ABSTRACT: The changes in lifestyle associated to sedentarism and bad food habits have contributed to the growth of obesity around the world. Therefore, the use of non-nutritive sweeteners has increased due to the rise of concerns about obesity. However, although some studies have shown the benefits of artificial sweeteners in weight control, others have indicated the opposite effects. According to several large scale studies as the San Antonio Heart Study and the National Health and Nutrition Examination Survey (NHANES), there is a positive association between artificial sweetener consumption and weight and/or BMI gain. Possible involved mechanisms by which NNS can aid in weight management must be considered, although in most of studies some data are inconsistent. One of the hypotheses is that a lack of activation in cephalic phase stimulation may increase the risk of obesity, while another is that activation through eating in general or exposure to sweet items could stimulate appetite and intake. There is also a view which relates NNS in insulin secretion and glucose metabolism. In relation to nutritive and osmotic effects, NNS may promote weaker satiety compared to NS, as the nature of the sweetener is also a factor. NNS can cause failure to release of gut peptides resulting in lower satiety and increased energy consumption. About palatability, NNS are often added to foods or beverages to improve the acceptability of low energy or energy reduced foods or diets, increasing their intake over more energy dense versions. Some studies assume that palatability promotes hunger and/or reduces satiety and stimulate intake.

KEYWORDS: Dietetic sweeteners; Weight loss; Obesity; Quality of life.

RESUMO: AAs mudanças no estilo de vida relacionadas ao sedentarismo e aos maus hábitos alimentares têm contribuído para o aumento da obesidade em todo o mundo. Dentre as consequências decorrentes das preocupações geradas por esse fenômeno, destaca-se o crescimento do consumo de adoçantes não nutritivos (NNS). Embora algumas análises tenham demonstrado benefícios dos adoçantes artificiais no manejo do peso outras indicaram efeitos opostos. De acordo com vários estudos de larga escala como o de *San Antonio Heart Study and the National Health and Nutrition Examination Survey* (NHANES) há uma associação direta entre a ingesta desses adoçantes e o ganho de peso e/ou IMC. Possíveis mecanismos envolvidos na influência dos NNS no controle ponderal devem ser considerados, embora existam alguns dados inconsistentes na maioria das pesquisas. Uma das hipóteses é que a falta de estimulação da fase cefálica da digestão como um fator de risco para a obesidade. Uma outra indica que a exposição a produtos doces poderia estimular o apetite. Existe também um questionamento relacionando os NNS à secreção de insulina e ao metabolismo da glicose. Quanto aos efeitos nutritivos e osmóticos, tais adoçantes poderiam oferecer menos saciedade quando comparados com os açúcares (NS). Uma das explicações para isso associa a menor liberação de peptídeos intestinais pelos NNS gerando assim menos saciedade e aumento do consumo energético. Sobre a palatabilidade, os NNS são frequentemente adicionados a comidas e bebidas, principalmente as de baixo teor calórico. Com isso, eles melhoram a aceitabilidade e podem concorrer com versões mais ricas em energia. Essa palatabilidade aumentada, por sua vez, de acordo com alguns estudos, incrementa a fome e estimula a ingesta alimentar.

DESCRITORES: Adoçantes dietéticos; Perda de peso; Obesidade; Qualidade de vida.

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INTRODUCTION

Due to the intense technological development over the last decades, there have been lots of changes in our way of life. One of the most important changes has happened in the food habits. Nowadays, our diet is characterized by foods eaten and/or prepared outside the home. These kinds of foods are mostly high-calorie and poor in nutritional aspects since they are constituted mainly by carbohydrates and fats. (J.POTI) In other words, the fast-food and sweet beverage consumption has increased which, combined with a sedentary lifestyle, and contributed to the obesity epidemic, especially in children and teenagers.

Between 1988 and 1995, 10 to 20% of men and 10 to 25% of women showed BMI (body mass index) ≥ 30kg/m² in Europe and in USA, 55% of population had BMI ≥ 25kg/m².According to the information based in the National Health and Nutrition Examination Survey (NHANES) 2009-2010, for adults over than 20 years, there was an increase in obesity between 1980 and 2010 in United States from 23% in NHANES III (1988-1994) to approximately 36% in 2009-2010¹.

