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Review

Non-nutritive sweeteners and type 2 diabetes: Should we ring the bell?

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ABSTRACT

Non-nutritive sweeteners (NNS) were thought to be healthy sugar substitutes used instead of sugar for caloric and glycemic control but evidences blaming them for contributing to type 2 diabetes (T2D) are rising. We aim to investigate whether NNS consumption prevents or causes T2D. Articles of all designs conducted on humans were retrieved from three databases in addition to manually reviewed articles. The literature is highly heterogeneous, and conclusions vary with different studies' types and designs. While some studies highlighted the neutral effect of NNS on T2D or reported inconclusive evidences to make their conclusion, others either found NNS culprit for increasing the risk for T2D or reported their protective effect against it. Those results were changing after adjustment for confounders. Due to the inconsistency in the literature, well-designed studies that take into consideration all types of confounders are needed.

Research in context: **Evidence before this study:** The epidemic of obesity is the result of many factors and causes several chronic diseases where its association with type 2 diabetes is well established. The first line of treatment for obesity is lifestyle changes including physical activity and dietary intervention where non-nutritive sweeteners have received a high attention; those were thought to be healthy sugar substitutes used instead of sugar for caloric and glycemic control but several evidences have blamed them for having a role in the development of type 2 diabetes. In our paper, we aim to investigate whether non-nutritive sweeteners consumption prevents or causes type 2 diabetes. To respond to this question, an extensive search of the literature was conducted between October and December 2018 using the key terms "non-nutritive sweeteners", "artificial sweeteners", "high-intensity sweeteners", "type 2 diabetes" and "prediabetes" on three databases including Pubmed, Science direct and Scopus. Additional search for relevant articles was carried out manually from the reference list of selected articles. Animal studies, studies involving sugar alcohols or those conducted on children, adolescents, pregnant women, or on participants with diabetes were excluded. Human studies conducted from January 2004 to October 2018 were included and divided into observational, interventional, and systematic review and meta-analysis for discussion and analysis

Added value of this study: In the literature, the term high-intensity sweeteners has been used interchangeably with non-nutritive sweeteners, artificial sweeteners or low-calorie

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sweeteners but few articles, if any, clarified the difference between them. In our review, we gathered the different definitions and classifications and summarized them to help the reader understand the difference.

Since artificial sweeteners are nowadays widely used and prescribed for caloric and glycemic control, and are unintentionally consumed because they enter in the manufacturing process of thousands of products and due to their potential side effects reported in several studies, we found it interesting to gather, summarize and discuss the available results assessing the role of non-nutritive sweeteners in the development of type 2 diabetes. Those results showed the heterogeneity of the literature and the difficulty in having a firm conclusion; this helps researchers to profit from our study and to conduct well-designed studies leading to firm conclusions and recommendations.

Implications of all the available evidence: Despite the absence of strong conclusion that confirms the fact that non-nutritive sweeteners consumption increases the risk for diabetes, no firm conclusion rejects this statement. In result, the existing evidences in addition to our study should ring the bell for clinicians and practitioners who are prescribing those sugar-alternatives as "healthy substitute" to white sugar. Moreover, this encourages the manufacturers to search for a healthy natural alternative to artificial sweeteners to be used in the manufacturing process.

Contents

1. Introduction

Diabetes, "one of the great health-care challenges of the 21st century" [1], has a huge economic burden over the globe [2]. It's a chronic condition where absent, insufficient or inactive insulin causes hyperglycemia leading to the disease. Untreated, diabetes increases the risk of disability [3] and causes several complications, delayed or prevented with early diagnosis and adequate intervention [4]. Worldwide, there are 425 million individual with diabetes expected to become 625 million by 2045. In 2017, "diabetes accounted for 10·7% of global all-cause mortality" among people aged 20–79 years and 51·8% of deaths before the age of sixty in the Middle East and North Africa were due to diabetes or its complications [4].

