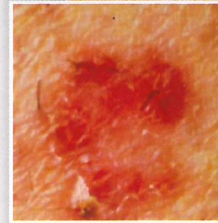
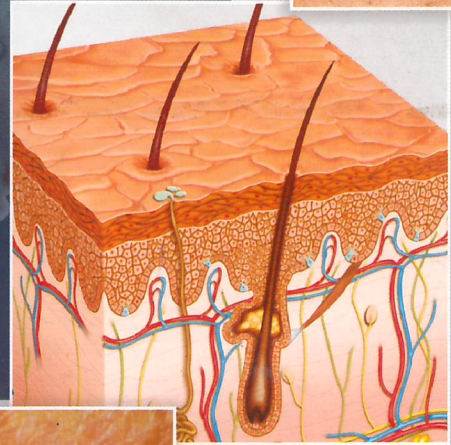
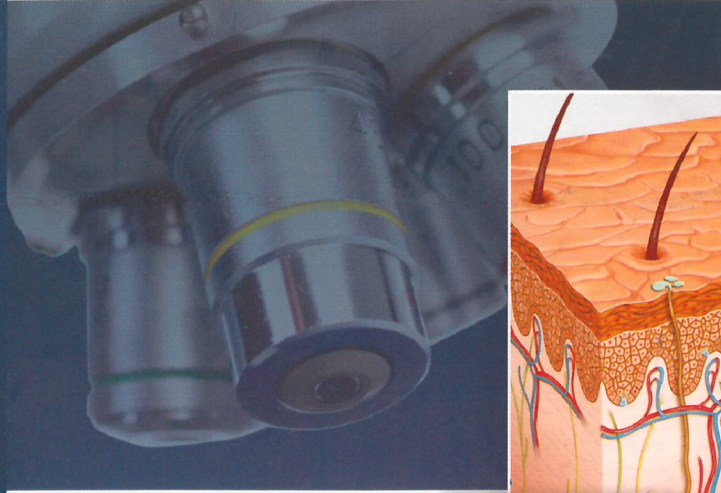


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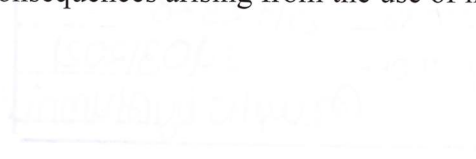
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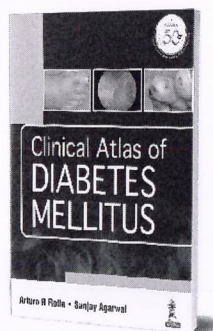
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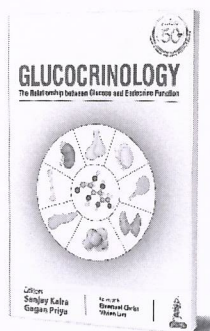
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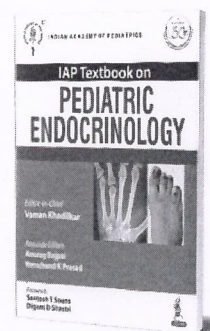
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### Artificial Sweeteners in Diabetes: How Safe?

Sandeep Rai, Madhur Rai

#### INTRODUCTION

Artificial sweeteners (AS) are one of the most common food additives worldwide. By definition, AS, otherwise referred to as very low-calorie sweeteners, non-nutrient sweeteners, non-caloric sweeteners or intense sweeteners, have a greater intensity of sweetness than caloric sweeteners such as sucrose, corn syrups and fruit juice concentrates. As a sugar replacement, they are added in

smaller quantities, hence, they provide no or only minimal calories. The Food and Drug Administration (FDA) has approved the use of six AS, which includes aspartame, sucralose, saccharin, advantame, neotame and acesulfame potassium (Ace-k), in food and beverages (Table 1). Federal regulations require that any food that contains aspartame bear this warning: "Phenylketonurics (PKU) Contains phenylalanine". This warning helps people with PKU avoid products that are a source of

TABLE 1: Artificial sweetener reference chart.

