

Pharmacotherapy of nonnutritive sweeteners in diabetes mellitus

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Introduction

Diabetes mellitus (DM) is the most common metabolic disorder and it is estimated that 300 million will subsequently have the disease by 2025¹⁻³ It is characterized by hyperglycemia as a result of insulin shortages, insufficient insulin action (resistance), or both.⁴⁻⁷ Insulin resistance increases the risk of type 2 diabetes.^{8,9} One characteristic that can be associated with insulin resistance is hyperinsulinemia that may result in deterioration of β -cell function, which is involved in the pathogenic process of diabetes.¹⁰ Insulinopenia, which occurs in type 1 diabetes (T1DM), is associated with decreased bone density and a state of low bone turnover.^{11,12} Insulin deficiency in turn leads to chronic hyperglycaemia (i.e. increased levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism.⁴⁻⁷ As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy,¹³⁻¹⁴ neuropathy,^{15,16} nephropathy,^{17,18} cardiovascular complications^{19,20} and foot ulceration.^{21,22} Thus, diabetes covers a wide range of heterogeneous diseases.

Symptoms

Symptoms are similar in both types of diabetes but develop more rapidly in type 1 diabetes and are most typical. The symptoms, as mentioned earlier, include polyuria, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis.⁴

Symptoms in type 2 DM are similar but insidious in onset. Most cases are diagnosed because of complications or incidentally. Most patients with type 2 diabetes die from cardiovascular complications and end-stage renal disease.¹⁷⁻²⁰ Geographical differences exist in both the magnitude of these problems and their relative contributions to overall

morbidity and mortality.^{23,24}

Prevention

A study showed improvement in carbohydrate and lipid metabolism in patients with type 2 DM who reverted to a traditional lifestyle.²⁵ Diet and exercise either alone or together reduced the progression of the disease by 40% after 6 years.²⁶ Similar studies done in Sweden also demonstrate the effectiveness of life-style changes in preventing diabetes.²⁷ A decade earlier, the Finnish Diabetes Prevention Study showed that lifestyle intervention reduced by 58% the risk of subjects with impaired glucose tolerance (IGT) progressing to type 2 diabetes.²⁸

Pharmacotherapy

It goes without saying that the aim of the treatment is primarily to save life and alleviate symptoms. Despite advances in preventive and treatment strategies, there has been an increase in cardiovascular risk factors, obesity, and renal diseases and therefore our secondary aim is to prevent long-term diabetic complications and thus increase longevity. The first aim is not difficult to attain.²⁹ In the previous review,³⁰ the concentration was on treatment prevalent at the time which included insulin and lifestyle modifications which were considered the cornerstone for the treatment and management of type 2 DM. Life style management includes diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones.⁴ The oral hypoglycaemic agents should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes.³¹ Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological). The emphasis in this review is to concentrate on the nonnutritive sweeteners in diabetes DM.

Sugars and sweeteners

Nonnutritive sweeteners are intensely sweet and very little quantities are required to make food and drinks palatable

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(they including saccharin, aspartame, cyclamate, acesulphame-K). They provide a useful means of reducing energy intake. Studies have also shown that under certain circumstances, mono- and disaccharides do not deteriorate glycaemic control or elevate lipid levels.³² Examples of such sweeteners are naturally occurring fructose and sorbitol which has been widely recommended for diabetics in the past [For further information on their use and side effects see reference 30 and 43].³³ It has been recommended that sucrose plus other added sugars provide no more than 10% of total energy requirement. This amount was further modified by WHO which suggests that total sugars should provide less than 10% of total energy. New sweeteners on the market include sucralose (Splenda) and stevia which will be discussed in more detail.

Saccharin

Saccharin was the first artificial sweetener to be introduced in the market. It was synthesized in 1879 by Remsen and Fahlberg. It had low production costs than regular sugar and was well accepted during World Wars I and II.³⁴ Saccharin is 200 to 700 times sweeter than sugar and has no calories. Brand names include 'Sweet'N Low, Sweet Twin, and Necta Sweet. It is used in tabletop sweeteners, baked goods, soft drinks, jams, and chewing gums.

