

## Review Article

# Reducing the Sugar Burden using Non-Nutritive Sweeteners: Review of Evidence and Recommendations

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## Abbreviations

ME: Middle East; NR-NCD: Nutrition-Related Non-Communicable Diseases; WHO: World Health Organization; NNS: Non-Nutritive Sweeteners; RCT: Randomized Controlled Trials; CVD: Cardiovascular Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; NHANES: National Health and Nutrition Examination Survey; MENA: Middle East and North Africa Region; FDI: Federation Dentaire Internationale; FAO: Food and Agricultural Organization; BMI: Body Mass Index; UAE: United Arab Emirates; US: United States; FDA: Food and Drug Administration; GRAS: Generally Recognized as Safe; Ace-K: Acesulfame-Potassium; NTP: National Toxicology Program; NIH: National Institute of Health; EFSA: European Food Safety Authority; FSANZ: Food Standards Australia and New Zealand; HC: Health Canada; JECFA: Joint WHO/FAO Expert Committee of Food Additives; ADI: Acceptable Daily Intake; NOAEL: No Observed Adverse Effect Level; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CINAHL: Cumulative Index to Nursing and Allied Health Literature; ADA: American Diabetes Association; NCI: National Cancer Institute

## Introduction

Consumption of added sugars has been implicated in increased risk of a variety of chronic diseases including obesity, Cardiovascular Disease (CVD), diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD) as well as cognitive decline and even some cancers [1-4]. Analysis of National Health and Nutrition Examination Surveys

## Abstract

Consumption of added sugars has been implicated in an increased risk of a variety of chronic diseases including obesity, cardiovascular diseases, diabetes as well as cognitive decline and some cancers. Middle East (ME) region suffers from high rates of nutrition-related non-communicable diseases (NR-NCDs), as well as a high intake of sugar, higher than the level recommended by the World Health Organization (WHO). FDA approved Non-Nutritive Sweeteners (NNS) are commonly used as sugar substitutes as they are sweeter than sugar and contribute negligible calories when added to food, making them a desirable substitute to sugar for dietary management of diabetes, obesity and the NCDs. Safety concerns have been raised in the ME region regarding the safety and efficacy of NNS and their efficient use in foods.

Data from animal and observational studies and evidence from systematic reviews and meta-analyses of Randomized Controlled Trials (RCTs) have shown the potential of NNS as a safe replacement for sugar but have, at times, reported caution for their use as harmful to health. This paper aims to review the available published data on the safety of NNS and provide evidence-based recommendations for their use in the Middle East region.

**Keywords:** Sugar; Sweetener; Non-nutritive sweetener; Low calorie sweetener; Artificial sweetener; High intensity sweetener; Safety

(NHANES, 1988-1994, 1999-2004, and 2005-2010) demonstrated a significant increase in cardiovascular mortality with increasing levels of sugar intake [5]. A systematic review, commissioned by the World Health Organization (WHO) in 2012, included a total of 68 trials, and concluded that reduced intake of dietary sugars was associated with a decrease in body weight [6]. A systematic review of 8 human epidemiologic studies on sugar and dental caries demonstrated a significant increase in the risk of dental caries with increasing level of sugar intake, especially above 10% of total calorie intake [7]. Further clinical trials have shown that excessive sugar consumption may be associated with an increased risk of cancer [8-10].

The Middle East and North Africa region (MENA) has very high intake of sugar, higher than the levels recommended by the WHO. Data on sugar consumption from the second edition of the Oral Health Atlas published by the Federation Dentaire Internationale (FDI) World Dental Federation in 2011 indicates that most countries in our region consume sugar at 15% of total energy intake i.e. approximately 75 g sugar per person per day (Table 1) [11]. WHO 2015 data indicates that calorie intake in the MENA region has escalated from 2290 Kcal per capita per day in the years 1964-1966, to 3090 Kcal per capita per day in the year 2015, and is estimated to reach 3170 Kcal per capita per day by the year 2030 [12]. The 2012 food-based dietary guidelines, promoted by Food and Agricultural Organization (FAO) and WHO, noted that overconsumption of foods rich in sugar leads to poor dental health and an increase in energy intake, which contributes to weight gain [13].

