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NON-CALORIC SWEETENERS AND BODY WEIGHT

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Abstract Both total caloric intake and consumption of free sugars is higher than recommended. This situation contributes, among many other factors, to the increase of overweight and obesity in the population. To maintain the sweet taste of foods and beverages while reducing the caloric content and the amount of free sugars in said products, many people choose to replace sugary products in their diet for options containing non-caloric sweeteners. This change in their dietary choice is accompanied by an increasing number of consultations with health professionals about the effects that non-caloric sweeteners could have on their body weight. Results reported in different scientific publications seem contradictory in relation to this topic: some of them, showing a positive association between the consumption of non-caloric sweeteners and energy intake and body weight, while others reporting that the consumption of these additives –in replacement of sugar– may lead to a reduction in caloric intake and body weight. The main objective of this article is to review the available evidence on the consumption of non-caloric sweeteners in relation to body weight, thus providing another tool for health professionals to make nutritional recommendations based on the best available evidence.

Key words: non-caloric sweeteners, artificial sweeteners, body weight

Resumen ***Edulcorantes no calóricos y peso corporal.*** Tanto la ingesta calórica total como el consumo de azúcares libres son mayores a los recomendados. Esta situación contribuye, entre muchos otros factores, al aumento del sobrepeso y la obesidad en la población. Para mantener el sabor dulce de los alimentos y bebidas, y a la vez reducir el contenido calórico y la cantidad de azúcares en los mismos, cada vez más personas optan por reemplazar los productos azucarados en su dieta por edulcorantes no calóricos. Este cambio dietario se acompaña de un creciente número de consultas con profesionales de la salud, sobre los efectos que los edulcorantes no calóricos podrían tener sobre el peso corporal. Resultados comunicados en diversas publicaciones científicas parecen contradictorios con relación a este tema, algunas informan una asociación positiva entre el consumo de edulcorantes no calóricos, la ingesta energética y el peso corporal, y otras muestran que el consumo de estos aditivos –en reemplazo del azúcar– lleva a una reducción de la ingesta calórica y a un descenso de peso. El principal objetivo de este artículo es repasar la evidencia disponible sobre el consumo de edulcorantes no calóricos con relación al peso corporal, brindando así una herramienta más para que los profesionales de la salud puedan hacer recomendaciones nutricionales basadas en la mejor evidencia disponible.

Palabras clave: edulcorantes no calóricos, edulcorantes artificiales, peso corporal

It is estimated that there are more than 2 000 million overweight or obese people in the world[1]. In addition, total calories in our diet are increasing while physical activity decreases; with the sedentary population being larger than the active population[2]. It is also estimated that more than 18% adults will be obese by 2025[3].

Obesity is related to metabolic disorders such as dyslipidemias, hypertension, insulin resistance, diabetes, inflammation and endothelial dysfunctions among others[4].

Although it has been clearly established that the causes of obesity are multifactorial, one of the factors that contribute to weight gain is the excessive consumption of free sugars. The World Health Organization (WHO) defines "free sugars" as those monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer and the sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates[5, 6], and advises to limit their consumption to less than 10% of the total calorie intake (strong recommendation), sug-

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gesting a reduction of up to 5%[7] as a conditional recommendation[7].

On the other hand, as sweet taste brings pleasure when consuming food and drinks, it is very difficult to reconcile the consumers´ preferences for sweet taste and comply at the same time with the current health recommendations.

An available tool to reconcile this preference for sweet foods and beverages with a decrease in sugar intake are non-caloric sweeteners (NCS), which are food additives that can be added to foods and beverages, thus allowing the sugar content to decrease while maintaining their sweet taste and palatability[8].

Table 1 lists the most commonly used NCS, their sweetness intensity (sensory evaluation using sucrose as a standard) and their acceptable daily intake (amount of a food additive that can be consumed daily as part of the diet, even during whole life, without any risk). The acceptable daily intake is established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[8].

The potential benefit of NCS lies in the substitution of the energy of added sugars, thus facilitating not just the reduction of total calorie intake, but also that of the above-mentioned sugars in particular.

However, many health professionals express several concerns about the effects that NCS could have on human health, particularly in relation to body weight.

In this sense, a controversy arises about whether the consumption of NCS could be useful to reduce energy intake (given the elimination of 4 calories per gram of sugar that is replaced by NCS) or if, on the contrary, it could be responsible for causing an increase in body weight in those who consume them. This last consideration is based on some positions that argue that the consumption of these food additives could increase appetite, thus generating an energy compensation, and in this way increasing the caloric intake with the consequent increase in body weight[9].

