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REVIEW ARTICLE

Decoding the mystery of non-nutritive sweeteners

Sachdev Meenakshi[1] · Viswanathan Mohan[2]

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Abstract

Background This commentary explores the landscape of non-nutritive sweeteners, further delves into the historical trajectory and the contemporary surge in the consumption of non-nutritive sweeteners (NNS), along with the accompanying controversies concerning their safety.

Objective The aim is to provide a comprehensive understanding of the influences of NNS, drawn from global studies and diverse perspectives.

Methods The commentary synthesizes findings from global studies, notably the NutriNet-Santé cohort, exploring associations between specific NNS and health consequences such as cerebrovascular events and malignancies. Additionally, it examines the research on consequences of NNS on gut microbiota and explores concerns linked to gestational diabetes, fetal exposure, and health of the offspring.

Results While caution is advised during pregnancy and fetal development due to potential risks, NNS show promise in weight management and short-term dietary goals when used cautiously in lower amounts. The commentary underscores the necessity for inclusive, long-term studies to guide evidence-driven policies and guidelines.

Conclusion While the article underscores the complexities and debates surrounding non-nutritive sweeteners (NNS), it also sheds light on the positive aspects. In the Indian context, where the intake of sweeteners is relatively low and mainly limited to beverages (tea or coffee), NNS appear to be safe, but prudent use is advocated. The article emphasizes the value of public education on NNS usage and concludes that, overall, NNS are reasonably safe when consumed in moderation. Continued research is needed to elucidate their intricate effects on health and impact on global health outcomes.

Implications The article concludes with clear guidelines for using NNS in India, highlighting the need for informed decision-making and ongoing research to elucidate their broader health consequences.

Keywords Non-nutritive sweeteners · Low-calorie sweeteners · Artificial sweeteners · Non-caloric sweeteners

✉ Viswanathan Mohan
drmohans@diabetes.ind.in
https://www.mdrf.in
https://www.drmohans.com

1 Dietary Department, Tamil Nadu Government Multi Super Specialty Hospital, Chennai, India

2 Department of Diabetology, Madras Diabetes Research Foundation, (ICMR Centre for Advanced Research On Diabetes) & Dr. Mohan's Diabetes Specialities Centre, (IDF Centre of Excellence in Diabetes Care), No 4, Conran Smith Road, Gopalapuram, Chennai 600 086, India

Navigating the sweet spectrum: the perplexing mystery of non-nutritive sweeteners

Throughout the ages, the sweet taste has remained one of humanity's most cherished flavors. However, for many years, it has been common knowledge that consuming excessive sugar can lead to detrimental health consequences. Non-nutritive sweeteners (NNS) have garnered a significant position among the most sought-after alternatives to sugar. They were primarily used before the 1950s for cost reasons because they were less expensive than sugar [1]. These sweeteners have the potential to satisfy sweet cravings without contributing to the excessive caloric load and risks of dental caries associated with sugar consumption [2, 3]. The growing prevalence of obesity, diabetes, and metabolic syndrome, along with increased consumer awareness, has triggered a progressive trend towards the use of low/zero caloric artificial sweeteners. NNS when consumed within acceptable daily limits (ADI) can help in limiting carbohydrate and energy consumption as a means to optimize weight [4]. Thus, their use has skyrocketed since the 2000s due to their presence in "lower calorie" food products and pharmaceuticals [5]. However, their usage has sparked controversies and concerns that merit thorough exploration in a balanced commentary.

Low-calorie sweeteners, artificial sweeteners, and non-caloric sweeteners have been designated as NNS by the American Heart Association since they do not provide any nutritional advantages such as of vitamins and minerals [6]. Aspartame, acesulfame-k, neotame, saccharin, and sucralose are USFDA (United States Food and Drug Administration)–approved NNS for use within the acceptable daily intake (ADI) levels in foods and beverages [7]. While these sweeteners have received approval from the USFDA, recently some concerns regarding the safety and long-term effects of certain sweeteners have arisen thereby leading the World Health Organization to advise restricting the consumption of non-sugar sweeteners in adults without diabetes, whenever possible [8, 9].

