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Review of Recommendations for the Use of Caloric Sweeteners by Adults and Children

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Abstract Sweeteners are natural or artificial substances that give food or a product a sweet flavour, and are divide by their nutritional value to caloric and non-caloric. Although they have been reported as safe, this review analyses the findings of various studies to obtain recommendations for their use based on their effect on energy consumption, weight, glucose and blood lipids. In addition to the compensation in energy intake, effects on appetite, hydration, preference for sweet flavours and cardiovascular function were reviewed. We searched MEDLINE, EMBASE, LILACS, and WHO ICTRP Search Portal without language restrictions. We included systematic reviews, controlled trials and observational studies comparing the administration of caloric and non-caloric sweeteners in adults and children. Two authors used AMSTAR tool, Risk of bias tool of the Cochrane Collaboration or ROBINS-I instrument for screening the studies according to their methodological quality and were included those have a low risk of bias. A reduction in blood glucose was more effective when sweetening foods with fructose compared with the use of sucrose in non-diabetic patients (–4.81 mmol/L; 95% CI –6.34 to –3.29, $p<0.05$). The reduction in body mass index was greater with the use of non-caloric sweeteners compared with sucrose in patients regardless of their weight (–0.3 to –0.9 kg/m^2, 95% CI –1.5 to 5). Although there is interest in identifying the efficacy of non-caloric sweeteners in preventing obesity and its complications, there is not sufficient evidence because of significant heterogeneity between the different studies and the lack of evidence in children. Thus, designing studies that will provide more evidence in this regard is necessary.

Keywords: *sweeteners, obesity, diabetes, cardiovascular diseases, chronic degenerative diseases, infection*

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1. Introduction

Sweeteners are natural or artificial substances that give food or a product a sweet taste, and are divided by their nutritional value according to the energy they provide. The caloric or nutritive sweeteners provide close to 4 calories per gram: sucrose, fructose, glucose/fructose syrup, lactose, glucose/dextrose, levulose/fructose, dextrose, maltose, polyalcohols. These sweeteners have been approved by the Food and Drug Administration (FDA) for consumption, mainly in children. However, it has been observed that they increase the risk of obesity and dental caries.

Non-nutritive or non-caloric sweeteners, such as sucralose, cyclamates, acesulfame-K, alitame, saccharin, neotame, aspartame, stevia, luo han guo (mogrosides in the pulp of the fruit), advantame, thaumatin and neohesperidin, are chemically processed and are very sweet, but low in calories. It has been suggested that their consumption decreases the risk of obesity; however, some have side effects [1].

Non-nutritive sweeteners can be obtained from natural sources by extracting different compounds from plant products. Among these are stevia (steviol glycosides, steviosides and rebaudioses) and luo han guo. In contrast, the artificial ones, including acesulfame K, sucralose, saccharin, cyclamate, neotame, aspartame and advantame, are synthetically obtained by processing different substances. In the last thirty years, the food industry has resorted to the use of sweeteners because they: 1) contribute sweetness to a product, enhance flavours, and neutralize astringent and spicy tastes; 2) preserve bacterial growth in the food; 3) enhance the flavour of cured meats; 4) develop colour and flavour in baked products; 5) provide body, palatability and texture to syrups, sweets and ice creams; and 6) improve the freezing point control and crystallization in ice creams and sweets. [1,2]

2. Non-nutritive Sweeteners (Non-caloric)

Because of the increase in the demand for these products owing to their very low caloric intake, the food industry has investigated new types of sweeteners with

greater sweetness and lower energy contribution. Among these are [1,3]:

2.1. Aspartame

A dipeptide formed by aspartic acid and phenylalanine. Methanol is produced when it is metabolized. It provides 4 kcal/g. Some of its advantages are: 200 times sweeter than sugar, enhances the taste of food, does not cause caries and works synergistically with acesulfame K. Its main disadvantages are: metallic taste, high cost, unstable at high temperatures, low solubility in water, it degrades with time and its sweetening capacity reduces in combination with flavourings.

