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Are Artificial Sweeteners Safe and Useful: What does the Evidence Suggest ?

Rudrajit Paul, Dipanjan Bandyopadhyay***

Introduction

Obesity and diabetes are major non-communicable diseases of modern times. As people are becoming aware of the dangers of metabolic syndrome, they often try to cut down on their carbohydrate or sugar intake. In this background, there is a rising public interest in so-called "zero calorie" artificial sweeteners. Artificial sweeteners are used in various food items available in the market and many manufacturers also use a blend of sugar and artificial sweeteners. The global market for artificial sweeteners is expected to grow from $ 7.2 Bn in 2018 to $ 9.7 Bn in 2024[1]. The soft drink industry is expected to have the maximum consumption of this ingredient due to demand for low calorie drinks or "diet" drinks[2]. Asia-Pacific region is the largest market for this food additive and is expected to grow quickly in the coming years[2].

In India, sweets are an integral part of everyday meals for most communities. Indians are the largest consumers of sugar in the world[3]. However, with the rising prevalence of diabetes and obesity, many Indians are becoming aware of the dangers of refined carbohydrates. In such a scenario, the demand for artificial sweeteners is rising rapidly[3]. The current market for this ingredient is estimated at 150 crores and is expected to have a double digit growth in the coming years[3]. For example, Saccharin, a commonly used sweetener in India, had a market volume of more than 4,600 tons in 2018 and is expected to reach 5,300 tons by 2024[4]. Since sweet dishes are an integral part of all religious rituals and family programmes in India, the demand for sweeteners will always be there. This is different from Western societies, where sweetened beverages and candy form the main route of intake of sugar.

In 1976, two researchers were working at Queen Elizabeth College, London with chlorinated sugar compounds. One of them, Leslie Hough, asked the other, Sashikant Phadnis, to test a compound. But Phadnis thought that he had been asked to "taste" it. So, he tasted the compound, called sucralose, and found it to be very sweet. Thus, sucralose was discovered accidentally.

Sweet taste is perceived by taste receptors expressed on taste cells. There are many types of taste receptors. For sweetness, it is T1R2 and T1R3. In T1R subunit, there is an extracellular domain called venus flytrap (VFT). Sucralose and natural sugars like sucrose or glucose bind to VFT domains of both T1R2 and T1R3 while Aspartame binds to only T1R2.

These artificial sweeteners or non-nutritive sweeteners (thus labelled by the AHA) are marketed directly in India and do not require any authorisation by health professionals. Thus, consumers are able to use them at their will, based on the advertisements and hearsay. But the consumers are often not conversant with the recommended daily intake limit or similar other scientific facts. This lack of awareness can cause excess consumption and related side-effects. For example, as people are becoming aware of the large amount of sugar added to popular carbonated beverages, many are thinking of switching to "diet" versions of those drinks. But these artificially sweetened beverages may not help in cutting down body weight at all. The San Antonio heart study in 2008 found that regular intake of artificially sweetened beverages led to an increased risk for obesity. But these facts are often suppressed during aggressive marketing.

The various online marketplaces have a wide variety of these sweeteners and consumers can decide for themselves. These sweeteners are marketed as a panacea for obese persons and celebrities often endorse them as means of staying healthy. However, the health effects of these sweeteners are a less discussed topic and consumers taking excess dose of these chemicals may present to the physician with side-effects. Thus, physicians should be aware of the biochemistry and pharmacology of these artificial sweeteners.

Common sweeteners used

Various artificial sweeteners are available in the market. The common ones are Acesulfame K, Aspartame, Neotame, Sucralose, Saccharin, Alitame and Cyclamate[5]. These sugar substitutes add sweet taste to food without adding the extra calories of sugar. Usually, these sweeteners have much

**Associate Professor, Department of Critical Care Medicine, IPGMER and SSKM Hospital, Kolkata - 700 020; **Associate Professor, Department of General Medicine, North Bengal Medical College, West Bengal.*
Corresponding Author: Rudrajit Paul, Associate Professor, Department of Critical Care Medicine, IPGMER & SSKM Hospital, Kolkata - 700 020. Phone: 9433824341; E-mail: r.paul.medicalcollege@gmail.com.

more sweetness compared to sucrose (for example, sweetness of Aspartame is 200 times sucrose and that of Saccharin is 300 times that of sucrose)[5]. Thus, they are needed in much smaller amount in food compared to sucrose. Sodium cyclamate is a compound with sweetness 30 - 50 times that of table sugar (Sucrose), thereby making it the least potent of all available artificial sweeteners. It is banned in the USA for fear of carcinogenicity, although it is approved in many other countries.