Diabetes is diagnosed based on one of the criteria mentioned in Table 1 and is classified into four categories: type 1 diabetes, type 2 diabetes (T2D), gestational diabetes, and a category including less common types of diabetes [5]. T2D is the most common accounting for 90–95% of all diabetes and is caused by the progressive loss of beta-cells function due to insulin resistance (IR) [5] where the majority of individuals with diabetes are overweight or obese. It's preceded by prediabetes where the blood glucose (BG) levels are above normal but are not high enough to be diagnosed as diabetes [5]. In the United states, around 84 million adults have prediabetes and 90% of them ignore that they have it [6] making them more prone to develop cardiovascular diseases and T2D [5]. All types of diabetes develop the same complications [5] that begin to form during the prediabetes phase, long time before the diagnosis of T2D where around one-third to one-half of persons with diabetes are undiagnosed because symptoms remain silent for many years [4]. Untreated, prediabetes progresses to T2D where comes the importance of lifestyle intervention that can decrease the incidence of T2D by 58% over three years [7]. Along with 150 min per week of moderate intensity physical activity, achieving and maintaining a 7% weight loss is the second goal of diabetes prevention program. While some foods were found to be associated with a decreased risk for T2D, others including sugars were blamed for increasing the risk for many health problems including diabetes [8]; this gave attention to non-nutritive sweeteners (NNS) as alternatives to sugar that are low in calories and safe

Table 1 – Criteria for the diagnosis of diabetes.

Test	Level
FPG[1]	≥126 mg/dL*
2 h plasma glucose during an OGTT[2]	≥200 mg/dL*
A1c levels[3]	≥6.5%*
Random plasma glucose levels[4]	≥200 mg/dL

Abbreviations: A1c: glycated hemoglobin; DCCT: diabetes control and complication trial; FPG: fasting plasma glucose; NGSP: national glycohemoglobin standardization program; OGTT: oral glucose tolerance test.

[1] After a fast of at least 8 h without any caloric intake.

[2] The patient is given 75 g anhydrous glucose dissolved in water and the levels of his plasma glucose are measured after 2 h.

[3] Using a method that is NGSP certified and standardized to the DCCT assay.

[4] In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

for diabetes prevention and management if used within the acceptable daily intake (ADI) levels and without compensation [5].

Sweeteners first appeared in the 19th century [9] and their definition and classification are inconsistent in the literature; while the European Food Safety Authority defines sweeteners as "Food additive substances used to impart a sweet taste to foods or in table-top sweeteners" and divide them into high-intensity sweeteners (HIS) and polyols while placing sugars on a separate category [10], the Food and Drugs Administration (FDA) defines sweeteners as "food additives that add sweetness with or without the extra calories", includes sugars in the definition of sweeteners and considers sugar alternatives (SA) as HIS. Those are divided into nutritive and NNS, where aspartame is considered as a nutritive sweetener while Saccharin, Acesulfame potassium (Ace-K), Sucralose, Neotame, Advantame, Steviol glycosides (known as stevia), and Luo Han Guo fruit extracts as NNS [11]. Other classifications are based on the energy contribution of SA (caloric or non-caloric), their source (natural or synthetic), their chemical structure [12,13], or their effect on postprandial glucose response [12] etc... In the literature, the term HIS has been used interchangeably with NNS, artificial sweeteners (AS), or low-calorie sweeteners. There's a long list of SA and many products enter the market yearly. The list of approved HIS differ among countries; while eleven are permitted in Europe [14], eight are regulated by the FDA [15] and approved in the United States including Saccharin, Aspartame, Ace-K, Sucralose, Neotame, Advantame, Stevia, and Luo Han Guo [11]. They are 30–13,000 times sweeter than sugar [16], have different functional properties and may be unintentionally consumed [17] because they enter in thousands of products [13]. For the purpose of this brief, the terms HIS or NNS will be used describing all SA including low or non-caloric sweeteners and natural or synthetic ones since all are used as sugar substitutes [11] where a minimal amount can enhance flavor without increasing caloric intake. Despite their wide usage and prescription as SA for caloric and glycemic control, several evidences were blaming NNS for having a role in the development of T2D.