ARTIFICIAL SWEETENERS					
Generic name	Brand name	Sweetness factor/ acceptable daily intake (ADI) mg of sweetener/ kg body weight/day	Uses	Additional facts/ metabolism	FDA approval
Saccharin	Sweet'N Low, Sweet Twin, Necta Sweet, Sweetex	200–700 times sweeter than sugar ADI-5 mg/kg	Tabletop sweetener, beverages, baked goods, jams, gum	Heat stable/Metabolism- Nil bitter metallic after taste	2001
Aspartame	Nutrasweet/Equal	200 times sweeter than sugar ADI-50 mg/kg	In processed foods and beverages	Not heat stable/ metabolized to: Phenylalanine aspartic acid methanol	1981
Acesulfame-K	Sunett, Sweet One	200 times sweeter than sugar ADI-15 mg/kg	General purpose	Heat stable to 392 °F/ metabolism-Nil	1998
Sucralose	Splenda/Sugar Free Natura	600 times sweeter than sugar ADI- 5 mg/kg	General purpose	Can be used in home baking/metabolism-Nil	1998
Neotame	Newtame	8000 times sweeter than sugar ADI-18 mg/kg	General purpose/ metabolism by esterase	Similar to aspartame	2002



phenylalanine. Although AS are generally considered safe for human consumption, there is increasing controversy regarding their potential ability to promote metabolic derangements in humans.

### ANY HEALTH RISKS OF USING ARTIFICIAL SWEETENERS?

This is still a highly controversial topic<sup>1</sup> AS have allegedly been linked to adverse effects such as cancer, weight gain, metabolic disorders, migraine, type-2 diabetes, vascular events, preterm delivery, hepatotoxicity, immune system disruptions and alteration of gut microbiota activity.<sup>2</sup> Although these potential health problems have long been studied, but a firm conclusion has yet to be reached on these allegations due to a lack of credible and consistent evidence. Some of these controversial areas are discussed below.

### ARTIFICIAL SWEETENERS FUELING THE DIABESITY EPIDEMIC?

A statement from American Heart Association and American Diabetes Association in 2011 pointed out that non-nutritive sweetener may be good for health by reducing or controlling weight and can have other beneficial metabolic effects too.<sup>3</sup> However, recent concerns regarding the safety of AS have arisen from few studies in humans. In a large meta-analysis of prospective studies<sup>4,5</sup> (17 cohorts with 38,253 cases) it has been shown that AS were associated with the risk of type 2 diabetes mellitus (T2DM). Another similar study demonstrated that diets sweetened with either natural or artificial sugars are linked with an increase in type 2 diabetes.<sup>6</sup> In a recently published study, which collected 10-year data from more than 10,000 women, who were consumers of AS as packet and tablets<sup>7</sup> showed an association between AS usage and risk of diabetes. More importantly they were also able to show a gradation of risk depending upon years of consumption and also the amount of AS consumed per day.

The explanation given for a probable association between AS and T2DM in observation studies is the reverse causation bias because of increase intake of AS is otherwise also seen among obese people.<sup>8</sup> Another convincing explanation is that an orosensory stimulus is silently generated by sweet foods, telling the body about the likely inflow of calories that is going to follow. This is followed by several gastrointestinal reflexes that finally relay in brain and intimate the hypothalamus through

negative feedback signals to decrease hunger sensation and increase satiety feeling as body has already received calories, however when sweetness is sensed without inflow of calories (AS ingestion), gastrointestinal reflexes do not send signals to hypothalamus to decrease the hunger sensation (Fig. 1). The brain recalibrates and persons hunger sensation continues and this leads to increase in "total calories consumed". This ultimately leads to weight gain and consequently increases the risk of diabetes.