According to WHO 2014 figures, the Eastern Mediterranean

**Table 1:** Average sugar consumption per person per day in 2011 [11].

Region	Global	MENA							
		UAE	Saudi Arabia	Kuwait	Lebanon	Egypt	Iran	Turkey	Jordan
Sugar intake (g/person/day)	109	76-100	76-100	76-100	>100	76-100	76-100	76-100	>100

MENA: Middle East and North Africa region; UAE: United Arab Emirates

Region has the third highest mean Body Mass Index (BMI), after North America and Europe. The highest levels of obesity worldwide for adolescents and adults aged 15 years and older are reported in Egypt, Bahrain, Jordan, Kuwait, Saudi Arabia and the United Arab Emirates (UAE). The prevalence of those who are overweight and obese in these countries ranges from 74-86% in women and 69-77% in men [14]. The increased rates of obesity and associated Nutrition-Related Non-Communicable Diseases (NR-NCDs) in the ME region is related to the overconsumption of harmful foods (high calorie intake) and lower consumption of protective foods. It is also thought that reduced rates of physical activity could be a contributing factor [15]. It is estimated that the prevalence of diabetes in the UAE increased by approximately 10% between 2005 and 2015 [16,17], an upward trend that shows no sign of abating. Similar concerning trends can be seen with the other NR-NCDs, including CVD and cancer. In 2015, CVD accounted for one third of deaths in the ME region, with a disease burden ranked higher than the global average [18]. Historically, cancer rates in the region were lower than the in Western countries; however, with huge economic, social and demographic changes over the past few decades, cancer is now the third leading cause of death, with incidence rates predicted to double from 2013 to 2020 [19].

Experts from the region recommend a reduction in the intake of foods and drinks high in sugar, in an attempt to curb diet-related diseases [13]. The WHO strongly recommends daily sugar intake for children and adults to be no more than 10% of total energy intake (approximately 50 g), and in some cases, even as low as 5% (approximately 25 g) [11,20]. Given the extraordinarily higher rates of obesity and diabetes in the Eastern Mediterranean region, 5% (~25 g) is seen as the most appropriate long-term goal for our region by the WHO [21].

NNS are commonly used as sugar substitutes or sugar alternatives because they are sweeter than sugar, and when added to foods, contribute only a few to no calories [22,23]. The use of NNS provides an important alternative for food and drink manufacturers (and ultimately consumers) to retain a sweet taste, whilst eliminating, or substantially reducing, the calories in a certain food or drink. These agents are used in a variety of food and drink products, including soft drinks, chewing gum, confectionery, frozen desserts, yoghurts, dessert mixes and puddings. They are widely used by people all over the world [23]. The literature suggests that Non-Nutritive Sweeteners (NNS), approved by the United States Food and Drug Administration (US FDA) have the potential of limiting sugar intake and curbing the associated disease risks, however, the safety of NNS have been questioned in several publications, including Randomized Control Trials (RCTs), observational studies and animal data [22].

This paper aims to review the available published data on the safety of NNS and provide evidence-based recommendations for their use in the Middle East region.

### Non-nutritive sweeteners approved as food additives

Most of the NNS are very low in calories or contain no calories

at all [23]. This review included aspartame as an NNS since its caloric value is almost negligible.

Currently, six different NNS are approved by as food additives, including saccharin, aspartame, acesulfame-potassium (acesulfame-K or Ace-K), sucralose, neotame and advantame [23]. They are selected by consumers and industry based on their adequacy for the preparation method being used and according to the type of food being prepared.

Stevioside and rebaudioside A (extracts of the *Stevia Rebaudiana* Bertoni plant), are used and regulated as dietary supplements [23]. However, *Stevia* leaf or its crude extracts are not considered generally recognized as safe ("GRAS"), and do not have FDA approval [24].

**Saccharin:** First discovered and used in 1879, saccharin is 200 to 700 times sweeter than table sugar (sucrose), and it does not contain any calories [23]. In the early 1970s, saccharin was linked with the development of bladder cancer in lab rats, which mandated additional studies of saccharin and the presence of a warning label on saccharin-containing products [23]. Since then, several human studies demonstrated that the results found in rats were not relevant to humans, and that saccharin is safe for human consumption [23,25,26]. In the year 2000, the National Toxicology Program (NTP) of the National Institute of Health (NIH) in the United States (US) concluded that saccharin should be removed from the list of potential carcinogens [23]. Products containing saccharin no longer have to carry the warning label in the US [23]. Saccharin is also approved by the European Food Safety Authority (EFSA) as an intense sweetener permitted for use in food preparation [27].

**Aspartame:** Aspartame is made of the two amino acids aspartic acid and phenyl alanine. It is about 200 times sweeter than table sugar [23], and was approved by the 1981 as a table top sweetener and in products such as chewing gums, cold breakfast cereals and dry bases foods (i.e., beverages, instant coffee and tea, gelatine, puddings, fillings, and dairy products and toppings).

