Nonnutritive Sweeteners, Fructose, and Other Aspects of Diet

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Two symposia at the American Diabetes Association (ADA) 70th Scientific Sessions, held on 25–29 June 2010, in Orlando, Florida, addressed aspects of the food industry's approach to satisfying the desire for sweets. One examined noncaloric/nonnutritive sweeteners and the other fructose, and a number of research presentations addressed other aspects of the relationship between diabetes and nutrition.

NONCALORIC/NONNUTRITIVE SWEETENERS—Beth Hubrich (Atlanta, GA), executive director of the Calorie Control Council, "an international nonprofit association representing the low-calorie food and beverage industry" (1), discussed new noncaloric/nonnutritive sweetener products available for consumers. The Calorie Control National Consumer Survey in 2007 showed that nearly 200 million individuals in the U.S., ~85% of the population, use such sweeteners; of those who do not, 38% do not like the taste and only 8–11% do not use them because of health concerns. The products' major uses are in soft drinks and sugar substitutes, and almost one-half of those using these products report daily use, increasing from 40% in 2000.

Acceptable daily intakes of the currently available such sweeteners, acesulfame potassium, aspartame, neotame, saccharin, steviua, and sucralose, are 15, 50, 18, 12, and 5 mg/kg body wt/day, respectively. These are the maximal amounts considered safe for daily consumption over an individual's lifetime, based on animal toxicology testing, with a 100-fold safety factor (2,3). Such intake would require an average adult, using aspartame as an example, to consume twenty 12-oz diet soft drinks, or 97 packets of sweetener, daily. Actual consumption levels for the 50th, 90th, and 95th percentiles of aspartame are estimated as being at most 4.8, 10.4, and 13.3 mg/kg body wt/day (4). Similar estimates apply to the other available sweeteners, suggesting that even individuals using large amounts of these products do not consume levels exceeding safety margins. Further, individuals using nonnutritive sweeteners tend, Hubrich stated, to have higher intake of fruits and vegetables and lower intake of fat and added sugars so have evidence of a healthier diet. Similar studies have been carried out in individuals with diabetes; those drinking diet soda have lower consumption of high-fat dairy products, processed meat, and refined sugar (5).

Stevia is a new nonnutritive sweetener representing a family of glycosides, in particular rebaudioside A. Used with bulking agents, this is available in products such as PureVia, Stevia in the Raw, and Sun Crystals in packets and in granulated form and in Splenda, a product now available in combination with fiber. Advantame, a sweetener being developed, made from aspartame in combination with vanillin, is 20,000 times sweeter than sucrose. Cyclamate, an older product, is ~30 times sweeter than sucrose, but blending of sweeteners may have synergistic effects, and various combinations using this agent are now being developed. Cyclamate was banned in the 1960s after an animal study suggested carcinogenicity, but a Food and Drug Administration (FDA) ruling in 1984 concluded that actual evidence is lacking that amounts used in man are carcinogenic. Other combination products include aspartame/saccharin, aspartame/acesulfame K, and sucralose/acesulfame K.

Alan M. Rulis, Exponent Scientific Consulting, Inc. (Washington, DC), discussed the development and implementation of legislative and regulatory policy, explaining how safety of nonnutritive sweeteners is determined (6). He was at the FDA for 30 years and from 1995–2004 was Director of the FDA's Office of Food Additive Safety. Rulis reviewed the history of approval of saccharin, developed in 1879 by Remsen and Fahlberg. Harvey Wiley, an early pioneer of food chemistry, food toxicology, and food safety, was the first commissioner of the FDA and thought saccharin to be unsafe, presaging the subsequent political battles over sweeteners in his disagreement with President Theodore Roosevelt about this. In 1958, it was put on the generally regarded as safe (GRAS) list, in 1977 the FDA proposed a ban on the product, the ban was then overridden by Congress, and in 2000 the warning label on saccharin was removed. Rulis explained that the FDA requires as a standard of safety "reasonable certainty of no harm" but specifically does not require "proof beyond any possible doubt that no harm will result under any conceivable circumstance" (7). "Harm to health" assessment requires estimation of probable consumer exposure in the context of relevant animal toxicological safety information. An appropriate safety factor is considered one-tenth that causing harm in animal studies, and to account for differences in human characteristics, this is divided again by one-tenth, leading to one-hundredth of the minimum amount toxic in animals as the amount (on a weight-adjusted basis) considered safe in humans. Against this must be balanced by the Delaney Clause requirement that "no additive shall be deemed to be safe if it is found to induce cancer in man or animal . . . after tests which are appropriate for the evaluation of the safety of food additives" [Amendment to the FD&C Act Sec 409(c) (3) (A)]. (It is interesting to note that direct testing to rule out human toxicity, then, does not seem to actually be required, a major distinction from the approach taken with pharmaceutical products.)