It had been generally recognized as safe (GRAS) until 1972, when it was removed from the GRAS list by the FDA. In 1977, the FDA proposed a ban on saccharin because of concern about rats that developed bladder cancer after receiving high doses of saccharin.^{35,36} Also food containing saccharin were required to carry a label warning that the sweetener could be a health hazard and that it was found to cause bladder cancer in laboratory animals. Most of the studies were carried out on 'one generation' studies but 'two generation' studies were conducted feeding the parent (F₀) and the following generation (F₁) with saccharin. In these studies, an increased risk for bladder cancer were consistently proven for the F₁ generation.³⁷ Male rats developed bladder tumors in up to 30% of all animals at a dose of 7.5% saccharin of their diet. In later trials, with larger number of F₁ generation rats, it was found that the risk of bladder cancer increases with a saccharin concentration of 4%.³⁸ This led to Canada prohibiting saccharin to be sold in Canada. However, according to the National Cancer Institute, further studies showed that saccharin did not cause cancer in humans, and that the bladder tumors in rats were related to a mechanism that is not relevant in humans. In 2000, the national Toxicology Program determined that saccharin should no longer be listed as a potential cancer-causing agent. In 2001, Federal legislation removed the requirements for the saccharin warning label. The conclusion that can be drawn from the studies is that saccharin induces bladder cancer in rats, when fed in high doses. Artificial sweeteners in high doses (>1680 mg/day), leads to an increased relative risk of 1.3 for bladder cancer in humans. The problem is that, a more precise determination of the exact agents is not possible, because many artificial sweeteners are combined in current food products.

Sucralose

Sucralose (Splenda) is an artificial sweetener that is not broken down by the body and therefore is non-caloric.^{39,40} In the European Union, it is also known under the E number (additive code) E955. It was discovered and patented in 1976 by scientist from Tate & Lyle, working with researchers Leslie Hough and Shashikant Phadnis at Queen Elizabeth College (now part of King's College London).⁴¹ Sucralose is approximately 600 times sweeter than sucrose (table sugar), twice as sweet as saccharin, and 3 times as sweet as aspartame.⁴² Sucralose is stable under heat and a broad range of pH conditions, which allows it to be used as a sweetening agent in a wide variety of foods.⁴³ Studies have shown that fasting glucose levels did not change in type 2 diabetes patients administered sucralose over 13 weeks,⁴⁴ suggesting that it can be used to increase dietary compliance and increase food palatability without altering long-term glucose homeostasis. It was first approved in Canada in 1991, and subsequently it was approved in Australia in 1993, New Zealand in 1996, United States in 1998 and the European Union in 2004. By 2008, it had been approved in over 80 countries, including Mexico, Brazil, China and Japan.⁴⁵ Sucralose can be found in more than 4,500 food and beverage products. It is used because it is a no-calorie sweetener, and does not cause dental cavities,⁴⁰ is safe for consumption by diabetics,^{44,46} and does not affect insulin levels.⁴⁷ According to the Canadian Diabetes Association, the amount of sucralose that can be consumed on a daily basis over a person's lifetime without any adverse effects is 9 mg/kg/day.^{48,49}

Toxicity data in over 100 animal and clinical studies unanimously indicated a lack of risk associated with sucralose intake.⁵⁰⁻⁵² However, some adverse effects were seen at doses significantly higher than the estimated daily intake (EDI), which is 1.1 mg/kg/day.⁵³ Adverse effects are seen at 1500 mg/kg/day which is known as the highest no adverse effects limit (HNEL).⁵³ There is a large margin of safety. Most of the ingested sucralose is not absorbed by the gastrointestinal (GI) tract and is excreted directly into the faeces, while 11-27% of it is absorbed.⁴¹ The absorbed sucralose is largely removed from the blood stream by the kidneys and eliminated in the urine, with 20-30% of the absorbed sucralose being metabolized.⁴¹ The eliminated urine is broken down by microorganisms in the environment albeit slowly and wastewater treatment has little effect on sucralose which is present at levels of several µg/l.^{54,55} The Swedish Environment Protection Agency warns there may be a continuous increase in levels if the compound is slowly degraded in nature.⁵¹ Sucralose has been observed to trigger migraine attack and long-term consumption in rats have resulted in weight gain.⁵⁶⁻⁵⁹

