Weight Control in Individuals With Diabetes

ZACHARY T. BLOOMGARDEN, MD

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A pilot project is underway to offer the *Perspectives on the News* commentaries as a monthly Web-based CME activity. Please access www.diabetes.procampus.net to view our initial efforts. We look forward to your comments.

Bariatric surgery

Carroll M. Harmon, Birmingham, Alabama, reviewed the topic of bariatric surgery in children. A typical response to the topic, he said, is of disbelief that such an approach would even be considered. Yet more than one million adolescents and young adults have BMI >40 kg/m^2, and obesity is by far the most common nutritional disorder among children in the U.S. Childhood obesity is associated with poor self-esteem, steatohepatitis, and a variety of cardiovascular and endocrine complications, with 80% of overweight children with one obese parent becoming obese adults. Harmon reviewed representative studies, showing that by standard measures, the quality of life of an obese child is similar to that of a child with cancer and fivefold worse than that of a healthy normal-weight child. Parent proxy reports suggest even greater impairment. Obstructive sleep apnea (OSA) is present in 55% of severely obese children with BMI >50 kg/m^2. Overweight children have a sevenfold greater risk of hypertriglyceridemia, and 86% of children diagnosed with diabetes are overweight or obese. The prevalence of childhood obesity among blacks and Hispanics is higher than among whites, with the likelihood of diabetes particularly great for African-American and Hispanic children. There is undoubtedly, Harmon concluded, interplay between genetic and environmental factors, with >600 genetic loci linked to obesity phenotypes and multiple single-gene mutations identified.

Treatment options for pediatric obesity are limited, with diet, exercise, and drugs, at best, able to produce moderate success. Thus, Harmon suggested, as bariatric surgery is becoming a widely accepted treatment option in obese adults, it may be appropriate for treatment of obese children. The procedures can be laparoscopically performed and lead to durable weight loss but are associated with mortality rates, which Harmon cited as ranging from 0.2–2% (1, and the study by Omalu et al. below), as well as having high complication rates. If obese children are already developing complications and have high likelihood of continuing to be obese in adulthood, however, Harmon argued that it is appropriate to consider bariatric surgery for selected individuals in this group. Both the malabsorptive plus restrictive Roux-en-Y and the restrictive adjustable gastric banding procedures are being performed in obese children (2), with the Roux-en-Y operation offered as one of a number of treatment options at the Children's Hospital of Alabama, using a multidisciplinary approach involving pediatricians, surgeons, nutritionists, nurses, psychologists, and social workers. In preoperative evaluation, children participate in a 6-month medical weight loss program and have at least three appointments with the surgeon, two psychiatric evaluations, and a board review to determine whether they are appropriate candidates. All patients and families are told that the long-term consequences are unknown and sign informed consent.

Harmon reviewed the results of bariatric surgery at his institution for the 30 children followed for at least 1 year. Mean BMI decreased from 56.5 to 35.8 kg/m^2, while that of a nonsurgical concurrently followed group decreased from 47 to 46 during the same time period. Insulin, glucose, triglyceride, and cholesterol levels decreased. Health-related quality of life improved in all parameters. Among children with OSA, whose baseline BMI was 61 kg/m^2, the apnea-hypopnea index decreased from 9.1 to 0.65 and BMI decreased to 42 kg/m^2, with weight decreasing from 173 to 118 kg. Of 10 children with type 2 diabetes, 9 required medication before and 1 after the surgery, with BMI decreasing from 51 to 33 kg/m^2, and with HbA_{1c} (A1C) decreasing from 7.3 to 5.6% and similar improvement in fasting insulin and glucose levels. Blood pressure and pulse decreased, the triglyceride level decreased from 215 to 85 mg/dl, and hepatic transaminase levels decreased. Although gastric banding is another option, Harmon mentioned that the procedure has not been approved by the Food and Drug Administration for use in children, and a 53-patient study of this approach showed a decrease in BMI from 48 to 40 kg/m^2 at 6 months, with a trend to weight regain at 18 months. Unanswered questions with all bariatric surgery include the maintenance of weight loss over time, the degree of resolution of comorbidities, whether there is life-long benefit to earlier rather than later weight loss, and, importantly, the potential for health complications of the surgery. Indeed, a number of adverse effects were seen in the 30 children. Nine had what Harmon termed minor complications, including requirement for endoscopic procedures, food obstruction, and wound infection. Four developed nutritional deficiency–related peripheral neuropathy, one developed beriberi felt due to poor compliance with recommended vitamin intake, and, most ominously, one child died after developing colitis postoperatively.