Aspartame is mainly used in liquid and powdered drinks, puddings, jellies, cereals, desserts, sauces and chocolates. It has been found that at high doses, it produces biochemical changes in plasma amino acids and secondary formaldehyde production during methanol conversion. However, clinical trials have reported that it is safe at 75 mg/kg/d. Other reported effects are headaches, hypertension, oedema, type IV hypersensitivity, changes in appetite and depressive states due to changes in the cerebral enzymatic activity of acetylcholinesterase. However, these reports have a limited number of patients and significant methodological deficiencies, and these effects have not been replicated in new investigations. [4]

Currently, its use is not recommended for phenylketonuric patients, as they cannot metabolize and degrade phenylalanine in the liver, due to a genetic lack of the enzyme, phenylalanine hydroxylase, leading to its accumulation and generation of ketone bodies that cause neuronal damage. [4,5]

2.2. Acesulfame K

A derivative of acetoacetic acid in combination with potassium. Its main use is to intensify the sweetness of food in combination with other sweeteners. It is absorbed in the small intestine and is excreted through the kidneys without being metabolized, hence it does not produce energy. Some of its advantages are quick perceptible sweetness, 200 times faster than sugar, it is resistant to heat and does not cause tooth decay. However, it has an unpleasant taste in high concentrations.

Acesulfame K is used in beverages, dairy products, jams, sweets, baked products, chewing gum, canned fruits and vegetables, fish, ice creams, gelatine, pasta and mouthwash. Different studies have shown no association between its consumption and the development of cancer, metabolic disorders, neurotoxicity, headaches, seizures or behavioural alterations, as has been suspected in previous years. [4]

2.3. Saccharin

An o-sulfobenzoic imide substance, which was the first non-caloric sweetener marketed during the world wars as a substitute for sugar, as it was rationed throughout Europe. It is absorbed by the intestine and excreted by the kidneys without being metabolized. No toxic effects are known.

Its advantages are that it is stable at high temperatures, pH variations, cooling and freezing, it is 200 to 700 times sweeter than sugar and is 100% soluble in water. However, it leaves a bitter taste. It is used as a substitute in instant drinks, sweets, juices, dairy products, jellies, jams, preserves, ciders, fish and canned fruits, sauces, chewing gum, multivitamins, ice creams, puddings, chocolates, toothpaste and mouthwash. [4]

2.4. Sucralose

Obtained from the chlorination of sucrose, in which three hydroxyl groups are replaced by chloride ions. It is not easily absorbed by the digestive tract, being eliminated with the faeces and the renal route without being metabolized or having any osmotic effect. It is 600 times sweeter than sugar.

Its advantages are its solubility in water, stability at high temperature and low pH, it functions synergistically with other sweeteners, it does not cause tooth decay and does not react with other food components. However, it is unstable in storage and susceptible to discoloration. It is used as a tabletop sweetener, in processed fruits, carbonated drinks, chewing gum, baked goods, jams, dairy products, frozen desserts, dressings and salads.

Sucralose is considered safe for patients with diabetes, which was demonstrated in a clinical trial with 128 people who were administered a dose three times greater than the estimated daily consumption and no adverse effects on glycaemic control were reported. [4,6]

2.5. Stevia

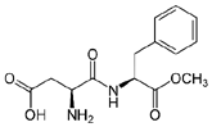
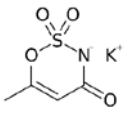
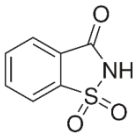
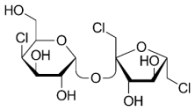
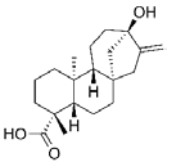
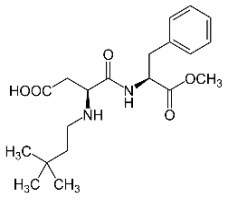
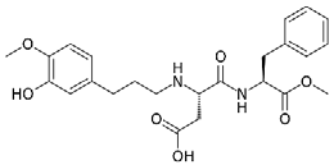
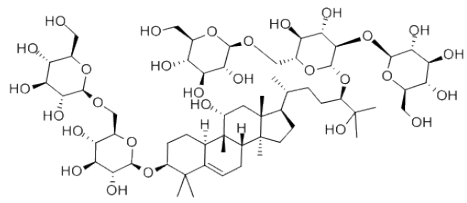
A natural sweetener, obtained from cooking and crushing the leaves of the perennial *Stevia rebaudiana* plant, whose leaves contain a mixture of steviol, steviosides, dulcosides, and rebaudiosides A, B, C and D, which can constitute 4% to 20% of the weight of the leaf depending on the variety and growing conditions.