Aspartame is one of the most exhaustively studied substances in the human food supply, with several studies supporting its safety [23,28-33]. In 1983, US FDA approved the use of aspartame in carbonated beverages and in 1996, for use as a "general purpose sweetener" [23]. It was also reviewed and approved by the EFSA [23,34]. Labels of aspartame-containing foods and beverages must include a statement informing individuals with a rare hereditary disease known as phenylketonuria that the product contains phenylalanine, as they have difficulties in metabolising it [23]. Recently, a review was conducted that revisited the safety of aspartame; the authors expressed caution in arriving at a definitive conclusion, as most of the safety studies evaluated were based primarily on animal models due to limited data from human studies [35].

**Acesulfame potassium:** Acesulfame potassium (Ace-K) is about 200 times sweeter than sugar and is often combined with other

sweeteners. US FDA approved Ace-K for use in specific food and beverage categories in 1988, and in 2003 approved it as a general purpose sweetener and flavour enhancer in food, except in meat and poultry. Unlike aspartame, it is heat stable, making it suitable as a sugar substitute in baked goods. Ace-K is typically used in frozen desserts, candies, beverages and baked goods. According to the FDA over 90 studies support the safety of Ace-K as an NNS [23,36,37]. Ace-K is also approved by the EFSA as an intense sweetener permitted for use in foodstuffs [27,38,39].

**Sucralose:** Sucralose is a non-caloric sweetener about 600 times sweeter than sugar, and was approved by the US FDA for use in 15 food categories in 1998 and for use as a general-purpose sweetener for foods in 1999. It is a general-purpose sweetener that can be found in a variety of foods including baked goods, beverages, chewing gum, gelatine and frozen dairy desserts. It is also heat stable like Ace-K [23]. Sucralose has been extensively studied and several safety studies in humans are available [23,40-45]. US FDA reviewed several safety trials before approving the use of sucralose as a general-purpose sweetener for food [23]. A recent EFSA review also reaffirmed the safety of sucralose as a food additive [27].

**Neotame:** Neotame is approximately 7,000 to 13,000 times sweeter than table sugar [23]. US FDA approved neotame in 2002 for use as a general-purpose sweetener and flavour enhancer in foods (except in meat and poultry). It is heat stable, and has proven safety; US FDA had reviewed data from animal and human studies designed to identify possible toxic effects, including effects on the immune system, reproductive system, and nervous system [23]. Similarly, after considering all the data on stability, degradation products and toxicology, the EFSA panel concluded that neotame is not of safety concern with respect to the proposed uses as a sweetener and flavour enhancer [46].

**Advantame:** Advantame is approximately 20,000 times sweeter than table sugar. US FDA approved advantame in 2014 for use as a general-purpose sweetener and flavour enhancer in foods (except in meat and poultry) [47]. It is heat stable, and has proven safety [48]; US FDA reviewed data from several animal and human studies designed to identify possible toxic effects for advantame, including effects on the immune system, reproductive and developmental systems, and nervous system, as well as pharmacokinetic and carcinogenicity studies, in addition to several exploratory and screening studies [23]. Similar evaluation by EFSA concluded that advantame and its metabolites pose no safety concern for consumers at the levels approved for use as a sweetener, which led to its approval as an NNS [49].

**Steviol glycosides:** Steviol glycosides are natural constituents of the leaves of *Stevia Rebaudiana* Bertoni, a plant native to parts of South America and commonly known as *Stevia*. There are three types of products available from *Stevia* i.e. high purity steviol glycosides, *stevia* leaf and its crude extracts; however only high purity steviol glycosides are approved by the US FDA [24]. They are reported to be 200 to 400 times sweeter than table sugar. High purity steviol glycosides are GRAS, and as such do not require US FDA approval as a food additive [23]. Based on its review of information and data submitted by industry in GRAS notices, has granted the GRAS status to certain high-purity steviol glycosides for use in food [24].

Similarly, high-purity steviol glycosides are also approved as safe for human consumption by the EFSA [50]. However, *stevia* leaf or its crude *stevia* extracts are not considered GRAS and do not have FDA approval for use in food [24].

