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Review

Soft drinks and sweeteners intake: Possible contribution to the development of metabolic syndrome and cardiovascular diseases. Beneficial or detrimental action of alternative sweeteners?

Concetta Schiano [a,*,1], Vincenzo Grimaldi [b,1], Michele Scognamiglio [c], Dario Costa [c], Andrea Soricelli [b,d], Giovanni Francesco Nicoletti [e], Claudio Napoli [a,b,c]

[a] Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "L. Vanvitelli", Naples, Italy
[b] IRCCS SDN, Naples, Italy
[c] Clinical Department of Internal Medicine and Specialistic Units, Division of Clinical Immunology and Immunohematology, Transfusion Medicine, and Transplant Immunology [SIMT], Regional Reference Laboratory of Transplant Immunology [LIT], Azienda Universitaria Policlinico (AOU), Naples, Italy
[d] Department of Exercise and Wellness Sciences, University of Naples Parthenope, Naples, Italy
[e] Multidisciplinary Department of Medical, Surgical and Dental Sciences, Plastic Surgery Unit, University of Campania "L. Vanvitelli", Naples, Italy

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ABSTRACT

The rapid increase in obesity, metabolic syndrome, and cardiovascular diseases (CVDs) has been related to the rise in sugar-added foods and sweetened beverages consumption. An interesting approach has been to replace sugar with alternative sweeteners (AS), due to their impact on public health. Preclinical and clinical studies, which analyze the safety of AS intake, are still limited. Major pathogenic mechanisms of these substances include ROS and AGEs formation. Indeed, endothelial dysfunction involving in the pathogenesis of micro- and macrovascular diseases is mitochondrial dysfunction dependent. Hyperglycemia and endoplasmic reticulum stress together produce ROS, contributing to the development and progression of cardiovascular complications during type 2 diabetes (T2D), thus causing oxidative changes and direct damage of lipids, proteins, and DNA. Epidemiological studies in healthy subjects have suggested that the consumption of artificial AS can promote CV complications, such as glucose intolerance and predisposition to the onset of T2D, whereas natural AS could reduce hyperglycemia, improve lipid metabolism and have antioxidant effects. Long-term prospective clinical randomized studies are needed to evaluate precisely whether exposure to alternative sugars can have clinical implications on natural history and clinical outcomes, especially in children or during the gestational period through breast milk.

1. Introduction

Until a few decades ago, overweight and obesity were considered a serious issue only in developed countries (WHO, 2018; Kim et al., 2017). The body mass index (BMI), which is the ratio between body weight (BW) expressed in kilograms, and the square of his height, expressed in meters, indicates whether an individual is in overweight (BMI > 25) or obese condition (BMI > 30) (WHO, 2018; Kim et al., 2017; Roberts, 2016). The World Health Organization (WHO) has stated that these characteristics have increased dramatically also in developing countries, where there are many urban agglomerations, with a prevalence mainly in adolescents (WHO, 2018). Changes in lifestyle and diet have caused an increase in the risk factors, which contribute to metabolic diseases, such as obesity, metabolic syndrome (MetS), type 2 diabetes (T2D), hypertension, dyslipidemias, stroke and cardiovascular diseases (CVDs) mortality (Costa et al., 2019; Scognamiglio, Costa, Sorriento, & Napoli, 2019). The increased consumption of soft drinks is associated with the onset of these pathologies (Cantoral et al., 2016; Carwile et al., 2015; Bray and Popkin, 2014). It is estimated that in the United States about 75% of all processed foods and drinks contain added sugars and that over 50% of the population regularly uses sugary drinks with an average consumption of 190 L/person per year, equivalent to about 450 ml/day. In Europe, consumption is around 240 ml/day and surprisingly, the younger population assumes about double quantity (Greenwood et al.,

* Corresponding author at: University of Campania "L. Vanvitelli", Department of Advanced Medical and Surgical Sciences, Naples 80138, Italy.
E-mail address: concetta.schiano@unicampania.it (C. Schiano).
[1] Equally contributed.

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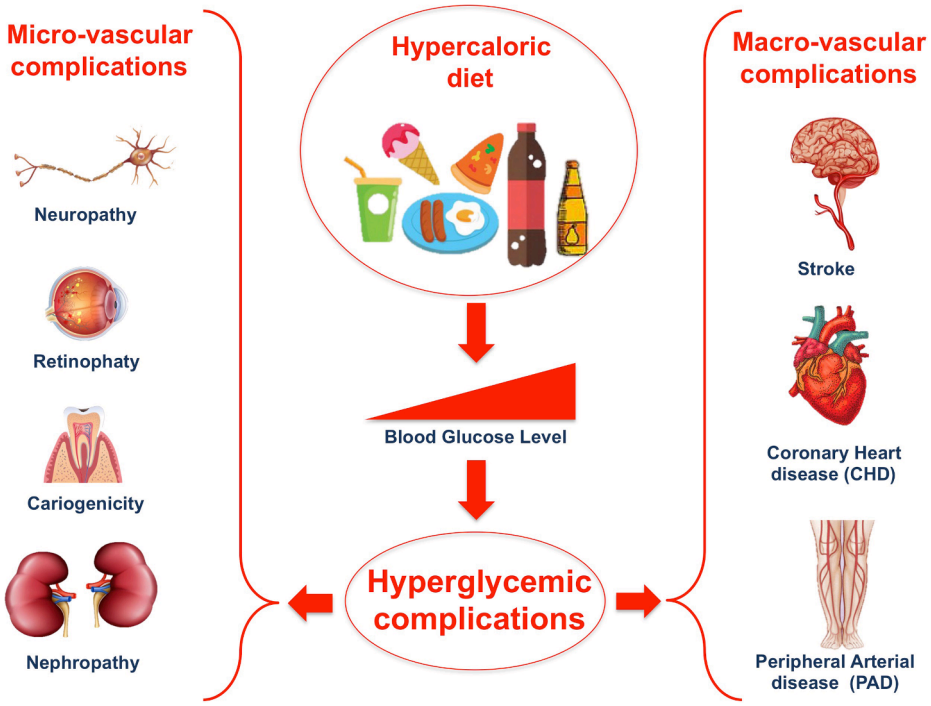

Fig. 1. Hyperglycemic condition and metabolic memory. An high calorie diet, consisting of drinks and foods with added sugars, can cause an increase in blood glucose. The main micro- and macro-vascular complications due to hyperglycemia conditions are shown in the figure. Specifically, retinopathy, nephropathy, cariogenicity, stroke, coronary heart disease (CHD), peripheral artery disease (PAD) and neuropathy.

2014). In order to decrease the incidence of cardio-metabolic diseases, WHO suggests controlling BW, by limiting calorie intake, a frequent strategy is to reduce the consumption of drinks containing glucose or fructose/fructose syrup and replacing sugars in the diet with low or non-caloric substitutes, called alternative sweeteners (AS) (Lizunkova, Enuwosa, & Chichger, 2019; Popkin and Hawkes, 2016; Katan et al., 2016; Kral et al., 2008) (Fig. 1). However, the pathogenic influence of AS on BMI is not yet fully understood. Moreover, in order to assess whether AS could be used to reduce CVD complications, this review provide an overview of the global trend in the intake of beverages with added sugars, reporting the effects mainly studied. Additionally, it was performed an updated summary of studies from both preclinical and clinical studies, linking excessive sugar consumption to microbiota deregulation, weight gain, obesity and related cardiometabolic conditions, including metabolic syndrome (MetS).