Rulis discussed acesulfame-K, discovered accidentally in 1967 by Karl Clauss of Hoechst. Its proposed use in beverages led to concern that there would be

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high potential intake levels and raised questions related to product stability. The product does hydrolyze to a small extent at low pH and under long-term storage conditions at high temperatures. Because a hydrolysis breakdown product leads to hypertrophy of follicular cells of the thyroid, the question of carcinogenicity was raised. Many other thyroid carcinogens were then studied to ascertain potential toxic dosages, with these doses extrapolated to propose what might be the maximal risk of the acesulfame K metabolite. With this calculation, which, surprisingly, did not itself actually require specific studies with the chemical in question, risk was determined to be extremely low and the product was approved. Sucralose was originally developed by McNeil, filed in May 1987, with final safety judgment and approval in 1997–1999. A rodent study showed what was felt to be excessive weight loss, but multiple additional studies failed to show evidence of this. Another question was raised as to whether sucralose is associated with increased hemoglobin glycation, but additional studies showed no such effect, leading to approval. Again, it is not clear that extensive human studies were carried out. Another path was taken for the stevia glycoside rebaudioside A, approval of which was based on the GRAS exemption, with application beginning in 2008 and FDA response 8 months later. The product was determined to be a "food additive," for which there was no evidence of lack of safety, based on the presence of data in the public domain accepted by qualified scientists. Of course, lack of evidence of harm is not the same as evidence of lack of harm! This logic may not be considered applicable to the development of food standards by the FDA.

France Bellisle (Quebec, Canada) reviewed potential mechanisms of the effects of nonnutritive sweeteners on food intake and appetite. Appetite, she said, may be considered a broad concept associated with the acceptance of foods and the willingness to ingest them, affected by palatability, with sweetness a strong appetite stimulus. Substances that confer sweetness, either sugars or intense sweeteners, might then stimulate food intake under circumstances either of hunger or of eating in response to hedonic stimuli. The enjoyment of sweet taste may be considered a reflex, as has been shown by studies of facial expressions of infants given a drop of sweet, sour, or bitter liquid (8). Another concept is that of satiety, the state of fullness or repletion after food intake inhibiting further consumption until hunger returns. It varies according to total energy load and density and with nutrient content, with protein possibly giving rise to greater satiety than carbohydrate, which in turn may be more satiating than fat. Other factors include food volume and sensory and cognitive factors enhancing or decreasing the intensity or duration of satiety.

Bellisle discussed the question of whether nonnutritive sweeteners may "uncouple sweetness and calories" (9), a notion that has led to the concept that dissociation between sweet taste and calories may disrupt hormonal and neurobehavioral pathways regulating hunger. This implies that nonnutritive sweeteners may not be as satiating as sugar or could actually cause hunger (10), tricking the body into overeating, or may overstimulate taste receptors, creating sweet taste addiction. Such sweeteners could then actually have adverse rather than beneficial effect. Bellisle pointed out that the effect of nonnutritive sweeteners on caloric intake depends greatly on the food, with 100 g of sugar- versus intense sweetener–containing soda having 40 vs. 2 kcal, fruit drink 56 vs. 11 kcal, and low-fat yogurt 75 vs. 44 kcal but chocolate 513 vs. 510 kcal. She reviewed a study comparing nonnutritive with nutritive sweeteners to assess whether the consumer compensates for the reduction in energy consumption, using a preload study design where, after a test substance is ingested, the subsequent hunger and desire to eat were measured. After ingestion of a plain yogurt-like product or after ingestion of the same product with aspartame (300 kcal each), appetite was somewhat reduced with either sucrose or maltodextrins (700 kcal each), suggesting that the development of satiety is an effect of the calories consumed rather than of the sweetness of the ingested food (11).