Some studies try to explain the association between sugar-sweetened beverage consumption and obesity by supporting the idea that unlike carbohydrates with high fiber content, caloric beverages are nutrient-poor and often lead to consumption of salty foods and fast foods. Also, some people say that sugar sweetened beverages produce a weak satiety which leads to compensatory dietary responses, although there are not any convincing evidence that supports this hypothesis².

The obesity is related to many metabolic and cardiovascular complications such as type 2 diabetes, hypertension, and coronary heart disease is a major concern².

Therefore, in order to reduce the caloric intake and, consequently, the weight, a good percentage of people substitute the caloric sweeteners for the low calorie ones. The reason is that they provide sweet taste without the extra energy derived from foods and drinks containing caloric sugars.

History of artificial sweeteners

![Chart showing the history of artificial sweeteners](Image)

Figure 1. Middle line: changes in the percentage of the population who are obese (BMI >30) from 1961 to 2006. Source: National Health and Nutrition Examination Survey (3). Bottom line: changes in the percentage of the population who are regular artificial sweetener users from 1965 to 2004. Source: National Household Survey (4). Top line: changes in the number of new artificial sweetener containing food products introduced to the American market from 1999 to 2004. Source: Mintel Market Analysis (5). Bars below the time axis indicates the type and availability of artificial sweeteners in the United States over time. Source: Kroger et al.⁶
The literature reports that most of the artificial sweeteners was discovered by accident, in which scientists tasted some unknown chemical substances. As these discoveries were reported new trends related to artificial sweetener use and obesity emerged in the United States (Figure 1). The oldest artificial sweetener, Saccharin, was discovered by Constantine Fahlberg at Johns Hopkins in 1879. Lots of diabetics used it to protect themselves against the diabetic manifestation. Also, Saccharin benefited the humanity during a sugar shortage in the period of World War II and served as a sugar substitute for women worried with their body shape.

Cyclamate was discovered in 1937 by Michael Sveda at the University of Illinois. It was often combined with saccharin to improve the taste. In 1958, Food Additives Amendment to the Federal Food, Drug, and Cosmetics Act declared that both compounds were “generally recognized as safe”. However, in 1969, the Food and Drug Administration (FDA) banned cyclamate due to its carcinogenic potentials. Concerns about saccharin’s safety also intensified, which contributed to the FDA announce its intention to ban saccharin in 1977. But, avid consumer protests led to a moratorium from the FDA announce its intention to ban saccharin in 1977. But, avid consumer protests led to a moratorium from

Later, other studies showed that there was no association between cyclamate and cancer. Bladder cancer which had often been related to saccharin ingestion was also found to be specific to rodent physiology. Therefore, cyclamate continues to be marketed in about 50 countries and the saccharin warning label was removed in 2000. However, the regular use of artificial sweeteners was rare until the next generation of compounds arrived.

In 1965, James Schlatter at Searle discovered aspartame while he was trying to create new ulcer drugs. Unlike the other artificial sweeteners that are usually excreted unchanged, aspartame can be metabolized. That’s why it is not strictly non-caloric (4 Kcal/g) and forbidden in people with phenylketonuria. Since aspartame is about 200 times sweeter than sucrose, small amount is enough to produce a sweet flavour, which makes its caloric contribution insignificant.

The FDA approved aspartame first for use in dry foods in 1981, then as a general sweetener in 1996. Monsanto bought Searle and converted it into NutraSweet in 1984. The patent on aspartame expired in 1992. Amid competition from generic manufacturers, NutraSweet engineered neotame, which was approved in 2002. Neotame is the most potent sweetener on the market, at 7,000 times the sweetness of sucrose.

Acesulfame potassium discovered it in 1967 by Karl Claus at the University of Illinois. Acesulfame potassium resembles saccharin and cyclamate in structure and taste. The FDA approved its use in dry foods in 1988 and as a general sweetener in 2003.

The most recent sweetener is sucralose which was discovered in 1979 by Shashikant Phadnis, a graduate student working for Tate and Lyle. It was approved in 1999.

