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Gastrointestinal and dietary aspects of diabetes

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At the 63rd annual scientific session of the American Diabetes Association (ADA), held in New Orleans, Louisiana, June 2003, a number of fascinating topics were discussed. This is the first of approximately six articles reviewing presentations at this meeting.

Diagnosis and treatment of gastrointestinal complications

Mark Burge, Albuquerque, New Mexico, introduced the topic of diabetic gastroparesis. The role of the stomach is to mix, pulverize, and deliver food to the duodenum. Gastric motor activity is controlled by many factors, including extrinsic parasympathetic and sympathetic and intrinsic enteric nerves and hormones such as gastrin, motilin, glucagon-like peptide-1, neuropeptide-Y, and nitric oxide. The glucagon-like peptide-1 agonist NN-211 delays gastric emptying in people with diabetes and may be beneficial for the overly rapid gastric emptying, which appears to worsen postprandial glycemia, of many individuals with type 1 diabetes. Gastric peristalsis is controlled by electrical impulses originating from gastric pacemaker cells, depolarizing three times per minute, with the fundus exhibiting receptive relaxation, while the antrum has regular contractions leading to vigorous mixing and grinding. Gastroparesis is potentiated by a number of factors, including gastric dysrhythmia, discoordination of antral contractions, failure of the fundus to relax, and hypomotility or inappropriate dilation of the antrum. Nausea, particularly following meals, vomiting, abdominal pain, bloating with malodorous eructation, early satiety, and anorexia are usual symptoms, although not typically with

weight loss, which may indicate an eating disorder or additional gastrointestinal illness.

There is poor relationship between the severity of gastropathy and the symptoms exhibited by a given person. For many patients, erratic glycemia, Burge noted, are "the only clue." This is complicated, however, as hyperglycemia delays gastric emptying of solids and liquids in individuals without diabetes; therefore, those with poorly controlled diabetes may only appear to have gastroparesis, showing the importance of achieving glycemic control. As symptoms alone are insufficient, it is important to objectively assess gastric function. Measurement of gastric emptying should be performed if possible when the patient is euglycemic, or if this is not possible, it is important to record the glucose level during the test. The scintigraphic assessment of gastric emptying of a technetium-labeled meal is most commonly performed, reporting the half-time for gastric emptying. For adequate assessment, 4-h gastric emptying studies are required, rather than using shorter studies and then extrapolating. Related tests include sonographic measurement of gastric emptying, acetaminophen absorption, electrogastrography, and intraluminal pressure measurement. Burge has assessed breath hydrogen concentration 12 h after the ingestion of a test meal, containing complex carbohydrate and lactulose, as a measure of total gastrointestinal transit time, which shows sensitivity of 100% and specificity of 90% in his studies. Gastroscopy or other evaluation may be required to exclude structural abnormality in selected individuals.

Richard McCallum, Kansas City, Kan-

sas, noted that the three-cycles-per-minute electrical rhythm of the antrum usually is not associated with a contractile response, but that after vagal stimulation signals such as motilin are released, the electrical signal causes gastric smooth muscle contraction. Physiologically, the interstitial cells of Cajal are spontaneously depolarizing gastric pacemaker cells that lead to contraction if excitatory signals are being conveyed in the gastric myenteric plexus. McCallum stated that domperidone is "pound for pound the best gastrointestinal drug in the world, an antiemetic centrally, powerful acting dopaminergic antagonist, and promot[ing] gastrointestinal motility in the small bowel." He added, "We use it extensively in patients who can't tolerate other prokinetics." Side effects include increased prolactin with galactorrhea, so the agent is not always tolerated. Hyperglycemia tachygastric develops in approximately one-third of patients and may be prostaglandin-mediated, and there is some evidence of a response to indomethacin, suggesting a role of prostaglandin synthesis inhibitors in treatment. McCallum noted that sildenafil relaxes the antrum and, therefore, would not be expected to be effective for gastroparesis, despite the potential role of nitric oxide-induced cGMP production. Interestingly, the agent has been successfully used for esophageal motility disorders such as achalasia.