2. Sweetener consumption

Sweeteners can help to reduce the positive energy balance for managing BW and blood glucose (Pepin, Stanhope, & Imbeault, 2019; Rogers et al., 2016). However, there are still conflicting data from short- and long-term consumption of both natural and artificial AS, such as aspartame, sucralose, and stevia derivatives (Lobach, Roberts, & Rowland, 2019; Farhat, Berset, & Moore, 2019; Nichol, Salame, Rother, & Pepino, 2019). Preclinical and clinical studies report that sweeteners can have negative effects on the intestinal microbiota, appetite control, and glucose metabolism (Daly, Darby, & Shirazi-Beechey, 2016; Suez et al., 2014). Specifically, in animal models their assumption for a period longer than 12 months, increased the food consumption, BW gain, the percentage of adiposity and also induced hyperinsulinemia, whereas reduced the postprandial thermogenesis when compared to animals exposed to carrier water or even to foods or soft drinks sweetened with calories (Wang, Browman, Herzog, & Neely, 2018; Ruiz-Ojeda, Plaza-Díaz, Sáez-Lara, & Gil, 2019; Tellez et al., 2013). The negative effects of AS were reduced in mice during a restrictive diet and were pronounced among male animals, genetically predisposed to obesity. Preclinical studies, therefore, indicated, on a biological level, likely mechanisms to explain the results of long-term observational studies conducted in humans, in which increases in BW and incidence of overweight and obesity were observed (Rogers et al., 2016; de Ruyter, Olthof, Seidell, & Katan, 2012; Ebbeling, Feldman, & Chomitz, 2012; Foreyt, Kleinman, Brown, & Lindstrom, 2012; Forshee and Storey, 2003). Finally, some evidence reports that ASs interact with the sweet taste receptors in the mouth and modify the intestinal secretion of molecules, such as glucagon-like peptide-1 (GLP-1), YY peptide (PYY), ghrelin and polypeptide glucose-dependent insulinotropic (GIP), which could affect blood sugar levels following AS consumption (Kim, Keogh, & Clifton, 2019; Temizkan et al., 2015). However, although AS could represent a valid substitute to sugar, according to recent clinical evidence, AS excess consumption can do not correlate with what is observed in preclinical studies. Indeed, it would appear that AS chronic consumption worse obesity, metabolic syndrome, T2D and related CVD (O'Connor et al., 2015; Gil-Campos, González, Díaz Martín, 2015; Pepino, Tiemann, Patterson, Wice, & Klein, 2013; Anton et al., 2010). *Pepino et al.,* showed that insulin-sensitive obese patients taking sucralose before a glucose load had a greater increase in the plasma glycemic peak and an increase in the insulin value than in the control group (Pepino et al., 2013). *Anton et al.,* again in obese patients, the consumption of AS, such as steviol glycosides, produced significantly lower postprandial glucose levels compared to the groups of aspartame and sucrose (Anton et al., 2010). Instead, *O'Connor et al.,* evaluated the association between different sugar-containing drinks and sugary drinks with AS on diabetic patients (O'Connor et al., 2015). Therefore, to understand the relationship between AS and metabolic diseases is needed. To date, there are few clear recommendations regarding the consumption of artificially sweetened foods and drinks in children. In general, as indicated by the Institute of Medicine and the American Academy for Pediatrics, AS are not recommended for children under 12 months of age, since there are no studies on the safety of sugar substitutes in infants. Additionally, foods and drinks containing sugar substitutes are generally not recommended even for infants over 12 months of age, as they are nutrient poor and would not allow for optimal growth and development. Indeed, it was

Table 1
Natural and artificial sweeteners by FDA and EU approved.

Sweetener origin	Name	Chemical formula	Sweeteness*	ADI by the US FDA (mg/kg)	ADI by the EU EFSA (mg/kg)
Artificial	Acesulfame-K	$C_4H_4KNO_4S$	200x	15	9
	Aspartame	$C_{14}H_{18}N_2O_5$	200x	50	40
	Cyclamate	$C_6H_{12}NNaO_3S$	30-50x	Not approved for consumption	0–11
	Neohesperidine DC	$C_{28}H_{36}O_{15}$	300-2000x	Not approved for consumption	5
	Neotame	$C_{20}H_{30}N_2O_5$	7000-13000x	0.5	2
	Saccharin	$C_7H_5NO_3S$	300x	15	5
	Sucralose	$C_{12}H_{19}Cl_3O_8$	600x	5	15
Natural	Steviol	$C_{20}H_{30}O_3$	30-300x	4	4
	Rebaudioside A	$C_{44}H_{70}O_{23}$	30-300x	4	4
	Stevioside	$C_{38}H_{60}O_{18}$	30-300x	4	4
	Thaumatin	$C_{25}H_{34}O_{15}$	1600-3000x	Not approved for consumption	Approved for consumption, but ADI not specified

Abbreviations: Acceptable Daily Intake (ADI); European Food Safety Authority (EFSA); European Union (EU); Food and Drug Administration (FDA); Neohesperidine dihydrochalcone (DC).
* Sweetness was compared with 10% sucrose solution.

demonstrated that substituting sugar-sweetened beverages with water decreases body fatness development in adolescence (Fabiano, Albani, Cammi, & Zuccotti, 2020). Moreover, most recently, *Eny et al.* have demonstrated that higher sugar-sweetened beverages consumption was associated with small elevations of cardiometabolic risk in preschool children (Eny et al., 2020).

Nonetheless, the American Dietetic Association assumed that AS could enable young consumers to enjoy the sweetness while continuing to manage weight, diabetes and other chronic diseases. However, especially for infants over 12 months, AS need to be used within the ADI range, which is specific to each FDA approved AS (see Table 1) (Dibay Moghadam, Krieger, & Louden, 2020; Fabiano et al., 2020; Kral et al., 2020; Sylvetsky, Rother, & Brown, 2011; Kral et al., 2008).

3. Literature search

In order to assess whether AS could be used for the treatment of CVDs and their complications, it was conducted a review of the scientific literature using three different electronic databases (PubMed, Google Scholar and Web of Science) and selected all the original searches publications involving the use of sweeteners in both animals and humans. Studies performed with both natural and artificial AS were included. To improve the analysis, clinical studies were also examined, which involved the use of alternative sweeteners, albeit with a varied scientific question. The literature search, conducted in June 2020, began by entering the following search terms in the databases: “Sweeteners” OR “Alternative Sweetener” OR individual sweeteners, such as “Acesulfame-K” OR “Aspartame” OR “Cyclamate” OR “ Saccharin ”OR Sucralose OR Stevia. This was supplemented by a second search in the same database using the following search terms: “Cardiovascular Disease” OR “Metabolic Syndrome” OR “Hyperglycemia” to ensure that relevant documents were not lost. Only English language articles published in peer-reviewed journals were included. In total, the literature search identified 223 documents relating to the combination of the terms “Alternative Sweetener AND Cardiovascular Disease”, 74 documents relating to “Alternative Sweetener AND Metabolic Syndrome”, 191 documents relating to “Alternative Sweetener AND Hyperglycemia ”, which were included for further analysis. Further research was also conducted to verify ongoing clinical trials, including both the type of observational and / or interventional study and extracted from the https://clinicaltrialswebsite.gov.