The objective of this article is to review the available scientific evidence regarding the consumption of NCS in relation to body weight and to analyze it in the light of evidence-based medicine.

Non-caloric sweeteners and energy compensation

Energy compensation occurs when the immediate reduction in calorie intake –due to the NCS replacement of sugars– is followed by a subsequent increase in calorie consumption[9].

Compensation mechanisms can be physiological or psychological[10,11]. In physiological compensation, the subject who is consuming a sweet food without sugar could be expecting to receive more calories, thus being hungrier and therefore eating more[10]. In psychological compensation, on the other hand, the subject thinks that he/she can afford eating more energy-rich foods because is already consuming fewer calories in food or drinks[10]. In addition, a “low calorie” label could cause the consumer to eat a larger portion of that product or to eat more accompanying foods[11].

It has been postulated that NCS are not capable of producing satiety, so that energy compensation could occur in the following meal[9, 12]. It becomes evident that for NCS to successfully contribute to reduce the calories of added sugars, they should also avoid compensation[12]. Therefore, it is relevant to evaluate to what extent an immediate reduction of the consumed energy -due to the lower consumption of sugars that have been replaced by

TABLE 1.– *Non-caloric sweeteners, relative sweetness and acceptable daily intake*

Non-Caloric sweetener	Relative sweetness*	Acceptable Daily Intake - JECFA (mg / kg of body weight /day)
Acesulfame-K	200	15
Aspartame	200	40
Steviol glycosides	200-300	4**
Saccharin	300	5
Sucralose	600	15

** In relation to sucrose (value = 1)*

*** Expressed in "steviol equivalents" (amount of steviol produced by each steviol glycoside after hydrolysis), since all steviol glycosides are metabolized to a common final metabolic product: steviol[8]*

NCS- is followed by an energy intake increase in subsequent meals, regardless of the macronutrient type.

In 2009, Mattes and Popkin reviewed the available evidence regarding the effects of NCS on compensatory appetite and food intake, describing eight potential compensatory mechanisms: cephalic phase stimulation, nutritive and osmotic effects, gut peptide response, palatability, informed use leading to overcompensation, loss of signal fidelity, activation of reward systems and training the palate[9]. This review concluded that, up to the time of publication, the available evidence either refuted or was insufficient to support each of these eight possible mechanisms through which NCS could increase appetite or energy intake[9].

However, more recent publications suggest that there is indeed an energy compensation after consuming foods and beverages containing NCS, but that this calorie compensation is partial[11-13].

As an example, during the first 24 hours after consuming aspartame, a 32% energy compensation was reported, with 68% of the original calories that were saved because of sugar replacement not being compensated[13].

When evaluating NCS-beverages, compensation was just 15% during the first 24 hours[13]. This lower compensation with beverages, could indicate that there is a more effective net calorie reduction by replacing sugar sweetened beverages by NCS-beverages, than by replacing sugars in foods[12].

The meta-analyses of randomized clinical trials (RCTs) indicate that after the consumption of food or beverages with NCS, there is just a partial compensation (a higher calorie intake that does not reach the caloric content of the sugar that was replaced). This compensation reaches 70% in children and 43% in adults, thus resulting in a net saving of 30% calories in children and 57% calories in adults[11].

To summarize, considering the best level of evidence available so far we can conclude that, after the consumption of food or beverages with NCS there is an energy compensation, but as it is just a partial compensation, the replacement of foods and beverages sweetened with sugar by those sweetened with NCS would lead to a net calorie reduction.

Non-caloric sweeteners and body weight

As indicated in the previous section, consumption of products with NCS instead of sugary products should reduce the overall caloric intake and this would eventually be reflected in body weight.

Rodent studies

A systematic review with meta-analysis carried out by Rogers et al. in 2016 analyzed the results obtained in several rodent studies that evaluated the animals' body weight after NCS consumption.

Although studies with positive, neutral and negative results in relation to weight gain have been found, most of these studies (over 45 articles of compulsory consumption and 10 articles of voluntary consumption) showed that NCS consumption did not increase the animals´ body weight[11].

Observational studies

Several epidemiological studies report a positive association between NCS consumption and body weight.

Two paradigmatic examples -because of their long follow-up and the large number of participants included- are the San Antonio Heart Study (2008)[14] and the Multi-Ethnic Study of Atherosclerosis (2009)[15].

The first one reported a positive association between the consumption of NCS-beverages and the incidence of overweight and obesity, during the monitoring of 5158 adults for a period of 7 to 8 years. At the end of the monitoring, the change in body mass index (delta BMI) was 47% higher ($p < 0.0001$) in the consumers of beverages with NCS in comparison to non-consumers (+1.48 kg/m2 vs. +1.01). kg/m^2)[14].