Stevia

Stevia is a genus of species of herbs and shrubs in the sunflower family (Asteraceae), native to South America, Central America and Mexico, with several species found as far north as Arizona, New Mexico and Texas.⁶⁰⁻⁶² They were first researched by Spanish botanist and physician Petrus Jacobus Stevus (Pedro Jaime Esteve),⁶³ from whom

the surname *stevia* originated.⁶⁴ The leaves of the stevia plant have 30-45 times the sweetness of sucrose.⁶⁵ The leaves can be eaten fresh, or put into teas and foods. The Guarani people have used the plant for more than 1500 years and the plant has a long history of medicinal use in Paraguay and Brazil, where it is known as stevia or honey leaf, Kaa-he-e.^{66,67} The sweet taste of the plant was first described by a Swiss botanist in 1899 in eastern Paraguay⁶⁸ and it was not until 1931 that two French chemists isolated the glycosides that give stevia its sweet taste.⁶⁹ These compounds were named Stevioside and rebaudioside (rebaudioside A, B, C, D, E) and are 250-450 times as sweet as sucrose, heat stable, pH stable and non-fermentable.⁷⁰⁻⁷³ Because of its sweetness, stevia has been grown commercially as a natural sweetener in many countries including Brazil, Paraguay, Japan, China, Korea, Malaysia, Taiwan, United States, Canada and parts of Europe.⁷⁴

Stevioside is considered to be a sugar substitute, both in the form of stevioside and stevia extract.^{75,76} They are used in variety of foods and products, such as pickled vegetables, dried seafood, soy sauce, beverages, candies, chewing gum, yogurt and ice cream, as well as in toothpaste and mouth wash. Stevia extract and stevioside are officially approved as food additives in Brazil, Korea and Japan^{64,77} and in the United States, they are permitted as a dietary supplement. The European Commission have not as yet approved stevia extract and stevioside to be used as food additives but in 2006, the meeting of the joint FAO/WHO Expert Committee on Food Additives (JECFA) announced a temporary accepted daily intake (ADI) of stevioside of up to 5.0 mg/kg body weight (BW).⁷⁸ Despite being a low calorie sweetener and dietary supplement for food^{60,72,75}, stevioside is used for treating hypertension and hyperglycaemia.^{79,80} Stevioside and related compounds are also reported to possess antitumor activity.⁸¹ Steviol glycosides do not induce a glycaemic response when ingested, making them attractive as natural zero-calorie or low calorie sweeteners to diabetics and others on carbohydrate-controlled diets. The presence of high concentration of stevioside and other glycosides in the leaves extracts, *S. rebaudiana* has been traditionally used in the treatment of diabetes. Jeppesen *et al*⁸² reported the antihyperglycaemic, insulinotropic and glucogonostatic effects of stevioside in type 2 diabetic Gotokakizaki (GK) rats as well as in normal rats. Stevioside was found to suppress significantly the glucose response and concomitantly increase the insulin response and thus may have the potential of becoming a new antidiabetic drug for use in type 2 diabetes.⁷⁷ In studies done on two model of diabetes in rats, i.e. STZ-induced diabetes rats and NIDDM induced by feeding fructose to rats, it was found that stevioside lowered blood glucose levels in both the models tested.⁸³ Toxicological studies have shown that stevioside does not appear to be mutagenic.^{84,85} However, from various mutagenic assays the genotoxic potential of steviol remains inconclusive.⁸⁶⁻⁸⁸