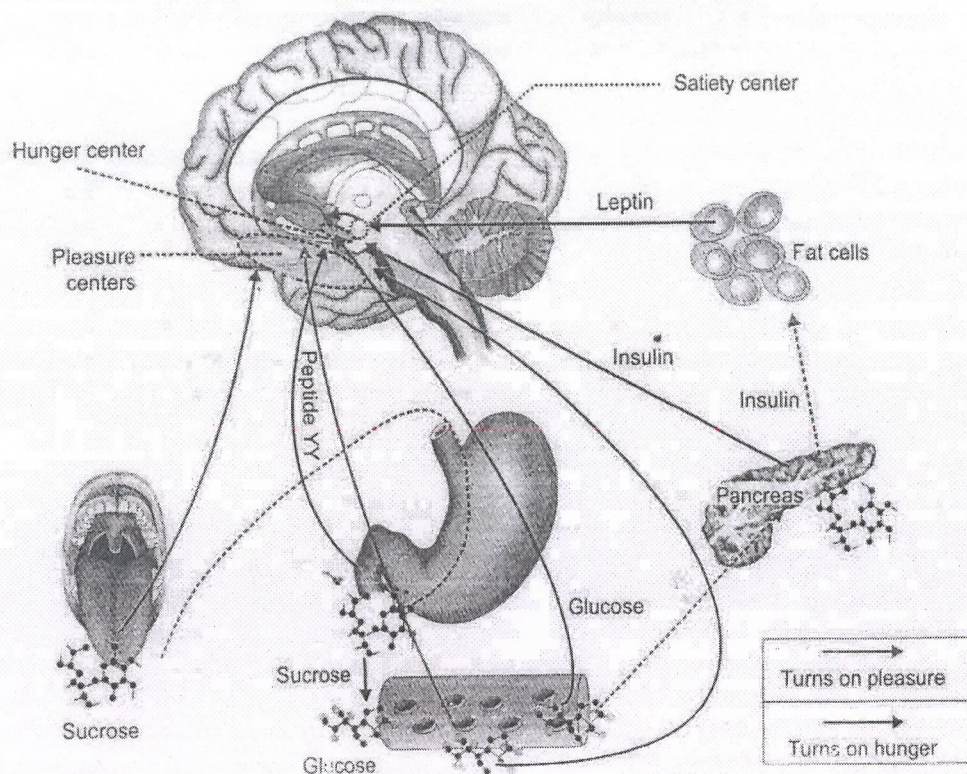
A study was conducted in the University of San Diego, California on volunteers who were given sips of water mixed with either sugar or sucralose. Functional magnetic resonance imaging scans of the brain were then recorded. Images showed that sugar activated areas of the brain which were involved in food reward, whereas sucralose did not have the same effect. These results proved that AS may not be effective in managing cravings for sweets.<sup>9</sup>

Another study was carried out on more than 3,000 individuals, which saw the impact of artificially sweetened drinks on the body weight. Results showed that those who consumed these drinks had a 47% higher increase in body mass index (BMI) than those who did not.<sup>10</sup> Another meta-analysis saw the effect of AS on body weight and cardio metabolic risk factors including.<sup>7</sup> Randomized controlled trials (RCTs) (1,003 participants; follow-up 6 months) and about 30 cohort studies (more than 400,000 participants; median follow-up 10 years) was critically analyzed. Evidence from RCTs does not support the benefits of AS for body weight management, and observational data suggest that routine intake of AS may be associated with increased BMI and cardiometabolic risk including coronary artery disease. In the cohort studies, it was found that consumption of AS was associated with increases in weight and waist circumference, and a higher incidence of obesity, metabolic syndrome, and type 2 diabetes.<sup>11</sup> However, publication bias was indicated for the studies with diabetes as an outcome.

### ARTIFICIAL SWEETENER SAFE IN PREGNANCY?

Although many AS are considered safe during pregnancy, women with any form of diabetes must limit their use of these substitutes. According to a study saccharin has been shown to cause effects as anemia, iron and vitamin A deficiency, depressed growth and elevated vitamin E in rats. They are also linked with premature deliveries prompted by two observational studies published in 2010 and 2012. Therefore, at present time, till further large





**Figure 1** Sucrose ingestion leads to calorie inflow and activates multiple gastrointestinal (GI) negative feedback signals to hypothalamus to decrease hunger sensation, while artificial sweetener ingestion is followed by no calories and therefore no feedback inhibition of hunger sensation, leading to increase food intake and weight gain.