### Non-nutritive sweeteners and disease risk

NNS have been extensively studied in terms of their associated risk with the development of non-communicable diseases such as cancer, cardiovascular disease, chronic kidney disease, asthma, allergies and mood or behaviour changes. Any evidence of a link appears to be inadequate [51]. NNS are some of the most extensively tested products by the US FDA, as well as many of the world's leading regulatory committees including the EFSA, Food Standards Australia New Zealand (FSANZ), Health Canada (HC) and the Joint WHO/FAO Expert Committee of Food Additives (JECFA). These regulatory bodies have extensively evaluated studies on the health impact of NNS and examined potential side-effects. They have consistently confirmed that all approved NNS are safe [52]. Some key aspects, including absorption, metabolism and excretion of these compounds have been documented in detail. Thus, appropriate interpretation and utilisation of these valuable data should suffice to address the controversies surrounding their use. As NNS have the potential to be useful tools in the management of diabetes and excessive caloric and sugar intake, it is important for healthcare professionals to be well-versed in their efficacy and safety, along with retaining a basic understanding of the differences among individual NNS agents and their metabolism [53]. Some key aspects of safety are discussed in a separate section of this article.

### Acceptable daily intake of non-nutritive sweeteners

Acceptable Daily Intake (ADI) is the amount of the food additive, expressed as mg/kg body weight, which can be ingested daily over a lifetime without incurring any health risk. Currently approved NNS agents are allocated a numerical ADI. This value is linked to the "No Observed Adverse Effect Level" (NOAEL) that is determined from the most sensitive studies in the most sensitive species tested (Table 2) [46,54].

A review by Martyn et al. [55] examined published data on the intake of all major NNS globally over the last decade, for regions including Europe, Japan, Korea, and other Asian countries, Latin America, and Australia/ New Zealand. Global estimates were evaluated by the JECFA. The study concluded that "overall, while the robustness of the data can obviously be improved in the future... the data provide a significant level of comfort that there does not appear to be a significant shift in NNS intake and levels of exposure are generally within the ADI limits for the individual sweeteners" [55]. Adequate studies in the MENA region on the intake and safety of NNS are lacking, and specific data for the region could not be reported on, however globally there has been a considerable increase in sweetener consumption since the mid-20<sup>th</sup> century [56].

### Methods

This systematic literature review was conducted based on the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Furthermore, to increase the rigor of the review, search term, databases and inclusion/exclusion criteria were agreed upon with consensus between the

**Table 2:** Information about non-nutritive sweeteners approved for use.

Sweetener	Chemical Composition	Multiplier of Sweetness Intensity Compared to Table Sugar (Sucrose) [23]	ADI (mg/kg/d)		Number of Sweetener Packets Equivalent to ADI* [23]
			[23]	EFSA	
Ace-K	N-sulfonyl amide [38]	200 x	0-15	0-9 [39]	23
Aspartame	Aspartyl-phenylalanine methyl ester [38]	200 x	0-50	0-40 [39]	75
Advantame	Derivative of aspartame [47]	20,000 x	0-32.8	0-5 [54]	4,920
Neotame	Derivative of aspartame [38]	7,000-13,000 x	0-0.3	0-2 [46]	23 (sweetness intensity at 10,000 x sucrose)
Saccharin	N-sulfonyl amide [38]	200-700 x	0-15	0-5 [39]	45 (sweetness intensity at 400 x sucrose)
Sucralose	Trichlorinated derivative of sucrose [38]	600 x	0-5	0-15 [39]	23
Steviol glycosides**	Rebaudioside A, Stevioside, Rebaudioside D [23]	200-400 x	--	0-4 [54]	--

\*Number of sweetener packets a 60kg person would need to consume to reach the ADI (calculations assume 1 packet is as sweet as 2 teaspoons of sugar); \*\*steviol glycosides are not approved as food additives, but as dietary supplements by the US FDA.

ADI: Acceptable Daily Intake; US FDA: United States Food and Drug Administration; EFSA: European Food Safety Authority.

reviewers prior to starting with the review process. Since the main aim is to increase awareness in our region regarding the NNS as a whole and not focusing on an individual type, the official MeSH and Emtree term “non-nutritive sweeteners” was the scope of the search in over two dozen databases, with an initial search done on PubMed (MEDLINE). However, only 10 of those databases stood out to be most relevant and useful to the purpose: Arab World Research Source, Biosis Citation Index, CINAHL Complete, Cochrane, Embase, Food Science and Technology, Global Health, PubMed, Scopus, and Web of Science. Appendix A consists of a detailed description of the search process, including the type of search, records retrieved and the input query.

In an attempt to provide an evidence-based look at the current perception regarding NNS, keywords used were strictly related to the official MeSH term “non-nutritive sweeteners” and they included the following: low calorie sweetener, non-nutritive sweetener, non-calorie sweetener, artificial sweetener and high intensity sweetener. Despite the pronounced similarity in the wordings, the use of these key terms facilitated the retrieval of data from the searched databases, which included everything relevant to the paper.