It is not absorbed by the intestine, but is degraded by the intestinal flora. In experimental studies with animals, a weak mutagenic effect of steviol and 15-oxo-steviol has been demonstrated, so only the use of purified extracts has been allowed to minimize these risks. Its advantages are: high sweetness level, soluble in water, it is not fermentable, it resists high temperatures and it functions synergistically with other combinations of sugars. However, in large quantities it tastes like liquorice and menthol, and it is not used to preserve food. It is used in confectionery, baked goods, beverages, dairy products, liquor, beer, soft drinks, ice creams and soy sauce. [7]

2.6. Neotame and Advantame

Derived from aspartame, they contain aspartic acid and phenylalanine, but with greater sweetening power (neotame is 7,000 to 13,000 times and advantame is 20,000 sweeter than sucrose). They can be consumed by people with phenylketonuria because the amount of phenylalanine in advantame is not significant. Both are stable at high temperatures, and advantame also is used in the food industry as flavour enhancers. [8,9,10]

Table 1. Side effects of Non-nutritive Sweeteners [12-17]

Molecule	Side effects
Aspartame 	It is not recommended for persons with phenylketonuria. The quantities of methanol provided by aspartame consumption are fewer than other common food sources and it could not cause any neurological effect. Its sweetness can be degraded with changes in pH and heat.
Acesulfame K 	None has been reported so far.
Saccharin 	Saccharin consumption during pregnancy can cause accumulation of this sweetener in the fetus because it crosses the placenta; however, it is not associated with malformations or abortions. A small study in humans reported higher glucose concentrations and significant changes in gut microbiota after seven days of consumption.
Sucralose 	Some human studies associate sucralose consumption with decreased insulin sensitivity and stimulation of GLP-1 (glucagon-like peptide 1) release; however, these findings have not been replicated.
Stevia 	The U.S. Food and Drug Administration only recommend the use of high-purity steviol glycosides; the use of stevia leaf and crude stevia extracts have no GRAS (Generally Recognized as Safe) classification because it contains a wide variety of other compounds not studied. Consumed at higher amounts can produce a bitter taste.
Neotame 	None has been reported so far.
Advantame 	None has been reported so far.
Luo Han Guo 	Consumed at high quantities may have an aftertaste.

2.7. Luo Han Guo

An extract of non-nutritive mogrosides obtained from the pulp of the plant, *Siraitia grosvenorii*. It is 100 to 250 times sweeter than sucrose. The acceptable daily intake has not been determined, yet, and although it has been very well accepted, like stevia, it is not yet marketed worldwide [8,11] (Table 1).

3. Methods

We searched MEDLINE, EMBASE, LILACS, and WHO ICTRP Search Portal. The date of the last search was January 2018 for all databases without language restrictions. We included systematic reviews, controlled trials and observational studies comparing the administration of caloric and non-caloric sweeteners in adults and

children. Two authors used AMSTAR tool for systemic reviews, Risk of bias tool of the Cochrane Collaboration for controlled trials or ROBINS-I instrument for non-randomized studies to screening their methodological quality. We resolved discrepancies through consensus and only those reports with an overall low risk of bias were included in this review.

4. Sweeteners and Chronic Degenerative Diseases

The health situation has changed in the last two decades because there is an excessive caloric intake of industrialized foods and a low energy expenditure due to sedentary lifestyle, which is associated with changes in the consumption patterns of sweetened beverages, increasing the risk of obesity, insulin resistance, type 2 diabetes mellitus and cardiovascular diseases in children and adults.

In the analysis sector of the sweetener market in Mexico, it has been reported that the annual average of sugar consumption has decreased by 2.7% from 2002 to 2011, which may be due to variations in the price, supply and demand of sugar, and changes in the dietary habits of the population, and because the consumption of high fructose corn syrup has increased at a rate of 40% on an annual average, constituting more than a quarter of the sweetener market in Mexico.

Characterizing the consumption of non-caloric sweeteners is complicated because several combinations are used in many products, without their exact content being specified, which makes it difficult to determine the ingested amount of each sweetener per day. However, it has been estimated that the general consumption of these products has grown by an average of 10.7% annually, representing around 5.5% of the sweetener market. [18]

Because of the continuous increase in the consumption of non-nutritive sweeteners (up to 15.1%) to promote weight reduction, the commercial food industry has taken this opportunity to add such sweeteners to their products, calling them dietetic foods, earning up to 1 trillion dollars in 2014. However, their side effects have not been analysed, thus the present review was carried out to obtain evidence and generate recommendations about their use in the general population. [19]