2. Methods

2.1. *Search strategy and selection criteria*

In this paper, we aim to investigate whether NNS consumption prevents or causes T2D. To respond to this question, an extensive search of the literature was conducted between October and December 2018 using the key terms "non-nutritive sweeteners", "artificial sweeteners", "high-intensity sweeteners", "type 2 diabetes", and "prediabetes" on three databases including Pubmed, Science direct, and Scopus. Additional search for relevant articles was carried out manually from the reference list of selected articles. Animal studies, studies involving sugar alcohols or those conducted on children, adolescents, pregnant women, or on participants with diabetes were excluded. Human studies conducted from January 2004 to October 2018 were included and divided into observational, interventional, and systematic review and meta-analysis for discussion and analysis.

3. Results

In observational studies including cross-sectional, case-cohort and prospective studies, conclusions are heterogeneous and vary among the same types of studies (Table 2).

While Leahy et al. [18] concluded that low calories sweetened beverages (LCSB) consumption was associated with decreased markers of prediabetes thereby decreasing the risk of T2D, Kuk and brown [19] concluded that aspartame but not saccharine had negative effects on BG levels among obese but not lean individuals making them at higher risk for T2D.

In many studies, NNS consumption was associated with an increased risk for T2D lost after adjustment for body mass index (BMI) and other variables; this was reported in a cross-sectional [20] and a case-cohort study [21] where the association between artificially-sweetened beverages (ASB) consumption and the increased odds of newly diagnosed diabetes reported before the adjustment became insignificant after adjusting for BMI and other confounders among obese but not normal [20,21] or overweight [21] individuals.

While in two prospective studies the consumption of diet soft drinks was not significantly associated with an increased risk for T2D among healthy women free from diabetes [22,23], the consumption of caffeine and caffeine-free beverages sweetened with AS was associated with an increased risk for T2D among females and males participants [24]; this association was lost after adjusting for BMI and energy intake among others especially in males. In females, intake of caffeine beverages with AS was not associated with an increased risk for T2D but the risk was increased among those consuming decaffeinated ASB [24]. This was consistent with other studies where the association between ASB consumption and IR [25] and risk for T2D [26,27] among participants free from diabetes was lost after adjustment for BMI [25–27] and waist circumference (WC) [27] among other confounders

Table 2 – Observational studies describing the association between NNS consumption and T2D risk before and after adjusting for confounders.

Reference	Type of study (Sample size)	Sources of NNS	Variables adjusted for	Before adjusting for confounders (NNS and risk for T2D)		After adjusting for confounders (NNS and risk for T2D)		
				Not associated with T2D	↑ risk for T2D	↓ risk for T2D	Non-significant risk	Positive risk
Leahy et al. [18]	Cross-sectional (25 817 non-diabetic adults aged 19 years and older)	Low-calorie sweetened beverages (all types of beverages)	Age, gender, ethnicity, current smoking, poverty income ratio, PAL, alcohol intake, BMI			X		
Kuk and Brown [19]	Cross-sectional (2 856 non-diabetic participants aged 40–74 years)	Aspartame and Saccharine from foods and beverages	–	X●	X●●			
Yarmolinsky et al. [20]	Cross-sectional (12 884 non-diabetic participants aged 35–74 years at baseline)	ASB	M1: sex, age, race/skin color, study center; M2: M1 + educational attainment, current smoking status, leisure time physical activity, HTN, family history of diabetes, dietary changes in previous 6 months, alcohol consumption, SSB consumption, unsweetened beverage consumption, diet/light food consumption, TEI, BMI, WHR		X		X	
Romaguera et al. [21]	Case-cohort (11 684 incident cases and a sub-cohort of 15 374 participants)	Artificially sweetened soft drinks	Adjusted model: sex, educational level, physical activity, smoking status, alcohol consumption, juices and total soft drinks were mutually adjusted; sugar-sweetened and artificially sweetened soft drinks were mutually adjusted plus adjustment for juice consumption; M2: adjusted model + energy intake; M3: M2 + BMI		X		X	