Aspartame is a dipeptide. It is heat labile and thus cannot be used for baking or cooking[5]. Right from the time of its approval, aspartame has been the subject of debate and public scrutiny. At one time, aspartame was rumoured to be carcinogenic. But subsequent human studies did not find any evidence to support this claim[5].

As of June 2019, the following sweeteners are approved in India (by FSSAI): Saccharin, Acesulfame, Aspartame, neotame, sucralose, and isomaltulose[6]. (However, it must be remembered that in the current age of frequent international travel, these countrywise approvals really do not matter. Anyone can go to USA or Europe and consume food products with artificial sweeteners. Then, they can come back to India with adverse health effects and present to the physician here. In India, these sweeteners are mixed in a variety of food items like chocolate, Pan masala, carbonated beverages, sweets, and chewing gum[6]. Aspartame has an even wider scope of application with usage in icecream, yogurt, flavoured milk, and jam, in addition to those mentioned above[6]. Sucralose (since it is stable at high temperature) is further used in cookies, pastry, doughnut, and custard powder[6]. Thus, for all varieties of sweet dishes and other food items where sweet additives are required, suitable artificial sweeteners are available.

In India, one important consideration for the use of non-nutritive sweeteners is during cooking. Daily Indian meals involve curries and in all parts of India, preparation of many curries requires sugar in addition to various spices. But all of these compounds are not heat stable. Thus, for use in cooking, only heat stable ones like acesulfame and Sucralose are to be used[6]. One disadvantage of acesulfame is that it sometimes leaves a bitter after-taste[5]. Thus, acesulfame may have to be combined with sucralose to avoid this bitter after-taste. This is especially true if acesulfame is used in alcoholic beverages[5]. Neotame is approved for use only in soft drinks and isomaltulose is approved only for sweet confectionary[6].

Most of these artificial sweeteners in food are not absorbed from the GI tract and are excreted in the faeces. Only those which are peptide by chemical composition like aspartame and alitame, are absorbed and metabolised by the amino-acid pathway.

In the USA, the USFDA has approved six sweeteners[7]: saccharin, aspartame, acesulfame potassium (Ace-K), sucralose, neotame, and advantame. Advantame is a compound which is 20,000 times sweeter than sucrose. It was approved in 2014. It is heat stable and can be used for baking. However, it is not recommended for use in poultry items.

Xylitol:

This is a 5-carbon compound which is sometimes used as a sweetener. It is synthesized from lignocellulosic biomass like hardwood, softwood, or agricultural wastes of maize or wheat. It is not a zero-calorie sweetener like the other compounds mentioned in this article, but calorie count is much less compared to sucrose. One particular effect of xylitol is reduction of *streptococcus mutans* in oral flora, thereby reducing the risk of dental caries.

Stevia:

Recently, a plant derived artificial sweetener, called Stevia has become available in the market. Stevia plant, native to South America, is a member of the sunflower family[8]. Knowledge about sweetness of various parts of this plant was known to the indigenous tribes of Brazil and Paraguay for centuries. Commercially, the ingredient is extracted from the leaves of the plant. The sweet ingredient is Steviol glycosides like Rebaudioside (A to F) and Dulcoside A[8]. This ingredient is used in a variety of food items like dairy products, ice cream, or canned fruit[7]. It is heat stable and thus, can be used for cooking or baking. FSSAI approved Stevia for the Indian market in 2015. But acceptance of stevia by Indians is slow. However, recently, some soft drink manufacturers in India have released stevia-based versions of their drinks and the market is slowly expected to grow.

FDA opinion on Stevia[9]

In the FDA website, as of 2018, it is written that high purity steviol glycosides are generally considered as safe (GRAS) and do not need FDA approval for use in food. But stevia leaves or crude extracts are not approved for use.