The last decade saw an explosive increase in the number of food products containing non-caloric artificial sweeteners. More than 6,000 new products were launched in the United States between 1999 and 2004. Currently, an ingredient search on foodfacts.com yields 3,648 products containing one or more of the five FDA approved artificial sweeteners. Sucralose is the most popular (1,500 products), followed by acesulfame potassium (1,103 products) and aspartame (974 products). Nowadays, artificial sweeteners are most commonly used, but, also, in a variety of other products, from baby food to frozen food. With such a diverse selection, it is more likely that people will encounter artificially sweetened items when making the day-to-day choices on food and beverages. The National Household Nutritional Survey estimated that as of 2004, 15 percent of the population regularly were using artificial sweetener. IRI Consumer Report stated that 65 percent of American households bought at least one sucralose-containing product in 2008. Therefore, the total number of artificial sweetener consumers, either regular or sporadic, is probably much greater.

**Justification for the study**

Face of the spreading epidemic of overweight and obesity worldwide, people resort to artificially sweetened foods and beverages containing nonnutritive sweeteners (NNS) with the aim of lose weight or, at least, control it. Most of studies on the subject have focused on the capacity of NNS to cause negative energy balance thought maintenance of the appeal and consumption of lower energy food by preserving its palatability.

In spite of these researches, there are other large scale studies as the San Antonio Heart Study and the National Health and Nutrition Examination Survey (NHANES) that suggest positive energy balance, in other words, a relation between the use of NNS and weight gain.

**The association between Non-nutritive sweeteners (NNS) and weight control**

The introduction of NNS into the food industry has been related to different perspectives present in the modern society.

At first, in an economic view, they are not only cheaper than NS but also more reliable. As a result, they attract huge investments based on the profits that they can offer. Moreover, their pleasant flavor, not so easily achieved with NS, increases the number of consumers.

In the health field, NNS has been recognized as one of the best alternatives for diabetic patients to reduce their intake of sugar and to guarantee weight control. Consequently, it
increases their quality of life not only for improving energy balance but also collaborating to dental health or reducing the possible risks for developing psychological disorders associated with the ingestion of high levels of calories.

The majority of the researches on NNS related to their metabolic influence indicate that instead of having intrinsic properties capable to modify the energy balance their biggest contribution may be related to a macronutrient shift. However, the degree of this influence is not determined and could be low in a way that in most cases NNS are used as dietary additions rather as substitutes for NS.

Recently, the major interest in the effects of NNS on a diet has been based on the hypothesis that their use may be causing weight gain or reduced weight loss in those people attempting to lose weight. This concern was first noted in 1986 based on the results from an American Cancer Society (ACS) survey conducted over 1 year in 78,694 women 50-69 years of age. After adjustment for initial body weight, those who used NNS were significantly more likely to gain weight than those who did not use but no conclusion was actually defined when taking into consideration the long-term effects on weight variance.

Despite the limits of the interpretation of the data, the hypothesis provided considerable debate during the following two decades since 1986. Some observational studies as the one which observed the cyclamate consumption in Catalonia, Spain (1992), noted an inverse association between the intake of cyclamate and Body Mass Index (BMI).

A large intervention trial aimed to promote weight loss through substitution of NNS for sucrose in the diet did not observed difference in weight loss between groups using and without aspartame. In this study the participants (n=163 adults) in a 3-week run-in, 16-week intervention, 1-year maintenance, and 2 year follow-up. At the end of the intervention, the former group better maintained the loss during the subsequent 2 years as it is possible to note in the graph bellow (Figure 2).

![Figure 2. Percentage change in body weight over 175 wk for women participating in a comprehensive weight-control program with (aspartame) and without (no-aspartame) aspartame-containing products. i ± SEM for each treatment group at l-wk intervals during 19 wk of active weight loss and at the end of 36 mo of maintenance and follow-up.](image)

