Review Article

Artificial sweeteners — clinical perspective

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Artificial sweeteners (AS) are substances with intense sweetening properties that can be added in small quantities to various foods to enhance its flavour without adding any extra calories. AS has always been under scrutiny and there are various controversies about health risks posed by its consumption. The commonly approved and available AS include saccharin, aspartame, sucralose, neotame and acesulfame potassium. Some natural derivatives like steviolglycosides and sugar alcohols have also been used as sweetening agents. The toxicity profile of these agents has been thoroughly studied and scrutinized and is generally considered safe by various national and international food regulatory authorities. However, the recent clinical trials have shown inconsistent results on weight gain and metabolic benefitwith regular consumption of AS. The current review will focus on effects of AS on clinical parameters like weight gain andglycaemic control and other metabolic risk factors. The safety of usage of AS in setting of pregnancy will also be analysed.

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Artificial sweeteners (AS) are known by several names, which include low-calorie sweeteners, high intensity sweeteners, non-nutritive sweeteners, sugar substitutes, etc. AS have a higher intensity of sweetness per gram than caloric sweeteners such as sucrose, corn syrups, and fruit juice concentrates[1]. As a caloric sweetener replacement, they are added in smaller quantities; and provide no or few calories. AS may assist in weight management, control of diabetes and prevention of dental caries[2]. There are other sugar substitutes like sugar alcohols or polyols that produces around 2 kcal/g; because they are not fully absorbed from the gut, polyols are less available for energy metabolism. Taken as a whole, AS are mostly not metabolized in the body and so, are generally considered safe for consumption. AS usage throughout the world, is evaluated by governing bodies; these include the Food and Drug Administration (FDA) of the United States and expert scientific committees such as the Scientific Committee on Food (SCF) of the European Commission, the Joint Expert Committee of Food Additions (JECFA) of the United Nations Food and Agricultural Organization (FAO) and the World Health Organization (WHO). In India, the usage of AS is governed by Food Safety and Standards Authority of India (FSSAI). The FSSAI has approved five AS: saccharin, aspartame, acesulfame potassium, sucralose and neotame. Stevia is also approved in India.

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Types of Artificial Sweeteners :

(a) Saccharin — Saccharin exceeds the sweetness of sugar by 200 to 700 times. It provides no energy because it is not metabolized by humans[3]. In March 1975, a Canadian study found that male rats experienced increased rates of bladder cancer after consuming high doses of saccharin[4]. Reports however stated that the amount of saccharin rats were eating was the equivalent of a person drinking 800 diet sodas a day. Other studies done during that period also raised doubts about association of high dose saccharin usage to bladder cancer. As a result, from 1981 until 2000, products containing saccharin required warning labels in the USA. The requirement was reversed after the US National Toxicology Program at the National Institute of Environmental Health Sciences found fault with the data and removed saccharin from the list of suspected human carcinogens[5].

(b) Aspartame — It is 160 to 220 times sweeter than sucrose. This sweetener does provide energy; however, because of the intense sweetness of aspartame, a minute amount needs to be added. So, the amount of energy derived is negligible. Foods that contain aspartame are contraindicated for those suffering from phenylketonuria[6]. A

comprehensive review of the safety of aspartame that covered previous publications as well as new information, supported its safety and negated claims of aspartame's association with a range of health problems including brain tumors[7]. The SCF also concluded that current intakes in European countries are well below the acceptable daily intake (ADI) set by JECFA and SCF (40 mg/kg body weight/day) and that aspartame is not a carcinogen and also is not associated with neurobehavioral disorders.8 Currently,aspartame is approved for use in over 100 nations.

(c) Neotame — It has a sweetness potency of approximately 7,000 to 13,000 times than sucrose. It is partially absorbed in the small intestine, rapidly metabolized by sterase, and excreted in urine and faeces. The label for products with neotame do not need to alert phenylketonurics. Neotame consumption at 100 times the ADI in animals did not produce neurotoxic or behavioural or reproductive toxicity effects. In human studies, there were no significant treatment effects of neotame ingestion compared to controls[9].

(d) Sucralose — It is 600 times sweeter than sucrose; it provides no calories as it is poorly absorbed (range 11% to 27%) and is excreted unchanged in the faeces. If at all any sucralose is absorbed, it is excreted unchanged through urine. FDA concluded from a review of more than 110 studies in human beings and animals that sucralose did not pose carcinogenic, reproductive, or neurologic risk to human beings[10].

(e) Acesulfame potassium — It is approximately 200 times sweeter than sucrose. Pharmacokinetic studies show that 95% of the consumed sweetener is excreted unchanged in the urine and does not provide any energy. Consumption of acesulfame-K does not influence intake of potassium[11]. It was evaluated for safety by JECFA in 1983[12,13]. The European Commission's SCF re-evaluated it and supported its safety but recommended an ADI at 9 mg/kg of body weight/day[14]. The amount of acesulfame-K added to food products is very small because of its intense sweetening power and it is often used in combination with other AS.