A number of presentations at the American Diabetes Association (ADA) Scientific Sessions addressed related aspects of bariatric surgery. Maser et al. (abstract 799) studied 28 individuals 6 months after bariatric surgery, who had a reduction in BMI from 48 to 37 kg/m^2, finding improvement in measures of cardiac autonomic neuropathy, including the expiration/inspiration and Valsalva

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Abbreviations: 2-AG, 2-arachidonyl glyceryl; ADA, American Diabetes Association; CB, cannabinoid; EC, endocannabinoid; GABA, γ-aminobutyric acid; GDM, gestational diabetes mellitus; MCH, melanin concentrating hormone; OSA, obstructive sleep apnea; RIO, rimonabant in obesity; WBC, white blood cell.

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RR variation ratios, which potentially reduces adverse cardiovascular outcome and mortality (abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 55 [Suppl. 1], 2006). Similar effects were seen in the 9 individuals with and the 19 without diabetes. In a separate study by these authors (abstract 798) of individuals with OSA, among nine individuals with elevated plasma renin, RR variation improved with continuous positive airway pressure treatment, although this was not seen in those with normal plasma renin level. In an analysis of 46 morbidly obese adolescents referred for bariatric surgery at Ohio State University, Schuster et al. (abstract 1,768) found OSA in 16. Those with versus without OSA were 50 vs. 13% male, BMI 57 vs. 49 kg/m^2, A1C 6.5 vs. 5.7%, and fasting insulin 65 vs. 39 μU/ml, respectively. Michalsky et al. (abstract 1,763) reported further characteristics of the group, finding 24% with hypertension, 42% with depression, 19% with type 2 diabetes, and 21% with asthma. Rodieux et al. (abstract 347) compared obese nondiabetic individuals having gastric bypass or banding, showing earlier insulin peak and greater clearance of a glucose load in the former, suggesting improved insulin secretion and sensitivity and increased peptide YY and enhanced suppression of ghrelin following the glucose load, perhaps playing a role in decreased food intake following this procedure.

Omalu et al. (abstract 297) reported a population-based study of cause-specific mortality among Pennsylvania residents who had bariatric surgery from 1995 to 2004. The 5-year cumulative mortality was 6.4%, with deaths following 159 of 2,949 procedures among men and 281 of 13,734 procedures among women. Forty-five deaths were from therapeutic complications and 47 from pulmonary emboli, most occurring within the 30 days following a procedure. An additional 16 deaths were from suicide, 76 from coronary heart disease, and 55 from sepsis. Bell et al. (abstract 1,703) studied 20 individuals having Roux-en-Y gastric bypass surgery, finding that after 6 months, BMI decreased by 32%, while serum osteocalcin increased by 58%, bone-specific alkaline phosphatase by 16%, and *N*-telopeptide cross-linked collagen type 1 by 80%, suggesting increased bone turnover with increased risk of osteoporosis, a potential negative effect of the procedure. The risk-benefit equation for bariatric surgery may not yet, then, be fully understood.

There is increasing understanding of factors related to childhood obesity. Baptiste-Roberts et al. (abstract 287) prospectively analyzed 27,591 mother-infant pairs followed until age 8. Infants whose mothers had gestational diabetes mellitus (GDM) had higher weight at birth, and at ages 3, 4, and 7 years, with weight at age 7 being 0.88-kg greater than that of infants whose mothers did not have GDM, even after adjustment for birth weight; consequently, maternal GDM increased the likelihood of overweight at age 7 years by 30%. Burgert et al. (abstract 293) found that 14% of 392 obese children had elevated alanine aminotransferase, which was associated with reduced insulin sensitivity, low adiponectin, and increased postload glucose, fasting triglyceride, and visceral and hepatic fat, which was assessed using magnetic resonance imaging. Winer et al. (abstract 294) from the same group reported that among 589 obese children and adolescents, reduced adiponectin levels were associated with elevations in C-reactive protein and low HDL cholesterol.

