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NON NUTRITIVE SWEETENERS - CURRENT PERSPECTIVE

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Abstract

High sugar diet plays a major contributing role in the increased prevalence of obesity and vital health concerns such as type 2 diabetes mellitus (T2DM), ischemic heart disease (IHD), hypertension, and cerebrovascular stroke. Therefore increased obesity related mortality has resulted in a surge of weight loss diets and products including non-nutritive sweeteners (NNS). NNS are food supplements that imitate the effect of sugar in taste with lesser calories. This has led to the increased global use of NNS. Diabetic subjects can enjoy the taste of meals by including NNS without increasing calorie intake. Various NNS are available in the market, giving a wide range of choice available to the diabetics. Their use has both pro and cons, therefore its use must be decided by the physician depending upon clinical profile of the patient. Judicious use of artificial sweeteners can thus help patients to lead a healthy and prosperous life without compromising with taste.

key words: *nonnutritive sweeteners, diabetes mellitus, calorie intake, obesity.*

Background and Aims

Every human being is born with a preference for sweet taste that remains throughout the life. Our palate yearn for ice-cream, our mouth waters at the image of glazed donuts, our dried throats lust for cold drinks, while visions of sugar plums dance in our mind. An average human being consumes about 120 gm of sugar per day to fulfill his cravings. Sugar rich diet plays a major contributing role in the increased prevalence of obesity, diabetes mellitus, ischemic heart disease, hypertension and certain cancers [1]. Therefore increased obesity related mortality has resulted in a surge of weight loss diets and products including Nonnutritive sweeteners (NNS). NNS are food supplements that mimic the taste of sugar with fewer calories. Consumption of NNS containing foods has increased among people of all ages, with 28% of the total population reporting their intake. In comparison to sucrose, NNS are at least 30 to 13,000 times sweeter to taste [2].

In the modern era, there has been a rising incidence and prevalence of diabetes which is globally devitalizing. Apart from being known as the diabetes capital of the world, India is also emerging to be the capital of obesity and heart diseases. India has a greater number of prediabetes subjects (nearly 77 million in number) as compared to 65 million diabetics. In around 15 to 20 years, it is estimated that this number will increase to a gigantic 100 million plus confirmed diabetics [3]. In the present scenario, diabetes is affecting more and more children and younger population because of

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lifestyles changes, physical inactivity, and consumption of junk food and increasing obesity. A matter of concern with diabetic patients is that they require sweeter food to appreciate the same taste as non-diabetics, therefore increasing the threshold level of sweeteners to 50 %.

With growing awareness of the link between diet and obesity, consumer concern over sugar levels in the diet is forcing a worldwide trend towards cutting down on sugar intake. The shift away from sugar is still years away but a trend towards low calorie sweeteners is occurring. The world is turning to artificial sweeteners and substitutes. The market for sugar substitutes is being fuelled globally by new age safer sweeteners. Replacing sugar with low calorie sweeteners not only helps diabetics plan their meals more flexibly by enhancing the pleasure of eating but also checks the calorie intake. These sugar substitutes have been classified into several categories.

NNS can be either natural or artificial. Natural sugar substitutes and sugar alcohols occur naturally in fruits and vegetables and can be manufactured industrially. They are not considered intense sweeteners as they are less sweet than sugar. Some important natural sweeteners include Brazzein, Erythritol, Curculin, Lactitol, Maltitol, Glycerol, Glycyrrhizin, Mannitol, Sorbitol, Xylitol, Stevia, Tegatose and Trehalose. Artificial sweeteners are sweeteners that do not occur naturally. These sugar substitutes provide sweetness without the addition of calories. Artificial sweeteners can be consumed safely up to the Acceptable Daily Intake (ADI) in the general population. NNS are alternatives for individuals who want to control their calorie intake and do not want to gain weight. Artificial sweeteners are regulated by U.S. Food and Drug Administration (FDA) as food additives. They must be approved by the FDA, which publishes a Generally Recognized as Safe (GRAS) list of additives. NNS available in the market has certain pros and cons, which makes it necessary for a physician to have knowledge before prescribing or advising them.

In the following paragraphs we are describing in detail the major NNSs available in the market.