A particular issue is that sugar-containing drinks may have "low satiety power," therefore adding an important energy load without eliciting adequate dietary compensation (12), although there is an argument against this notion. Bellisle showed studies in which energy from drinks added to calories without triggering compensatory decreases in solid food intake, implying that removing sugar from drinks would not be likely to increase food intake. She reviewed the Su.Vi.Max study, in which she was an investigator, following 1,200 French adults and comparing regular consumers with nonconsumers of nonnutritive sweeteners. The former were heavier but ingested fewer calories and, in particular, less sugar, suggesting that the nonnutritive sweeteners did not enhance appetite overall or for sweet products (13). This finding was corroborated by analysis of individuals consuming diet sodas in the U.S. in the Multiethnic Study of Atherosclerosis (MESA). These individuals were more likely to exercise and less likely to smoke cigarettes, although their body weight and waist circumference were greater than that of individuals consuming sugar-sweetened beverages (5). Similarly, diet soda was not a marker for "unhealthy lifestyle" but was, rather, associated with more ingestion of whole grains, fruit, low-fat dairy products, desserts, and coffee and less of processed meat, refined grains, and sugar-sweetened soda. A study of grocery purchase patterns of 1,574 individuals found that those purchasing diet soda made better nutrition choices (14). Bellisle discussed a meta-analysis of 16 randomized controlled trials in which replacing sugars by nonnutritive sweeteners was associated with a 10% reduction in daily energy intake, with an average 0.2 kg/week greater weight loss and with less weight regain after weight loss. Although there is an animal model showing that overeating follows exposure to saccharin- and sucrose-containing beverages (15), Bellisle commented that there is no evidence that human consumption of diet beverages increases either appetite or energy intake (16) and, indeed, that frequent users of nonnutritive sweeteners showed the same level of appetite for sweet-tasting substances as those not drinking such products (17). A study of individuals who had maintained >10% weight loss for >5 years showed that they consumed less dietary fat and more artificially sweetened beverages and were more physically active (18). Functional magnetic imaging studies do show, Bellisle stated, that although both sucrose and the nonnutritive sweetener sucralose activate primary taste pathways, only sucrose activates domaminergic midbrain areas, suggesting that the brain is capable of distinguishing the two and that only the former might effectively reduce food intake. On balance, however, Bellisle concluded that that the use of nonnutritive sweeteners is beneficial and allows substantial difference in energy intake. She pointed out that there is a beneficial, presumably cognitive, effect and that consumers of these sweeteners

appear to integrate their use of these beverages with an overall pattern of healthy food choices.

FRUCTOSE—In a symposium on dietary sweeteners containing fructose, Julie A. Miller-Jones (St. Paul, MN) discussed misconceptions about fructose and high-fructose corn syrup (HFCS), reviewing the history and chemistry and some commonly held myths about the product. She pointed out that "fructose has been in the news," with some well-respected investigators arguing that it is related to metabolic syndrome and abnormal lipid panels while others have argued that "there is insufficient evidence to . . . restrict high fructose corn syrup . . . [but rather that] advice to limit consumption of all added caloric sweeteners, including fructose, is warranted" (19). Both fructose, a ketose, and glucose, an aldose, are reducing sugars, which combine to form sucrose. Fructose is found in fruit, honey, and table sugar. Sources of dietary fructose include agave, the richest natural source of fructose, with 85% of carbohydrate in this form; honey, with approximately 50%; and fruit juices. HFCS is made from acid- or amylase-treated corn starch and contains 42–55% fructose; Miller-Jones commented, "It's higher than corn syrup . . . but it's not high." In contrast, apple and pear juice have >66% fructose; asparagus, raspberries, spinach, and watermelon have 56–65% fructose; and most fruits and nuts have 42–55% fructose. In most foods, fructose and glucose are present in equal proportion, an availability ratio that has changed little over the past 40 years. HCFS is similar in sweetness to sucrose, is fermentable by yeast, has greater moisture retention and, because of the reducing sugar aspect, increases browning of foods but is less likely to crystallize.