However, findings from the San Antonio Heart Study indicated a direct relation. The trial joined 5158 adults, 3682 (74%) of whom completed the study between 1979 and 1988. A dose-response relation was observed between NNS beverage consumption and the incidence of overweight or obesity among individuals with a baseline BMI < 25 as well as those with a baseline BMI < 30 kg/m², after adjustment for baseline BMI, age, ethnicity, sex, years of education, and socioeconomic status. Elevated odds ratios were noted for individuals consuming 11-21 or ≥ 22 beverages containing NNS per week (1.60 and 1.79 in the former group and 1.92 and 2.08 in the latter group) (Figure 3).
Figure 3. A) ORs for becoming overweight/obese by 7- to 8-year follow-up, according to artificially sweetened beverage consumption quartile at baseline. It represents 428 incident cases among 1,250 with BMI <25kg/m²; B) ORs for becoming obese by 7- to 8-year follow-up, according to artificially sweetened beverage consumption quartile at baseline: shows ORs for the incidence of BMI ≥30kg/m²: 390 incident cases Overall P = 0.005; trend P < 0.0001. Adjusted for gender and ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency, and smoking status.

The mean BMI gain was 1.47 in the combined group of users of NNS and 1.01 in non users. At the end of these findings, it is necessary to consider the possibility of occurring some bias. The most probable one would be related to limiting analyses to use of beverages containing NNS while some studies consider the effects more consistently associated NNS stimulation of appetite and intake.

THE USE OF NNS AND THE ENHANCEMENT OF THE APPETITE: POSSIBLE MECHANISMS INVOLVED

Metabolic responses induced by the cephalic phase stimulation

The cephalic phase stimulation represents a physiologic responses to sensory stimulation which is suggested by some studies as a fundamental mechanism capable to provide an efficient digestion and absorption of foods as well as the use of the energy and nutrients.

There are contradictory researches related to the true consequences of the cephalic stimulation. Some of them hypothesize that lack of this activation may increase the risk of obesity. Others hypothesize that activation of this phase contributes to increasing the food consumption and so, may turn out to be a problem for weight control.

One proposed mechanism for the latter view is related to an effect of NNS on insulin secretion and glucose metabolism. However, more clear evidence is missing.

Even if sweet exposure provided by NNS does increase insulin release, it cannot be assumed that it will enhance hunger. Elevated concentrations of insulin in the brain decrease feeding in animals but hunger in humans doesn’t seem to be related with insulin concentrations during euglycemic clamp studies. These studies also demonstrate that hunger does not pursue glucose concentrations.

Moreover, it is necessary to consider that other cephalic phase responses might influence mechanisms promoting hunger and not only the insulin release. For
example, the thermogenic response after the palatable stimuli\textsuperscript{24}, is associated with reduced hunger\textsuperscript{25} but this response may not be activated by all sweeteners as, for example, aspartame. In this context, the results founds in the actual researches does not conclude that NNS stimulate hunger via cephalic phase responses.

**Nutritive and osmotic effects of the foods in the digestive process**

Through the digestive process, it is also necessary to consider the influence developed by the stomach and by the intestines in the signals of satiety.

The stomach provides appetitive responses based on the volumetric distension as it was demonstrated by the mechanical inflation of a balloon and its influences in the hunger\textsuperscript{26} while the intestines are more likely to response based on the nutritive properties of the food\textsuperscript{27}.\textsuperscript{10}Some researches\textsuperscript{28,29} have already demonstrated that gastric stretch and intestinal nutrient signals have synergistic effects on satiety. However, these characteristics are not the only ones to be analyzed in a way that other influences made by intestinal osmoreceptors and gastric chemoreceptors\textsuperscript{30} may occur.

Considering the influence of NNS in these mechanisms, some studies have been made with different types of beverages divided in two groups: those containing NS and others containing NNS. The conclusions, despite being uncertain, associate NNS with weaken satiety properties.

This evidence may be related to the following observed properties: beverage containing NS have a higher energy content and osmotic load\textsuperscript{31}. The more energetic content a beverages has, the more slowly it will empty from the stomach\textsuperscript{30} independently of the osmotic effects\textsuperscript{32}. And the opposite of this evidence is also true\textsuperscript{33} or else, the higher the osmotic load the slowest is the empty independently the energetic content.

Regarding the osmotic effects on gastric emptying, a research\textsuperscript{33} has already showed that they are transient, or else, after 30 min of ingestion of beverages with significant differences in osmotic properties, emptying rates gets very similar as the greater gastric volume generated by the high osmotic load promotes increased emptying.