This review provide an overview of the global trend in beverage

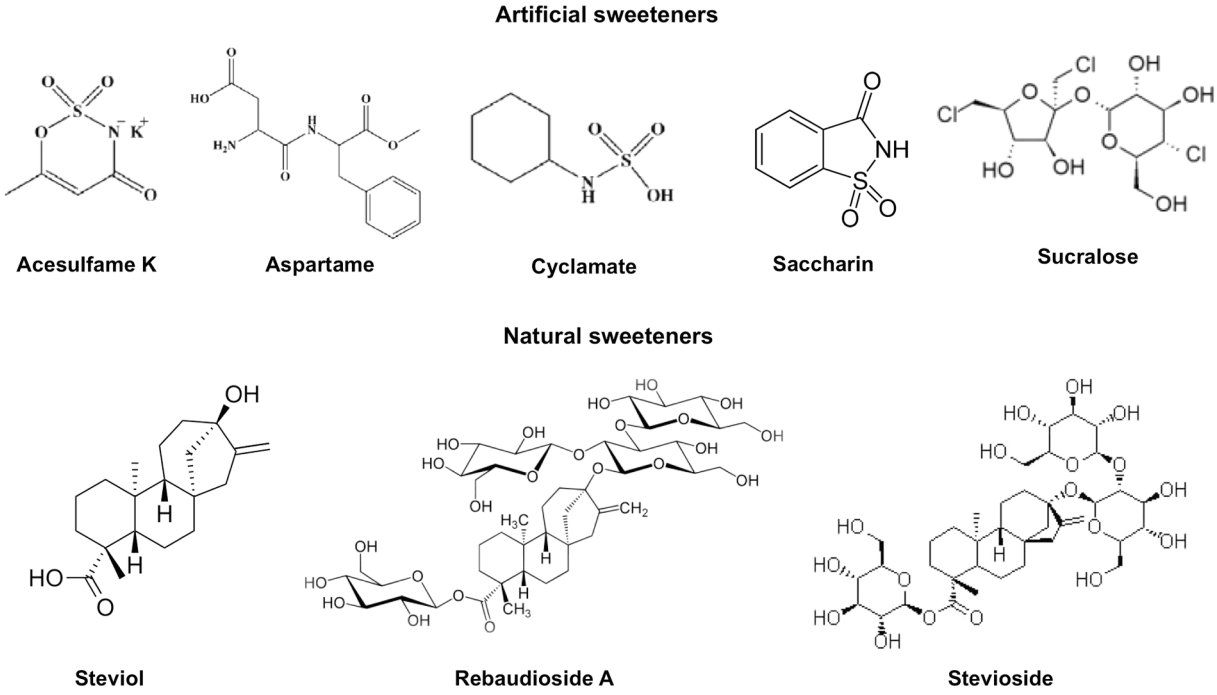

Fig. 2. Artificial and natural alternative sweeteners. Chemical structures of artificial and natural alternative sweeteners commonly used in soft drinks and foods.

intake with added sugars and an updated summary of evidence from preclinical and clinical trials, linking excessive sugar consumption to microbiota deregulation, weight gain, obesity and related cardiometabolic conditions, including MetS. The results of cross-sectional or case-control studies were not included to avoid confusion in the reader. Finally, observational and interventional studies are considered, highlighting the importance of moderately using AS-sweetened beverage options in the diet, limiting the consumption of soft drinks, in order to have a beneficial effect on cardiometabolic diseases in men.

4. Sweeteners: Main characteristics

Sweeteners are substances used to give a sweet taste to the food and/or drinks to which they are added (Martyn et al., 2016). Although the European Food Safety Authority (EFSA) or the US Food and Drug Administration (FDA) do not consider a classification of sweetener based on origin, this report analyzed them, following a classification into two groups: synthetic sweeteners (also called non-calorie sweeteners), with little or no nutritional power and natural sweeteners (also called caloric sweeteners) (Martyn et al., 2016; Huth, Fulgoni, Keast, Park, & Auestad, 2013), for a better understanding of the characteristics and an easier reading of the studies conducted.

Today, many low- or zero-calorie drinks and foods are available (Smeets, Weijzen, de Graaf, & Viergever, 2011). This section describes the natural and artificial AS marketed or under development most commonly used worldwide (Fig. 2). Acesulfame-K, aspartame, cyclamate, saccharin, sucralose, and stevia are the sweeteners approved for consumption (Huth et al., 2013; Huvaere, Vandevijvere, Hasni, Vinkx, & van Loco, 2012). Other sweeteners, such as neohesperidine DC, neotame, and thaumatin were not included because they have more limited use. Sweeteners are widely used, alone or in combination, by the food industry for also sweetening candies, chewing gums, and jams (Grembecka, 2015; Huvaere et al., 2012). Their sweetening power is 30 to 500 times higher than sucrose, the common sugar used (Hunter, Reister, Cheon, & Mattes, 2019). However, many consumers prefer products with natural sweeteners (Banga et al., 2019). The use and dosage of the different AS in food and soft drinks are established based on the acceptable daily intake (ADI) values assigned after reviewing their safety assessment studies. ADI is calculated according to the following formula: sweetener mg/BW (kg)/day. The numerical value corresponds to the maximum quantity that can be safely taken throughout the day. For this reason, it is also defined as 1% of the NOEL level, as no observable adverse effects, determined by human and animal safety assessment studies. Since non-caloric sweeteners are generally much sweeter than sucrose, therefore, can be used in small quantities. Non-caloric ASs are classified into chemically synthesized sweeteners, including aspartame saccharin, and sucralose; and natural sweeteners extracted from plants, such as stevia glycosides, thaumatin and monellin (Gupta, 2018). In Table 1, synthetic and natural ASs approved by the Food and Drug Administration (FDA) of the United States (US) and/or EFSA of the European Union (EU) with their ADI, respectively, have been reported.

4.1. Artificial sweeteners

Artificial sweeteners (AS) are substances obtained by chemical synthesis, with a high sweetening power without the extra energy derived from foods and drinks containing caloric sugars (Mueller et al., 2015; Bellisle and Drewnowski, 2007). Currently, ASs, such as acesulfame, used as acesulfame-potassium, saccharin and aspartame play a vital role in the food industry (Basílio, Silva, Pereira, Pena, & Lino, 2020). Although the studies conducted to date report enough benefits, several data refer to adverse reactions in customers. In this regard, EFSA is currently re-evaluating several sweeteners, including aspartame, acesulfame-K and saccharin, which will be completed by 31 December 2020. AS have a taste similar to the sucrose, but a much higher sweetening power (intensive sweeteners up to 500–1000 times greater), although they activate human taste pathways differently from sucrose (Frank et al., 2008). The limiting factors for the use of AS are represented by the association between their intake and incidence of the MetS, insulin resistance, and incidence of T2D (Ojo and Brooke, 2014; Swithers, 2013; Lutsey, Steffen, & Stevens, 2008; McNaughton, Mishra, & Brunner, 2008). The most common synthetic ASs are acesulfame K, aspartame, cyclamates, and saccharin, which are used by the food industry in the production of "light" food and drinks.