The second study, which followed 6814 adults, reported that daily consumption of soft drinks with NCS was associated to a 36% higher risk ($p < 0.001$) of developing metabolic syndrome (HR: 1.36, CI 1.11 - 1.66) and a 67% higher risk ($p < 0.001$) of suffering from type 2 diabetes (HR: 1.67, CI 1.27-2.20)[15].

Meta-analyses of observational studies

In agreement with the data from most of the epidemiological studies, the meta-analyses of these studies reach the same conclusions[16-18].

As an example, Ruanpeng et al.[16] conducted a bibliographic search where they identified 3 studies that evaluated the relationship between the consumption of soft drinks sweetened with NCS and the risk of obesity, reporting a relative risk of 1.59 (CI: 1.22 - 2.08). While the authors note that their study was the first meta-analysis that showed that regular consumption of artificially sweetened soft drinks was significantly associated with an

increase in the overall risk of overweight and obesity, it is worth noting that the three included studies (12,987 adult patients) were observational: those already seen, San Antonio Heart Study[14] and Multi-Ethnic Study of Atherosclerosis[15] plus a telephone survey conducted by French et al. (1015 participants between 16 and 65 years old)[19].

That same year, Azad et al.[17] published another meta-analysis after a bibliographic research that allowed them to include 30 cohort studies, to evaluate the relationship between NCS consumption and BMI. The meta-analysis of these observational studies showed a minimal increase in BMI, hypertension, metabolic syndrome and diabetes.

Miller et al.[18] also meta-analyzed prospective cohort studies, concluding that although NCS intake was not associated with an increase in fat mass, it was significantly associated ($p < 0.05$) with a slightly higher BMI (relative risk 0.03, CI: 0.01-0.06).

It is very important to note that these meta-analyses are not "meta-analyses of RCTs", which are at the top of the evidence pyramid, but are "meta-analyses of observational studies", thus having practically the same limitations found in the primary studies which originated them.

Limitations of observational studies

As previously seen, the conclusions of several observational studies and their meta-analyses suggest that NCS could lead to a compensatory effect that could eventually increase food intake, with an increase in body weight as the final outcome. However, it is important to note that this type of study, because of its design, can just show an association but not a causal relationship. That is why associations derived from observational studies should always be interpreted with caution.

In these studies, the observation of a positive association between the consumption of NCS and body weight could be due to confounding factors. This becomes clear when, while making statistical adjustments to eliminate said confounders -such as, for example, adiposity- this association dissipates or tends to disappear[20].

Another point to take into account in observational studies is that it is very difficult to determine the directionality of the effect: are NCS causing an increase in body weight (causality)? Or are overweight or obese people the ones who tend to consume more NCS (reverse causality)? In this case, the phenomenon known as reverse causality would explain how the greater consumption of NCS could be the consequence of the interest of individuals with excess weight to decrease their body weight and not the cause of weight gain in this population.

For the above reasons, there is currently broad international scientific consensus regarding the correct interpretation and scope of the results of observational studies. The Academy of Nutrition and Dietetics (USA) states in its official position that although some observational studies report that people who use NCS are more likely to gain weight, this does not mean that NCS cause weight gain, but rather that NCS are more likely to be consumed by people with overweight or obesity[21].

On its part, the Nutrition Committee of the Spanish Association of Pediatrics concludes that "some observational studies have also linked the BMI increase with the consumption of NCS, even though these data should not be interpreted as evidence of a causal relationship but rather as a sign that the probability of consumption is greater in the obese and sedentary population (reverse causality)"[22].

Accordingly, the joint position of the American Heart Association and the American Diabetes Association states that among observational studies, the challenges of accurately assessing NCS intake, the multiple potential confounding factors, and the difficulty in determining the directionality (possible reverse causality), represent important limitations[12].

When making an evidence-based nutritional recommendation and if there are available some studies with a better level of evidence than that of the epidemiological studies -as is the case of well-designed RCTs- it is justified to rely on the latter, since these studies are the ones that offer the best evidence of a possible cause-effect relationship and of the effectiveness of an action.

Intervention studies

Unlike the observational studies, most of the RCTs that evaluate the consumption of NCS in relation to energy intake and body weight –because of their higher cost and difficult implementation– tend to be short-term studies, thus limiting the knowledge of weight modification during prolonged periods.

In the last years, several systematic reviews of RCTs with meta-analysis have been published[11, 17, 18].