Treatment for patients failing to respond to pharmacologic agents included surgical placement of jejunostomy for maintaining nutrition and the use of gastric pacing. Two approaches have been used: high-energy low-frequency waves to stimulate contraction and high-frequency low-energy stimulation to activate central antiemetic sites, which is technically more readily administered. The Medtronic low-energy higher-frequency (12–14 cycles/s) stimulator does not stimulate motor contraction to "pace the stomach" and was approved in March 2000. The device is implanted by laparotomy or laparoscopy with two elec-

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Abbreviations: ADA, American Diabetes Association; RDA, recommended daily allowance.

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trodes proximal to the pylorus. In a group of 17 individuals with diabetic gastroparesis randomized to alternating active treatment or sham treatment for 1 month, half experienced a >50% decrease in nausea and vomiting, with additional decreases in bloating, fullness, abdominal pain, satiety, and anorexia (1). McCallum has now treated a total of 38 subjects with diabetes and gastroparesis who had previously had numerous hospitalizations for this condition. Improvement begins after ~2 weeks, and by 6 months, there is typically >50% reduction in nausea and vomiting and improvement in quality of life, with weight gain and better glycemic control, although with only a modest improvement in gastric emptying. After 1 year, hospitalization rates are very low. There is a low (~5%) rate of infection and of migration of the device. McCallum speculated that the device leads to return of function of the interstitial cells of Cajal. Antral biopsy of these patients has shown, however, that interstitial cells of Cajal are absent in approximately one-third of cases; therefore, some patients will fail to respond to the low-energy stimulator.

These patients may need direct stimulation of muscle with higher-energy impulses. Animals with vagotomy have a gastroparesis-like state with glucagon administration and show erratic rapid gastric electrical activity that can be “paced through” to normalize gastric emptying. Using bipolar electrodes placed along the greater curvature of the antrum in individuals with gastroparesis, it is similarly possible to “pace” the stomach, resulting in an improvement of delayed gastric emptying symptoms and a >50% decrease in gastric emptying time to the normal range after a 3-month trial. The use of botulinum A toxin may give brief improvement by opening the pylorus, what McCallum termed “the equivalent of a pyloroplasty,” but will be unsuccessful if antral function is abnormal. Although gastrojejunostomy has occasionally been performed with the rationale of decompressing the dilated stomach and allowing feeding, he suggested that this approach often leads to severe fluid and electrolyte disturbance and should be avoided. Some patients require total gastrectomy with esophageal-jejunal anastomosis, but this extreme approach must be reserved for those who fail to respond to all other approaches.

McCallum presented three cases illus-

trating other aspects of treatment. The first was of a 44-year-old woman who had had diabetes for 25 years and a 40-lb weight loss that was regained with total parenteral nutrition. She had 72% retention at 4 h during a gastric emptying study. A pacemaker and feeding jejunostomy were placed surgically, the latter as “a safety net, an insurance policy” given the need for the surgical procedure, but they were not actually required. At 6-month follow-up, she was improving. She planned to obtain domperidone from New Zealand (it is less expensive there than in Canada) to enhance gastric emptying and to try metronidazole for presumed bacterial overgrowth.