Acceptable Daily Intake :

The concept of ADI was introduced in 1961 by JECFA. ADI is expressed in mg of additive per kg of body weight and it is the amount of the substance if consumed on a daily basis over a lifetime will not result in any adverse effects. Based on results from animal toxicology studies the no-observed-effect level (NOEL) for a particular AS is determined. NOEL is divided by 100 to determine the ADI for a food additive, a 100-fold safety factor to avoid any possible side effects in humans[3]. If estimated daily intake (EDI) exceeds the ADI, there may be limitations on the use of the sweetener. For sweeteners, testing may be augmented to address specific end points like neurotoxicity testing and effects on humans with relevant conditions like effects on glucose homeostasis in those with diabetes. A recent evaluation of AS intake worldwide revealed that intake of AS are well below acceptable levels[15].

Artificial Sweeteners: Effect on Clinical Parameters :

AS are generally believed to be safe from toxicity point of view. As they hardly provide any calories, they have also long been considered beneficial for those with diabetes and where weight gain is a concern. But over the last decade, new data has emerged that has challenged the notion of metabolic safety of AS.

Risk of Developing Diabetes :

The Health Professionals Follow-Up Study, a prospective cohort study of 40,389 healthy men,concluded that sugar sweetened beverages (SSB) clearly increased the risk of type 2 diabetes. Intake of artificially sweetened beverages (ASB) was shown to be associated with type 2 diabetes in the age-adjusted analysis (HR: 1.91) but failed to show any association in the multivariate-adjusted analysis (HR: 1.09)[16]. The Manhattan study, in which 2019 participants free of diabetes were on longitudinal follow up, showed that consumption of diet soda was associated with risk of incident diabetes. The association depended on BMI at the time of diet assessment though a further sub-analysis in overweight or obese subjects revealed that the association persisted irrespective of BMI in those groups[17]. The Women's Health Initiative (WHI), analysis of a cohort of 64,850 women, revealed that ASB consumption was associated with a higher risk of diabetes with an HR of 1.21 comparing ASB consumption of =2 serving/day to never or <3 serving/month. The study concluded that, consumption of SSB increased the risk of diabetes by 43% where as ASB intake was associated with a 21% increased risk[18]. Other studies[19-21], including two meta-analysis[22,23], also suggest that although less compared to sugar and SSB, there is an increased chance of developing diabetes with regular AS consumption particularly in obese individuals. One possible explanation behind the association between AS intake and risk of diabetes in observational studies is reverse causation bias, which relates to the fact that obese individuals are more likely to consume AS. Alteration in gut flora induced by AS has been proposed as a mechanism to induce glucose intolerance. The glucose intolerance induced in mice by AS was corrected by addition of antibiotics[24].

Risk of Obesity :

Although AS were designed to restrict calories and promote weight loss, the findings in observational and interventional studies have not been encouraging. Several large epidemiological studies have shown that regular con-

sumption of AS is associated with weight gain[25-28]. Consensus from interventional studies suggest that AS do not help to reduce weight when used alone[29,30]. A review of AS usage in children also showed epidemiological link between weight gain and consumption of AS[30]. In the Baltimore Longitudinal Study of Aging, after a10-year mean follow up, AS users had (0.80 kg/m^2) higher BMI, (2.6 cm) larger waist circumference and (36.7%) higher prevalence of abdominal obesity compared to non-users[31].

Regular users of AS are hypothesized to have increased desire for high calorie and sweet foods. AS may interfere with the physiological mechanisms that enable to predict the caloric content of food based on sweet taste causing overconsumption of calories. Sucralose was shown to modulate physiological parameters involved in normal body weight regulation by activation of sweet taste receptor in the brain that might potentially affect appetite regulation by providing an inaccurate signal regarding the actual levels of extracellular glucose in the brain[32,33]. Thesweet-taste receptors in the intestine could interact with AS and stimulate glucagon-like peptide 1 (GLP-1) secretion which in turn leads to insulin release from pancreas. Rise in insulin secretion can increase appetite and result in weight gain[34].