Brufani et al. (abstract 1,753) performed oral glucose tolerance testing on 174 children with BMI >2 SDs above the age-matched level, finding 9 with impaired glucose tolerance and 1 with diabetes; fasting glucose was higher among the children with impaired glucose tolerance, while fasting insulin and c-peptide levels were similar, with the authors suggesting reduced insulin sensitivity. However, one might equally argue that failure to increase insulin levels with increasing glucose suggests decreased β-cell secretory function. Crimmins et al. (abstract 1,754) found that 10- to 18-year-old childrens' prevalences of overweight were 18 and 19% in 1,746 adolescents studied in 2001 and 2005, respectively, which is at odds with the suggestion from cross-sectional studies that childhood overweight is increasing.

Rimonabant and other treatment

The development of new pharmacologic approaches for the treatment of obesity will be crucial to the overall treatment of individuals with type 2 diabetes. David Cummings, Seattle, Washington, and Geoge Kunos, Bethesda, Maryland, discussed the endocannabinoids (ECs) as important regulators of food intake, body weight, and metabolism. Marijuana (cannabis sativa) commonly gives not only a mood-enhancing effect but also an appetite-stimulating effect, colloquially described as "the munchies." In 2600 BC, Huang Ti recommended cannabis for relief of cramps, rheumatic, and menstrual pain, and cannabis has recently reentered medical treatment for use in states associated with anorexia, such as AIDS wasting, weight loss in Alzheimer's, and chemotherapy-induced nausea and vomiting. Research into cannabinoid biology began with Gaoni and Mechoulam's identification in 1964 of THC (Δ 9-tetrahydrocannabinoid), the most important chemical component of cannabis. Two fatty acid–derivative ECs, anadamide (arachidonyl ethanolamide), named from the Sanskrit word "ananda" for "bliss," and 2-arachidonyl glyceryl (2-AG), have been characterized (3). The two ECs are expressed differently in different tissues and are likely to have somewhat different effects. In 1988, brain cannabinoid (CB) receptors were identified, with the CB1 receptor cloned first and found to be a member of the family of G-protein–coupled receptors (expressed at high level in the brain and at lower levels in peripheral tissues), while the CB2 receptor was subsequently characterized as having actions in the immune system and hematopoeitic tissues but also present in other tissues, including the brain. The CB-1 and -2 receptors have ~43% homology. The first CB1 receptor inhibitor, rimonabant, was described in 1994 by Rinaldi-Camona et al. at Sanofi as a result of combinatorial chemistry and large-scale screening, with potential for use in treatment of obesity. The CB1 receptor has been proposed to regulate food intake and sleep. The brain EC system is normally silent, becoming activated transiently under circumstances associated with pain and anxiety, inhibiting motor behavior, causing sedation, and promoting food intake and loss of aversive memory. ECs act as retrograde inhibitors of synaptic transmission. Effects of the EC system include actions mediating synaptic plasticity, with central and peripheral analgesia and anxiolysis seen. The EC system mediates reward effects of drugs and alcohol and has additional actions including neuroprotection, motor suppression, seizure suppression, and antiemetic effects. Peripheral EC effects include vasodilation and bradycardia, increased lipogenesis in adipose tissue and liver, increased osteogenesis, increased hepatic fibrogenesis, and many other actions. The EC system also plays a role in body-weight regulation, decreasing energy expenditure with effects on long-term adiposity signals such as

adiponectin, insulin, and leptin, as well as modulating the effects of short-term signals including gastrin and cholecystokinin. ECs interact with other neurotransmitters in the hypothalamus, hindbrain, and mesolimbal reward system, as well as peripherally, in the gastrointestinal tract, in adipocytes enhancing lipogenesis, in muscle blocking glucose uptake, and in liver increasing lipogenesis. Thus, the EC system acts to increase feeding, absorption, metabolism, and storage of energy. An important feature of EC blockers is evidence of improvement in features of metabolic syndrome beyond the degree to which this can be explained by weight loss alone.