Aspartame

Aspartame is a non saccharide artificial sugar substitute, first synthesized in 1965 and codified as E951 in the European Union. It is the most extensively scrutinized food supplement available in the market. 50 mg/kg body weight is the acceptable daily intake of aspartame as recommended by the FDA. It is a methyl ester of the dipeptide of the natural amino acids L-aspartic acid and L-phenylalanine. However it cannot be called a true “non-caloric” sweetener because it is absorbed and metabolised after being broken down in the gut. Aspartame disintegrates into aspartic acid, phenylalanine and methanol, which are responsible for providing 4 calories per gram of aspartame. But aspartame provides negligible calories because it is about 200 times sweeter than natural sugar; therefore very minimal amount is required to produce a sweet taste [4]. It is often mingled with other artificial sweeteners like acesulfame to provide a similar taste as with natural sugar. Aspartame is unappealing as a baking sweetener because it is unsuitable at high temp and high pH due to its hydrolysis into its constituents. However its stability can be improved by enclosing it in maltodextrin or fats. It has a half-life of around 300 days at room temperature and *p*H 4.3 but it is very unstable at *p*H 7, with a half-life of only a few days [5]. Therefore aspartame is used as an artificial sweetener in soft drinks as they have a pH ranging from 3 to 5 where aspartame is stable.

As with any other food additive, aspartame is also linked with some adverse effects. In North America, a large number of people (around 70 million people) consume aspartame frequently, but the reported side effects are minimal, averaging to around few hundred annually [4]. More than half of the complaints are nonspecific like headaches, vertigo, and mood swings [6]. Consumers may also experience gastro-intestinal side effects and hypersensitivity in the form of urticaria and rashes. Seizure is a very rare adverse effect. Side effects usually occur only when intake exceeds recommended dose. Aspartame disintegrates into a compound Diketopiperazine which may be accountable for these adverse effects [7].

Aspartame decomposes into phenylalanine, aspartic acid and methanol on ingestion. Formaldehyde and formic acid are formed from the disintegration of methanol and are really toxic at excessive doses. Aspartame is contradicted in patients with phenylketonuria because they cannot metabolise phenylalanine and therefore products containing aspartame should carry a warning [8].

A study published in 1996 claimed a 10% increase in brain tumors with increased use of aspartame in the 1980s [9]. This was a misconception because increased incidence of brain tumours occurred in early 1980s before the introduction of aspartame. Moreover, aspartame intake during pregnancy and lactation was not found to increase risk for brain tumors among children [10].

The U.S. Food and Drug Administration (FDA) approved aspartame in 1974 and since then it has been a part of several health related rumors and controversies. FDA narrates this NNS as "one of the most thoroughly tested and studied food additives the agency has ever approved" and has a clear cut safety. Finally in the year 1987, the U.S. Government Accountability Office stated the food additive approval procedure has been carried properly for aspartame. Since then, it is being used for human consumption worldwide in more than 90 nations and is found safe. Prevailing evidences indicate that, at recommended doses, aspartame is safe to use as a non nutritive sweetener. It is now being widely used all over the world and is even slowly taking the place of saccharin in the Indian subcontinent.

Sucralose

Sucralose is a nonnutritive sweetener, also known by the name of E955 in Europe and first sold under the name of Splenda. It's absorption by human body is minimal and therefore passes out of the body in its original form. Sucralose is approximately 3.3 times sweeter than aspartame, twice as sweet as saccharin and 600 times sweeter than table sugar. It can be used as an additive in products requiring a longer shelf life because of its stability under extreme temperatures and over a wide range of *p*H [11]. It is used as a food additive in consumable products such as chocolates and soft drinks. Sucralose is labeled as a zero calorie sweetener because any product providing less than 5 calories is defined as 'zero calorie' by FDA. Although sucralose is a zero calorie sweetener, additives such as dextrose or maltodextrin provide approximately 2-4 calories per teaspoon. It is being extensively used in a variety of populations including pregnant and nursing females because of an excellent safety profile.

In 1976 Sucralose was brought to light in Queen Elizabeth College by Leslie Hough and Shashikant Phadnis. Tate & Lyle patented the substance in 1976 and Canada became to the first country to give approval for its use in 1991 [12]. It is accepted in over 80 countries, including India, China, Mexico, Brazil and Japan. In 2006 an amendment was made in USA

in the regulations for foods by FDA to incorporate sucralose as a nonnutritive sweetener in consumable items. It has various advantages for diabetics as it is safe for use, do not alter insulin levels and also do not promote dental cavities [13].

The absorption of sucralose is very low (around only 11-27%) leading to an increased fraction being directly expelled with stools. Only 20-30% of absorbed sucralose is metabolized and a large fraction is excreted in urine by the kidneys. Therefore every bit of ingested sucralose can be retrieved from the excreta. However it is biodegradable and creates no environmental menace [14].

Sucralose has become a commercial victory because in comparison to other low calorie sweeteners, it is better in terms of taste, safety and stability. Its use has a large margin of safety because there is a large difference between estimated daily intake (EDI) as compared to highest no adverse effects limit (HNEL) [15].