Tagatose

Tagatose, a naturally occurring hexose, was found to have an antidiabetic property in animal feeding study⁸⁹ followed up with human studies which confirmed its promise as a

potential treatment for type 2 diabetes and obesity.⁹⁰⁻⁹² It occurs naturally in small amounts in dairy products.^{93,94} Tagatose was originally developed as a sugar substitute for calorie and weight control and has 1.5 kcal/g compared with table sugar's 4 kcal/g.⁹⁵ In the US it qualified as generally recognized as safe (GRAS) for use in foods under the FDA-regulated program.⁹⁶ Tagatose is branded 'Naturlose®' for medical and health application. Tagatose was authorized to be used in foods by the Korean Food and Drugs Administration on the 23rd of July 2003⁹⁷ and by the Standards Australia New Zealand on the 21st of February 2004.⁹⁸ On December 14, 2005, tagatose was formally approved as a 'novel food ingredient' in the European Union (EU) without any restrictions on usages.⁹⁹

Tagatose was observed to produce low glycaemic and insulin responses, only 3% of that was ascribed to glucose.¹⁰⁰ Short-term clinical trials have shown that pre-administration of tagatose blunts the rise in blood glucose and insulin otherwise observed after glucose or sucrose loading in both healthy and diabetic subjects^{101,102} and the inhibition of postprandial glucose was seen even when tagatose was administered 4 h and 15 min before lunch in healthy subjects.¹⁰³ Further studies showed that the daily intake of tagatose by type 2 diabetics resulted in a decline of glycosylated haemoglobin (GlyHb) in both short-term and long-term trials.^{90,91} The only questionable drawback to tagatose compared with other oral antidiabetic agents (OAs), is that it has to be given in a large dose. Tagatose might be administered in doses up to as much as 15 g tid, much larger than a pill of regular OA. However, this can be resolved by putting tagatose on cereals, in juice, other foods, mints, or candy bars.¹⁰⁴

Toxicity studies demonstrated that tagatose is not genotoxic.¹⁰⁵ In sub-chronic toxicity test conducted on male and female (20/sex/group) of CrI:CDBR rats, only transient soft stools were observed from the higher dose groups.¹⁰⁶ This was attributed to incomplete absorption of tagatose. Tagatose has no effect on the liver enzyme levels (ALT, AST, GGT and ALP).¹⁰⁶ Embryotoxicity and teratogenicity studies conducted in CrI:CDBR rats showed no maternal toxicity, embryotoxicity or teratogenicity.¹⁰⁷ Finally, in clinical trials, tagatose has shown strong evidence for the control of HbA1C, postprandial hyperglycaemia and hyperinsulinemia, while also reducing weight at a medically desirable rate. Added benefits include increased HDL levels, enhanced butyrate production (to combat colon cancer), antioxidant and prebiotic properties. Tagatose has been declared GRAS under FDA food ingredient rules, and has been widely consumed in food products as a sweetener for many years with no toxic events being reported.

Advantame

Advantame is a novel sweetener that is 116 times sweeter than aspartame and 20,000 times sweeter than sucrose.^{108,109} Another study has demonstrated advantame to be 37,000 times sweeter than sucrose.¹¹⁰ Due to its intense sweetness, advantame can be used in much smaller amounts than other currently marketed sweeteners and its calorific contribution is insignificant.^{108,109} It is an N-substituted (aspartic acid