Source: Gabymichel, BruceBlas, Mikael Haggstrom, Haggström, M (2014). "Medical gallery of Mikael Haggström 2014". *WikiJournal of Medicine* 1 (2)

scale studies are done, pregnant women must be advised to avoid these sweeteners.<sup>12</sup> It is also critical to investigate the effect of AS in other populations, such as infants and young children, lactating women, and those with metabolic diseases.

### ARTIFICIAL SWEETENERS AND THE RISK OF CANCER?

In 1970, a research was conducted which showed the association of saccharin with bladder cancer in laboratory rats. Another study raised a needle of suspicion when it showed that aspartame intake is associated with malignancies like leukemia, lymphoma and multiple myeloma (in men).<sup>13</sup> However, this particular study was limited by inability to quantify exact consumption of aspartame because of variable presence of aspartame among the dietary sources. Another limitation of this study was the inability to explain the rationale behind male preponderance of carcinoma risk. Similarly, another

study assessed the possible effects of five non-nutritive sweeteners on cell proliferation, morphology and cell's deoxyribonucleic acid (DNA). It was also seen that sodium saccharin and sucralose caused more DNA fragmentation in all cell lines than any other artificial sweeteners.<sup>14</sup>

However, Weihrauch et al. after reviewing the literature meticulously, opined that there was no significant evidence of AS consumption and cancer risk with currently available AS.<sup>15</sup> Similar conclusions were also drawn by another large study which prospectively analyzed data from more than 400,000 men and women over a 5 years period and did not find any association between aspartame consumption and risk of hematopoietic or brain tumours.<sup>16</sup>

### EFFECT OF ARTIFICIAL SWEETENERS ON GUT BIOME

Artificial sweeteners influence the microbial composition of the oral mucosa, and they are viewed positively by the



dental community. It is therefore not surprising that AS have recently been shown to alter the gut microbiota, primarily in rodent models. Experimental evidence for -induced alterations in gut microbiota in humans is limited. AS exposure for 1 week was associated with changes in the gut microbiome and glucose metabolism in a small human sample.<sup>17</sup> Notably, several of the bacterial taxa that changed following AS consumption were previously associated with type 2 diabetes in humans,<sup>18</sup> including over-representation of Bacteroides and under-representation of Clostridiales. However, the lack of a control group makes these findings less interpretable. Nevertheless, further study in this area is warranted, given the emerging role of the gut microbiome in health and disease. In another study, the relative toxicity of six FDA-approved AS and that of ten sport supplements containing these AS were tested using genetically modified bioluminescent bacteria from *E. coli*. The bioluminescent bacteria, which luminescence when they detect toxicants, act as a sensing model representative of the complex microbial system. Both induced luminescent signals and bacterial growth were measured. Toxic effects were found when the bacteria were exposed to certain concentrations of the AS.<sup>19</sup>

## NOVEL SWEETENERS

Novel sweeteners are hard to fit into a particular category because of what they're made from and how they're made. Stevia is extracted from the leaves of the plant species *Stevia rebaudiana*, native to Brazil and Paraguay. Stevia contains steviol glycosides, which are used as AS. FDA has not questioned the GRAS (generally, recognized as safe) status of certain high-purity steviol glycosides for use in food. However, stevia leaf and crude stevia extracts are not considered GRAS and do not have FDA approval for use in food. Tagatose is also considered a novel sweetener because of its chemical structure. Tagatose is a low-carbohydrate sweetener similar to fructose that occurs naturally but is manufactured from the lactose in dairy products. The FDA categorizes Tagatose as a GRAS substance.