The search was not limited to a publication year, nor to a document type; hence, the search targeted journal articles, books, theses, letters and conference papers. Additionally, given that the conducted review was a global comprehensive search, all English written documents in the literature were screened, without any restriction to publication years. However, out of scope documents, including findings related to paediatrics, organ toxicity, chemical assays, metabolites, and pharmacokinetic studies, were excluded from the review.

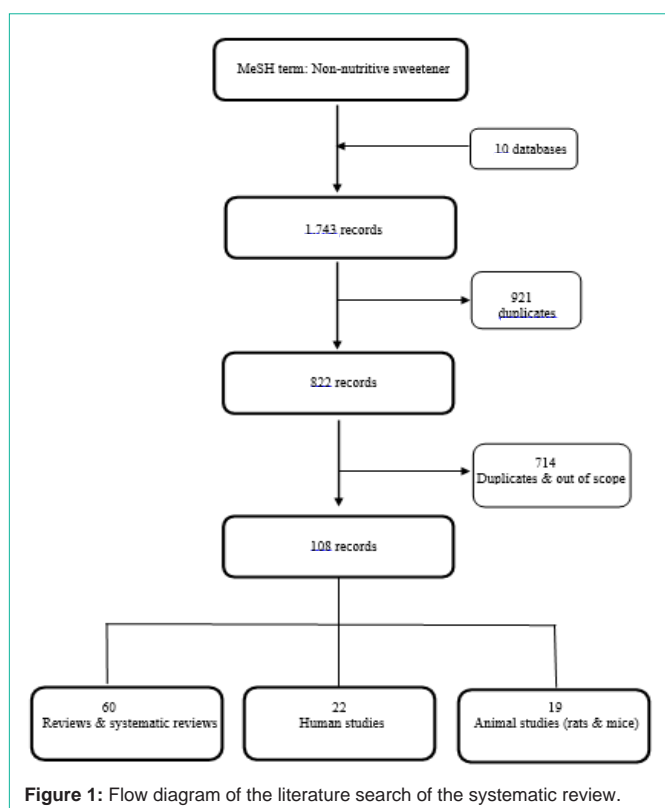
Each reviewer independently searched the databases by screening the titles, abstracts, headings, and keywords, which was subsequently followed by a thorough examination of the articles that were eligible. Afterwards, findings were discussed between reviewers in order to decide on the final papers to be included based on their relevance to the objectives of the review and according to the inclusion/exclusion criteria mentioned earlier. Abstracted information was based on certain characteristics (title, abstract, keyword, heading), and any disagreement was resolved by discussion between the reviewers to

reach a final decision.

The initial search resulted in a total of 1,743 records, which were reduced to 822 after removing duplicates among the 10 databases. A further filtration considering the inclusion and exclusion criteria (i.e. articles not in English or out of scope) generated a final count of 108 records. A manual screening of the findings resulted in the following breakdown: 60 reviews and systematic reviews, 22 human clinical trials, 19 animal studies (mainly rats and mice) and 7 articles about NNS in general. A further scrutiny of the articles led us to choose a total of 86 articles that were deemed suitable for the aim of this review. These were chosen based on topics relevant to our area of interest, such as the influence of NNS on sweet taste cravings, safety in pregnant women, impact on glycaemic response, role of NNS in diabetes management, effect of NNS on weight gain and cardio metabolic risks, assessment of cancer risk with NNS usage, and contribution of NNS to dental health. Figure 1 is a flow diagram of the included articles in the systematic review. A table containing all 86 articles considered for this review is included as Appendix B.

### Evidence addressing specific concerns with non-nutritive sweeteners

**Influence of NNS on sweet taste cravings:** Studies reported that NNS may prevent individuals from associating sweetness with caloric intake and, as a result, alter their intake, craving more sweet food and choosing this over nutritionally valuable food, contributing to weight gain [50,51]. Similarly, some articles on rodents showed that when they were exposed to NNS, either in utero or through breastfeeding, they exhibited heightened preferences for NNS in adulthood [58-60]. On the other hand, current evidence from adult and paediatric cohorts, does not show any consistent association between NNS intake and increased cravings for sugar or sweet products and suggests that NNS usage tends to lower the intake of sweet-tasting substances, suggesting a potential role in satisfying the desire for sweetness [61]. A recent systematic review by Appleton KM et al. [62] confirmed that the available evidence does not indicate that repeated exposure to sweetness can lead to habituation of sweet taste in children or adults [62]. The latter review also reported that exposure to sweet tastes from dietary sources with low quantities of sugars, for example those sweetened with NNS, may not only