Table 2 – (Continued)

Reference	Type of study (Sample size)	Sources of NNS	Variables adjusted for	Before adjusting for confounders (NNS and risk for T2D)		After adjusting for confounders (NNS and risk for T2D)		
				Not associated with T2D	↑ risk for T2D	↓ risk for T2D	Non-significant risk	Positive risk
Palmer et al. [22]	Prospective cohort (43 960 non-diabetic African American women aged 21–69 years at baseline)	Diet soft drinks	–	X				
Schulze et al. [23]	Prospective cohort (91 249[x] and 51 603[xx] female nurses free from diabetes, cardiovascular diseases and cancer aged 24–44 years at baseline)	Diet soft drinks	M1: age; M2: M1 + alcohol intake, physical activity, family history of diabetes, smoking, postmenopausal hormone use, oral contraceptive use, intake of cereal fiber, magnesium, trans-fat, ratio of PUFA to SFA and consumption of sugar-sweetened soft drinks, diet soft drinks, fruit juice and fruit punch (other than the main exposure depending on the model); M3: M2 + baseline BMI; M4: M3 + TEI				X	
Bhupathiraju et al. [24]	Prospective cohort (74 749 women from the NHS aged 30–55 years and 39 059 men from the HPFS aged 40–75 years free from diabetes, cardiovascular diseases and cancer at baseline)	Caffeinated and decaffeinated artificially sweetened carbonated beverages	M1: age and time interval; M2: M1 + smoking status, alcohol use, postmenopausal hormone use, physical activity, family history of diabetes, alternate HEI, consumption of other beverage other than the main exposure depending on the model (total coffee, caffeinated tea, fruit punch, SSB or ASB), presence of HTN, HCT, adherence to a low calorie diet, reported weight change; M3:M2 + TEI, BMI		X		X[■]	X[■■]

Table 2 – (Continued)

Reference	Type of study (Sample size)	Sources of NNS	Variables adjusted for	Before adjusting for confounders (NNS and risk for T2D)		After adjusting for confounders (NNS and risk for T2D)		
				Not associated with T2D	↑ risk for T2D	↓ risk for T2D	Non-significant risk	Positive risk
Ma et al. [25]	Prospective cohort (1 685* participants without pre-diabetes and 2 076** non-diabetics)	Diet soda	M1: baseline HOMA-IR, age, sex, current smoking status, HTN, PAL, BMI, DGAI score, intakes of energy, alcohol and fruit juice, mutual adjustment for SSB and diet soda intake; M2: M1 except that the DGAI score was replaced with intakes of individual foods including coffee, whole grains, fruit, vegetables, red meat, nuts and fish		X		X	
de Koning et al. [26]	Prospective cohort (40 389 healthy males aged 40–75 years at baseline)	ASB	Age, smoking, physical activity, alcohol intake, multivitamin use, family history of T2D, high triglycerides, high blood pressure, use of diuretics, weight change, adherence to a low calorie diet, TEI, BMI		X		X	
O'Connor et al. [27]	Prospective cohort (24 653 non-diabetic participants aged 40–79 years at baseline)	ASB	M1: age, sex, occupational social class, education level, family history of diabetes, PAL, smoking status, alcohol consumption, season, mutual adjustment for intake of other sweet beverages; M2: M1 + TEI; M3: M2 + BMI, WC		X		X	
Nettleton et al. [28]	Prospective cohort (6 814 Caucasian, African American, Hispanic and Chinese adults aged 45–84 years)	Diet soda	M1: study site, age, sex, race, ethnicity, energy intake; M2: education, physical activity, smoking status, supplement use; M3: M2 + WC and BMI		X			X