Guidelines and research on NNS: showing their safety

Numerous research studies and reviews have showcased the safety of NNS. The RSSDI-ESI (Research Society for the Study of Diabetes in India (RSSDI) and the Endocrine Society of India (ESI) recommendations 2020) advocates that artificial sweeteners when consumed in prescribed doses within the ADI are deemed to be safe [10]. Recently, a WHO (World Health Organization) meta-analysis indicated that NNS may have no effect on glucose metabolism and result in decreased body weight when combined with short-term dietary restriction [11]. The American Diabetes Association (ADA) advised, in the recent past, replacing up to one-third of white granulated sugar with artificial sweetener in diabetes-aware recipes [12]. NNS-containing beverages, when used as a replacement for sugar-sweetened beverages (SSBs), may provide cardiometabolic benefits among overweight/obese/type 2 DM (T2D) individuals [13]. A recent study from India investigating the effects of replacing added sugar with NNS in overweight and obese participants demonstrated significant reductions in adiposity indices and improvements in cardiometabolic parameters [14]. Furthermore, the study findings indicate that this substitution also led to reduced cardiometabolic risk factors among individuals with type 2 diabetes T2D [15].

Unsweetening the debate: evaluating NNS and the diseases risk data

Nonetheless, recent discoveries in several research studies have examined the potential adverse health consequences stemming from the excessive and extended consumption of NNS especially when used maybe solely for calorie restriction or weight reduction in people without diabetes, as detailed below:

A European Prospective Investigation into Cancer and Nutrition cohort of 477,206 participants from 10 European countries with a follow-up for 11.5 years found that daily consumption of approximately 6 servings per week of combined soft drinks (sugar sweetened and artificially sweetened) was positively associated with hepatocellular carcinoma [16]. After analyzing data from 24 population-based epidemiological studies, which included a total of 93,095 participants and 20,749 individuals with metabolic syndrome (MetS), a meta-analysis revealed significant positive associations between NNS and MetS risk. Their findings indicated that the risk of MetS increased by 31% with each 250 ml/day increase in NNS-sweetened beverage consumption [17]. The WHO meta-analysis on NNS published in 2022 suggests that NNS may temporarily substitute sugar in overweight/obese patients, yet it is unclear about the risks of cardiometabolic diseases and other long-term effects [8, 9]. Following this, the CARDIA study concluded that habitual, long-term aspartame and saccharin intake independent of total caloric intake and diet quality are related to greater volumes of visceral, intermuscular, and subcutaneous adipose tissue [18]. Recently, ADA 2023 proposed the link between artificial sweeteners consumption and an increasing incidence of T2D suggesting that these may not be safe sugar substitutes [19].

Bitter truths and sweet surprises: the gut-NNS connection

The impact of sweeteners on gut microbiota composition is still under debate. Even though there are some lacunae in the evidence associated with the health effects of NNS in both healthy and non-healthy populations, the USFDA, EFSA (European Food Safety Authority), and Codex Alimentarius consider them safe and well-tolerated, as long as the consumption is limited to NNS-specific ADI [20]. A number of the bacterial groups that exhibited alterations after consuming NNS had previously been linked to type 2 diabetes in humans [21]. However, a recent 12-week study investigated the effects of sucralose in coffee, tea, and fruit juices on the gut microbiome of 38 Asian Indian adults with type 2 diabetes. While no significant changes were observed in the gut microbiome, sucralose consumption resulted in significant reductions in body weight and body fat percentage [22]. The findings from both short- and long-term human cohorts consuming NNS indicate that individuals have unique responses to NNS, which may be linked to the variations in their gut micro biota composition and function [23]. RSSDI 2022 recommends that artificial sweeteners should be restricted as they alter the diversity of the gut micro biome and can increase insulin resistance [24].

Table to cradle: are NNS safe in pregnancy?

According to a study, sucralose and stevia are considered to be the safest sugar substitutes for pregnant women. However, there is limited research on the safety of acesulfame-K and polyols during pregnancy. Saccharin is not recommended for pregnant women as it crosses the placenta. Pregnant women with hyper phenylalaninemia should avoid aspartame [25].