replace consumption of free sugars but could also reduce the desire for sweetness [62]. Additionally a recent meta-analysis of clinical studies on NNS and sweetness concluded that NNS may offer, to some extent, the advantage of satisfying desire for sweetness when consumed shortly before or with a meal [63]. A study supported by the Netherlands Organization for Health Research and Development in 4-12 year old children found that NNS consumption tends to reduce, rather than increase, the intake of sugar-containing foods and facilitates weight loss, as indicated by reduced weight gain and fat accumulation in normal-weight children [64]. Another study among 7-11 year old Dutch primary school children showed that sugar-sweetened and sugar-free beverages produced similar satiety, and children consuming sugar-free beverages did not make up for the missing calories from other sources [65]. This perhaps explains why the sugar-free group had less body fat than the sugar group [65].

**Safety of NNS in pregnant and lactating women:** Data reviewed by Araujo JR et al. [66] concluded that animal studies showed long-term consumption of NNS, particularly aspartame, starting during the peri-gestational period, may predispose the offspring to develop obesity and metabolic syndrome later in life [66]. However, the authors expressed caution in extrapolation to humans since well-designed clinical studies evaluating NNS metabolic effects in humans are still lacking [66]. In the review by Sylvetsky et al. [58] it was also determined that NNS ingested by lactating mothers are passed to their infants in breast milk [58]. However, the author raised concern as to whether the concentration of NNS found in breast milk exerts any biological effects [58]. This requires further study. Leading global dietary authorities such as the US FDA, EFSA, FSANZ, HC, and JECFA have confirmed the safety of all approved NNS for all

population groups, including pregnant and breastfeeding women [52]. They noted that the available data do not suggest any adverse effects such as increased risk of toxicity, adverse pregnancy outcomes or neonatal issues when NNS is substituted for sugar in pregnancy within the established ADI [67,68]. Other published reviews did not find a clear relationship between early sweet taste experiences (from fruit and vegetable extracts & sweetened water) in utero and during early infancy, and later acceptance for sweet taste [69].

**Impact of NNS on glycaemic response:** The past decade was marked by significant interest in the ability of NNS to have an adverse effect on blood glucose control [43]. Grotz VL et al. [43] conducted a literature search and found that there were some studies which hypothesized that sucralose and other NNS can adversely affect blood glucose regulation, e.g., by affecting total insulin secretion, glucose uptake and/or glucose utilization either by direct effect or *via* effects on glucagon-like peptide-1 or gastric inhibitory polypeptide [43]. However the authors suggest that these studies were mostly conducted in animals, and testing methodologies and other factors may limit reliability of extrapolating results of studies in animals to overall effects on blood glucose control in humans [43]. On the contrary, multiple trials across the globe have provided evidence in support of NNS; claiming they do not affect postprandial blood glucose levels or promote insulin secretion in humans [27,43,70-73].

In parallel, several human studies in children and healthy, normoglycemic, normal-weight adult cohorts, as well as at-risk, diabetic, and overweight populations, demonstrate that NNS do not have any adverse impact on glucose uptake and glycaemic control [40,43,74-84]. Several meta-analyses support the inert nature of NNS with respect to glycaemic control [51,71,73]. There is also a lack of evidence from human *in vivo* studies for any clinical effect of NNS on the secretion of incretins [76].

### Role of NNS in diabetes management

A systematic review by Romo-Romo A et al. [71] included observational studies, clinical trials and meta-analyses, and assessed the association between NNS consumption and the development of metabolic diseases including type 2 diabetes, obesity, and metabolic syndrome [71]. The authors observed that some studies suggest an association between NNS consumption and development of metabolic diseases; however, the authors concluded that the evidence level of observational studies cannot establish causality [71]. Additionally, they also concluded the results obtained from clinical trials are contradictory, due to the heterogeneity in the population included, NNS studied, placebo use, exposure time and outcomes evaluated [71].

Alternatively, several health organisations globally such as the American Diabetes Association (ADA), EFSA, Academy of Nutrition and Dietetics in the US, and Diabetes UK recognise the role of NNS as a safe replacement to added sugar in healthy and diabetic populations [27,85,86].

In the US, a study by Anton et al. [83] in 2010 showed that sucralose, aspartame and stevia, decrease blood glucose and insulin response compared to sucrose, and concluded that stevia preloads significantly reduced postprandial glucose levels compared to sucrose preloads ( $p < 0.01$ ), and postprandial insulin levels compared to both

aspartame and sucrose preloads ( $p < 0.05$ ) [83].