Table 2 – (Continued)

Reference	Type of study (Sample size)	Sources of NNS	Variables adjusted for	Before adjusting for confounders (NNS and risk for T2D)		After adjusting for confounders (NNS and risk for T2D)		
				Not associated with T2D	↑ risk for T2D	↓ risk for T2D	Non-significant risk	Positive risk
Sakurai et al. [29]	Prospective cohort (2 037 Japanese men aged 35–55 years)	Diet soda	M1: age; M2: M1 + BMI; M3: M2 + family history of diabetes, smoking, alcohol drinking, habitual exercise, presence of HTN, presence of dyslipidemia, receiving the diet treatment for chronic disease, TEI, total fiber intake; M4: M3 + consumption of SSB (for diet soda), fruit juice consumption, vegetable juice consumption, coffee consumption		X			X
Fagherazzi et al. [30]	Prospective cohort (66 118 non-diabetic women)	ASB	M1: years of education, smoking status, physical activity, HTN, HCT, use of HRT, family history of diabetes, self-reported use of antidiabetic drugs, alcohol intake, omega-3 fatty acid intake, CHO intake, coffee, fruit and vegetables, processed-meat consumption, dietary pattern; M2: M1 + TEI (excluding energy from alcohol and CHO); M3: M2 + BMI		X			X
Fagherazzi et al. [31]	Prospective cohort (61 440 healthy women aged 40–65 years at baseline)	Artificial sweeteners from packets or tablets	M1: univariate; M2: M1 + baseline alcohol consumption, CHO intake, daily energy intake from protein and lipids, level of education, smoking status, HTN, HCT, family history of diabetes, physical activity; M3: M2 + BMI		X			X

Abbreviations: ASB: artificially sweetened beverages; BMI: body mass index; CHO: carbohydrates; DGAI: dietary guidelines adherence index; HCT: hypercholesterolemia; HEI: healthy eating index; HOMA-IR: homeostatic model assessment of insulin resistance ; HPFS: health professionals follow-up study; HRT: hormone replacement therapy; HTN: hypertension; M: model; NHS: nurses' health study; NNS: non-nutritive sweeteners; PAL: physical activity level; PUFA: poly unsaturated fatty acid; SFA: saturated fatty acid; SSB: sugar sweetened beverages; T2D: type 2 diabetes; TEI: total energy intake; WC: waist circumference; WHR: waist to hip ratio.
● Saccharine.
●● Aspartame.
ˣ for diabetes analysis.
ˣˣ for weight change analysis.
■ In males consuming caffeinated and caffeine free carbonated beverages sweetened with artificial sweeteners and in females consuming caffeinated carbonated beverages sweetened with artificial sweeteners.
■■ In females consuming caffeine free carbonated beverages sweetened with artificial sweeteners.
* The sample used to analyze the association between cumulative mean consumption of SSB or diet soda and incident prediabetes.
** The sample used to analyze the association between beverage consumption and changes in HOMA-IR.

making ASB inoffensive in the development of obesity and T2D [26].

From the other side, several prospective studies showed a positive association between AS consumption and the increased risk for T2D even after adjusting for confounders. One study concluded that daily diet soda consumption was associated with an increased risk for T2D, attenuated while remaining statistically significant after further adjustment for baseline BMI and WC [28]. Consistently, another study reported that diet soda consumption was associated with an increased incidence of T2D even after multivariable adjustment where the consumption of 1serving/day of diet cola increased the risk for diabetes by 70% among males free from diabetes [29]. Similarly, the consumption of AS from beverages [30] or packets/pills [31] was associated with an increased risk for T2D among women; frequent daily consumers of AS from packets/pills had 63% higher risk for T2D while those with lower consumption had 32% higher risk for T2D [31]. The association diminished but remained statistically significant after adjustment for BMI and other confounders [30,31].