The second patient was a 51-year-old female with a 10-year diabetes history and a 1-year history of gastroparesis who experienced severe nausea and vomiting 10 times a day at 3- to 4-day intervals. Psychogenic vomiting, also termed rumination syndrome or conditioned vomiting, is a syndrome of vomiting within 5–10 min of eating, with the patient then swallowing and regurgitating in a “ritual” cycle. Some patients “become conditioned” after months or years of delayed gastric emptying. The disorder can only be diagnosed when it occurs within minutes, whereas “the classic gastroparetic” vomits food ingested many hours previously. Treatment is with cisapride (no longer commercially available because of the potential for ventricular arrhythmia and hence requiring electrocardiographic monitoring), domperidone, erythromycin (acting as a motilin agonist), and low-fat, low-fiber, small, frequent feedings with the use of a backup nutrient liquid such as Ensure at night. McCallum suggested the use of transdermal scopolamine, as nausea is an important symptom requiring ongoing prophylactic treatment. The phenothiazine derivative promethazine may also be useful for nausea, although, like scopolamine, its anticholinergic effect may lead to a small further decrease in gastric emptying. Tegaserod, a serotonergic agonist developed for irritable bowel syndrome, promotes upper gut motility and may play a role. New motilin agonists such as GM-611 (Chugai Pharmaceuticals) are being developed and may prove useful. Bacterial overgrowth is common and should be treated with metronidazole, amoxicillin-clavulanic acid, neomycin, or probiotics such as acidophilus-containing products. Clonidine treatment

may be effective, always starting with a low dosage to avoid hypotension. For nocturnal stool incontinence, octreotide may be administered at bedtime and “will block all diarrhea,” but the agent may further decrease gastric emptying and should usually not be given during the day. Patients with diabetes and severe diarrhea should have evaluation to exclude other gastrointestinal illness such as celiac disease.

The final case was of a 48-year-old woman with an 18-month history of gastrointestinal symptoms, treated with 10 mg metoclopramide s.c. McCallum suggested that this is an important agent, acting both via cholinergic and antidopaminergic pathways to enhance gastric emptying, and should particularly be given in the morning when nausea is most severe, as the patient must not begin vomiting, which can lead to uncontrolled diabetes and a cycle of worsening requiring hospitalization. Tachyphylaxis is frequently seen, however, and ~40% of patients are unable to tolerate the agent because of extrapyramidal side effects. In this case, a gastrostomy had been placed for continuous drainage and a jejunostomy for feeding, the former causing severe potassium deficiency. He treated her pain with transcutaneous fentanyl, although methadone may be better than other opiates because of fewer gastrointestinal and neurologic side effects. He termed this patient “a gastric cripple,” stating, “We can return that woman to a functional life within three months,” and advising that such patients have “the gastric pacer.”

The role of protein in diet

Marion Franz, Minneapolis, Minnesota, introduced a symposium on the role of protein in diabetes, addressing issues of nutrition and metabolism. There is a great deal of research on one of the macronutrients, carbohydrate, but evidence is relatively limited addressing the roles of protein. Protein intake is remarkably consistent across all age-groups (~16% of energy intake), amounting in general to 100–125 g in men and 80–100 g in women, levels approximately twice the recommended daily allowance (RDA) needed to replace body protein losses. In the U.K. Prospective Diabetes Study dietary recall, protein intake was 21% of total energy intake in subjects with type 2 diabetes, who consumed ~1,800 and 1,400 kcal (men and women, respective-

ly), suggesting that as energy intake is reduced, protein intake remains relatively constant. Over the past 90 years, protein intake has been remarkably consistent in the U.S. population, while carbohydrate and fat intake have been reciprocally related. One reason for the difficulty in changing protein intake is that there are very few foods solely containing protein, so that “cold cuts,” for example, are mainly fat, with egg white and shrimp the foods highest in protein. Protein digestion begins in the stomach, is continued by pancreatic proteinases, with subsequent protein breakdown into di- and tripeptides and then absorption as amino acids across the intestinal mucosa, entering the portal vein, although glutamine, glutamate, and aspartate are used in part for fuel by gut mucosal cells. The nonessential amino acids are deaminated and their nitrogen converted to urea, with 50–70% of a typical protein meal used in this fashion for conversion into glucose. None of this glucose, however, appears in the general circulation, perhaps because the protein was slowly digested, the glucose was stored as glycogen in the liver, or the amount converted into glucose had not been accurately calculated. The effect of protein depends on the availability of insulin and on glycemic control. Adequate insulin is required for control of protein catabolism and gluconeogenesis.