Results from the 2001-2012 NHANES showed that the consumption of NNS beverages compared to water was associated with reduced intake of carbohydrates and sugar, with no adverse relationships to glycaemic responses [87]. Other systematic reviews and meta-analysis of RCTs showed that NNS consumption was not found to elevate blood glucose level [88].

### **Effect of NNS on weight gain, obesity and cardiometabolic risks**

The potential effects on weight gain, body composition and obesity in human and animal studies were reviewed by Archibald AJ et al. [89]. The study provided an overview of the current body of literature regarding prenatal and childhood exposure to NNS worldwide. It reported that “there is an emerging body of evidence from human and animal studies suggesting that early-life exposure to NNS may have adverse effects on cardio-metabolic health and development possibly leading to increased risk of obesity-related outcomes”. However, the authors noted that some studies found no association, or at least did not provide evidence of confounding variables, thus they concluded that “current evidence remains inconclusive due to the paucity of RCTs, lack of evidence from low and middle-income countries, limitations of observational studies, and lack of mechanistic studies” [89].

Some of the available literature on animal and limited human studies raise a concern regarding the increased weight gain and adverse cardiometabolic risks of NNS [90-93]. Azad M.B et al. [94] published a systematic review in 2017 to determine whether routine consumption of NNS was associated with long-term adverse cardiometabolic effects. The authors found that the evidence from RCTs did not clearly support the intended benefits of NNS for weight management, and observational data suggested that routine intake of NNS may be associated with increased BMI and cardio metabolic risk [94]. However, this observation has been addressed by Sievenpiper, J. L. K. et al. [95] who highlighted that important methodological considerations were overlooked in this systematic review. Furthermore, they noted that the findings were discordant with higher quality evidence from RCTs and were at high risk of reverse causality, among other important limitations, including publication bias, inconsistency, indirectness and imprecision in the pooled estimates [95]. Additionally, Nakajima, KI et al. [96] suggested that a potentially overlooked factor that might influence the effect of NNS on cardiometabolic health may be the timing of ingestion [96]. Evidence from well-designed studies shows that NNS beverages do not negatively impact the cardiometabolic risk factors [97].

In a review evaluating the latest research on the effects of NNS on the host microbiome, the gut-brain axis, glucose homeostasis and energy consumption; as well as their potential impact on obesity, Pearlman M et al. [98] noted that NNS are marketed as a healthy alternative to sugar and as a tool for weight loss. However, the authors acknowledged that many of the studies evaluating the effects of NNS on metabolic parameters were using rodent models, and although these models provide some insight into the effects of NNS, the outcomes are inconsistent in humans [98].

A brief report “NNS: Disturbing the Energy Balance Equation

in Adolescents?” was published on obesity in December 2017. The authors modelled dietary intake data collected for 2-19 year olds participating in the 2009-2010, 2011-2012, and 2013-2014 NHANES. Interestingly, the study results indicated that NNS beverage consumption is associated with obesity in US adolescents but showed no association between consumption of NNS foods and obesity. The authors did not discuss additional correlations that were identified in their models and concluded that observational findings should be further investigated to determine if NNS intake is related to obesity [99]. In addition, the authors noted that the study relied on self-reported dietary recall and there were differences in reporting by older children and parents of young children. They concluded that the observational nature of this study excludes any determination of relationship between cause and effect [99].

Comparing the efficacy of NNS or water for weight loss during a 12-week behavioural weight loss treatment program, Peters J.C et al. [100] suggested that NNS beverages can be part of an effective weight loss strategy. An article by Anton S.D. [101], however, suggested that these findings should be interpreted with caution, since longer term outcomes would be required to confirm these results and the potential mechanism(s) for the superior effects of NNS on weight loss outcomes observed in the original study remain unknown. Results from an additional one year RCT suggested that NNS beverages may be an effective tool for weight loss and maintenance within the context of a weight management program [102]. This result is consistent with the few other published long-term human trials that evaluated NNS for weight loss [103,104].

Evidence from well-designed, controlled human studies consistently showed that the consumption of NNS and/or foods and drinks containing them can be a useful tool in managing or lowering excess body weight [64,83,103-106]. Systematic reviews and meta-analyses of human studies also support these results [63,107,108]. A recent meta-analysis by Miller PE et al. [107] provided a rigorous evaluation of the scientific evidence on NNS and body weight and composition. The authors concluded that the findings from observational studies showed no association between NNS intake and body weight or fat mass; however, they also noted that the data from RCTs, which provide the highest quality evidence for examining the potentially causal effects of NNS intake, indicates that substituting NNS options for regular-calorie versions, results in a modest weight loss and may be a useful dietary tool to improve compliance with weight loss or weight maintenance plans [107]. Similarly, a meta-analysis conducted by de La Hunty et al. [108] demonstrated that using foods and drinks sweetened with aspartame instead of sucrose results in a significant reduction in both energy intake and body weight [108].