portion) derivative of aspartame that is similar in structure to neotame, another N-substituted aspartame.¹¹⁰ It has been used as a sweetener in coffee, iced tea, powdered beverage formulations, and as a flavor enhancer in beverages, chewing gum and yoghurt. It is stable compound even at high temperatures and finds use in a broad range of food and beverage applications, including low-pH products. It is a suitable sweetener alternative for diabetics as it was shown not to affect glucose homeostasis. Advantame offers an alternative to the already approved sweeteners in the market. In the US population the mean intake of advantame is estimated to be between 1.2 mg/person/day or 21 µg/kg body weight/day. In the high consumer US population, the mean intake was estimated to be 3 mg/person/day or 46 µg/kg body weight/day. Advantame is rapidly absorbed, but only to a limited extent, in the range of 4-23%. Absorption is mainly as ANS9801-acid, which is a de-esterified advantame which is formed in the gastrointestinal tract as a result of hydrolysis of the parent compound. It is mainly excreted in the faeces of rats, dogs and humans (> 80% in each case), with urinary excretion representing a minor route. In subchronic and chronic toxicity studies, advantame administered at a concentration of 0, 1500, 5000, 15,000 and 50,000 ppm (corresponding to doses of 0, 118, 415, 1231 and 4227 mg/kg body weight/day in males and 0, 146,481, 1487 and 5109 mg/kg body weight/day in females) to groups of 20 male and 20 female rats for a period of 13 weeks.¹¹⁰ No significant effects were seen on body weight, food consumption, or on food conversion efficiency. No neurotoxicity was observed during the course of testing. The no-observed-adverse-effect level (NOAEL) was concluded to be 50,000 ppm in the diet. Similar results were observed by Warrington et al, 2011.¹⁰⁹ The only clinical signs were light colored faeces that were observed for animals receiving 15,000 and 50,000 ppm which were not apparent by the end of recovery period.

Neotame

Neotame is, chemically, a dipeptide methyl ester of aspartame with a sweetness potency in humans 7000-13,000 times that of sugar. Toxicity studies including carcinogenicity, reproduction, teratogenicity and in utero/postnatal evaluations at doses up to 40,000 times 90th percentile estimated human exposure (FDA 2002)¹⁰⁶ showed that neotame was well tolerated in all species tested including rats, mice, beagle dogs and New Zealand rabbits.¹¹¹⁻¹¹³ Regulatory review of neotame safety studies has been completed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and in Australia, New Zealand and the US and other reviews are still continuing.¹¹¹⁻¹¹³

The only side effects reported were reductions in food consumption (FC), body weight (BW), and body weight gain (BWG) compared to controls at doses requiring high dietary concentrations.¹¹⁴ These were due to poor palatability of neotame-containing diets (more than 35,000 ppm) and were not associated with toxicity in any species tested.¹¹⁴ This is also true for other high intense sweeteners such as sucralose¹¹⁵ and saccharin.^{116,117} The concentration of high-intensity sweeteners, including neotame, used in

animal studies are many 100-1000-fold greater than those intended for human consumption, thus specific qualities of taste and palatability are not relevant to human exposure but critical to study outcomes. It also means that it is safe to use neotame in humans within the amount used in the diets which is small.

Aspartame

Newborns have a preference for Sweet-tasting foods¹¹⁸ Studies have proved that and the fondness for sweet foods is inborn.¹¹⁸ Honey was the first recorded sweetener, which was used in ancient cultures of Greece and China.¹¹⁹ It was later replaced with saccharose, common sugar, which was originally obtained from sugar cane. Sugar beets were the major source of saccharose during the world wars and the first artificial sweetener was saccharin, which was synthesized in 1979 by Remsen and Fahlberg. The sweetener was well accepted during World War I and II because of its low production costs and the shortcomings of regular sugar.³⁴ In 1981, aspartame was introduced into the market as 'Nutrasweet' and for the first time, dairy products such as yoghurts were calorie-reduced and were sold as 'diet' or 'light'.¹¹⁹ The first three substances, saccharin, cyclamate and aspartame, are referred to as 'first generation sweeteners' which was followed by new generation or second generation sweeteners such as acesulphame-K, sucralose, alitame and neotame, which have quite a different key market areas. However, even the second generation sweeteners have similar limitations to the older ones. The taste is often accompanied by a bitter and metallic aftertaste and does not provide a 'realistic' and 'voluminous' mouth-feel of regular sugar. The quality of sweetened products has increased with the combination of many artificial sweeteners.