On the other side, regarding the nutritive influence, there are no clear evidences of its direct effects. A hypothesis has been showed\textsuperscript{26} that not only the nutritive load but also the nature of the sweetener may influence the digestive process and satiety. As it is possible to observe in Figure 4, sucrose empties from the stomach more quickly than an isoenergetic load of maltose, but the former results in greater fullness.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Gastric emptying profile of orally administered sucrose and maltose solutions and unsweetened water control. Indicates that the emptying rates of both isoenergetic sucrose and maltose are significantly slower than that of water from t ¼ 30 min (P < 0.05) and the emptying rate of maltose is significantly slower than sucrose for the majority of time points from t ¼ 40 to t ¼ 160 min}
\end{figure}

Fonte: Lavin et al.\textsuperscript{26}, p.82.
About the gut there are no clear evidence of its influence in the appetitive signals and furthermore its contribution may be hidden by cognitive, sensory and metabolic mechanisms. The complexity of this regulation has been shown in a study where long-term gastrectomized individuals differ little from healthy control ones in appetitive sensations and food intake.

In this way, we can observe that, changes in the osmotic and nutrient properties of foods with NNS are not directly supposed to enhance hunger or diminish satiety and others influences not so clearly established must be considered.

**Activation of gut peptide response and its influence in the satiety**

Studies have shown that a potent incretin and satiety factor is the glucagon-like peptide-1 (GLP-1). It is already known that dietary carbohydrate influences in different levels the release of this gut peptide. While the carbohydrates may guarantee an adequate stimulus for secretion of glucagon-like peptide-1 (GLP-1) a failure of NNS to stimulate the release of such peptide, as observed in the Figure 5, related to the aspartame effects, could explain the lower satiety and increased energy intake these substances may provoke.

**Influences of flavor properties in the total amount of food intake**

One of the biggest reasons to add NNS in foods is to guarantee a favorable taste and they are added to stimulate the intake of low-energy food or to items with health benefits as the high-fiber or nutritive foods.

In any case, the possibility that palatability stimulates hunger or reduces satiation and so facilitates intake may be related to the association of NNS with gain weight. However, support for this view is very restricted.

One study noted that hunger increased in anticipation of eating a preferred food, but most trials have monitored appetite within an eating occasion. Greater palatability has been associated with augmented unchanged, or diminished hunger after adjustment for intake. Studies monitoring appetitive effects beyond the meal have also different results (Figure 6).

Moreover, it is also necessary to consider that the relation may not be static in a way that with frequent exposures to a food, it changes and possibly, the acceptability of less palatable foods gets higher with familiarity as we can observe in Figure 7 presented in the later cited trial. In this context, we could not find any conclusive evidence that palatability influences appetitive.

![Figure 5. Physiological mechanisms mediating aspartame-induced satiety. Plasma GLP-1 concentrations following consumption of aspartame or its constituent amino acids compared to the control (mean ± S.E.M., n = 6). GLP-1 secretion was significantly suppressed following the liquid meal after prior ingestion of aspartame and the constituent amino acids](image-url)
Figure 6. Mean (SE) ratings of desire to eat at times before, during and after consumption of preferred food (●) and less preferred food (○). Mean (SE) ratings of prospective consumption at times before, during and after consumption of preferred food (●) and less preferred food (○). Statistical significance of comparisons between the two meals is * $p<0.05$, ** $p<0.01$

Figure 7. Mean ratings "satiety (fullness)" from 1 (weak) to 25 (strong) after bread perceived as low, medium, high; in pleasantness from day 1 to day 5 (N.35). The ratings are shown from just before the lunch (0 min), right after the lunch (45 min) until 90 min after the lunch (135 min)
MECHANISMS BY WHICH NNS MAY ENHANCE ENERGY INTAKE OR BALANCE

While there is no doubt that the exchange of NNS for NS on a diet makes you increase the percentage of calories derived from fat consumption, theories say that perhaps this exchange also stimulates an absolute increase in the fat consumption and a possible increase in total energy consumption, or weight gain.