Saccharin

Saccharin, the oldest artificial sweetener, is available on the market for more than a century. In the European Union it is known as E954. Benzoic sulfilimine is the basic constituent of saccharin which is sweeter as compared to sucrose and gives no calories. The sodium salt of saccharin is used as an artificial sweetener and is around 300 times sweeter as compared to simple sugar. It is a true "non-caloric" food additive because it is resistant to degradation and therefore excreted by the body intact. Unpalatable aftertaste adds a disadvantage, but it can be curtailed by adding a minimal amount of supplements like amino acid glycine and cyclamate. Saccharin is very effective in diabetic population because it does not get absorbed and digested in the gastrointestinal tract, thus not affect insulin levels [16]. It is commonly used in chocolates, bakery items, deserts, fruit jams and soft drinks, in addition to being used as a tabletop sweetener. It also is used in other household products such as toothpaste, lip gloss, mouthwash, vitamins, and pharmaceuticals. It is an excellent candidate as an additive in low-calorie and sugar-free products because of its stability over a wide range of temperatures. Five mg per kg body weight per day is the recommended Adequate Dietary Intake (ADI) for adults and children [17]. Intake of foods containing saccharin is high in India, as it is the cheapest and most widely used NNS product.

A chemist named Constantin Fahlberg, first produced saccharin in Johns Hopkins University in 1878, working on coal tar derivatives. But it was during the 1960s and 1970s it gained popularity as a non calorie sweetener. In 1972, saccharin was removed from the GRAS list in the United States because of its likely association with bladder carcinoma in rats as shown by experiments. However, scientists later discovered that rodents, unlike humans, have specific proteins in their urine , which combine with saccharin and calcium phosphate to produce micro crystals, thus damaging the epithelial lining of the urinary bladder and increasing the risk for bladder cancer [18]. Therefore in the year 2000, warning labels were removed from saccharin. A study in Italy examined the association between saccharin and other NNS with gastric, pancreatic, and endometrial cancers between 1991 and 2004 and concluded that consumption of NNS products such as saccharin and aspartame are not related with the risk for cancer in the human population [19].

The analyses of the U.S. Department of Health and Human Services National Toxicology Program had led to removal of saccharin from its list of carcinogens in 2000. Later, the U.S. FDA and the state of California changed their stand on saccharin, certifying its

safety for human consumption. The U.S. Environmental Protection Agency (EPA) has officially withdrawn saccharin and its salts from the list of unsafe constituents and edible products. In the present scenario, saccharin is permitted to be used in most nations including the Indian subcontinent and other countries like Canada also are thinking of lifting their previous ban on it as an artificial sweetener

Cyclamates

Cyclamates include three similar compounds, namely sodium cyclamate, calcium cyclamate, and cyclamic acid and are about 30 times sweeter than natural sugar. Cyclamates are often used together with other NNS because of their low potency among artificial sweeteners available in the market. Their main advantages include chemical stability and a lower cost than saccharin or aspartame. Although most of cyclamate dose is eliminated unchanged by the body, some is converted to a compound known as cyclohexylamine, whose safety has been doubtful. In the year 1958, cyclamates were given a “Generally Recognized as Safe” (GRAS) status in the United States. However, the FDA prohibited its use in the U.S in 1969, with citation of the Delaney Amendment because of its link with bladder carcinoma in rats [20]. In United Kingdom, however, it was accepted for use in the same year and is now being used in cheaper sweetener consumable goods. Its metabolic product cyclohexylamine can be a causative agent for testicular atrophy in rats at large doses, but this problem has not been encountered in humans. The Health Protection Branch in Canada has approved cyclamate as a tabletop sweetener. Overall 55 countries including Canada have given approval for its use. However it is still prohibited for use in India and USA. The U.S. ban on cyclamates is still in effect, but may be withdrawn because FDA has concluded that neither cyclamates nor cyclohexylamine are carcinogens by reviewing a large number of studies on animals [20].

Stevia

Stevia is a nonnutritive natural sweetener extensively used by the people of Paraguay for centuries and is being used for use for over 400 years across the globe. A Spanish botanist and physician named Petrus Jacobus Stevus first explored this NNS and therefore the word Latin stevia comes from his surname. It is a genus of around 240 species of shrubs and herbs in the Asteraceae family [21]. In the present, it is grown and consumed in many parts of the world including East Asian countries (Thailand, Japan, Korea, Taiwan, China, Malaysia), Israel, South America and Philippines. China is the world's largest exporter of stevioside. In India it is cultivated as Madhu pattha or Madhu patra. The Guaraní peoples of Paraguay used stevia to treat heartburn and other ailments. Two major compounds (Rebaudioside and Stevioside) are chiefly accountable for its sweet taste. Stevia has advantages in terms of being heat and pH stable, non-fermentable, has a negligible effect on blood glucose and is around 150 times sweeter than natural sugar [22]. It is beneficial as a food additive for diabetic population because of its added benefit in reactivating insulin secreting pancreatic beta cells, thus boosting glucose tolerance [23]. It also has a role in reduction of tooth decay, therefore can act as a substitute for sugar in tooth pastes.