Franz summarized the latest ADA recommendations pertaining to dietary protein. For individuals with controlled type 2 diabetes, and perhaps for those with type 1 diabetes, protein ingestion does not increase plasma glucose concentrations. With less than adequate glycemic control, protein requirements may exceed the recommended dietary allowance, although not exceeding usual dietary intake levels. For people with nephropathy, although there is somewhat less evidence, protein intake should be reduced to $0.8 \text{ g} \cdot \text{kg body wt}^{-1} \cdot \text{day}^{-1}$, and for those with microalbuminuria, protein intake should be $0.8\text{--}1.0 \text{ g} \cdot \text{kg body wt}^{-1} \cdot \text{day}^{-1}$; there is no evidence as to whether animal or plant sources of protein are preferable. If renal function is normal, there is no evidence as to the benefits of changing dietary protein intake. The long-term effects of diets high in protein and low in carbohydrates are unknown, although it appears that such diets do lead to weight loss and improvement in glycemia, although not necessarily to a greater extent than

that with other diets. There is no evidence that protein slows carbohydrate absorption or that adding protein to food ingested for hypoglycemia or ingesting protein-containing foods at bedtime is helpful for the prevention of subsequent hypoglycemia, although these measures have typically been recommended for subjects with type 1 diabetes. Franz reviewed a study showing that for glucose levels $>180 \text{ mg/dl}$, a bedtime snack is not required. For levels between 120 and 180 mg/dl, snacks with or without protein have similar effects, whereas with lower glucose levels, bedtime snacks are not only useful but necessary, again without particular evidence of a benefit from protein.

Errol Marliss, Montreal, Canada, discussed the implications of altered protein turnover in diabetes. Glucose production, related to the fall in insulin with rise or lack of change in glucagon, leading to gluconeogenesis, is accelerated under conditions of insulin deficiency. With exogenous amino acids and glucose, as seen after a meal, glucose production increases further in the insulin-deficient patient. There is not, however, evidence of abnormal protein metabolism in treated subjects with diabetes. This may be due to the focus on the fasted state of most existing research. Worse degrees of glycemic control are associated with various degrees of protein catabolism. Oral hypoglycemic agents and exogenous insulin increase protein synthesis and decrease protein catabolism. In studies of obese individuals, a low-energy high-protein diet tends to be associated with similar degrees of protein balance with and without diabetes. Marliss concluded that with hyperglycemia, dietary protein requirements may increase, and he recommended that individuals with diabetes avoid very-low-protein diets.

Mary Gannon, Minneapolis, Minnesota, reviewed the effects of dietary protein on circulating insulin and glucose concentrations. The amino acids that result from protein digestion have long been known to be available for gluconeogenesis, with 56 g glucose theoretically available to be produced for every 100 g meat protein ingested and the glucose-generating capacity of 100 g of various proteins ranging from 50 to 80 g. Glucose concentrations do not, however, change after ingestion of protein. This appears to be mainly due to the increase in insulin

after protein ingestion. Gannon noted that when 50 g protein was given to control and type 2 diabetic subjects, there was no increase and a small decrease in glucose, respectively, in association with an increase in insulin levels, which occurred to a greater extent in people with diabetes. The integrated insulin response after protein ingestion is 28% of that after glucose ingestion in nondiabetic individuals, with the two additive, while the insulin response to protein is as great as that to glucose in subjects with type 2 diabetes and the response to glucose plus protein is greater than the sum of the individual responses. Studying a variety of protein sources given with dietary carbohydrate, cottage cheese, beef, turkey, gelatin, egg white, fish, and soy all stimulate insulin secretion to varying degrees. Increasing dietary protein from 15 to 30% for 5 weeks, approximately the half time of HbA_{1c} , without changing calories or weight, was shown in 12 subjects with diabetes to not affect urine microalbumin or creatinine clearance, with a 38% decrease in integrated postprandial glucose levels and 0.8% decrease in HbA_{1c} from baseline levels of $\sim 8\%$, an effect, Gannon noted, that is similar to that for oral hypoglycemic agents, suggesting a particular benefit of high dietary protein in subjects with diabetes.