4.1.1. Acesulfame-K

Acesulfame-potassium (K) was discovered in 1970. It is 130 times sweeter than sucrose and is stable at different conditions of temperature and pH, which can be found in soft drinks and foods. Although safety studies show that acesulfame-K is not carcinogenic, cytotoxic or teratogenic (Tian et al., 2020; O'Sullivan, Pigat, O'Mahony, Gibney, & McKevitt, 2017; Fowler, 2016), a study reported that this synthetic sweetener was found in the breast milk of breastfeeding mothers, which had consumed soft drinks in the past 2 days. At lower concentrations, acesulfame-K was also found in the breast milk of a few mothers, who reported that they had not consumed sweeteners because it was probably present in traces in other foods (Sylvetsky et al., 2011). No scientific studies were found that reported effects in breastfed infants. Currently, only research has been conducted in animal models (Uebanso et al., 2017). In particular, *Uebanso et al.* examined acesulfame-K effects, at maximum ADI, on the gut microbiome in mice, and comparing them with sucralose assumtion (Uebanso et al., 2017). Both sucralose and acesulfame-K did not increase food intake, body weight gain, or liver weight, nor epididymal or cecum fat, whereas only the intake of sucralose increased the concentration of hepatic cholesterol and cholic acid. Finally, consumption of sucralose, but not acesulfame-K, affected the relative amount of the fecal microbiome (Uebanso et al., 2017). Moreover, pregnant and lactating mice were exposed to acesulfame-K and sucralose at doses approved for human consumption. In the pups, negative effects have been observed at the hepatic and intestinal level. In particular, the authors highlighted the down-regulation of some liver detoxification pathways and changes in the composition of the intestinal microbiota, similar to the alterations of the microbiome that occur in subjects affected by obesity and MetS (Olivier-Van Stichelen, Rother, & Hanover, 2019; Zhu et al., 2017; Sedova et al., 2007). Therefore, although these are only the first results in the animal model, pregnant or breastfeeding women should limit their consumption of AS, because their effects on children's metabolism are not yet fully known. In this regard, human trials would be needed.

4.1.2. Aspartame

Aspartame is a dipeptide methyl ester discovered around 1960 and approved as the first sweetener in 1981 (Durán Agüero, Angarita Dávila, Escobar Contreras, Rojas Gómez, & de Assis Costa, 2018). Although it has an energy content equivalent to 4 Kcal/g, (such as sucrose) the quantities used in the formulation of dietetic and low-calorie foods are so small that its calorie intake is irrelevant. Its preferential use is for the preparation of low-calorie drinks, yogurt, desserts, jellies, instant drinks, fruit juices, confectionery, and pharmaceutical products. The solubility enhances with higher or lower pH as well as with increased temperature (Chattopadhyay, Raychaudhuri, & Chakraborty, 2014). Since aspartame it is not cariogenic and is about 180 times sweeter than sucrose in aqueous solution, it is the most used sweetener in the world (Tian et al., 2020). The level of aspartame is not measurable exactly, because it is rapidly metabolized into aspartic acid and phenylalanine after ingestion (Durán Agüero et al., 2018). For years, it has been shown that the different concentrations of aspartic acid and phenylalanine in humans while taking aspartame have been considered not clinically relevant. However, since it contains phenylalanine, its consumption is limited for people with phenylketonuria. Animal studies have suggested adverse consequences on metabolic programming through exposure to

aspartame during pregnancy. Furthermore, despite some hypotheses, there is no solid evidence that aspartame is carcinogenic (Martyn et al., 2018; Kirkland and Gatehouse, 2015).

4.1.3. Cyclamate

Cyclamate was discovered in 1937 but has been used as a sweetener since 1950. It is used in the form of sodium salt, while calcium salt is consumption, particularly during a low sodium diet. Cyclamate is 30 times sweeter than sucrose (Chattopadhyay et al., 2014). By itself, cyclamate is not toxic, however, after ingestion and following intestinal metabolism, it produces cyclohexylamine, which is much more toxic (Renwick, Thompson, O'Shaughnessy, & Walter, 2004).

4.1.4. Saccharin

Saccharin was discovered in 1878 and it has been used for over a century. Its use was considerable especially during the two world wars, when there was a lack of sugar. Saccharin has been widely used because of its low production cost and the lack of common sugar (Gupta, 2018; O'Sullivan et al., 2017). It is 200 to 500 times sweeter than sucrose (Gupta, 2018). At the molecular level, it is an aromatic organic compound used in the form of sodium salt or calcium. Both salts are highly soluble in water (Chattopadhyay et al., 2014). It is about 300 times sweeter than sucrose. Saccharin is pharmacologically inert and side effects are very rare (Gupta, 2018). Consumers and the doctors, dentists and dietitians, who counsel saccharin, have overwhelmingly supported its benefits (Fitch & Keim, K.S.: Academy of Nutrition and Dietetics, 2012). It is know that healthcare professionals prefer the use of saccharin, as a non-calorie AS, for weight reduction into obese, for diabetics, other than to reduce dental cavities (Lohner, Kuellenberg de Gaudry, Toews, Ferenci, & Meerpohl, 2020; Al Humaid et al., 2018; Horwitz, McLane, & Kobe, 1988; Kline, Stein, Susser, & Warburton, 1978). Several scientific research studied saccharin effects. However, although there is controversial data regarding its safety, available research indicates that saccharin is safe for human consumption (Basílio et al., 2020; Azeez, Alkass, & Persike, 2019; Amin and AlMuzafar, 2015; Andrejić et al., 2013). Baffling data was mainly based on the results obtained by feeding male rats with high doses of sodium saccharin, which induced bladder tumors in the animal model (Frija et al., 2019; Price et al., 1970). However overall, scientific data supporting the safety of saccharin indicates that: more than 30 human studies indicate the safety of saccharin at human consumption levels; in 14 animal studies, saccharin has not been shown to induce cancer in any organ, even at exceptionally high dose levels; saccharin is not metabolized and does not react with DNA, therefore it cannot be defined as a classical carcinogen (Basílio et al., 2020; Azeez et al., 2019; Amin and AlMuzafar, 2015; Andrejić et al., 2013). Saccharin is approved in more than 100 countries around the world and has been tested and determined as safe by the World Health Organization's Joint Expert Committee on Food Additives (JECFA) and the European Union's Scientific Committee on Food. Based on current research, the JECFA doubled its previous ADI (acceptable daily intake) for saccharin. Finally, the JECFA committee noted that animal data that previously raised questions about saccharin are not considered relevant to humans.

4.1.5. Sucralose

Sucralose was discovered in 1976. This sweetener is a product of sugar, however, it is not metabolized and represents a zero-calorie sweetener. Sucralose is 450–650 times sweeter than sucrose, has a sweet and pleasant taste and its temporal intensity profile is very close to that of sucrose and is non-toxic (Olivier-Van Stichelen et al., 2019). Several studies have shown that sucralose was mutagenic at high concentrations (Eisenreich, Gürtler, & Schäfer, 2020; de Oliveira et al., 2015; Berry et al., 2016; Grotz, 2008; Sasaki et al., 2002). In a murine model, sucralose intake has been shown to increase the expression of the efflux transporter P-glycoprotein (P-gp) and cytochrome P-450 (CYP-450) in the intestine (Tian et al., 2005). P-gp and CYP-450 are involved in the early stages of liver detoxification during drug metabolism. Moreover, it promoted food intake through a neuronal fasting response (Wang et al., 2016; Watowicz, Anderson, Kaye, & Taylor, 2015). Both preclinical and clinical studies have shown that sucralose modifies glucose and insulin levels (Pepino et al., 2013). However, the effect of sucralose on first-pass drug metabolism has not yet been investigated in humans. Furthermore, sucralose has been shown to alter the microbial composition in the gastrointestinal tract, reducing beneficial bacteria (Turnbaugh and Gordon, 2009; Abou-Donia, El-Masry, Abdel-Rahman, McLendon, & Schiffman, 2008).