4.1. Sweeteners in the Control of Diabetes Mellitus

Several researchers have evaluated the consumption of non-nutritive sweeteners by patients with diabetes, observing a prevalence of up to 96%, being significantly higher in men ($p = 0.01$), with a preference for acesulfame K in 90% of the population, followed by aspartame in 86%, sucralose in 80%, stevia in 22% and saccharin in 0.7% (20). Because of their high consumption, since 1800 different clinical trials have been conducted to determine which sweetener is more effective in maintaining normal glucose and blood lipid concentrations without adverse effects. Among these we note the following:

In 2011, Wiebe *et al*., conducted a systematic review with network meta-analysis to compare the effectiveness of sweeteners added to food to control blood glucose concentration 2 h after of food intake. In this study, 53 clinical trials were included, with a total of 1126 overweight, obese and/or diabetic patients over 16 years of age, who were given diets with different types of sweeteners (glucose, fructose, sucrose, sugar alcohols, aspartame, saccharine, sucralose and stevia). At the end of the study it was concluded that the use of fructose reduced glucose concentrations compared with diets with sucrose (–1.12 mmol/L; 95% CI –1.95 to –0.27, $p<0.05$) and glucose (–4.8 mmol/L; 95% CI –6.34 to –3.29, $p<0.05$), without increasing blood cholesterol levels (Figure 1) [21].

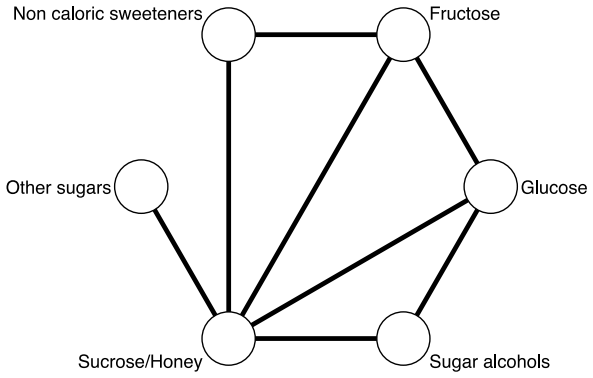


Figure 1. Network Meta-analysis of Six Interventions in Glycemic Control (mmol/L) in the Blood, 2 h After Ingestion

In 2009, Sievenpiper conducted a systematic review, in which he analysed 16 clinical trials with 236 patients with diabetes mellitus type 1 and 2, and compared them using the same interventions, reporting that there was no statistically significant difference in the reduction in concentration of glucose, total cholesterol, low density lipoprotein (LDL) or high density lipoprotein (HDL) in the blood, which was attributed to the substantial heterogeneity in his analysis. [22]

In 2008, Livesey evaluated the effects of a fructose-containing diet in a study that included 112 clinical trials with 106 healthy individuals and individuals with some metabolic alteration (insulin resistance, diabetes mellitus type 2, hyperlipidaemia), who were given fructose-sweetened foods. He compared the results with patients who received another type of sweetener in their diet (glucose, sucrose or maltodextrins), observing a reduction in the concentration of glycosylated haemoglobin and triacyl-glycerol in the patients that fructose was added to their diet (–0.02 mmol/L; 95% CI –0.03 to –0.01, $p<0.05$). [23]

Regarding the relationship between the consumption of beverages containing non-caloric sweeteners and the development of diabetes mellitus, De Koning conducted a cohort study with a follow-up of 20 years. He reported observing an increase in the risk of developing the disease. However, after a multivariate analysis it was concluded that this relationship was spurious, as it mainly depended on the basal health conditions of the subjects and the diet they consumed daily. [24] Given these results, the American Dietetic Association stated that non-nutritive sweeteners were safe for consumption because they do not affect the glycemic response in patients with diabetes mellitus. [25,26]

4.2. Sweeteners and Energy Ingestion

We found a review conducted by Gardner (2012), in which 12 studies were included, which compared the compensation of energy intake of participants who consumed foods containing aspartame with subjects who added sucrose to their food. The author found that 32% of the original energy deficit was not compensated for during the 24 h after the intake of foods with aspartame, resulting in a reduction in calories. [3]

Similar results were observed in:

A clinical trial conducted by Raben in 2002, which compared the consumption of energy after the intake of sucrose-containing foods with subjects who ingested food containing non-nutritive sweeteners. After 10 weeks of follow-up, there was a significant increase in body weight, fat mass, blood pressure and caloric intake in the subjects consuming sucrose-containing food compared with patients who consumed foods containing non-nutritive sweeteners. [27]

A study by Suez *et al.*, which included seven participants who consumed for a week the total admissible daily intake of saccharin, observed that the glucose concentration in the participants rose considerably from day 5 of intervention. [28]