Over the period from 1970, according to disappearance data, available added sugar calories have increased 19% but the per capita increase in total calories has been 24%. It does appear that we have to some extent substituted fructose for sucrose. The greatest increase, however, is in added fats and in cereal and grain products. The most recent National Health and Nutrition Examination Survey (NHANES) of 15,189 individuals, suggests an increase in daily sugar intake of 83.1 g equivalents from 1994–1996 levels. Approximately 76% of the U.S. population consumes <20% of their energy as sugar, while 13% consume >25% of their calories as added sugar, particularly teenagers and young adults, coming mainly from sodas and, to a lesser extent, sweetened grain products, leading Miller-Jones to state, "The message that we want to drive home is, 'Eat more fruit.'"

Fructose is associated in epidemiologic studies with greater weight, triglyceride, blood pressure, and insulin resistance levels and in animal and human feeding studies with small dense LDL cholesterol, nonalcoholic fatty liver disease, and greater levels of protein glycation. Fructose intake, based on disappearance data studies, has correlated over the past five decades with increasing obesity prevalence (20). Studies specifically examining HFCS show its level to correlate strongly with the prevalence of obesity and overweight (21) and, similarly, use of sweetened beverages correlates with body weight (22). "The tragedy," Miller-Jones stated, "is that you can [consume >800 kcal in a soft drink] and not think you've consumed calories. . . . It's the big gulp that's the problem." Although an animal model has shown greater weight gain with HFCS (23), she suggested that these findings of the study were methodologically problematic. The one effect of HFCS that does appear reproducible, in her assessment, is its association with elevation in triglyceride levels (24), with other effects simply related to increased consumption of calories. 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 (25). The combination of 60% fat and fructose caused obesity, high triglyceride, and glucose intolerance in another animal model (26). The increasingly recognized effect of fructose on uric acid levels (27) was not discussed. Another question Miller-Jones raised is whether rodents are an imprecise model for effect of fructose, given that de novo lipogenesis constitutes 60–70% of fat synthesis in rodents—far more than the 10–20% in humans.

Extremely high fructose intake levels are uncommon, Miller-Jones stated, "in nature." She reviewed a meta-analysis of clinical studies showing no effect of <3 month studies of moderate or high fructose intake either in normal or in diabetic individuals on body weight, going on to cite a recent review, which stated, "Ingestion of fructose in a normal, dietary manner . . . does not cause biologically relevant changes in triglyceride or body weight [even] when consumed at levels approaching 95th percentile estimates of intake" (28). The issue may then be the adverse effect of high-level consumption of any sugar. In a study of 34 men fed either 25% sucrose or 25% HFCS, both diets increased triglyceride levels similarly (29), although another study comparing 25% fructose with glucose feeding showed the former to increase lipids and intra-abdominal fat (30). Perhaps because fruits are relatively high in fructose, epidemiological studies have actually shown an inverse association of fructose intake with diabetes prevalence (31). Miller-Jones concluded that excess calories, rather than HFCS, are what cause adverse effects (32). Her thesis, then, is that sucrose and HFCS are virtually the same, other than in cost, and that "large amounts of all sugars should be avoided. . . . A calorie is a calorie whether it comes from glucose, fructose, or a combination of both." She described as "our real problem" the dilemma described in a review by David Jenkins, "Too much sugar, too much carbohydrate, or just too much?" (33).

Michele M. Doucette (Denver, CO) further discussed the notion "that all naturally occurring sweeteners are equally caloric. . .[although] fructose consumed in isolation and in high amounts can cause abnormal metabolic profiles." She suggested that sucrose is likely to have similar effects and reviewed the relationship between total added sugars and obesity and diabetes. "The obesity epidemic is not abating," she stated, with obesity overtaking overweight in population prevalence beginning in 2006. Obesity is of course associated with type 2 diabetes, with a comparison of NHANES 1976–1980 and 2005–2006 showing particular increase in obesity among individuals with diabetes in the more recent survey.