4.2. Natural sweeteners

Artificial AS are widely used in a variety of foods and beverages as a sugar substitute, mimicking the effect of sugar on taste without adding calories. However, consumers have a negative perception of artificial sweeteners not only because of adverse sensations, such as bitterness. Therefore, the food/beverage industry has focused on the use of natural AS. Although recent studies suggest that natural ASs can reduce hyperglycemia and improve lipid metabolism, diabetes and MetS still represent a global problem and excessive sugar consumption plays an important role. More promising data comes from the use of natural AS, which may be a better alternative to sugar and artificial AS. A number of natural sweeteners, which are becoming popular food ingredients for consumers, are: raw honey, one of the oldest natural sweeteners (Olas, 2020); molasses derived from sugar cane (Valli et al., 2012); maple syrup (Sato, Nagai, Yamamoto, Mitamura, & Taga, 2019) and coconut sugar (Choy et al., 2018). However, to date, only few information are available regarding the metabolic impact of chronic consumption of natural sweeteners, which are usually only considered for their sugar content and not for the other nutrients they contain. In this regard, in very recent studies, *Valle et al.* evaluated the metabolic impact of consuming other natural sweeteners, such as maple syrup, brown rice, agave, and corn syrups, molasses or honey, compared to an equivalent amount of sucrose. Obese rats fed a diet, which included these types of natural sweeteners, showed reduced insulin resistance compared to animals fed sucrose (Valle, St-Pierre, Pilon, & Marette, 2020; St-Pierre et al., 2014). It is therefore likely that the daily substitution of sucrose with natural AS will produce lower glycemic and insulinemic responses, resulting in better long-term metabolic health. Natural sweeteners are low calorific, non-toxic and super sweet (100 to 10,000 times sweeter than sucrose) in nature and can avoid the adverse effects associated to the use of synthetic sweeteners. These substances are preferred over AS since they do not have any adverse impact on health (Tandel, 2011; Geuns, 2007). The active sweet principles stored in plants can include: terpenoids, steroidal saponins, dihydroisocoumarins, dihydrochalcones, proteins, polyols, and volatile oils.

4.2.1. Steviol glycosides

Regarding its potency, steviol glycosides represent the best natural sweetener and are already widely distributed throughout the world (EFSA, 2014). Steviol glycosides have been used in large quantities in Japan with no documented side effects probably their safety comes from the low absorption in both humans and rats in the stomach and ileum (Sylvetsky et al., 2019). Stevia has been used since ancient times for different purposes around the world (Goyal & Samsher, & Goyal, 2010). For centuries, the Guarani tribes of Paraguay and Brazil used Stevia (mainly *S. rebaudiana)* as a sweetener in medicinal teas for the treatment of heartburn and other disorders (Brandle and Telmer, 2007). Steviol glycosides are AS extracted from the leaves of the Stevia rebaudiana plant. The steviol glycosides have zero calories and are 150–350 times sweeter than sugar, therefore an excellent sweetener (Perrier, Mihalov, & Carlson, 2018). Literature reported results that include metabolism, safety, impact on blood glucose, energy intake and changes in body weight, blood pressure, dental caries, and taste properties (Kim et al., 2019; Pham, Phillips, & Jones, 2019; Brambilla, Cagetti, Ionescu,

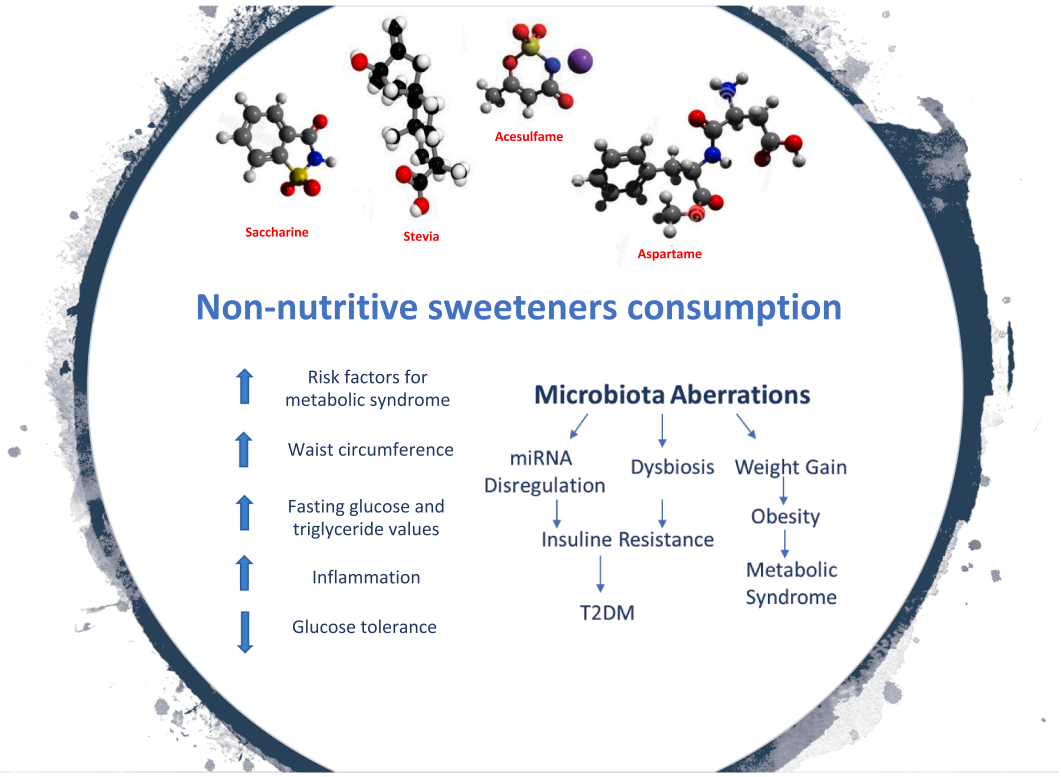

Fig. 3. Effects of AS and Metabolic Syndrome. Alternative sweeteners consumption and their implications on the development of Metabolic Syndrome with particular involvement on the gut microbiota, which leads, through various ways, to increased glucose intolerance and T2D onset.

Campus, & Lingström, 2014; Gupta et al., 2013; Anderson, Curzon, Van Loveren, Tatsi, & Duggal, 2009). Studies investigating the action of steviol glycosides on the gut microbiome instead, showed no evidence of an adverse effect on human health only for rebaudioside A (Lobach et al., 2019). Different studies in obese and diabetic patients have shown that the replacement of sucrose with steviol is associated with lower postprandial glycemic and insulinemic levels, suggesting a beneficial effect of this sweetener on glycidic metabolism (Anton et al., 2010). The intake of steviol was associated with significantly lower postprandial glycemic and insulinemic levels compared to the levels achieved after preloading with sucrose and aspartame. Moreover, after preloading with steviol and aspartame, participants consumed significantly less food during the day than preloading with sucrose (Anton et al., 2010; Mohamed, Ceunen, Geuns, Van den Ende, & De Ley, 2011). The replacement of traditional sucrose with steviol could represent an effective strategy for weight management and a potentially advantageous tool for the containment of post-prandial glycemic levels.