Julie Eisenstein, Boston, Massachusetts, reviewed the relationship between dietary protein and weight loss. Although, she noted, epidemiologic studies suggest a positive correlation between dietary protein and weight gain, the popular conception is that dietary protein can be helpful in causing weight loss. “Calories are not the whole story here,” she pointed out. Although the RDA is $0.8 \text{ g protein} \cdot \text{kg body wt}^{-1} \cdot \text{day}^{-1}$, actual protein intake in the U.S. ranges from 10 to 35% of total energy, with adults in the U.S. typically consuming $\sim 50\%$ more protein than the RDA. High-protein diets, she suggested, should be defined as 25% of dietary calories in weight maintenance and twice the RDA in weight loss, and very-high-protein diets should be defined as 35% of dietary calories and three times the RDA. Energy expenditure is comprised of the resting energy expenditure, typically 60–70% of the total, the thermic effect of eating, usually comprising 10–15% of energy, and physical activity, which is tremendously variable from one person to another. Proponents of high-

protein diets suggest that protein decreases energy intake by decreasing hunger and/or increasing satiety and that energy expenditure may be increased with such diets.

There are a limited number of studies in this area of nutrition, and it is noteworthy that a high-protein calorie-restricted diet may actually not be high in protein, but instead may be low in other macronutrients. In short-term studies, a high-protein meal is associated with decreased subsequent food ingestion, suggesting suppression of hunger. Long-term studies, however, show equivocal evidence of decreased energy intake. An additional factor is that the thermic effect of feeding as a percent of energy intake appears to double after a protein meal compared with a fat or carbohydrate meal. Furthermore, the decrease in resting energy expenditure after weight loss may be lessened in individuals following a high-protein diet.

“The ultimate question is, ‘Do high protein diets lead to greater weight loss?’” Analyzing nine earlier studies with similar calorie intake, Eisenstein stated that there was no evidence of difference in either weight loss or fat loss, which “discounts dietary protein having a major role.” A more recent 6-month study of ad libitum high versus normal protein diet, however, showed lower calorie ingestion for those on the former diet. The two most studies appeared in the May issue of the *New England Journal of Medicine*. The first, which compared 25 vs. 12% protein diets for 6 months, showed a similar advantage in weight loss, with improvement in insulin sensitivity and fasting triglyceride levels (2). The second study instructed patients in the “Atkins diet” approach and showed greater weight loss at 6 months, although not at 12 months (3). Eisenstein concluded that in diets of similar calorie content, there is no evidence of benefit, but that with ad libitum diets, there is some evidence of benefit of high-protein approaches, although more data on long-term safety are needed.

Madelyn Wheeler, Indianapolis, Indiana, ended the symposium with a discussion of the relationship between dietary protein and early renal disease, addressing two questions, “Is protein amount or source a risk factor for the development of microalbumin?” and “Can protein amount or source be of benefit?” The highest quintile of protein intake is 19%

or more of energy, which would be 1.3 g/kg protein in a 65 kg woman, while the average intake is 14–16% ($1-1.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), of which 70% is of animal origin. Low levels of dietary protein are <12% of energy intake, or $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, which is the RDA for “good quality protein.” A low-protein diet for a typical person ingesting 1,800 calories, therefore, includes ~56 g protein/day. Some studies show a relationship between dietary protein and microalbuminuria (4), but other studies have not confirmed this relationship (5). It may be that high dietary protein intake is particularly associated with microalbuminuria in people with particularly high protein (>20% of energy) intake who have multiple risk factors such as both diabetes and hypertension (6).