Initial studies in animal carried out in 1984 showed that aspartame did not have any cancer-inducing effects, even in very high doses.^{120,121} but 15 years after its approval, questions arose as to its cancer causing abilities.¹²² This received tremendous attention from the mass media, as well as the scientific communities. The authors hypothesized that the increasing brain tumours in humans since the 1980s could possibly be due to the introduction of aspartame. They supported their hypothesis with an FDA trial in 320 Sprague-Dawley rats fed with aspartame for 2 years, 12 of which developed brain tumours.¹²³ This could not be confirmed by later trials.¹²⁴ In a case-controlled study on aspartame consumption in children with brain tumours, no elevation in brain tumor risk to the child was observed from maternal consumption of aspartame during pregnancy nor during any trimester of pregnancy nor during breast feeding.¹²⁵ Owing to the existing studies, the following statements can be made about the carcinogenic potential of artificial sweeteners. Heavy artificial sweeteners use (>1680 mg per day) leads to an increased relative risk of 1.3 for bladder cancer in humans. Despite unscientific articles in the mass media and scientific press, there is no evidence that the aspartame bears a carcinogenic risk.

Alitame

Alitame is an artificial sweetener developed by Pfizer in

the early 1980s and currently marketed in some countries under the brand name Aclame.¹²⁶ Like aspartame, alitame is an aspartic acid-containing dipeptide. Most dipeptides are not sweet, but the unexpected discovery of aspartame in 1965 led to a search for similar compounds that shared its sweetness. Alitame is one such second-generation dipeptide sweetener.

Alitame has several distinct advantages over aspartame. It is about 2000 times sweeter than sucrose, about 10 times sweeter than aspartame, and has no aftertaste. Its half-life under hot or acidic conditions is about twice as long as aspartame's, although some other artificial sweeteners, including saccharin and acesulfame potassium, are more stable. Unlike aspartame, alitame does not contain phenylalanine, and can therefore be used by people with phenylketonuria. Alitame has been approved for use in Mexico, Australia, New Zealand and China and the European Union but does not have FDA approval-meaning it cannot be used in the United States (US). According to the Codex draft General Standard for Food Additives (GSFA), alitame is permitted for use at a maximum level of 40–300 mg/kg in a wide range of foods and beverages, including bakery wares, water-based flavoured drinks, dairy-based drinks, dairy-based desserts, cream, edible ices, jams, confectionery and some dietetic foods [Table 1]. It is permitted for use within good manufacturing practice in table-top sweeteners and in some sugars (brown) and syrups (maple). It is to be used in flour products (including noodles and pasta), some processed fruit and vegetables, custard, jelly, sauces and toppings. In contrast, the Joint Food Standards Code allows its use only in specific bakery wares, not including bread (Australia New Zealand Food Authority, 2002).¹²⁷ Alitame is known to have “a clean, sweet taste”¹²⁷ “From an oral load of alitame, 7–22% is unabsorbed and excreted in the feces. The remainder is hydrolyzed to aspartic acid and alanine amide. The aspartic acid is metabolized normally, and the alanine amide is excreted in the urine as a sulfoxide isomer, sulfone or conjugated with glucuronic acid”.¹²⁷ Essentially, this is telling us that alitame is not hazardous and goes through normal processes in the body, even though it is metabolized to some degree. In Europe it is known as E956. Two-year carcinogenicity studies conducted in CD-1 mice, Long-Evans rats and Sprague-Dawley rats showed neoplastic changes in the following organs: Kidney, liver, pancreas, lung heart, thymus, mesenteric nodes, adrenal cortex, parathyroid, uterus, cervix, brain, Zymbals's glands, skin, bone, abdominal cavity and soft tissues. The no-observed-effect-level (NOEL), based on body weight changes, was 0.3% in the diet, equal to 230 mg.kg/bw/day for males and 250 mg/kg/bw/day for females.^{128,129}