5. Contribution to the development of metabolic syndrome

AS consumption provides a very low calorie or zero-calorie alternative intake that provides minimal or no carbohydrates or energy. Their dietary consumption can modulate energy balance and may influence feeding and metabolism through a variety of peripheral and central mechanisms (Reid et al., 2016; Burke and Small, 2015; Lefterova and Lazar, 2009). Recent evidence highlighted that AS consumption has been associated with increased risk factors for MetS, as represented in Fig. 3 (Hess, Myers, Swithers, & Hedrick, 2018, Green and Syn, 2019; Romo-Romo et al., 2016). In particular, the association between waist circumference and total AS, such as saccharin, sucralose, and acesulfame-K was demonstrated (Hess et al., 2018; Miller and Perez, 2014; Morenga, Mallard, & Mann, 2013). In addition, it was found positively associated between fasting glucose and triglyceride values with total AS and aspartame consumption (Hess et al., 2018).

5.1. Sweeteners and human gut microbiota

Composition and function of the microbiota were affected by external factors, such as environmental stressors, antibiotics and diet (David et al., 2014) as aberrations in the gut microbiota have been associated with the development of insulin resistance, obesity, and also MetS (Fig. 3) (Torre, Keller, Depeyre, & Kruseman, 2016; Cani, Everard, & Duparc, 2013). To date, there are conflicting results on the specific roles of AS on the microbiota (Castaner et al., 2018; Bian et al., 2017). In human studies, it was demonstrated that AS consumption may induce changes in microbiota composition (Roca-Saavedra et al., 2018). Dysbiosis was observed following AS consumption in animal studies (Suez et al., 2014). In several diet-induced animal models of MetS by using AS, changes in microbiota composition (Bacteroidetes to Firmicutes) were positively correlated with reduced glucose tolerance contrarily to observed for overweight people dysbiosis would seem to increase intestinal permeability and thus promote the development of a pro-inflammatory niche that stimulates β-cell autoimmunity (Bibbò, Dore, Pes, Delitala, & Delitala, 2017). AS consumption modulates gut microbiota composition and associations with an increased risk of MetS, obesity, and T2D were demonstrated (Imamura et al., 2016; Grundy et al., 2005).

5.2. Epigenetic mechanisms and AS consumption

The growing interest in the epigenetic involvement in human disease, in particular on the role of miRNAs changing cell function has focused attention on miRNA implications on gut microbiota function (Fig. 3). miRNAs regulate at least 30% of human genes, playing critical roles in cell proliferation, differentiation, apoptosis, and hematopoiesis (Bartel, 2004). miRNA expression can be altered by stress and diet and AS consumption may modify miRNA expression by altering bacterial composition and lead to metabolic changes (Zacharewicz, Lamon, & Russell, 2013). MiRNA by acting at the DNA level or directly on RNA in

the mitochondria could help to restore gut microbiota composition (Liu and Weiner, 2016). Besides, up- or down-regulation of certain specific miRNAs has been correlated with the development of insulin resistance and increased severity of T2D (Latreille et al., 2014). Regular AS consumption induces changes in the composition of the gut microbiota with a consecutive development of insulin resistance (Rowland et al., 2018). MiRNAs, as regulators of many metabolic processes, could be useful therapeutic agents. MiR-126 expression that is significantly reduced in diabetic patients, in which an impaired proangiogenic capacity causes diabetic vasculopathy, manipulation of miR-126 expression could induce migration and proliferation of vascular endothelial cells and facilitate their repair (Jansen et al., 2013). The explanation would be due to the fact that separation of sweetness from calories interferes with physiological responses and the interaction of AS with sweet-taste receptors in the gut negatively affects glucose absorption provoking inducing fat accumulation and weight gain (Moran et al., 2014). On the other hand, deteriorated caloric compensation can lead to an excess of energy supply, which ultimately leads to weight gain (Hill, Wyatt, & Peters, 2012). The reduced caloric compensation results in increased weight gain in animal studies. AS reduces the validity of sweet taste as a signal to predict caloric intake that leads to a positive balance of energy and weight gain (Swithers, Martin, & Davidson, 2010).

6. Contribution to the prevalence of cardiovascular diseases

It is now known that hyperglycemia is associated with an increased risk of cardiovascular disease (CVDs) that occurs in diabetic patients (Napoli and Ignarro, 2009; Weng et al., 2020; Monnard and Grasser, 2018) (Fig. 1). Animal studies have suggested that AS consumption may affect glucose or insulin homeostasis; it can alter the intestinal microbiota, increase appetite and promote weight gain however evidence of these associations in humans is limited (Toews, Lohner, Küllenberg de Gaudry, Sommer, & Meerpohl, 2019; Pepino, 2015; Suez et al., 2014). Furthermore, studies that have assessed the relationship of AS consumption with incident T2D are also confounding; some studies reported that higher intake of diet soda and/or consumption of AS is associated with a higher risk of T2D, while others find no association (Gardener, Moon, Rundek, Elkind, & Sacco, 2018; Vos et al., 2017; O'Connor et al., 2015; Nettleton et al., 2009; Palmer et al., 2008). An association study found that although the consumption of diet soda and AS was high, neither was associated with the risk of diabetes (Jensen et al., 2020; Sanz-Paris et al., 2016, Scharf and DeBoer, 2016). The principal hyperglycemic pathologic complications can be classified as macrovascular complications, which are the CVDs as acute myocardial infarction (AMI), stroke, and peripheral artery disease (PAD); and micro-vascular complications, such as kidney disease, retinopathy and neuropathy, as shown in Fig. 1 (Miceli et al., 2019; Sommese et al., 2018; Yamagishi, Nakamura, & Matsui, 2017; Shammas et al., 2017; Yang et al., 2017; Evans, Wang, & Morris, 2002). Other risk factors include insulin resistance, endothelial dysfunction, caused by excessive vasoconstriction and/or reduced vasodilatation, high levels of reactive protein C, medium-intimate thickness and accumulation of coronary calcium (Napoli et al., 2006a; Sharif et al., 2019; Narain, Kwok, & Mamas, 2016). Oxygen radicals can increase the expression of procoagulant and pro-inflammatory factors, induce apoptosis, and alter the production of nitric oxide (NO) (Napoli and Ignarro, 2009). Oxidative stress can be also produced by glucose and fructose, which non-enzymatically reacting with some proteins, lipids, and nucleic acids, produce senescent macromolecules termed advanced glycation end products (AGEs), which are rapidly metabolized and eliminated from humans (Vlassara and Striker, 2013, Napoli, Lerman, de Nigris, Loscalzo, & Ignarro, 2002). AGE high production and cellular accumulation increase oxidative stress induction through the interaction with a specific surface receptor, called receptor for AGEs (RAGE) (Schmidt, 2017). Accumulating evidence has shown that AGE-RAGE axis induces oxidative stress through several ways: by inhibiting NO production into

Table 2
Clinical trials and alternative sweetener effects.