However, clinical trials have not confirmed the impact of this substitution on weight gain, and they only present bordering evidence on increasing the consumption of fats. Thus, several studies showed that this substitution would not lead to full compensation of the energy from sugars with calories from fat, and although some studies show that there is an increase in absolute consumption of fats, others point to a lack of significant changes in lipid intake.

However, some studies have shown that the hypothesis that use of NNS could replace the use of NS (prerequisite for reaching such conclusions) is not true, and the use of NNS do not reduce the use of NS.

Regarding the molecular level, there are receptors in the intestine, similar to oral receptors for sweet tastes (TR1s), which, when activated by NS or NNS, enhance insertion of GLUT2 in the enteroctye cell, leading to a rapid increase in the transport of glucose. Hence, starting from the assumption that the high activity of GLUT2 is associated with obesity, substitution of NS for NNS would not be really beneficial to health.

INFORMED USE LEADS TO OVERCOMPENSATION

In Brazil and many other countries it is compulsory to present nutrition information in most food products. However, depending on how this information is interpreted by consumers, it may be even harmful, leading to an increase in energy consumption.

Thus, some individuals may overestimate the caloric loss that a product that makes use of NNS can bring, so they could exaggeratedly relax other actions that help in weight control. Examples: reduction in concern with physical activities; excessive consumption of these products, although they may have a relatively reduced unitary calorie content, ultimately contributing to a greater absolute energy intake; consumption of other caloric foods in excess, because the NNS creates a feeling of “clear conscience.” Moreover, beliefs about the energy content of certain foods can have psychological effects on hunger stronger than the actual caloric value of these foods.

There is not an established concept of what we can expect from products that use NNS, regarding the daily energy consumption. In one study, the consumption of cereals containing aspartame led to a higher daily caloric intake (notorious, although not statistically significant) than in subjects consuming a cereal (of equivalent energy value) which contained sucrose. However, several other studies did not show similar results.

Hence, the harm that the use of NNS can bring is more related to an inappropriate use of it, than from the inherent characteristics of the product.

LOSS OF SIGNAL FIDELITY

Despite being inherent to humans to consider the sweet taste pleasant, much of the flavor that we feel in foods is related to a mechanism of associative learning. In other words, part of the sensory signaling that arrives at our brains when putting a food in the mouth is connected to previous experiences we had with that food. Thus, this information can be used to estimate instinctively what kind of food we should look for and in what quantity, and which mechanisms of digestion can be pre-activated in order to maintain a stable energy balance.

Nevertheless, a chronic ingestion of a food with taste similar to certain products, but with reduced caloric amounts, would lead to a remodeling of noncognitive information on this product so that, gradually, progressively larger amounts could be ingested, until it reaches the initial energy intake of the individual. Thus, when, in sequence, that individual is again submitted to the ingestion of the original high-calorie product, he will consume high amounts of it, leading to excessive energy balance. These findings were verified in rat and human studies, although the latter is not restricted to the use of NNS.

So, to obtain more precise data and adequate knowledge on the association between taste and energy balance, more studies that focus on the use of NNS and monitor the implications of its chronic use in hunger are needed.

ACTIVATION OF REWARD SYSTEMS

The concept of reward in the diet is very difficult to define. It is complex for its multifaceted presentation, including characteristics such as taste, desire and learning. However, it is almost certain its role in the modulation of appetite, one of the major pillars of food intake. Within this sphere, it is known that the sweet taste is a stimulus for neural dopamine release, which are mediators of reward system and can stimulate food intake. There is also some association between a lack of activation of these reward systems and greater food intake.

Furthermore, studies show that high palatability can initiate a process of feeding in the absence of energy needs and even improve the absorption of energy supply. Therefore, the addition of NNS on a supply was related to an increased consumption. In addition to that, by being associated with the learning process, when there is repeated
exposure, less palatable foods gain more acceptances while highly pleasurable food loses palatability with frequent exposure. Individuals with high efficient systems of reward can eat induced by palatability, what explains a direct relation between pleasure to eat and food consumption or BMI. However, there are other studies that indicate there is no significant difference between lean and obese individuals, and others that state that skinny guys have even a great pleasure for food, indicating that obese people could have an uncontrollable “desire” to eat rather than more pleasure.

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