In their meta-analysis, Rogers et al. concluded that consumption of NCS instead of sugars, reduces acute energy intake in adults (-119 kcal per day)[11]. An important limitation of acute intake studies is that, by measuring it in a single meal, potential adjustments in later intakes could be lost.

When analyzing intervention studies lasting more than 24 hours, the groups assigned to NCS also showed the lowest absolute energy intake values: in 9 comparisons against sugar they found a daily energy reduction of -75 to -514 kcal[11].

Finally, in relation to body weight, the researchers found 8 studies (691 adults) with follow-ups between 1.25 and 40 months, that showed a relative weight loss (-1.41 kg) in those subjects who consumed products with NCS, compared to those who consumed sugary products[11].

The importance of comparators

When interpreting the combined analyzes of the RCTs that evaluate the relationship between NCS consumption and energy intake or body weight, it is essential to take into account the nature of the comparator.

The desired reduction in calorie intake (and possibly in body weight) is achieved because of the calorie restriction that happens when the consumption of sugars decreases and not because of the consumption of NCS *per se*. Therefore, if caloric comparators (such as sugar) are used in comparison with NCS, one would expect to see positive results, whereas if non-caloric comparators are used in comparison with NCS (water, placebo, nothing), one would not expect similar results.

In accordance with this, in 2017 Azad et al.[17] conducted a systematic review of RCTs with meta-analysis (including 7 RCTs of 11,774 potentially relevant articles), where they assessed the relationship between NCS consumption and BMI. Unlike other meta-analyzes of RCT[11, 18], the authors concluded that none of the selected studies showed any effect on BMI (neither positive nor negative).

As previously exposed, it would be expected that the effect of NCS would be different depending on the calories the comparator has, and which are therefore available to be displaced (0 calories in the case of water or placebo vs. 4 calories per gram of sugar)[23]. Given that the comparators evaluated in the RCTs that were included in this meta-analysis were non-caloric[24-30], the design does not allow for the evaluation of the effect of displacing calories while replacing sugars by NCS[23].

Returning to Rogers´ meta-analysis[11], when non-caloric comparators were analyzed and energy intake was evaluated in short-term RCTs, similar results to those of Azad et al.[17] were obtained, without appreciating an apparent benefit with the consumption of NCS. Once again, it is worth noting that a decrease in calorie intake or in body weight after consumption of NCS is not expected if these are not used in replacement of caloric sweeteners such as sugar, since the decrease in energy intake (and its potential benefit in body weight) is not given by consuming NCS but by consuming less sugars.

When analyzing all the meta-analyses of available RCTs, and independently of the comparator used, we can see that NCS consumption is at least neutral or decreases the energy intake and body weight in adults.

Statistical significance and clinical relevance

In 2014, Miller et al. performed a meta-analysis of 15 RCTs (1951 participants with follow-ups of between 3 and 78 weeks) which also included body composition analysis[18]. Their conclusions were that the consumption of NCS reduced modestly but significantly ($p < 0.05$) the body weight by -0.80 kg (CI: -1.17, -0.43), the BMI by -0.24 (CI: -0.41, -0.07), the fat mass in -1.10 kg (CI: -1.77, -0.44) and the waist circumference in -0.83 cm (CI: -1.29, -0.37).

Although all these outcomes seem to favor NCS, it is important to emphasize the fact that being statistically significant does not necessarily imply to be clinically relevant; an example would be the reduction of waist circumference in less than one centimeter which, even though it is statistically significant, is not so relevant from a clinical point of view.

Long-term evidence: Water or beverages sweetened with NCS?

The short-term nature of intervention studies limits their ability to observe long-term body weight changes.

One of the clinical trials with the longest follow-up was carried out by Peters et al. in 2016[25]. It included 303 overweight or obese adults in a one-year controlled hypocaloric weight control program and divided them into two groups: one group consumed water and the other one consumed beverages sweetened with NCS. The subjects assigned to water consumption decreased their body weight by -2.45 ± 5.59 kg, while those assigned to beverages sweetened with NCS reduced their body weight by -6.21 ± 7.65 kg ($p < 0.001$). Changes in waist circumference also favored the group assigned to NCS-beverages (mean -8.67 vs. -4.17 cm) ($p < 0.001$). Finally, while 44% of those subjects assigned to NCS-beverages reduced at least 5% of their initial body weight, only 25% of the subjects in the group assigned to water achieved that goal ($p < 0.001$)[25].