However in India, various online stores sell Stevia leaf also. Any reader of this article can now visit any online store and buy stevia leaves at his/her will. Whether use of these leaves is advisable and if so, how they should be used, is a matter of debate, but there is no regulation on their retail.

Recent interest in "rare sugars"[5]

Recently, there is considerable interest in the field of dietetics in rare sugar compounds. These are monosaccharides which are not metabolised in the body.

They can act as food sweeteners and one advantage, compared to other artificial sweeteners, is that there is no bitter after-taste.

Some examples include Xylitol, Tagatose and D-psicose. Readers are encouraged to read the relevant literature on their properties for further information.

Possible health effects

Low or zero calorie sweeteners are expected to reduce the intake of carbohydrates without compromising the taste of food. Reduced intake of carbohydrates is expected to reduce body weight. *But is the cause-effect relationship so simple?*

In 2012, a landmark meta-analysis on the effect of sugar intake on body weight was published in the BMJ[10]. This meta-analysis, commissioned by the WHO, tried to find out the quantitative effect of excess sugar intake on body weight, based on published trial data. However, most of the trials included in this meta-analysis had very small number of participants. For example, the trial by Markmann *et al* in 2000 included only 20 subjects and that by Poppitt in 2002 included 28 subjects[10]. Thus, the results from these trials may not be generalised. Moreover, many of these trials showed that increase in sugar intake led to increase in waist circumference but the increase in actual body weight was modest[10]. For example, the 2011 Nurses' Health study I and II in USA found that increase in sugar intake by 1 serving/day led to increase in body weight of around 0.5 kg over a 4-year period[11]. For the present article, the significance of these data lies in the fact that replacement of sugar with artificial sweeteners will not lead to a radical decrease in body weight. If the total calorie intake remains same, then only artificial sweeteners *will not help in reduction of obesity*.

Now the question arises, how much amount of these artificial (or high-intensity) sweeteners is safe? For this, the FDA uses a parameter called ADI: Acceptable daily Intake. This is the amount of substance which is considered safe for daily consumption over the course of lifetime of a person. For example, ADI of saccharin is up to 5 mg/kg and for Stevia it is 4 mg/kg. Thus, Stevia has a narrow window of use and Stevia-based drinks cannot be taken in large quantities. But the problem is there is no authoritative mechanism for limiting the sale of these items and a person may consume as much as he/she wants at a time. The consumer product companies would just write a statutory warning in the label and thus, wash their hands off. This raises the possibility of side-effects from excess use.

Another problem is that the ADI for each sweetener compound may vary according to the recommending authority. For example, as stated above, the ADI for saccharin is 5 mg/kg according to the European Food safety Authority but according to the Joint Food and Agriculture Organization of the United Nations, the figure is 15 mg/kg[12]. For sucralose (perhaps the commonest sweetener used in India) the Joint Food and Agriculture Organization of the United Nations limit is 5 mg/kg; but European limit is 15 mg/kg.

Also, organisations like the FSSAI have demarcated maximum permissible concentration of sweeteners in each food item[6]. If these guidelines are followed strictly, then the chance of adverse reactions is very low. For example, for carbonated beverages, the limit of saccharin is 100 ppm and for chocolates, it is 500 ppm[6]. For aspartame, the limit for custard powder is 1,000 ppm and for chocolate, it is 2,000 ppm. Similar guidelines may be found for each sweetener and for each food item.

In 2019, in the BMJ, another important meta-analysis was published. This one analysed the link between intake of non-sugar sweeteners and health outcomes[12]. The trials included in this meta-analysis were mostly small and there were some lacunae on the reporting of data. Analysis revealed that the reduction in body weight after use of non-sugar sweeteners (NSS) was modest at best[12]. For obese individuals, the mean reduction in body weight was 2 kg (pooled data of 3 studies). But many trials found no significant weight reduction after the use of NSS. So, at this time, NSS cannot be recommended for control of obesity.