Kunos further discussed the effects of ECs on retrograde neural transmission, noting that CB1 receptors are the most highly expressed receptors in the mammalian brain, present presynaptically, mainly at the inhibitory γ-aminobutyric acid (GABA) and excitatory glutamate neurons, with the EC, produced in the postsynaptic neuron, acting to inhibit neural transmission, further suggesting that the ECs perform a modulatory function. CB1 receptors are involved in hunger-induced food intake. In a mouse not expressing the CB1 receptor, the degree of increase in food intake with food deprivation is decreased, and this is seen to a similar extent with administration of rimonabant to normal mice. In contrast, genetically obese hyperphagic *ob/ob* or *db/db* mice either lacking leptin or, with abnormal leptin receptor, show increased hypothalamic EC levels, suggesting a leptin-related mechanism. There are cannabinoid-sensitive hypothalamic projections of neurons producing the orexigenic peptide melanin concentrating hormone (MCH) to the mesolimbic reward pathway, a mechanism by which an agent acting in the hypothalamus can influence food reward. Leptin leads to tonic release of GABA from these neurons, normally inhibiting their output; with leptin-deficient animals, the tonic inhibition is removed leading to release of MCH. Rimonabant can block these receptors, leading GABA release to be suppressed, with subsequent MCH release.

Biosynthesis of anandamide and of 2-AG both involve several steps, diacyl glycerol being one of the precursors of 2-AG. The existence of parallel synthetic pathways implies that it would be difficult to develop a therapy inhibiting EC synthesis, but it may be possible to develop a pharmacological approach modulating degradation of one or the other compound to activate or deactivate the EC system. Mice deficient in fatty acid hydrolase have a 10-fold increase in anandamide levels without change in 2-AG. The ECs have hypotensive effects, and inhibition of fatty acid hydrolase normalizes blood pressure in rats with angiotensin II–induced hypertension, improving cardiac abnormalities in this model as well. Monoglyceride lipase degrades 2-AG, and administration of a monoglyceride lipase inhibitor has been found to enhance stress-induced analgesia. A particularly interesting approach would be the development of inhibitors not crossing the blood-brain barrier, to allow specific pharmacologic peripheral effects.

Uberto Pagotto, Bologna, Italy, discussed a number of animal models allowing greater understanding of the physiologic roles of the EC system. ECs are active in promoting food intake in the invertebrate hydra vulgaris, a high degree of evolutionary preservation. CB1 receptors are present in neurons involved in food intake, and CB1 antagonists acting in the limbic system may decrease the reward properties of food intake, while 2-AG infusion directly into the nucleus accumbens and anandamide administration into the ventromedial hypothalamus increase food intake, an effect blocked by rimonabant. Hypothalamic EC levels decrease after food intake, a feedback inhibition pathway (4). Thus, the CB1 receptor appears to play an important role in the regulation of food intake at the level of the hypothalamus. Pagotto noted that there is also an EC system in the gastrointestinal tract. Intestinal EC levels increase with food deprivation and decrease after feeding. CB1 receptors show overlay with cholecystokinin-containing neurons in the gastrointestinal tract. Mice not expressing the CB1 receptor ($CB1^{-/-}$) show decreased body weight and reduced fat mass, with pair-feeding experiments showing decreased body mass independent of food intake, so that CB1 blockade must have more than a pure anorectic effect. In vitro, rimonabant administration decreases, while CB1 receptor agonists increase white adipose tissue lipogenesis. The CB1 receptor is expressed more highly in adipocytes than in preadipocytes, suggesting it to play less of a role in adipocyte differentiation. CB1 receptor agonists upregulate genes involved in lipogenesis in the liver.