NCT Number	Condition	Intervention	Enrollment	Aim (Acronim)
NCT02646956	Development	Sweeteners	82	To determine whether there are age-, diet- and genetically-related differences in the perception of sweeteners, both nutritive and non-nutritive (TNNS).
NCT02928653	Body Weight	Soft drink	187	To compare the effects of daily consumption of aspartame, rebaudioside a, saccharin, sucralose, and sucrose on body weight and composition in a standardized protocol (LCS).
NCT02371694	Diabetes Type 1	Soft drink	30	To determine the postprandial glucose dose–response curves response to varying fat amounts by studying various parameters (REQINSOIL).
NCT01324921	Diabetes Type 2	Soft drink	37	To compare the postprandial glycemic and insulinemic response of subjects with type 2 diabetes consuming a typical breakfast meal or no breakfast.
NCT02297880	Eating Behavior	Soft drink	170	To examine the effects of low calorie sweeteners containing beverages on appetite and intake in healthy individuals.
NCT02031497	Glucose Homeostasis	Soft drink	60	To evaluate the effect of a regular consumption of a carbonated drink with sweeteners, in a normal diet, compared with unsweetened sparkling water on insulin sensitivity in healthy normoweight and overweight subjects (SEDULC).
NCT02520258	Glucose Metabolism Disorder	Soda containing only aspartame	75	To evaluate the effect of some artificial sweeteners like

(continued on next page)

Table 2 (*continued*)

NCT Number	Condition	Intervention	Enrollment	Aim (Acronim)
				those in diet soda on changes in how the body responds to and uses sugar.
NCT02589002	Glucose Metabolism Disorders	Sucralose	66	To evaluate the effect of sucralose on insulin sensitivity and beta-cell function.
NCT02800707	Glucose Tolerance	Sucralose/ Stevia	40	To determine the influence of two non-caloric sweeteners on glucose metabolism via the gut microbiome in adult men and women.
NCT03703141	Healthy	Sucralose	95	To demonstrate whether acute or chronic sucralose exposure affects insulin or carbohydrate metabolism or alters systemic inflammatory markers and microbiota in young, healthy adults.
NCT02580110	Healthy Subjects	Sucralose/ Stevia	39	To investigate, in healthy humans, effects of 3 commonly used sweeteners on cardio metabolic risk markers, cognitive functions, and influences on gut microbiota composition.
NCT01200940	Healthy Volunteers	Sucralose/ Aspartame/ Acesulfame-K	118	To study the effects that artificial sweeteners have on hormone levels, blood sugar, and appetite.
NCT02335021	Insulin Resistance	Sucralose	97	To investigate the effects of dietary exposure to artificial sweeteners on taste sensitivity, preference and brain response in adults (AFS-adult).
NCT01103921	Metabolic Syndrome/ Dyslipidemia	Aspartame	214	To examine the effects of consumption of sugar-sweetened beverages on blood triglycerides and cholesterol, cholesterol concentrations, and the body's sensitivity to insulin (DRS).
NCT01272427	Obesity	Sweeteners	36	To demonstrate that glucose and whey protein given 30 and 60 min before a pizza meal will exert different effects on food intake in adolescent children, and will depend on pubertal stage.
NCT02413424	Obesity	Sucralose	38	To examine whether sugar-replacement sweeteners that are currently on the market change how well the body works to control blood sugar (NNS).
NCT04016337	Obesity	Soft drink	138	To study the beneficial effects of sugar-free, rich-in-phytochemicals drink consumption on postprandial hyperglycemia, in order to provide alternatives to excessive sugar intake and counteract the postprandial response linked to sugar consumption in subjects with low levels of chronic inflammation such as overweight people (BEBESANO).
NCT01196351	Obesity Prevention	Non-caloric sweetener	35	To demonstrate that the effect of exercise increases short term appetite and food intake, and interferes with satiety and satiations to a preload in normal weight, overweight and obese boys (VeT).
NCT01996514	Obesity Prevention	Non-caloric sweetener	59	To demonstrate that food advertisements in a TV program watched during a meal, would block satiety responses to pre-meal energy

(*continued on next page*)

Table 2 (*continued*)

NCT Number	Condition	Intervention	Enrollment	Aim (Acronim)
				consumption and delay satiation in OW/OB but not in NW boys and girls.
NCT01115088	Obesity/ Diabetes Type 2	Aspartame/ Sucrose/ Stevia	30	To evaluate the effects of three different types of sweeteners on food intake, hunger and satiety levels, as well as insulin and glucose measures.
NCT02335008	Oral Perception	Sucralose	30	To test the hypothesis that repeated consumption of artificial sweetener reduces sweet taste intensity (AFS_pilot).
NCT03023137	Pregnancy	Sucralose	480	To evaluate how lifestyle interventions during pregnancy affect obstetric results, neonatal metabolism and the intelligence of the offspring (W&D).

the endothelial cell (Sahajpal, Goel, Chaubey, Aurora, & Jain, 2019; Bellier et al., 2019); by producing peroxynitrite, a toxic NO product (Napoli et al., 2006b; Sahajpal et al., 2019; Bellier et al., 2019) and by stimulating the formation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase in endothelial cells, mesangial cells, and renal proximal tubular cells (Yamagishi and Matsui, 2018; Kajikawa et al., 2015). Moreover, the AGE-RAGE complex promotes atherosclerotic plaque formation, but also impairs the reverse cholesterol transport decreasing the expression levels of adenosine triphosphate binding membrane cassette transporter A1 (ABCA1) and ABCG1, thereby, accelerating atherosclerosis in hyperglycemic condition (Crismaru et al., 2020). Finally, this complex could increase atherosclerotic disease progression inducing the apoptotic cell death of endothelial progenitor cells (EPCs) and simultaneously suppressing their migration and tube formation in vitro (Napoli, Benincasa, Schiano, & Salvatore, 2020; Napoli et al., 2011; Schmidt-Lucke et al., 2005). Indeed, high circulating levels of AGEs have been associated with endothelial dysfunction in CVD patients, including diabetic and end-stage renal failure patients (Tarbell, Mahmoud, Corti, Cardoso, & Caro, 2020). In order to study AS assumption on the endothelial system, in recent study, it was demonstrated that natural and artificial sweeteners did not significantly modify cell proliferation and cell cycle distribution of endothelial cells (ECs) in vivo; did not induce cytotoxic effects and did not compromise the angiogenic capability (Schiano et al., 2020). Moreover, genes, such as C-X3-C motif chemokine ligand 1 (CX3CL1) and hypoxanthine phosphoribosyltransferase 1 (HPRT1) were non-differentially expressed with all sweeteners investigated at the difference of glucose and fructose treatment (Schiano et al., 2020). In order to study the effects of AS on metabolic health, it was observed a reduction in the number of circulating progenitor endothelial cells (EPC), which are fundamental in vascular repair and regeneration, after the administration of these compounds in drinking water in mice. The number of EPCs was less reduced when an inflammatory process was underway. Thus, even in this preclinical model, the sweeteners induced apparently opposite effects based on the health of the recipient (Schiano et al., 2019).

7. Clinical trials

More than 200 randomized controlled trials have been launched to date, of which 137 have been completed and only 22 have published results reports. Thirty-four studies recruited exclusively women, 31 men, and while 15 are observational, the majority were interventional studies (N.221). As reported in Table 2, during these clinical studies, glucose levels were assessed following the intake of AS, such as aspartame, saccharin, steviol glycosides and sucralose, assessing blood glucose concentrations over time in 18% of cases, while 19% evaluated the effects of AS on obesity/MetS. Overall, the results confirmed that the consumption of AS does not increase the blood glucose level and its concentration decreased over time. However, the glycemic index varied based on BW, age and the presence of T2D in the participants. Only a few studies have evaluated the effect of AS in pregnancy. In order to investigate whether AS can affect the fetus, the researchers showed at the ability of AS to cross the placenta (NCT03954418). The aim of another clinical study was to determine the concentration of AS in amniotic fluid and breast milk samples and to correlate these data with mothers' intake of AS (NCT03972176). Finally, in the third clinical study, it was evaluated whether a balanced diet (with also the intake of sucralose) combined with regular exercise and thus improving glucose homeostasis could increase the percentage of children to take home in women with consecutive early miscarriages (NCT03023137). Only the study with completed enrollment status was reported in the Table 2. The Table 2 shows the main ongoing clinical trials of the type of observational and/or interventional study to study the effects of sweeteners, extracted from the site https://clinicaltrials.gov. Clinical trials (which enrolled more than 30 participants) were reported with specific scientific aim.