A systematic review by Rogers (2016), who evaluated the caloric intake after the consumption of unsweetened beverages, drinks with sugar and beverages with non-caloric sweeteners, noted that the consumption of non-caloric sweeteners only reduced the energy intake when compared with drinks sweetened with sugar (–94 kcal; 95% CI –122 to –66, $p<0.05$). [29]

Based on the abovementioned findings, the American Association of Cardiology examined whether changes in the polymorphism of the sweet taste receptors, Taste 1 receptor Member 2 and 3, affect the preference for sweet-tasting foods, favouring their intake; resulting in increase on appetite because of their effect on insulin secretion; increase the thirst sensation due to their palatability and high osmolarity, thus favouring the intake of beverages; which consumption increases in energy intake that leads to a greater risk for obesity. However, no conclusive results were obtained. (Table 2) [3,30,31,32,33].

4.3. Sweeteners and Body Weight

Several researchers have proposed that the interaction of these sweeteners with sweet taste receptors located in pancreatic beta cells and enteroendocrine cells promotes the secretion of insulin and GLP-1 (a peptide similar to glucagon type 1), and increase glucose transport at the intestinal level, upon an increase in the expression of the transporters, sodium/glucose cotransporter 1 (SGLT1) and glucose transporter 2 (GLUT2), leading to elevation in the blood glucose concentration. [26]

However, these theories are contradictory to the evidence reported previously:

In Miller's systematic review, he documented that the consumption of non-caloric sweeteners caused a small but significant decrease in body weight (–0.80 kg; 95% CI –1.17 to –0.43), body mass index (–0.24 kg/m^2; 95% CI –0.41 to 0.07), fat mass (–1.10 kg; 95% CI –1.77 to –0.44, $p<0.05$) and waist circumference (–0.83 cm; 95% CI –1.29 to -0.37). [34]

Rogers identified a significant decrease in body weight in both adults and children after consuming beverages with non-nutritive sweeteners compared with drinks sweetened with sugar (–1.35 kg; 95% CI –2.28 to –0.42, $p<0.05$), concluding that these sweeteners could positively influence energy saving, and therefore favour weight loss when used as a substitute for sugar consumption and under a structured food plan to avoid overcompensation of energy savings. [29]

A Sievenpiper review in 2012 included 41 clinical trials in which 756 diabetic patients. This study compared fructose as a dietary supplement with other sources of carbohydrates in the diet to examine the effect on body weight. He observed that after 7 days of intervention, there was a significant weight reduction in patients who consumed fructose (–0.55 kg; 95% CI –1.09 to –0.02, $p<0.05$), concluding that fructose could be effective in reducing body weight. [35]

In the paediatric population, there is very little evidence in this regard. However, a study analyzed the body mass index of 193 families, who had children and adolescents who usually consumed foods with non-caloric sweeteners and compared them with families consuming sugar-sweetened foods. After 6 months, this study reported that children in the families who consumed foods with non-caloric sweeteners, decreased their body mass index significantly. [36]

Similar findings were observed in a clinical trial performed in 2006, which was conducted on 103 patients between 13 and 18 years of age who regularly consumed sugar-sweetened beverages (diet drinks, ice tea, lemonade and punch). For 25 weeks, their usual consumption of sugar-sweetened beverages was displaced to noncaloric beverages. The authors observed a significant reduction in body mass index (-0.63 ±0.23 kg/m^2), offering additional support for American Academy of Pediatrics guidelines to limit the consumption of sugar-sweetened beverages. [37]

Table 2. Theories on the Effect of Sweeteners on Appetite (Modified from 20).

Potential mechanisms	Description of the phenomenon
Stimulation of the cephalic phase	It has been observed that non-nutritive sweeteners affect this phase, thus the feeling of hunger and appetite
Nourishing and osmotic effects	Because of their low energy and osmotic load, sweeteners may alter the speed of gastric emptying and absorption of other factors of digestion, affecting the feeling of hunger
Palatability	Non-caloric sweeteners increase palatability, which stimulates hunger and/or reduces satiety
Overcompensation	The energy saving due to the substitution by the use of a sweetener leads to subsequent compensation
Loss of signal fidelity	The properties of metabolic signals are lost and directed towards a signal for over consuming energy
Activation of reward systems	Non-caloric sweeteners may play a role in food intake reward
Palate training and reinforcing something familiar	Repeated exposure to non-nutritive sweeteners perpetuate preference for sweet foods in the diet