## ALTERNATIVES TO ARTIFICIAL SWEETENERS

Various natural sweeteners, which are safer, can be used instead of AS. Many of these include added benefits of being rich in minerals and vitamins. These include honey, coconut nectar, fruits, maple syrup, molasses, sugar alcohols, stevia, agave nectar, apple sauce and

others. The key word here is alternatives meaning and they also contain sugar, but in less amount and should be used instead of refined sugar. Stevia is probably the healthiest option, is 100% natural, and contains zero calories, followed by xylitol, erythritol and yacon syrup. These contain less sugar compared to sucrose. Xylitol is a sugar alcohol that contains 40% fewer calories than sugar. Eating it may offer dental benefits. Erythritol is a sugar alcohol that tastes almost exactly like sugar, but it contains only 6% of the calories. It is an excellent sugar alternative. "Less bad" sugars like maple syrup, molasses and honey are slightly better than regular sugar, but should still be used sparingly. As with most things in nutrition, moderation is the key.

## CONCLUSION

Artificial sweeteners are a ubiquitous part of modern life, especially of diabetes care. While it is nearly impossible to replicate "real-life" consumption in randomized controlled trials, epidemiological studies report positive associations with obesity and metabolic impairments. In contrast, human randomized controlled trials suggest that AS may be a useful, or at least neutral tool for weight management. Given the discrepancies in the available evidence, the extent to which AS are helpful or harmful for weight management and chronic disease prevention warrants further well designed, large scale studies. With all the evidence available till date, it is advisable that AS, if at all have to be used, should only be used occasionally and not chronically for long term, and that too, in a limited amount. Physicians who advise these AS to their obese or diabetic patients need to take a step back and re-evaluate their recommendations especially in light of the newer studies on various unfavorable metabolic effects that are emerging now. In fact, we may be dealing with a Wolf in a Sheep's clothing.

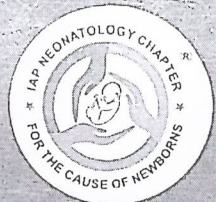
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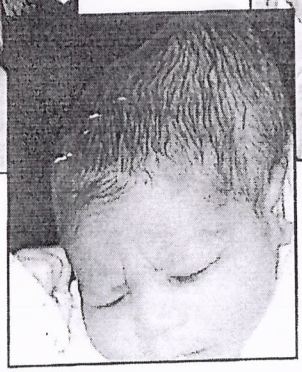
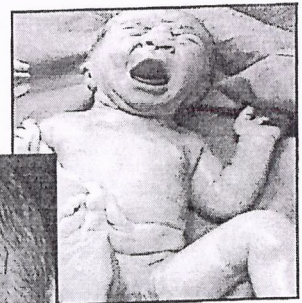
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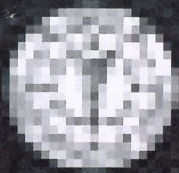


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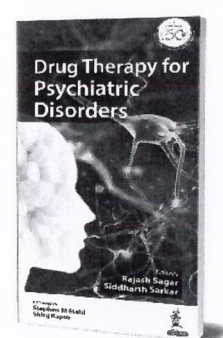
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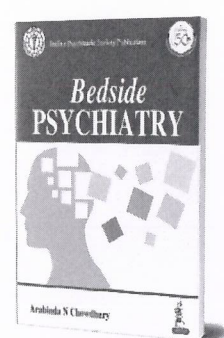
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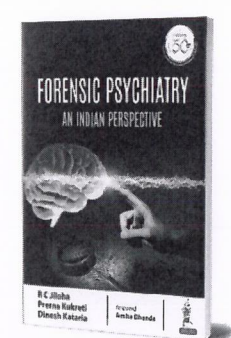
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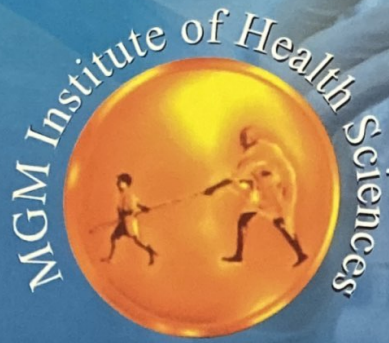
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# Strengthening the Profession of Nursing

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Proceedings of the National Conference

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2019

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*Editors*

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