The U.S. FDA banned stevia in 1991 and marked it as an "unsafe food additive" after receiving a complaint from an incognito industry. However, the 1994 Dietary Supplement Health and Education Act forced the FDA to change its decision to allow stevia to be consumed as a dietary supplement, although not as a food additive. In 2006, the World Health

Organization (WHO) executed a comprehensive assessment of experimental data available with stevia and came on a conclusion that it is not genotoxic in vitro or in vivo. No proof of carcinogenic potential was found with stevia in this report [24]. World Organization Expert Committee on Food Additives very recently gave approval to stevia to be used as sweetener.

Xylitol

Xylitol is a naturally occurring sugar alcohol, providing only around 70-80% energy as compared with sugar. It is comparable to sugar in sweetness and is widely used as a non-nutritive sweetener. Absolutely pure Xylitol is a white, crystalline carbohydrate that occurs naturally in fruits and fibre rich vegetables and as well as in many hardwood trees like corn, oats, husks, and mushrooms. The human body also produces xylitol during normal metabolic process.

Although being recognized in 1891 by the German chemist Emil Fischer, xylitol was almost unacknowledged until World War II. In Finland due to sugar scarcity, the countrymen started using xylitol and concluded that people using xylitol had better health as compared to those who did not used it [25].

Metabolic effects of lactitol and xylitol were compared with those of glucose intake on plasma insulin, glycemia and C-peptide in a recent study. They found that upon ingestion of lactitol or xylitol, plasma insulin, glucose and C-peptide concentrations do not change as compared with ingestion of glucose [26]. More than 35 countries have given an approval for its use. It is used as an additive in consumable items, medicines and oral hygiene products such as toothpaste, mouthwashes and fluoride tablets. It is marketed as "safe for diabetics" and has practically no aftertaste, Xylitol has well established beneficial effects on oral health. It has a well-studied role in preventing demineralization of tooth enamel, retardation of progression of plaques & dental cavities, increasing saliva production and protecting salivary proteins [27]. Xylitol use can lead to improvement of breath odour and reduction of oral and nasopharyngeal infections and may also prevent osteoporosis [28].

Xylitol has a low glycemic index and is not completely absorbed. It is flawless in maintaining adequate levels of insulin in blood because of insulin independent metabolism [29]. It slows down stomach emptying and the unabsorbed fraction acts just like fibers, thus maintaining healthy intestinal function. All these contribute to weight loss. Therefore all these added advantages, lead to increased consideration of sugar alcohols to be used in food items especially made for diabetics and people on energy restricted diets.

Newer NNSs

Alitame, neotame are other newer nonnutritive sweeteners which are structurally similar to aspartame. Alitame is 2000 times as sweet as sucrose [30] while neotame is approximately 7000 to 13000 times sweeter. They are awaiting approval from FDA and presently not available in India.

Discussion

In the prevailing modern area, nonnutritive sweeteners have an important role. They lead to weight reduction and improved oral hygiene with the added advantage of providing a wide variety of food for diabetics. Diabetic population is on a drawback with diminished perception of sweet taste and they have increased threshold level for sweeteners as compared to other people. Therefore, a diabetic requires sweeter food to appreciate same taste as compared to non diabetic. NNS are a great option for diabetics to enjoy the taste food restricted from them.

However, consumption of artificial sweeteners may impair the body's ability to count its caloric intake based on the sweetness profile of food. So persons using these NNS may end up with eating much more than required and may increase their obesity risk [31].

A major issue is with the safety profile of NNS; especially in susceptible populations because of their potential harmful effects in children, pregnant women, breastfeeding mothers, individuals with low seizure thresholds, and individuals at risk for migraines. Another serious issue is that consumers often do not have adequate information. When used in moderation within the maximum daily intake, these NNS are safe for consumers. However consumers must also make a conscious effort to monitor their daily intake. While many skeptics & media hype continue to claim that NNS are a cause of obesity, cancers or behaviour disorders, various studies have concluded that there is no valid proof and experimental studies to relate them with NNS. The Academy of Nutrition and Dietetics recommends using artificial sweeteners in moderation, in conjunction with a healthy diet based on the recommendations provided in the Dietary Guidelines for Americans [8].

Conclusion

In conclusion, the choice and amount of sweetener to be used should depend on the clinical profile of the individual thus outweighing the benefits against the risks and thus leading to a healthy life.

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