Impact on Glycemic Control in Diabetics :

Diabetics are advised to restrict simple carbohydrates like glucose, sucrose, fructose, etc. Foods containing AS provide alternatechoices, making possible increased variety, compliance to prescribed meal plans and in some cases, improved psychological well-being.A multicenter, double-blind, placebo-controlled, three month randomized study, in diabetics, in which sucralose was administered at a dose approximately three times the maximum estimated daily intake, showed no adverse effect on any measure of blood glucose control in individuals with type 2 diabetes[35]. A review on AS also concluded that it did not adversely impact glycemic control in individuals with diabetes[36]. A recent meta-analysis concluded that consumption of AS did not increase plasma glucose concentrations. The glycemic impact of AS intake did not vary according to the type of AS, but did differ to some extent depending on age, body weight, and status of diabetes[37]. In another study, it was demonstrated that intake of diet soda before a glucose load increased GLP-1 secretion in non-diabetic controls and in those with type 1 diabetes but not in type 2 diabetic subjects. Glucose-dependent insulinotropic polypeptide (GIP) and peptide YY (PYY) secretion were not altered by consumption of diet soda. The clinical significance of this finding is however not yet clear[38]. The current understanding is that AS does not impact glycaemic status in diabetic subjects. Whether it has any additional and indirect action on incretins and other gut hormones in diabetic subjects needs further evaluation.

AS Usage in Childhood :

As a means to help curtail the obesity epidemic, dietary changes to prevent weight gain in children and adolescents have been encouraged. A key question is whether replacement of sugar-sweetened products with those containing AS in children is truly beneficial. The general trend is that AS may reduce total caloric intake when consumed between meals, but when consumed with meals, children may compensate for low-calorie snacks or drinks by increasing meal-associated calories. A review of AS usage in children also showed epidemiological link between weight gain and consumption of AS[30]. Another interesting aspect that draws attention on AS usage among children is addiction to sweet foods. Though most addiction research examines more common drugs of abuse, such as alcohol, cocaine, morphine, and nicotine, various studies have drawn parallels between drug seeking behavior and food seeking behavior. This has led some to believe that sugar and other sweet substances could become physiologically addictive[39]. Majority of pediatric epidemiologic studies have found a positive correlation between weight gain and ASB intake. Blum *et al* examined ASB consumption and BMI Z-scores in 164 elementary school-aged children. This longitudinal study found that increased diet soda consumption was positively correlated with follow-up BMI Z-score after two years[40]. Comparable results were found by Berkey *et al*, who examined the relationship between BMI and diet soda consumption in over 10,000 children (aged 9 to 14 years) of Nurses' Health Study II participants over the course of one year[41]. Thus,recent epidemiological and clinical findings question whether recommendations for the use of AS in children is appropriate.

AS Usage in Pregnancy :

Although AS such as aspartame, acesulfame-K, and saccharine are generally considered safe with respect to acute toxicity, the overall safety of regular consumption during pregnancy is still disputed because the outcomes of AS usage on the fetus are not clear. Human studies found that the breakdown products of aspartame cross the placenta[42]. But, consumption of aspartame during pregnancy is not expected to be a concern when staying within the ADI[43]. There is limited research on the safety of acesulfame potassium during pregnancy, but studies have found that this sweetener does cross the placenta. However, these results were reported for concentrations of acesulfame potassium that were substantially greater than typical human exposure[44]. A case-control study also reported that risk of spontaneous abortions in women was not increased in those who consumed saccharin[45]. Some studies do report that high intake of both AS and SS beverages is associated with an increased risk of preterm delivery[46]. The

study involved 59,334 pregnant women and evaluated the association between intake of sucrose-sweetened soft drinks, carbonated or not, and preterm birth (< 37 weeks) infants as the primary endpoint. A high intake of ASB was associated with preterm delivery; the adjusted OR for those drinking >1 serving/d was 1.11 (95% CI: 1.00, 1.24). The trend tests were positive for both SSB & ASB types[46]. Reinforcing this data, a study linked the high intake of ASB with prematurity; the adjusted OR for those who drank > 1 serving/day was 1.11 (95CI = 1.00 - 1.24)[47]. Further studies are needed to reject or confirm these findings. Maternal consumption of AS during pregnancy may also influence infant BMI[48]. Findings illustrated positive associations between intrauterine exposure to ASB and birth size and risk of overweight/obesity at 7 years[49]. Carbonated ASBs were also associated with registry-based asthma and self-reported allergic rhinitis, while early childhood outcomes were related to non-carbonated soft drinks[50]. These results suggest that consumption of ASB during pregnancy may play a role in offspring allergic disease development. Consumption of AS during pregnancy might have a negative effect on the pregnancy outcome in terms of preterm delivery. There are also some doubts about long term outcome in children who had exposure to AS in utero and more data is required before recommendations about routine usage of AS in pregnancy can be advocated.

Conclusion :

Though AS consumption is not associated with toxicity like carcinogenesis, but there are unresolved questions regarding its metabolic safety. At this time, the available data is insufficient to conclusively determine whether the use of ASin beverages and foods reduces weight or prevents diabetes. The evidence reviewed suggests that when used judiciously, AS could facilitate reductions in consumption of calories as compared to sugar and SSB. But, these theoretical advantages might not translate to expected clinical benefits because of compensatory increase in energy intake from other sources, alterations in gut flora and abnormal response of gut hormones. Further studies are required to ascertain the metabolic safety of these substances.

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