It is expected that diabetic patients using NSS should have lower blood glucose levels as they are replacing sugar with a no-calorie substitute. But in practice, data shows that the reduction in fasting blood glucose is modest at best for persons using NSS[12]. Published data also show that the use of aspartame in diabetics may act as a chemical stressor and lead to increased cortisol levels and thus, increase in blood glucose levels[13]. It may also alter gut microbial activity and increase insulin resistance paradoxically. Recently (2017) a European study revealed that chronic consumption of NSS actually led to increased risk of type 2 diabetes, when adjusted for BMI[14]. In this study, it was also shown that NSS conferred an increased risk of diabetes in a dose-dependent manner. The use of NSS may be associated with paradoxical weight gain due to increase in appetite and thus, increased calorie consumption as a whole[15]. *So, the simple explanation that replacing sugar with NSS will control blood sugar levels is not true*.

In 2012, the American Heart Association also published a statement on NSS[16]. In this, the association concluded that there is still insufficient evidence to recommend NSS as a health supplement[16]. Also, they made some interesting observations. It was recorded that the use of NSS did not

have any clinically meaningful effect on glycaemic control in diabetics[16]. The association of "diet" soft drinks or artificially sweetened beverages (ASB) with cardiovascular events is debatable. While some studies have found a statistical association of ASB with coronary events and chronic kidney disease, other studies have reported no association. One problem with these studies is that most American and European studies have reported data on NSS used in beverages. But in India, most sugar intake is in form of sweets or dairy products. Thus, whether the metabolic effect of NSS in these products will be similar to ASB is a matter of research. Also, whether NSS added to cooking will have the intended health effects is a matter of speculation.

Molecular effect of NSS in the brain

A 2016 study from Sydney found that chronic sucralose diet in animals paradoxically increases food intake[17]. Thus, although the intake of sugar is reduced, the organism can end-up eating more as a whole, thereby increasing calorie intake[17]. Some changes in the pleasure-reward pathways in the brain is said to be responsible for this effect. The applicability of this data in humans is still debatable. However, some molecular mechanisms have been proposed which may explain this paradoxical increase in energy intake after taking NSS[16]. One such theory is that, intake of sugar leads to release of gut peptides which causes satiety in the hypothalamus. But intake of NSS does not release gut peptides and thus, the person ends up eating more.

Other health hazards

Another health hazard often cited of NSS is the risk of carcinogenicity[15]. Cyclamate was the first compound to be implicated in causing cancer, and thus banned in the USA[15]. Although later studies refuted this claim, still the compound remains banned in the USA. For other sweeteners, no link has been found with cancers[15]. In the 1970s, saccharin was linked to bladder cancer in rats. But subsequent human studies did not find any risk[18]. Now-a-days, a number of artificial sweeteners are combined in the same food item (as stated above for Acesulfame). Thus, individual effect of one compound is difficult to gauge.

Aspartame is metabolised to phenylalanine. Thus, patients with phenylketonuria should never be given this compound[15]. Aspartame, in general, can also cause chronic fatigue[15].

There is some data on the potential for excitotoxicity of Aspartame and Neotame. But whether this is clinically meaningful at the usual level of intake is doubtful[19].

Consumers in many countries have concerns about the health safety of NSS[16]. In a survey conducted in the USA, 64% of the subjects indicated that they were concerned about the safety of these sweeteners[16]. Thus, manufacturers often use certain tricks of wordplay to bypass this anxiety. For example, Stevia is marketed as "natural" sweetener, obtained from leaves of certain plants. Sucralose is marketed as "made from natural sugar" as it is a chlorinated form of sucrose.

Physicians working in India will often come across patients taking a lot of herbal supplements as medicines. Many of them have the notion that honey or jaggery is allowable in diabetic patients, instead of sugar. But this myth should be dispelled. Both honey and jaggery contain sucrose, and thus the net effect on calorie intake is the same. They are not sugar substitutes. Chawanprash is another ayurvedic concoction widely used in India. Recently, consumer companies have launched "sugar-free" chawanprash. These contain the artificial sweeteners discussed above. Consumers should be made aware of this change.

Conclusion (Take-home messages)

- Artificial sweeteners available in the market are generally safe for consumption, with certain restrictions.
- Artificial sweeteners are not a solution for diabetes control or obesity.
- There is a chance in alteration of appetite or feeding behaviour of a person taking artificial sweeteners.
- In India, heat-stable sweeteners like sucralose can be used for cooking but their health effect is still not known.

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