4.4. Sweeteners and Cardiovascular Function

Regarding the cardiovascular risk of sweeteners, Fung and Ling conducted cohort studies in 2009 and 2011 in which they included 2500 adults, to analyse the association between the intake of sweetened beverages and the presence of coronary heart disease. It was reported that the consumption of two or more drinks with added sweeteners increased up to 2% the risk of coronary heart disease, renal failure and metabolic syndrome in these patients after consumption for a period of 9 to 12 years. However, the authors concluded that despite observing this association, it does not determine a causal relationship, and therefore more studies are required to characterize this phenomenon. [38,39]

Similar findings were reported in the Azad meta-analysis, which observed an increased risk of developing hypertension (HR 1.12, 95% CI 1.08 to 1.13, I2 53%, $p<0.05$), cerebral vascular events (RR 1.14, 95% CI 1.04 to 1.26, I2 0%, $p<0.05$) and different cardiovascular events (RR 1.32, 95% CI 1.15 to 1.52, I2 0%, $p<0.05$). However, they lack evidence and these associations require more experimental studies. [40]

4.5. Sweeteners and Infections

Finally, it has been observed that xylitol, a caloric sweetener, reduced infection by *Streptococcus Pneumoniae* and *Haemophilus Influenzae* in nasopharyngeal cells, hence it was suggested that it could decrease the risk and frequency of acute otitis media infections in children under 12 years of age. Under this premise, in 2013, Azarpazhooh conducted a systematic review that included three clinical trials with 1826 children who were given a xylitol diet or placebo. He observed that there was a significant reduction in the risk to develop an episode of acute otitis media (RR 0.75; 95% CI 0.65 to 0.88, $p<0.05$). However, this effect was not consistent in children who already had a respiratory tract infection during the intervention, suggesting that it may be a useful alternative as a coadjuvant in the prevention of otitis media. [41]

5. Conclusions

After analysing all the evidence, including a network meta-analysis where seven types of sweeteners were compared, seven systematic reviews in which 53 clinical trials were included with more than 5000 patients, and different observational cohort studies, we concluded the following:

A) Regarding the control of the concentration of blood glucose, foods sweetened with fructose were found to be more effective compared with the use of sucrose, glucose or other sugars 2 h after consumption in non-diabetic patients (–4.81 mmol/L; 95% CI –6.34 to –3.29, $p<0.05$).

B) With respect to the change in body mass index, non-caloric sweeteners are more effective compared with sucrose in patients regardless of weight (–0.3 to –0.9 kg/m^2; 95% CI –1.5 to 5).

C) For energy consumption, the consumption of non-caloric sweeteners only reduced the energy intake when compared with drinks sweetened with sugar (–94 kcal; 95% CI –122 to –66, $p<0.05$).

D) Fructo-oligosaccharides were found to be more effective than sucrose for the control of total blood cholesterol levels (0.26 mmol/L; 95% CI 0.03 to 0.48, $p<0.05$) both in healthy patients and in patients with diabetes mellitus type 2.

Despite the interest in identifying the efficacy of non-caloric sweeteners as a potential tool for preventing obesity and its complications, the evidence has not been sufficient because of the significant heterogeneity between the different studies and the lack of evidence in children. Therefore, we do not have enough information to establish recommendations on the use of these additives to improve health. However, clinical trials, controlling multiple factors such as the consumption of healthy diets, exercise programs, lifestyle and adherence to dietary programs should be designed, to correctly identify the effect of sweeteners on health, and in this way generate new health care programs, which may reduce the prevalence of obesity and its associated diseases.

References

[1] American Dietetic Association. “Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners”, *J Am Diet Assoc*, 104(2): 255-275. Feb.2004.

[2] Valdés, S., Ruiz, M. “Edulcorantes en alimentos: aplicaciones y normativas”, *Alimentación online*, 13: 38-44. May.2009. [Online] Available: http://www.alimentacion.enfasis.com/notas/13134-edulcorantes-alimentos-aplicaciones-y-normativas/. [Accessed Feb. 2, 2018].

[3] Gardner, C., Wylie-Rosett, J., Gidding, S., Johnson, R.K., Reader, D., Lichtenstein, A.H., et al. “Nonnutritive Sweeteners: Current Use and Health Perspectives: A Scientific Statement from the American Heart Association and the American Diabetes Association”, *Circulation*, 126(4): 509-519. Jul.2012.