An observational study linked consumption of NNS-containing beverages to an increased risk of gestational diabetes mellitus (GDM) [26]. According to a systematic review and meta-analysis study, NNS consumption was associated with an increased risk of preterm birth, higher birth weight, and a shorter gestational age [27]. NNS was also speculated to have the ability to influence fetal metabolic programming. These observations raise the concern about transplacental fetal exposure to NNS [28]. Traces of limited NNSs can be found in amniotic fluid and breast milk, attracting attention to the probable effect of long-term exposure on the health of the fetus/infant. This effect of chronic exposure of the fetus/infant to low levels of several NNSs is not clear [29]. Based on human studies, maternal NNS consumption during pregnancy has been associated with an increase in offspring's weight. Additionally, it is intertwined with higher infant BMI at 1 year, as well as an increased risk of the infant being overweight [30, 31]. One study found a significant positive correlation between intrauterine NNS exposure and birth size, as well as an elevated risk of overweight or obesity in children aged 7 years [32]. The safety and potential consequences of NNS consumption during pregnancy warrant further investigation, as limited research suggests associations with adverse outcomes for both mother and infant. It would be prudent to advise all pregnant women to avoid NNS during the pregnancy period.

Deciphering the enigma: aspartame and dietary methanol

A large French population–based prospective cohort study (NutriNet-Santé 2009–21) of 103,388 adults with a follow-up duration of 9 years revealed that aspartame consumption was linked to an increased risk of cerebrovascular events, and excess acesulfame potassium and sucralose consumption was linked to an increased risk of coronary heart disease [33]. Moreover, when compared with 102,865 non-consumers, the intake of aspartame and acesulfame-K was associated with an elevated overall risk of obesity-related malignancies. Notably, aspartame exhibited a more significant risk, particularly in relation to breast cancer with a follow-up duration of 7.8 years [34].

Aspartame was classified by IARC (International Agency for Research on Cancer) as possibly carcinogenic to humans (IARC Group 2B) based on a few evidence of carcinogenicity in humans. However, despite this classification, JECFA (Joint FAO/WHO Expert Committee on Food Additives) reaffirmed the acceptable daily intake of 40 mg/kg body weight for aspartame. In response to this, WHO has reported continuing to monitor with vigilance along with IARC and support further research on the connection between aspartame exposure and long-term health effects [35].

Breaking sweet barriers: exploring non-nutritive sweeteners in type 1 diabetes research

While most children with type 1 diabetes can consume NNS within safe ranges (NNS-specific ADI), caution is necessary for those consuming higher levels of the NNS [36]. Furthermore, study findings suggest that children with type 1 diabetes in Canada generally consume NNS below acceptable daily intake (ADI) levels, indicating a low likelihood of significant impacts on blood glucose control or body weight. However, the study's small sample size and limitations emphasize the need for further research to validate or refute these results [37]. In general, NNS are not advised for children below 12 years of age.

Tying the threads: bitter or better?

Despite the growing body of research and heightened interest in NNS, our understanding of their effects remains significantly limited. Notably, there is a paucity of human studies on nutritive sweeteners, underscoring the need for more comprehensive investigations. To address this knowledge gap, the establishment of robust randomized control trials (RCTs) incorporating substantial population samples over extended periods is of paramount importance. By subjecting NNS to rigorous scrutiny through such well-designed RCTs, we can thoroughly assess potential adverse effects and safety considerations associated with these non-caloric sweeteners.

While certain long-term cohort studies have identified correlations between non-nutritive sweetener consumption and disease risks, it is essential to acknowledge the inherent limitations of these investigations, often confined to specific populations or geographic regions. Consequently, their generalizability on a global scale is restricted. To overcome this limitation, it becomes imperative to conduct further long-term cohort studies that encompass diverse populations from various regions worldwide. Specifically, more studies are needed in Indian populations' where the consumption of NNS is not huge or is it in large quantities as in the West and in the Middle East. Such an inclusive approach aims to yield a comprehensive evaluation of the safety and potential health implications of NNS.

By assimilating data from wide-ranging and diverse populations, the insights gained from these longitudinal studies hold promising prospects for informing the development of health protocols, facilitating evidence-based decision-making, and ultimately safeguarding public health. As researchers, our commitment lies in striving for a nuanced and thorough understanding of the effects of NNS, laying the groundwork for evidence-driven policies and guidelines that can positively impact global health outcomes.