In contrast, another intervention study of similar characteristics (89 adults with overweight or obesity in a six-month hypo caloric diet), showed a discretely greater weight loss in the group assigned to water: -8.8 ± 1.9 kg vs. -7.6 ± 2.1 kg ($p < 0.015$). They also found a more appreciable improvement in some metabolic variables (greater weight loss, fasting insulin and HOMA-IR index) in the water group, in comparison with the NCS-beverage group[26]. Although both groups showed an improvement in their metabolic variables -as was also appreciated by Peters et al.[25]- in this case, the positive effects were more evident in the group consuming water.

Although there is little research expressly comparing water consumption versus NCS-beverages consumption, and although some RCTs seem contradictory, it can be concluded that in no study the NCS favored weight gain. This is consistent with the vast majority of the short-term intervention studies analyzed previously, where NCS consumption showed a neutral effect or a slight reduction in body weight but did not led to weight gain.

Although the gold standard for hydration is water, it seems plausible that in some cases, beverages sweetened with NCS can help with the adherence to long-term weight loss programs or with weight loss treatments in adults, mainly in those who do not like to drink water.

In accordance with this line of thought, the working group of the American Heart Association concluded in its 2018 statement that for those adults who are usually heavy consumers of sugary drinks, beverages with NCS can be a useful replacement strategy to reduce the intake of sugary drinks[31], adding that this approach could be particularly useful for people who are used to a sweet-tasting drink and for whom water, at least initially, is not a desirable option[31].

Position of different medical societies

Considering the higher quality of evidence (RCTs and meta-analyses of RCTs over epidemiological studies and their meta-analyses), several scientific societies have issued their position in relation to NCS consumption and body weight.

The Academy of Nutrition and Dietetics (USA) notes that consumers can safely use a range of sweeteners (nutritive and NCS) when consumed within a meal plan that is guided by current dietary recommendations, dietary reference intakes, as well as by their individual health goals and personal preferences. They also add that when nutritive sweeteners are substituted by NCS, they can help consumers to limit the consumption of carbohydrates and energy as a strategy to control their glucose level or body weight[21].

In their joint position, the American Heart Association and the American Diabetes Association point out that NCS may facilitate the reduction of added sugars intake, weight loss or control, and the promotion of beneficial effects on related metabolic parameters. They also comment that products that contain NCS can help weight control when they are used instead of caloric products, as long as they are not being compensated in another way[12].

In its Medical Nutrition Therapy Recommendations (2017), the American Diabetes Association notes that NCS have the potential to reduce the total calorie and carbohydrate intake, if used in place of caloric sweeteners and if the latter are not compensated with the intake of other caloric foods, also affirming that NCS are safe to use within the levels of the defined acceptable daily intake[32].

Finally, the position of Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes, states that NCS are safe and can be recommended to people with diabetes[33].

In conclusion, after the consumption of food or beverages with NCS, there is a caloric compensation that is partial (a higher energy intake that is still lower than the energy content of the replaced sugary food) and variable (70% in children and 43% in adults), thus providing a net saving of calories when sugary foods and beverages are replaced by those with NCS.

While there is a positive association between the consumption of NCS and the incidence of overweight and obesity, this is mainly seen in observational studies, which cannot show a causal relationship and whose results could be explained by reverse causality.

RCTs, that offer the best evidence of a cause-effect relationship, conclude that the replacement of sugars by NCS is at least neutral or decreases the caloric intake and the body weight in adults.

In some cases, replacing sugary foods and beverages with their NCS versions could also be a useful dietary tool to improve compliance with a weight reduction program or with body weight maintenance plans.

There is still a need to perform RCTs that assess the consumption of NCS and its relationship with body weight at longer periods.

Currently, the higher quality of evidence (RCTs, systematic reviews and meta-analyzes of RCTs) shows that consumption of NCS -in replacement of sugars- could be useful for reducing calorie intake and relative body weight

in adults. Therefore, the replacement of sugars present in food and beverages by NCS, could be beneficial to decrease the intake of total calories and particularly that of free sugars, which in turn would have beneficial effects on the metabolic parameters that are related to obesity.

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Inundated via social media with the opinions of multitudes, users are diverted from introspection; in truth many technophiles use the internet to avoid the solitude they dread. All of these pressures weaken the fortitude required to develop and sustain convictions that can be implemented only by traveling a lonely road, which is the essence of creativity.

Inundados por los medios sociales con la opinión de multitudes, los usuarios son desviados de la introspección; en verdad muchos tecnófilos usan Internet para evitar la soledad que ellos temen. Todas estas presiones debilitan la fortaleza requerida para desarrollar y sostener convicciones que sólo pueden ponerse en marcha recorriendo un solitario camino, que es la esencia de la creatividad.

Henry A. Kissinger

How the Enlightenment ends. *The Atlantic*, June 2018