[4] González A. “Posición de consenso sobre las bebidas con edulcorantes no calóricos y su relación con la salud”, *Rev Mex Cardiol*, 24(2): 55-68. Apr.2013.

[5] Magnuson, B.A., Burdock, G.A., Doull, J., Kroes, R.M., Marsh, G.M., Pariza, M.W., et al. “Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies”, *Crit Rev Toxicol*, 37 (8): 629-727. Oct.2007.

[6] Bloomgarden Z. “Nonnutritive sweeteners, fructose and other aspects of diet”, *Diabetes Care*, 34: e46-51. May.2011.

[7] Anton, S.D., Martin, C.K., Han, H., Coulon, S., Cefalu, W.T., Geiselman, P., et al. “Effects of Stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels”, *Appetite*, 55: 37-43. Aug.2010.

[8] US Food and Drug Administration. Food Additives & Ingredients - Additional Information about High-Intensity Sweeteners Permitted for use in Food in the United States [Online]. Center for Food Safety and Applied Nutrition. Available: http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm397725.htm [Accesed Mar.18, 2018].

[9] Chattopadhyay, S., Raychaudhuri, U., Chakraborty, R. “Artificial sweeteners - a review”, *J Food Sci Technol*, 51(4): 611-621. Apr.2014.

[10] Warrington, S., Lee, C., Otabe, A., Narita, T., Polnjak, O., Pirags, V., Krievins, D. “Acute and multiple-dose studies to determine the safety, tolerability, and pharmacokinetic profile of advantame in healthy volunteers”, *Food Chem Toxicol*, 49: S77-83. Nov.2011.

[11] Li, X.E., Lopetcharat, K., Drake, M.A. “Parents' and children's acceptance of skim chocolate milks sweetened by monk fruit and stevia leaf extracts”, *J Food Sci*, 80(5): S1083-1092. May.2015.

[12] Academy of Nutrition and Dietetics. “Position of the Academy of Nutrition and Dietetics: Use of Nutritive and Nonnutritive Sweeteners”, *J Acad Nutr Diet*, 112: 739-758. May.2012.

[13] Butchko, H.H., Stargel, W.W., Comer, C.P, Mayhew, D.A., Benninger, C., Blackburn, G.L., et al. “Aspartame: review of safety”, *Regul Toxicol Pharmacol*, 35:S1-93. Apr.2002.

[14] Pope, E., Koren, G., Bozzo, P. "Sugar substitutes during pregnancy", *Can Fam Physician*, 60(11): 1003-1005. Nov.2014.

[15] Romo-Romo, A., Aguilar-Salinas, C.A., Gómez-Díaz, R.A., Brito-Córdova, G.X., Gómez-Velasco, D.V., López-Rocha, M.J., et al. "Non-Nutritive Sweeteners: Evidence on their Association with Metabolic Diseases and Potential Effects on Glucose Metabolism and Appetite", *Rev Invest Clin*, 69(3): 129-138. May-Jun.2017.

[16] Pepino, M.Y., Tiemann, C.D., Patterson, B.W., Wice, B.M., Klein, S. "Sucralose affects glycemic and hormonal responses to an oral glucose load", *Diabetes Care*, 36(9): 2530-5. Sep.2013.

[17] Brown, R.J., Walter, M., Rother, K.I. "Effects of diet soda on gut hormones in youths with diabetes", *Diabetes Care*, 35(5): 959-64. May.2012.

[18] 12/18Secretaría de Economía de México. Análisis de la situación económica, tecnológica y de política comercial del sector edulcorantes en México. [Online]. Available: http://www.economia.gob.mx/files/comunidad_negocios/industria_comercio/Analisis_Sectorial_Mercado_Edulcorantes.pdf [Accesed Mar. 18, 2018].

[19] Mattes, R., Popkin, B. "Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms", *Am J Clin Nutr*, 89: 1-14. Apr.2009.

[20] Romo-Romo, A., Almeda-Valdés, P., Brito-Córdova, G.X., Gómez-Pérez, F.J. "[Prevalence of nonnutritive sweeteners consumption in a population of patients with diabetes in Mexico]", *Gac Med Mex*, 153(1): 61-74. Jan.2017.

[21] Wiebe, N., Padwal, R., Field, C., Marks, S., Jacobs, R., Tonelli, M. "A systematic review on the effect of sweeteners on glycemic response and clinically relevant outcomes", *BMC Medicine*, 9: 123. Nov.2011.