Diverse research data highlights the potential adverse health effects of artificial sweeteners, sparking public debate. Further study is needed to understand their impact on inflammatory pathways and non-communicable disease development. Though NNS may help limit the total energy intake (TEI) of sugar to lesser than 10%TEI, the long-term safety of NNS still remains uncertain. A higher risk of hypertension, insulin resistance, raised blood glucose, abdominal obesity, and dyslipidemia has been associated with long term and consumption of NNS in large quantities whether this is related to excess calorie consumption or other confounders is not clear. The impact of NNS on the cardiovascular system is still unclear, and further research is required [38]. Until comprehensive, long-term studies offer conclusive evidence, it is advisable to avoid intake of large doses of NSS [8]. This calls for informed choices and awareness, aiming for safer alternatives and promoting healthier lifestyles. Moreover, it is not clear whether the adverse effects of NNS apply to all or only to specific ones like Aspartame.

What did the WHO meta-analysis conclude?

The 2022 meta-analysis conducted by the World Health Organization (WHO) examined and advised that NNS consumption below the acceptable daily intake is generally considered safe. While the analysis did not establish a direct link to cardiometabolic disorders, it highlighted the need for caution regarding potential long-term effects. Short-term use may benefit those dealing with weight issues. An additive does not pose safety concerns provided the anticipated daily intake is less than or equal to the ADI [7]. There is an urgent need for appropriately planned randomized controlled studies to review their effectiveness in different populations. The WHO made it very clear that their cautions regarding NNS did not apply to those with diabetes. It was mainly means for those using NNS in large quantities with weight reduction as their goal for which the WHO felt that the NNS was better avoided.

What about use of NNS in India?

In India, most of the NNS intake is related to their coffee and tea where only a small amount of the NNS is added. However, it is important to note that aspartame is not heat stable hence better avoided in hot beverages [39]. The consumption of sweetened beverages using artificial sweeteners is, as of now, not very high in India. Given the low intake of sweeteners which are well within the acceptable daily intake (ADI) allowed for sweeteners, there is not much of concern, as of now, regarding the use of sweeteners in India. However, learning from the experience in the West where there is indiscriminate and large-scale use of sweeteners has resulted in some adverse effects, it would be prudent to advise use of artificial/alternate sweeteners only in limited quantities and not to go overboard with their use. Moreover, the use of artificial sweeteners to prepare deserts or sweets, where sweeteners would be used, should be discouraged. We should also educate people that just because sugar is replaced with a sweetener, a sweet dish like a dessert does not become healthy, since it may still be calorie dense, which also depends on the type and quantity of fat and carbohydrate used for the preparation. ADA recommends health care providers should continue prescribing reduction in consumption of sugar and calories with or without the usage of NNS. At the same time, moderate quantities of sweeteners can be consumed by people living with diabetes with a sweet tooth, provided it reduces the total calorie and carbohydrate consumption. Since NNS have been subjected to thorough safety assessments by regulatory bodies, one could be reassured that as of now, population-specific USFD-approved sweeteners can be considered reasonably safe within their acceptable daily intake [40].

'TEN ' Guidelines for use of Non-nutritive sweeteners (NNS) in India

1. Avoid all NNS in pregnancy.
2. Preferably avoid all NNS in children.
3. Aspartame should not be added to hot beverages.
4. Aspartame must be avoided by those with Phenylketonuria.
5. Do not use NNS to prepare desserts and sweet dishes where large quantities may be required for optimizing taste.
6. Remember just because sugar is removed and replaced with NNS, a dessert or sweet can still be unhealthy because of high calorie and fat content.
7. Do not use NNS as part of weight reduction program as their efficacy is not established.
8. Use of NNS particularly stevia or sucralose in small quantities along with tea and coffee appears to be safe.
9. WARNING: Do not exceed Acceptable Daily Intake (ADI) of sweeteners.
10. More Indian data (particularly long term) is required.

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Declarations

Competing interests Zydus Wellness has supported studies on Sucralose done by the Madras Diabetes Research Foundation.

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