Acesulfame-K

Acesulfame Potassium (K), discovered accidentally in 1967 by Karl Clauss of Hoechst, was approved for use by the FDA as a safe artificial sweetener in July, 1988.¹³⁰ It is a derivative of acetoacetic acid. Acesulfame K is 200 times sweeter than sugar and has zero calories. Brand names include ‘Sunett’ and ‘Sweet One’. ‘Sunett’ is a mixture of acesulfame-K with Splenda. The FDA approved the

sweetener in 1998 for use in beverages.¹³¹ In December 2003, it was approved for general use in foods, but not in meat or poultry. It can be found in baked goods, frozen desserts, candies, beverages, cough drops, and breath mints. Long-term toxicity, carcinogenicity and reproductive toxicity tests on acesulfame-K and also on compounds, traces of which may form after prolonged storage, demonstrated that acesulfame-K is acceptable and safe for all potential consumers of intense sweetness.¹³² More than 30 countries have approved the use of acesulfame-K in food, beverages, cosmetics and pharmaceuticals. Unfortunately, in other studies, several potential problems associated with the use of acesulfame have been raised. They are based largely on animal studies since testing on humans remains limited. The findings showed the following:

Acesulfame-K stimulates insulin secretion in a dose-dependent fashion thereby possibly aggravating reactive hypoglycemia (“low blood sugar attacks”).¹³³ Acesulfame-K apparently produced lung tumors, breast tumors, rare types of tumors of other organs (such as the thymus gland), several forms of leukemia and chronic respiratory disease in several rodent studies, even when less than maximum doses were given.^{134,135} According to the Center for Science in the Public Interest, it was petitioned on August 29, 1988 for a stay of approval by the FDA because of “significant doubt” about its safety. In view of the present significant *in vivo* mammalian genotoxicity data, acesulfame-K should be used with caution.

Cyclamate

Cyclamate (cyclamic acid and its salt) was discovered in 1937 at the University of Illinois following an accidental contamination of a cigarette with a derivative of cyclohexylamine. DuPont patented cyclamate in 1940, and it became available to consumers in 1950. It entered into the US market after its FDA approval in 1951.¹³⁶ Cyclamate provided a better taste than, and in addition, blended well with saccharin. Both substances were mixed together with other additives and sold as ‘sweet’n’low’, which became a huge success in the USA. It was not only used in tablet or liquid form (‘table top sweetener’), but also proved suitable for soft drinks [Table 2]. Consumption of cyclamate increased steadily over time up to 1969, when it was banned in the USA, UK and other countries due to safety concerns related to its carcinogenicity.^{136–138} Cyclamate is converted to a metabolite, cyclohexylamine, which has been reported to be rather toxic.¹³⁹ In experiments carried out in rats and dogs, cyclohexylamine caused testicular atrophy and impairment of spermatogenesis.^{140–142} However, subsequent studies have contradicted the earlier work, and cyclamate continues to be used in many countries.¹⁵⁸ The contradiction to the work of Takayama et al¹⁴³ was that the number of animals tested was small, which was too low to reach any significance or to confirm a negative result.¹⁴⁴ There are no descriptive or case-controlled studies of cyclamate in humans, because it was approved after saccharin, and products contained mixtures of both artificial sweeteners and on the assumption that most consumers used the

mixture containing saccharin and cyclamate since the introduction of cyclamate. The prevailing opinion today is

Table 1: Theoretical maximum level of alitame estimated by the budget method

Category	Per cent containing alitame	Theoretical maximum level (mg/kg)	Highest maximum permitted level (mg/kg)		
			Australia Zealand	New	General Standards for Food Additives
Solid foods	50	40	60		100
Beverages	50	40	300		300

Joint FAO/WHO expert on committee on food additives (JECFA) acceptable daily intake (ADI) for alitame, 0–1 mg/kg body weight

that neither cyclamate nor cyclohexylamine is likely to be carcinogenic to humans, especially at the levels recommended for diet foods (see Table 2).