What drives obesity is energy balance, related to genetics, ethnicity, food consumption patterns, and activity patterns, which have not increased in keeping with the increase in energy intake. "There's food abundance, there's vending machines . . . they're eating out more . . . portion sizes have increased." What is needed, then, Doucette said, is a "socioecologic framework for preventing obesity" addressing food intake and physical activity, with appropriate understanding

of the roles of social norms and values as well as individual factors in changing both elements of this balance.

She asked, "How does this all connect in with added sugars?" Naturally occurring sugars intrinsic in whole fruit, grains, vegetables, and milk products may be compared with extrinsic sugars added during food processing or consumption. Loss-adjusted food availability data from 1980–2006 showed an increase in sugar consumption from 106 to 130 g/day. There are a variety of dietary guidelines, with most agreeing that ~10% of total calories consumed should be as sugars.

"We're eating a lot of the foods that are more energy dense and less nutrient dense . . . much less of the healthy foods," Doucette said. Too many soft drinks, sugar sweets, and sweetened grains and too few fruit drinks and milk products are consumed. The mean daily amount of sugar added to the diet is ~50 g/day. One difficulty is that the nutrition facts panel in food labels does not directly give added sugar content. Common sugars in foods include sucrose, fructose, lactose, maltose, glucose, dextrose, corn syrups, honey, molasses, and fruit juice concentrates; interestingly, corn syrup is not considered an added sugar; useful Web sites with information about sugars in food are labelwatch.com, fatsecret.com/calories-nutrition, and thedailyplate.com. Doucette suggested that the "source of added sugar is not the primary concern. Most important is the amount of total calories." She discussed the newly released 2010 dietary guidelines, which suggest nutrient-dense foods, vegetables, fruits, and high-fiber whole grains, with low levels of solid fats, added sugars, and sodium, suggesting that diet be integrated in practical terms that promote personal choices.

FOOD AND NUTRITIONAL SUPPLEMENT PRESENTATIONS AT THE ADA MEETING—Kitabchi et al. (abstract 108-LB) compared effects of 30% protein, 40% CHO, and 30% fat vs. 15% protein, 55% CHO, and 30% fat 500 kcal hypocaloric diets in 11 obese nondiabetic premenopausal women over 3 months; the two diets led to a comparable fall in weight, blood pressure, C-reactive protein, tumor necrosis factor-α, and interleukin-6, but the former led to greater improvement in glucose tolerance and two oxidative stress markers, dichlorofluorescein and malondialdehyde. Darakhshan et al. (abstract 1772) treated 13 obese individuals with 4-week hypocaloric high protein vs. conventional diets, also finding no significant difference in weight loss or total fat, but with a significant decrease in adipocyte diameter and plasma leptin with the former; they suggested the strategy of alternating between the two diets with controlled washout intervals for obesity management. Pasupuleti et al. (abstract 110-LB) administered a dietary supplement containing "soy and whey . . . peptides . . . minerals, antioxidants, vitamins, cinnamon extracts, insulinotropic amino acids/peptides, and soluble and insoluble fiber and then formulated with milk protein and organic soy milk" versus placebo to 59 type 2 diabetic individuals for 12 weeks, finding A1C reductions of 1.6 vs. 0.7%, respectively, and fasting glucose reductions of 39 vs. 5 mg/dL. Malik et al. (abstract 1766) reported that participants in the Nurses' Health Survey with higher dairy intake during adolescence had reduced risk of diabetes; Rosal et al. (abstract 1767), however, reported that dairy beverages constituted 9% of caloric intake among adult Latino diabetic patients with A1C >7.5%, whereas juices, fruit drinks, and regular sodas accounted for 7% of total calories, together offering readily addressed areas for reduction in energy intake.

Chacko et al. (abstract 109-LB) administered 500 mg magnesium daily (as the citrate) versus placebo in a 4-week crossover trial of 14 overweight nondiabetic healthy individuals, showing a significant decrease in fasting C-peptide with downregulation of complement C1q, proplatelet basic protein, and tumor necrosis factor–related protein 9 genes and upregulation of the transient receptor potential channel genes *TRPM6* and *TRPM7*, compatible with magnesium's known favorable metabolic effects. Ali et al. (abstract 1763) randomized 59 individuals with impaired fasting glucose, impaired glucose tolerance, or metabolic syndrome to chromium picolinate 500 or 1,000 μg daily or placebo daily, showing no effect on insulin sensitivity, fasting or 2-h glucose, weight, blood pressure, A1C, lipids, or urine albumin levels.