### **Assessment of cancer risk with NNS usage**

According to the currently available literature, the possible link between NNS and cancer seems to be negligible [21,102-113]. Early studies on cyclamate suggested that when it was given in combination with saccharin it caused bladder cancer in laboratory animals [121]. However subsequent carcinogenicity studies turned out to be negative [103,116]. As association between sucralose and cancer has also been proposed [122], however, this too is unsubstantiated [110].

Three case-control studies have shown no overall excess of bladder

cancer in association with use of NNS, nearly all of which contained saccharin [111]. Epidemiological studies in humans did not find the bladder cancer-inducing effects of saccharin and cyclamate that had been reported from animal studies in rats [123]. Saccharin has been extensively researched; over 5000 patients with bladder cancer have participated in case-control studies over 27,000 diabetics have been observed for 234,000 person-years. The cumulative relative risk from these case control studies is less than 0.98, while the standardized mortality ratio for bladder cancer in diabetics is only 70. After Analyzing these studies the authors concluded that saccharin is not related to human bladder cancer [124]. Additionally, a review of epidemiologic evidence conducted by Marinovich M et al. [112] found no consistent association between the use of aspartame and cancer risk [112]. Health authorities such as US FDA, WHO, EFSA, National Cancer Institute (NCI) have noted, on many occasions, that NNS are safe and do not cause cancer.

### Contribution of NNS to dental health

Oral health-related diseases such as dental caries are on a rapid rise in the Middle East region, largely attributed to poor awareness as well as contributing factors such as increased sugar consumption, inadequate oral hygiene practices and a high prevalence of smoking [125]. Carbohydrates present in the mouth are fermented by naturally occurring bacteria, resulting in the production of acid that leads to demineralization of the teeth and caries. NNS, however, cannot be metabolized by oral bacteria to form acids. This lack of sugar-related fermentation may offer protection from dental caries [126]. NNS are even utilised to improve the palatability of toothpastes, mouthwashes and fluoride supplements, thereby encouraging greater use. Indeed, the EFSA has approved the claim that chewing gum with NNS helps maintain tooth mineralisation and neutralise acids [127].

### Limitations

The main aim of our review was an attempt to create an awareness in MENA region regarding NNS and specific concerns regarding their usage. However, there was no region-specific data available and hence articles were chosen to give a global perspective to the reader. Only English language articles were considered during literature review.

### Conclusion

Following this review of available literature, NNS may appear to be safe for use as a sugar replacement, when used within the ADI limits. NNS may be effective in reducing energy intake, not increasing the sugar cravings and lowering the glycaemic response. They are also considered to be safe for consumption by pregnant and lactating women by leading global dietary authorities. Data also suggests they are safe for use by diabetic and obese individuals. They do not cause dental caries and the claims of possible risk of NNS to induce cancer are not substantiated by the available evidence. However, specific safety profiles for individual NNS need to be considered by healthcare professionals before making any recommendations. In the ME region, there are increased rates of obesity and associated NCDs. High sugar intake, which in turn leads to high calorie intake, is one of the major causes of these diseases. NNS could be a means of tackling the issue of sugar burden in the MENA region.

It is clear that more region-specific studies are needed on sugar and NNS intake, and their association with obesity, metabolic risk

factors, cardiovascular diseases and cancer, with the aim of generating culturally-specific, evidence-based recommendations for sugar intake reduction. Given their prevalence and widespread use, NNS and their physiological impact, remains an important topic of research. It is therefore important to caution against potential hazards or risks of NNS usage. Community education and awareness are crucial for disseminating the potential role of NNS as a safe alternative to sugar. Recommendations are needed for the industry when it comes to product's reformulation along with guidelines on packaging such as declaration of the chemical composition of the NNS in use.

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### Author Contributions

N.H. outlined and drafted the manuscript. A.A.D., K.A.-M., W.H.A., M.M.E.-D., L.C.I., S.M.S. provided critical comments and concepts during the meeting that were incorporated into the manuscript. They also reviewed and revised the draft manuscript and approved the submitted version.

### Conflicts of Interest

Each author received travel expenses and an honorarium for participating in the consensus meeting sponsored by PepsiCo, Inc, held on 4<sup>th</sup> May 2018, in Dubai, UAE.

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