Short-term studies have addressed the early phase of renal disease, with one study showing that high ($1.5 \text{ vs. } 0.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) dietary protein intake was associated with hyperfiltration (7), although another study of $1.45 \text{ vs. } 0.76 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ protein showed no effect on the glomerular filtration rate (8). In a practical sense, studies have shown that it is very difficult to decrease protein intake to levels $<1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$; therefore, it has been difficult to adequately compare long-term effects of different diets. In individuals with macroalbuminuria, there is only equivocal evidence of benefit. As far as the protein source, there is some evidence of benefit of a low-calorie soy protein diet (9), but the comparison of low-calorie plant protein with animal plus plant protein has shown no difference in albuminuria or glomerular filtration rate. One study suggested lesser levels of albuminuria with a diet containing protein derived from chicken than one using beef (7). Wheeler suggested that the interrelationships between various protein-containing foods may be important, as may be the “quality” of various proteins.

Dietary micronutrients and diabetes

Elina Hypponen London, U.K., discussed the relationships of vitamins D and E and of nicotinamide to the prevention of development of type 1 diabetes. Vitamin D should be considered a hormone rather than a nutrient, with metabolic actions mediated by receptors. Deficiency causes rickets in children and osteomalacia in adults, while excess causes hypercalcemia, but there is also evidence of an impor-

tant immunomodulatory role affecting several Th1-type cytokines and dendritic cell maturation that may potentially alter the pathogenic steps leading to type 1 diabetes. Administration of 1,25 dihydroxy vitamin D decreases progression to diabetes among NOD mice, with evidence of a dose-related effect, although only at doses associated with hypercalcemia. Nonhypercalcemic analogs may also prevent isletitis and play a role after there is already evidence of β -cell destruction. In humans, the EURODIAB study of vitamin D supplementation in infancy appeared to decrease the development of type 1 diabetes (10), and there is evidence that cod liver oil intake during pregnancy decreases type 1 diabetes risk (11). In a study of children whose mothers were pregnant during 1966, there was a “strikingly consistent association” between lack of vitamin D supplementation and type 1 diabetes risk (12). For those children regularly receiving vitamin D supplements, there was a dose effect, with higher doses further decreasing risk. Children with possible rickets during the first years of life had a particularly high risk of type 1 diabetes. Hypponen pointed out, however, that vitamin D supplementation recommendations have been decreased and that this may be a factor in the recent increase in type 1 diabetes frequency. There are also genotypic differences between individuals at greater and lower risk of type 1 diabetes, with the possibility that decreased formation of 1,25 di-OH vitamin D may play a role.

Vitamin E is a fat-soluble vitamin with antioxidant properties. As oxidative stress contributes to β -cell destruction, vitamin E and other dietary antioxidants may be beneficial. This is particularly evident in the alloxan diabetic mouse model, and there is evidence that vitamin E deficiency plays a role in animal models. In humans, serum α -tocopherol levels have been shown to be lower in subjects subsequently developing diabetes than in control subjects. Vitamin E in large doses may be immunostimulatory, however, so this should be studied with care. A pilot study from New Zealand suggested a benefit of nicotinamide, but in a large randomized clinical trial of diabetes prevention, the European Nicotinamide Diabetes Intervention Trial, antibody-positive first-degree relatives of children with diabetes showed no benefit at the 5-year follow-up. In an earlier meta-

analysis, nicotinamide did not decrease HbA_{1c} or insulin dosages (13). Nicotinamide may also worsen insulin resistance; therefore, its use is not currently suggested.

David R. Jacobs, Minneapolis, Minnesota, discussed magnesium, calcium, and vitamin E in type 2 diabetes. Antioxidant levels are lower in individuals developing type 2 diabetes, and low vitamin E levels appear to be associated with insulin resistance. There is, however, no evidence supporting a benefit of supplemental vitamin E. The Heart Outcomes Prevention Evaluation study of vitamin E showed that among the 5,720 subjects without diabetes, there was no effect in decreasing diabetes, and among the 3,577 subjects with type 2 diabetes, there was no effect in reducing complication levels (14). In the Insulin Resistance Atherosclerosis Study of individuals not taking supplements, those with higher serum vitamin E levels had reduced risk, whereas those taking vitamin E did not show such a relationship (15), suggesting that “it’s really not the vitamin E.” Asked about whether there is evidence of decreased inflammation with vitamin E, he suggested that “it’s probably going to be more complicated than single micronutrients.”