Results of human interventional studies were also heterogeneous (Table 3). In a cross-over study, participants were randomized to compare the effect of consuming a beverage sweetened either with sucrose or with a HIS on energy intake and on BG and insulin levels where HIS were divided into natural or artificial. During the test, participants were given a test breakfast in the morning and a test beverage in the mid-morning followed by a lunch after 1 h while testing their BG and insulin levels. Then, they were dismissed 2 h after lunch. Larger spikes in BG and insulin levels were recorded in the sucrose group after consuming the test beverage whereas the levels remained steady among those consuming HIS until after lunch where the spike in insulin and glucose was higher among HIS consumers even after adjusting for confounders. Overall, there was no difference between both groups in total energy intake and in the total area under the curve (AUC) for glucose and insulin noting that the type of sweetener didn't show any effect on the results [32]. Using the same design, ten males were recruited from the study above to investigate the effect of replacing a sucrose beverage with a beverage containing natural or AS. Participants underwent the same protocol but their BG and insulin levels were tested over a period of 24 h. There was no significant difference in the total AUC for glucose and insulin even after controlling for confounders with no difference between natural or AS [33].

A study of a longer period randomized participants into two groups to investigate the metabolic effects of a diet rich in sucrose compared to that rich in AS [34]; twelve were given sucrose containing meals and the rest was given meals with AS while keeping the rest of their diet normal. After ten weeks, participants were placed in a respiratory chamber, were given breakfast and lunch and underwent blood tests before and after the meals. The sucrose group had larger spikes in post-prandial glucose and insulin after the breakfast with a significant difference in the incremental area under the curve (iAUC) for glucose but that of insulin failed to reach significance even after adjusting for confounders.

Another study randomized participants into two groups; the first was given sucralose pills over four weeks and the

Table 3 – Interventional studies describing the association between NNS consumption and T2D risk.

Reference	Type of study (Sample size)	Duration	Type and source of NNS in the experimental group	Control group	No difference between NNS and control	Beneficial effect of NNS on T2D risk	NNS ↑risk	No effect of NNS on T2D risk
Tey et al. [32]	Randomized cross-over double blind (30 healthy normal weight males aged between 21 and 50 years)	6 h each test session for 4 sessions	Aspartame (artificial sweetener), stevia and monk-fruit (natural sweetener) from a test beverage	sucrose sweetened beverages	X			
Tey et al. [33]	Randomized cross-over double blind (10 healthy normal weight males aged between 21 and 50 years)	1 day each test for 4 sessions	Aspartame (artificial sweetener), stevia and monk-fruit (natural sweetener) from a test beverage	sucrose sweetened beverages	X			
Raben et al. [34]	Randomized controlled trial (23 healthy overweight participants aged between 20 and 50 years)	10 weeks	Artificial sweeteners from food and beverages	Sucrose from food and beverages		X		
Lertrit et al. [35]	Randomized cross over double blind (15 healthy participants aged > 18 years)	4 weeks each phase for 2 phases	Sucralose pills	Placebo (empty pills)			X	
Ma et al. [36]	Randomized single blind (7 healthy normal weight participants aged 24 ± 2 years)	4 h each session for 4 sessions	Intragastric infusion of sucralose in normal saline (80 g and 800 mg)	normal saline or 50 g of sucrose in water				X
Grotz et al. [37]	Randomized double blind (46 healthy males)	20 weeks*	Sucralose pills	Placebo (cellulose)	X			

Abbreviations: NNS: non-nutritive sweeteners; T2D: type 2 diabetes.
* consisting of 4 weeks screening, 12 weeks test and 4 weeks follow-up.

Table 4 – Systematic reviews describing the association between NNS consumption and T2D risk.