Dondoi and Mogos (abstract 1774) treated 42 type 2 diabetic individuals receiving 1,500 mg metformin daily with 2 g n-3 fatty acids daily, as well as 1 g vitamin C daily to prevent oxidation of the former; homeostasis model insulin resistance decreased 13%, and those with hypertriglyceridemia at baseline decreased triglyceride levels from 425 to 183 mg/dL. Costacou et al. (abstract 1757) followed ~600 type 1 diabetic individuals for 18 years, finding a 48% lower likelihood of coronary disease among men in the highest versus lower three quartiles of n-3 fatty acid dietary intake; there was no effect in women. Correction for HDL and LDL cholesterol and triglycerides, however, made the former association nonsignificant. Dragomir et al. (abstract 193) allocated 290 type 2 diabetic individuals to diets with or without supplemental fish oil capsules containing 1 g eicosapentanoic acid, 1 g docosahexanoic acid, and 0.1 g α-tocopherol acetate for 12 months, showing the supplemented group to have significantly lower carotid intima-medial thickness progression. Utzschneider et al. (abstract 197) randomized 19 nondiabetic individuals to high- versus low-fat isocaloric diets for 4 weeks, finding greater reduction in liver fat by magnetic resonance spectroscopy with the latter in association with reduction in total and HDL and LDL cholesterol and increase in plasma triglycerides.

Kim et al. (abstract 1762) analyzed dietary habit questionnaires in 2,865 type 2 diabetic patients from the Korean National Diabetes Program and found lower BMI to be associated with eating 3 meals versus 1–2 meals daily (despite fewer reported calories with the latter), with regularly timed meal schedules, and with slower rather than more rapid eating patterns. Stull et al. (abstract 1769) reported greater improvement in insulin sensitivity (hyperinsulinemic-euglycemic clamp) of 32 obese, nondiabetic, and insulin-resistant subjects with two daily servings of a 16-oz. liquid shake containing 22.5 g freeze-dried blueberry powder than with an equicaloric placebo shake.

Kirwan et al. (abstract 196) studied 22 older obese adults during a 12-week exercise training period with high- versus low-glycemic index foods and found similar improvement in weight, insulin sensitivity, and visceral fat but reduced postload insulin, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide levels only in the latter group. Silva et al. (abstract 1768) analyzed 3-day weighed-diet records of 175 type 2 diabetic individuals and found that the metabolic syndrome (defined by the presence of any three of five factors: central obesity [waist circumference ≥94 cm for men and ≥80 cm for women], triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, blood

pressure ≥130/85 mmHg, and fasting glucose ≥100 mg/dL) was associated with the glycemic index of the overall diet, with the breakfast glycemic index appearing to account for all of the difference between those with and those without the syndrome.

Pittas et al. (abstract 198) compared 608 women with newly diagnosed type 2 diabetes and 559 control subjects in the Nurses' Health Study and found 25-OH vitamin D levels in the highest versus lowest quartile to be associated with 48% lower likelihood of diabetes. Jarvandi et al. (abstract 1758) did not find an association of dietary vitamin D with blood pressure but found that during the months with low sun exposure, individuals who did or did not use vitamin supplementation had a mean systolic blood pressure of 134.5 vs. 139 mmHg, respectively, adjusted for age, sex, BMI, physical activity, ethnicity, smoking, alcohol, number of antihypertensive medications, and total energy and nutrients addressed in DASH diet recommendations.

Ketterer et al. (abstract 1764), noting the presence of insulin receptors in several brain areas including the olfactory bulb, found that a hyperinsulinemic-euglycemic clamp reduced olefactory function, which suggests a potential regulatory step for hunger and satiety and leads to the question of what if any changes occur in these parameters in diabetes and with insulin resistance.

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