Most calcium other than that in bone and teeth is in the cytosol acting as an intracellular messenger. Dairy products are the primary food source. Jacobs described a study comparing 20 subjects treated with vitamin E whose brachial artery diameter was greater and oxidative stress decreased, in association with increased intracellular magnesium and calcium levels. Subjects with type 2 diabetes treated with metformin show a lesser frequency of vitamin B12 deficiency with calcium supplementation. Calcium supplementation also appears to increase the beneficial effect of β blockers on left ventricular hypertrophy. Both oral calcium and dairy products appear to be associated with decreasing body fatness. The Coronary Artery Risk Development in Young Adults study, at the 10-year follow-up of 3,157 individuals, showed that dairy products are associated with decreased insulin resistance (16).

Magnesium is extremely important in energy metabolism and may increase insulin sensitivity and decrease diabetes incidence. Low serum magnesium is associated with greater frequency of hypertension, CHD, and diabetes. Serum

and cellular magnesium levels are reduced in individuals with diabetes. Trials of magnesium supplementation in subjects with diabetes have not, however, shown consistent improvement in glucose control, although in a study from Mexico of subjects treated with glyburide with rather low magnesium levels, there is evidence of benefit. Magnesium levels are also lower in individuals with albuminuria and those with lower extremity ulcers and show little response to catecholamines in people with obesity. Whole-grain cereals are high in both fiber and magnesium and may be of particular benefit, with “foods and not supplements” being the optimal approaches for improvement in both magnesium and other nutrients. He also noted that “the low fat craze” leads to ingestion of “lower quality foods.”

Byron Hoogwerf, Cleveland, Ohio, discussed the relationship between micronutrients and the complications of diabetes. Oxidative modification appears to occur with diabetes, with evidence that antioxidants can be beneficial in vitro and in animal models. Endothelial nitric oxide production is decreased with oxidant stress, potentially linking atherosclerosis with these processes. D- α tocopherol supplementation improves measures of diabetic retinopathy and nephropathy in animal models. With vitamin C administration, forearm endothelium-dependent vasodilation improves in subjects with diabetes. Clinical studies have not, however, shown benefit. In addition to the Heart Outcomes Prevention Evaluation study (discussed above), the Heart Protection Study assessed the effect of an antioxidant vitamin combination, including 600 units vitamin E, as well as vitamin C and β carotene, and did not show an effect on clinical events in the overall group or in individuals with diabetes or in those without a history of CVD (17).

Janet C. King, Oakland, California, concluded with a discussion of the implementation strategies for prevention using micronutrients. The current ADA recommendations are 60–70% carbohydrate, 15–20% protein, <10% saturated fats, and <300 mg cholesterol, and “there is no clear evidence of benefit from vitamin or mineral supplementation.” “Should the ADA define healthy food strategies or supplements?” Biologically plausible evidence-based recommendations are not available for micronutrients, although

King discussed the conceptual difficulty of creating randomized controlled trials that would show a long-term preventative or therapeutic benefit of early micronutrient treatment. Vitamin C, carotenoids, zinc, niacin, vitamin E, and chromium are among the substances that could be considered. There is some evidence of a beneficial association between plasma vitamin E and C levels and diabetes and its complications, but not of relationship between these outcomes and the use of supplements, suggesting the importance of food strategies rather than of supplemental vitamin products. There is some evidence of the benefit of supplements, as in the effects of calcium in decreasing osteoporosis, of folic acid in decreasing homocysteine, and of multivitamin supplements in decreasing birth defects, but no direct evidence that they would be appropriate for individuals with diabetes.

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