Reference	Type of study (Sample size)	NNS and T2D risk		
		No conclusive evidence	↑ the risk for T2D	Not beneficial in risk prevention
Lohner et al. [38]	Scoping review (15 SR, 155 RCT, 23 non-randomized controlled trials, 57 cohort, 52 case-control, 28 cross-sectional, 42 case series/case reports)	X		
Bruyère et al. [39]	Systematic review and meta-analysis (383 studies)	X		
Romo-Romo et al. [40]	Systematic review (14 prospective studies, 28 clinical trials and 2 meta-analysis)	X		
Wiebe et al. [41]	Systematic review and meta-analysis (53 RCT)	X		
Tucker and Tan [42]	Systematic review (41 interventional studies)			X
Greenwood et al. [43]	Systematic review and meta-analysis (11 prospective studies)		X	
Imamura et al. [44]	Systematic review and meta-analysis 21 prospective studies		X	

Abbreviations: NNS: non-nutritive sweeteners; RCT: Randomized controlled trial; SR: systematic review; T2D: type 2 diabetes.

second was the control group in a cross-over randomized design. They underwent an oral glucose tolerance test at the end of each phase, followed by an intravenous glucose tolerance test the next day. There was no difference in the AUC for glucose between both groups, but sucralose consumers had lower insulin sensitivity and higher AUC for Glucagon-like peptide-1 (GLP-1) [35]. This was inconsistent with Ma et al. [36] where sucralose, but not sucrose, when taken in isolation by intragastric infusion didn't increase GLP-1, gastric inhibitory polypeptide (GIP), insulin, and glucose levels among participants.

Contrarily, high doses of sucralose had no negative effects on BG control where insulin, glucose, and glycated hemoglobin (A1c) levels remained in normal ranges similar to placebo [37] making sucralose a good option for those seeking BG control like individuals with diabetes or those at risk of developing the disease.

Results of systematic reviews and meta-analysis were highly heterogeneous (Table 4); while the majority of systematic reviews [38–41] and meta-analysis [39,41] reported that there is no conclusive evidence that NNS increase the risk for T2D, others showed that NNS have no effects [42] on T2D prevention or found them to be associated with an increased incidence of T2D [43–44] independent of adiposity [44] or attenuated by adjustment for BMI [43].

4. Discussion

The unclear association between NNS and the risk for T2D is affected by many factors including adiposity, reverse causality, gut microbiota among others. Obesity is a confounding factor in the relationship between NNS and metabolic diseases [40] but the true direction of the association is unclear; it's unknown whether NNS consumption is directly associated with T2D independent of obesity, or if the association is due to reverse causality where individuals with diabetes tend to consume NNS for caloric and glycemic control or if adiposity has a role in the association between NNS and T2D. Since adiposity is reflected mainly by BMI and WC, adjustment for these factors is important to clarify the role of adiposity. Therefore, adjustment for BMI in the study of Kuk and Brown [19] was of ultimate importance to understand whether obesity has caused this impaired plasma glucose levels, or whether aspartame consumption increased the risk for T2D independently of obesity.

The majority of the studies adjusted for BMI and other confounders; In Bhupathiraju et al. [24] the association lost after adjusting for BMI and total energy especially in males, was attributed to reverse causality but they were unable to explain the reason behind the difference between caffeinated and decaffeinated ASB among females and have linked it to unhealthy lifestyles not included in their study. The association between NNS and the risk for T2D reported among overweight and/or normal but not obese subjects may be either due to confounding where those with excess weight could have made lifestyle changes that might have affected the results [20], or due to a possible role of adiposity, or due to reverse causality [21] which also explains the results of other studies [26,27]. In Ma et al. [25], different assays were used to measure insulin at baseline and during follow-up which might have affected the results, but their results were supported by the increased risk for prediabetes.

Contrarily, the association between NNS consumption and the risk for T2D remained after adjustment for BMI and other variables indicating an independent association between ASB and T2D partly mediated by BMI [30] as well as both direct and indirect effect of NNS on T2D partly mediated by adiposity [31]. It's worthwhile to note that in Nettleton et al. [28] participants were not previously healthy, inclusion criteria were unclear and diabetes risk factors were not considered which might have affected their results.