[22] Sievenpiper, J.L., Carleton, A.J., Chatha, S., Jiang, H.Y., de Souza, R.J., Beyene, J., et al. "Heterogeneous effects of fructose on blood lipids in individuals with type 2 diabetes: systematic review and meta-analysis of experimental trials in humans", *Diabetes Care*, 32 (10): 1930-1937. Oct.2009.

[23] Livesey, G., Taylor, R. "Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies", *Am J Clin Nutr*, 88 (5): 1419-1437. Nov.2008.

[24] De Koning, L., Malik, V.S., Rimm, E.B., Willett, W.C., Hu, F.B. "Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men", *Am J Clin Nutr*, 93: 1321-1327. Jun.2011.

[25] Franz, M.J., Powers, M.A., Leontos, C., Holzmeister, L.A., Kulkarni, K., Monk, A.W., et al. "The evidence for medical nutrition therapy for type 1 and type 2 diabetes in adults", *J Am Diet Assoc*, 110: 1852-1889. Dec.2010.

[26] Romo-Romo, A., Aguilar-Salinas, C.A., Brito-Córdova, G.X., Gómez Díaz, R.A., Vilchis-Valentín, D., Almeda-Valdes P. "Effects of the Non-Nutritive Sweeteners on Glucose Metabolism and Appetite Regulating Hormones: Systematic Review of Observational Prospective Studies and Clinical Trials", *PLoS One*, 11(8): e0161264. Aug.2016.

[27] Raben, A., Vasilaras, T.H., Møller, A.C., Astrup, A. "Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects", *Am J Clin Nutr*, 76:721-729. Oct.2002.

[28] Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C.A., Maza, O., et al. "Artificial sweeteners induce glucose intolerance by altering the gut microbiota", *Nature*, 514(7521): 181-186. Oct.2014.

[29] Rogers, P.J., Hogenkamp, P.S., de Graaf, C., Higgs, S., Lluch, A., Ness, A.R., et al. "Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies". *Int J Obes (Lond)*, 40(3): 381-394. Mar.2016.

[30] Kun, E., Horvath, I. "The influence of oral saccharin on blood sugar", *Proc Soc Exp Biol*, 66: 175-179. 1947.

[31] Yamazaki, M., Sakaguchi, T. "Effects of D-glucose anomers on sweetness taste and insulin release in man", *Brain Res Bull*, 17: 271-274. Aug.1986.

[32] Fitzsimons, T.J., Le Magnen, J. "Eating as a regulatory control of drinking in the rat", *J Comp Physiol Psychol*, 67: 273-283. 1969.

[33] McKinley, M.J., Johnson, A.K. "The physiological regulation of thirst and fluid intake", *News Physiol Sci*, 19: 1-6. Feb.2004.

[34] Miller, P.E., Perez, V. "Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies", *Am J Clin Nutr*, 100(3): 765-777. Sep.2014.

[35] Sievenpiper, J.L., Souza, R.J., Mirrahimi, A., Yu, M.E., Carleton, A.J., Beyene, J., et al. "Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis", *Ann Intern Med*, 156 (4): 291-304. Feb.2012.

[36] Bodearmel, S.J., Wyatt, H.R., Stroebele, N., Smith, S.M., Ogden, L.G., Hill, J.O. "Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: the America on the Move family study", *Pediatrics*, 120: e869–79. Oct.2007.

[37] Ebbeling, C.B., Feldman, H.A., Osganian, S.K., Chomitz, V.R., Ellenbogen, S.J., Ludwig, D.S. "Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study", *Pediatrics*, 117: 673-680. Mar.2006.

[38] Fung, T.T., Malik, V., Rexrode, K.M., Manson, J.E., Willett, W.C., Hu, F.B. "Sweetened beverage consumption and risk of coronary heart disease in women", *Am J Clin Nutr*, 89: 1037-1042. Apr.2009.

[39] Lin, J., Curhan, G.C. "Associations of sugar and artificially sweetened soda with albuminuria and kidney function decline in women", *Clin J Am Soc Nephrol*, 6: 160-166. Jan.2011.

[40] Azad, M.B., Abou-Setta, A.M., Chauhan, B.F., Rabbani, R., Lys, J., Copstein, L., et al. "Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies", *CMAJ*, 189(28): E929-E939. Jul.2017.

[41] Azarpazhooh, A., Limeback, H., Lawrence, H.P., Shah, P.S. "Xylitol for preventing acute otitis media in children up to 12 years of age", *Cochrane Database Syst Rev*, 8: CD007095. Aug.2016.