8. Challenges and future perspectives

The main reasons that led industries to add sugars to food and drink are varied, such as to balance sweetness and acidity in fruit-based products such as drinks, preserves, and sauces; to stabilize the flavor in low-fat ice cream, to reduce the bitterness of cocoa in chocolate. Currently, cumulative evidence show results obtained from experimental models on the negative effects of high sugar intake in the diet, but no clear evidence indicated daily caloric thresholds for sugar intake that can have negative effects on human health. Recent reports indicate the need to limit foods, such as added sugars, which induce reactive oxygen species (ROS) formation and contain AGEs, to prevent the development of metabolic diseases and related comorbidities. Indeed, during CV damage, high glycemic levels function through different mechanisms, such as ROS and AGEs formation. Endothelial dysfunction plays a central role in the pathogenesis of micro and macro-vascular diseases. Endothelial dysfunction is triggered after mitochondrial dysfunction caused by hyperglycemia and endoplasmic reticulum stress, which together generate ROS, contributing to the development and progression of cardiovascular complications in diabetic patient. At the molecular level, they cause irreversible oxidative changes, which directly damage lipids, proteins, and/or DNA, altering the intracellular signaling pathways. To date, most studies have analyzed the possible association between alternative sugars and the risk of dental caries, T2D and depression, while there are still few studies reporting the effects of sweeteners on the CV system. Specifically, randomized controlled trials do not clearly demonstrate the expected benefits of consuming alternative sweeteners for the management of BMI. On the contrary and in a worrying way, there is a surprising congruence between the results obtained in animal models and a series of large-scale long-term observational studies in humans, for the search for weight gain, adiposity, the

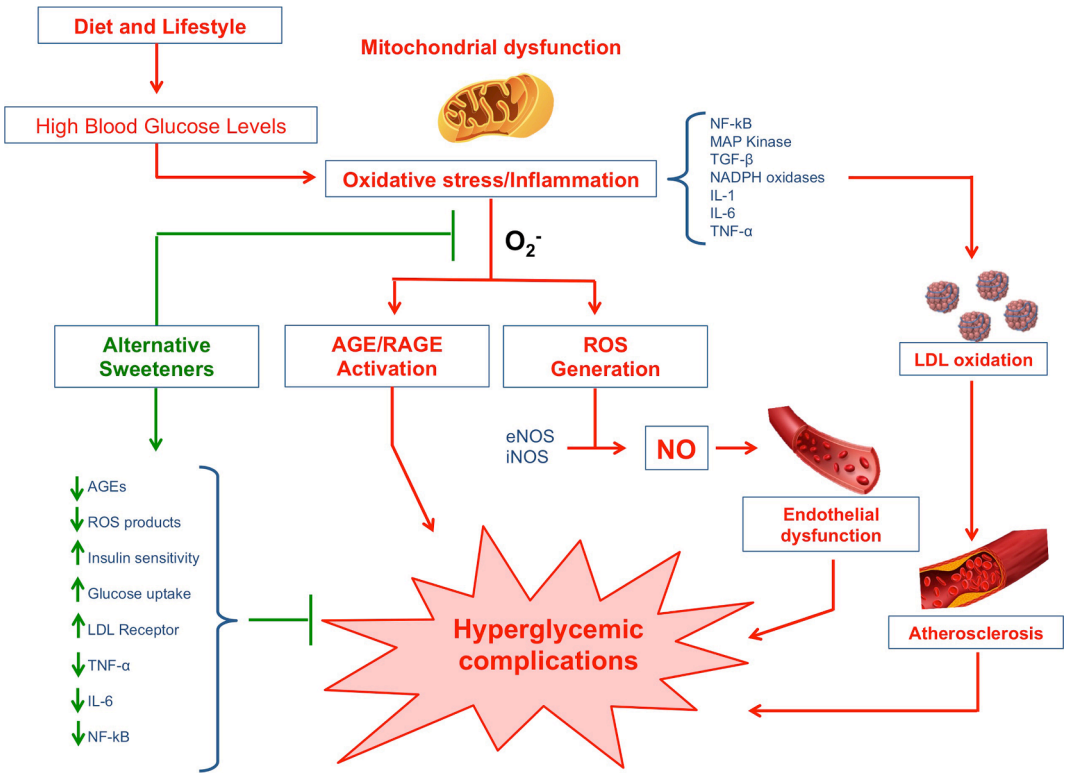

Fig. 4. Alternative sweeteners and potential action mechanisms. Potential action mechanisms underlying the effects of AS on the development of T2D and cardiovascular complications. By interacting with the sweet taste receptor family (T1R), AS produce an increase in insulin sensitivity, glucose uptake and LDL receptors. On the other hand, they could reduce AGEs, ROS, and inflammatory molecules, such as TNF-α, IL-6, intracellular NF-kB. However, through the activation of the associated G protein, excessive AS consumption could explain their contribution to weight gain/obesity, insulin resistance, intestinal permeability and inflammatory diseases, thus contributing to the onset of diseases metabolic and related comorbidities.

incidence of obesity, significantly increased cardiometabolic risk and even total mortality among subjects with chronic daily exposure to low-calorie sweeteners (Simon et al., 2013). Still, other studies are needed, in particular for saccharin, acesulfame-K, and steviol glycosides, which have been studied less frequently than aspartame and for periods not exceeding 16 weeks. Prospective and pharmacokinetic clinical studies are needed to determine whether early exposure to alternative sugars through breast milk can have clinical implications on the children or during the gestational period on the fetus. Further randomized controlled studies are also needed to compare different types and formulations of sweeteners and to evaluate the effect of replacing sweeteners with sugar (Fig. 4). It would be advisable to use sweeteners with caution until the risk/benefit ratio of these substitutes is fully demonstrated.

9. Conclusions

This review aims to provide updated information on the effects of ASs on CVDs and related complications, as well as on body weight and glycemic control. Currently, there are five AS and stevia, as natural sweetener approved for use. For each sweetener, the FDA and EFSA indicate an ADI, which is the amount of sweetener considered safe to consume daily. Today, the consumption of ASs is increasing in all age groups, especially in children. However, since there are few explicit recommendations for the consumption of ASs in pediatric age, the best drink is always water, although the consumption of AS drinks instead of sugary drinks could be a useful strategy to reduce metabolic risk among strong consumers achieving less harmful effects on health. However, further studies are needed to evaluate the potential metabolic consequences of ASs consumption at various stages of life and to better understand the underlying biological mechanisms.

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Author contributions

CS, VG and MS performed Medline; CS, DC, and VG wrote the review; AS, GFN and CN supervised the work. All authors have read and agreed to the published version of the manuscript. CS, VG and CN funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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