Based on the results of the reviewed observational studies, no firm conclusions could be drawn due to the heterogeneity of the studies that differed in the population, the type and form of sweeteners, the monitoring periods, how AS intake was assessed and the bias due to different methods in analyz-

ing different variables where in many studies weight, questionnaires and other variables were self-reported in addition to the inability of some observational studies to reveal causality, where comes the importance of reviewing interventional studies to understand the true association.

In interventional studies, results of Tey et al. [32,33] when taken as a whole, showed that LCSB have minimal effect on BG levels when compared to sucrose, but both studies were of a short duration and individuals were healthy normal weight males where comes the importance of reviewing studies of longer duration conducted on both sexes from all BMI categories because the majority of NNS consumers have diabetes or have excess weight and use them for caloric and glycemic control. The study conducted over a longer period showed that post-prandial insulin, glucose, and lipid levels were significantly higher among sucrose consumers suggesting a potential benefit in substituting a high sucrose diet with a diet containing NNS [34] which was inconsistent with Tey et al. [32] where the levels were increased among NNS consumers. However, comparison can't be made because the sweeteners used, the participants, and the study design and duration are not similar. Consistently with Tey et al. [32,33], an insignificant difference in the AUC for glucose was reported between the sucralose and placebo groups, but sucralose consumers had increased GLP-1 levels and were at a higher risk for T2D due to the decrease in insulin sensitivity and increase in insulin release as indicators for IR [35] along with a reduction in acute insulin response which is the first indicator for defects in beta-cells function [45]. This highlights the effect of chronic exposure to sucralose on the risk for T2D which contradicts the results of Ma et al. [36] reported previously. By giving sucralose in form of pills or by intragastric infusion, both studies [35,36] bypassed the sweet taste receptors in the mouth suggested to have a potential role in insulin and other hormones release, which doesn't occur in real life. Moreover, Lertrit et al. had a small sample size with the majority of their participants being females in addition to the absence of baseline glucose and insulin levels which would have been helpful to compare the results [35]. Similarly, Grotz et al. [37] excluded females and provided sucralose in form of pills bypassing the sweet taste receptors in the mouth.

The reviewed interventional studies were of a short duration, had different protocols, used different sweeteners and were conducted over different populations making conclusions hard to be drawn where comes the importance of reviewing systematic reviews and meta-analysis for having the highest quality of evidence among all study designs.

From systematic reviews and meta-analysis, no solid conclusion could be drawn and comparison can't be made because those are conducted on different studies' types and designs. Taking this into consideration, results may be biased and causality is difficult to determine making the current level of evidence insufficient to conclude whether NNS consumption is associated with diabetes or has favorable or detrimental effects on the disease.

Due to the detrimental effect of sugar and sugar-sweetened beverages, researchers were investigating the possibility of replacing sugar and sugar-sweetened beverages with NNS and ASB; while some studies concluded that it's better for obese or those at risk of weight gain or T2D to consume ASB instead of sugar-sweetened beverages [18,22,46], others have concluded that ASB shouldn't be encouraged [40] or recommended instead of water [39,47] for being non-healthy options in the prevention of diabetes [44] but can be used if consumed within the ADI and without compensation [40,46]. Those could exert potential health improvements but more structured and relevant studies are required to assess their outcome [41].

To our knowledge, this is the first mini-review that explained and compared the different definitions and classifications of sweeteners, and from the few reviews that studied the variables adjustments while including all forms of sweeteners in the analysis. Limitations include not analyzing all studies and restricting them to those conducted on adults free from diabetes while excluding children, adolescents, and pregnant women who constitute a large proportion of the population.

Due to the lack of conclusive data and because NNS are being largely consumed and prescribed, and since the majority of interventional studies assessed the role of NNS in isolation and not as part of a habitual diet, there is an urgent need of well-designed studies that take into consideration all types of confounders and factors that play a role in the development of T2D.

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Authors contribution

All authors contributed equally in this work; they all designed revised and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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