Cyclamate is not metabolized by the human body, and thus it is considered a nonnutritive sweetener. In comparison to other sweeteners, cyclamate is perhaps the least sweet, being only 30-80 times as sweet as sucrose in actual food uses. This again depends on upon its concentration, pH, flavouring agents and other ingredients that are part of the food product. Aspartame, by comparison, is about 200 times sweeter than sucrose, whereas saccharin is about 200-700 times sweeter. At high concentration, like other sweeteners, cyclamate has some unpleasant aftertaste.¹¹⁴ At low concentration, cyclamate has some bitter-masking ability which makes it attractive for use in pharmaceutical products. The food and Agricultural Organization/World Health Organization has determined an acceptable daily intake (ADI) value (the maximum amount that could be consumed daily for a lifetime without appreciable risk) for cyclamate to be 11 mg/kg body weight.¹⁴⁵ However in the UK, a temporary maximum ADI of only 1.5 mg/kg body weight has been established until the results of further research are known.

Fructose

Fructose, a ketose (simple sugar), is a monosaccharide, which the body can use for energy. In combination with glucose, an aldose, it forms sucrose, Fructose is found in honey, fruits and table sugar. Sources of dietary fructose

Table 2: Diet food products containing cyclamate levels

Cyclamate levels	Diet food
25 mg/g	Table top sweeteners
0.8 mg/ml	Milk beverages
4 mg/ml prepared drink	Beverages and beverage bases
27 mg/ml	Gelatin, puddings, filling
1.6 mg/ml	Salad dressings
30 mg/ml	Jellies, Jams, preserves
30 mg/ml	Sweet sauces, toppings, syrups
20 mg per stick	Chewing gum
5 mg/g	Hard confectionery

2.6 mg/g Baked good, baking mixes include agave, the richest source of natural fructose, with 85% of carbohydrate in this form; honey with approximately 50% and fruit juices. Apple and pear juice have > 66% fructose; asparagus, raspberries, spinach and watermelon have 56-65% fructose; and most other fruits and nuts have 42-55% fructose.¹⁴⁷ Because it does not cause blood sugar to rise tremendously (has low glycemic index), it was once thought that fructose was a good substitute for sucrose (table sugar). However the American Diabetes Association (ADA) and nutritional experts have questioned its usefulness. Evidence suggests that the rise in consumption of refined sugars high in fructose is one contributing factor to the rise in obesity, insulin resistance, dyslipidaemia and hypertension and high risk for type 2 diabetes and cardiovascular diseases.^{147,148} The genesis and progression of the metabolic syndrome involves deregulation of signaling and metabolic pathways^{149,150} in the liver and the adipose tissue. Studies specifically examining high fructose corn syrup (HFCS) show its level to correlate strongly with the prevalence of obesity and overweight.¹⁵¹ However other studies have shown that overconsumption of fructose, rather than normal consumption, cause dyslipidaemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes.¹⁵² It was observed that you could drink >800 kcal in a soft drink and not think that you've consumed calories...It's the big gulp that is the problem. At very high levels of ingestion, comprising 25% of energy intake, fructose- rather than glucose-sweetened beverages are associated with increased levels of intra-abdominal fat, increased lipids, and decreased insulin sensitivity.¹⁵³ In animal models, the combination of 60% fat and fructose caused obesity, high triglyceride, and glucose intolerance.¹⁵⁴ In another animal models, high glycaemic diets and high consumption of the natural sugar fructose have been shown to induce a number of metabolic complications including hyperinsulinemia, hyperglycemia, hypertension, and insulin resistance.¹⁵⁵ Similarly studies in humans have demonstrated that fructose infusions can induce hepatic insulin resistance.¹⁵⁶ It has been observed that extremely high fructose intake levels are uncommon in nature and that ingestion of fructose in a normal dietary manner does not cause biological changes in triglyceride or body weight

when consumed at levels approaching 95th percentile estimates of intake.¹⁵⁷ This raises the question that the adverse effects observed are due to high-level consumption of any sugar rather than the HFCS.¹⁵⁸ The newly released 2010 dietary guidelines suggest nutrient-dense foods, vegetables, fruits, and high-fiber whole grains, with low levels of solid fats, added sugars, and sodium inferring that diet be integrated in practical terms that will promote personal choices.

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