Normally, EC activity is transient, but in obesity, the EC signal is more constantly active, with hypothalamic EC overreactivity playing a role in hyperphagia in a number of rodent models. The epididimal fat pad and pancreas EC systems are also upregulated in obesity, with 2-AG levels higher and more sustained. Circulating levels of anadamide and 2-AG are increased in individuals with obesity and diabetes. Perhaps a high-fat diet upregulates anandamide synthesis and/or decreases its degradation. CB1 receptor expression is also increased in the obese rat, with increased CB1 receptor levels in muscle from the *ob/ob* mouse, while rimonabant increases oxygen consumption in these animals, suggesting an effect of the EC system on energy expenditure. Rimonabant also increases β3 adrenergic receptor expression and increases circulating adiponectin levels, so that in obesity, in addition to an immediate effect by decreasing appetite, rimonabant may subsequently act to improve insulin sensitivity and to increase energy expenditure. Thus, there is concern that rimonabant might have adverse effects by raising metabolic rate or causing tacchycardia, although these have not been observed in clinical studies.

Jean-Pierre Despres, Quebec, Canada, described the rimonabant in obesity (RIO) program pooled data, involving a total of 6,627 individuals randomized to 5 or 20 mg rimonabant or to placebo. He noted that visceral fat is associated with a cluster of atherothrombotic inflammatory abnormalities, as defined by the Adult Treatment Panel-III and the International Diabetes Federation. ECs are overproduced in obesity and are targets for obesity treatment, and Despres showed that, among obese men, the degree of visceral obesity is associated with the 2-AG level, with 2-AG tertiles predicting higher triglyceride and insulin levels, lower HDL and adiponectin, and worse glucose tolerance. The four RIO studies, three of which have been published (5,6,7), were designed similarly, with a 1-month placebo run in, so that the "baseline" measurements were actually performed after patients had already lost 2 kg in weight and had had a 2-cm decrease in waist circumference. At 1 year, the placebo group lost 4 kg in weight and 4.5 cm in waist circumference, similar to the outcome of the lifestyle intervention of the Diabetes Prevention Program (8). In the as yet unpublished RIO-Diabetes study, also presented by Scheen et al. (abstract 560), 1,047 type 2 diabetic individuals were treated for 1 year with a 600 kcal/day cal-

orie-deficit diet with 0, 5, or 20 mg rimonabant daily. A1C decreased from 7.3 to 6.7% with the 20-mg rimonabant dose, while decreasing 0.1% with the 5-mg dose and increasing 1% with placebo. The effects were similar among those individuals receiving metformin and those treated with a sulfonylurea. In the 20-mg dose groups receiving metformin and sulfonylurea, fasting glucose decreased 13 and 11 mg/dl, respectively; triglycerides decreased by 9% for both; weight decreased 6 and 5 kg, respectively; and HDL cholesterol increased 17 and 14%, respectively. Placebo-adjusted weight loss was 3.9 kg at 1 year, less than in the studies of nondiabetic individuals whose weight loss was 4.7–5.4 kg, a finding Despres noted to be typical of weight loss studies comparing diabetic with nondiabetic individuals. Among the patients without diabetes, with rimonabant waist circumference decreased 8.5 cm at 1 year. HDL cholesterol was consistently higher and A1C consistently lower with rimonabant treatment than with placebo for any degree of weight loss, suggesting that approximately half of the effect of the drug may reflect a direct effect; although Despres pointed out that there were falls in both HDL and triglycerides during the run-in period, potentially leading to an overestimate of the effects of rimonabant on HDL, although to an underestimate of the triglyceride effects. In the RIO-Lipid study, the prevalence of metabolic syndrome decreased from 53 to 25% with rimonabant, in association with a reduction in insulin and in small, dense LDL levels. Rimonabant decreased leptin and increased adiponectin, with the response appearing to be greater than that seen with similar weight loss among individuals receiving placebo. Despres et al. (abstract 345) reported the effect of rimonabant on glucose tolerance in 2,540 nondiabetic individuals in the RIO-Lipids and RIO-Europe trials. After 1 year, 2-h glucose levels decreased from 115 to 108 mg/dl with placebo but from 111 to 99 mg/dl with 20 mg rimonabant daily. Among those with abnormal glucose tolerance, 52% of those receiving placebo versus 65% of those receiving rimonabant normalized, while 13 versus 6% had developed diabetes at the conclusion of the 1-year study, respectively.

Smith et al. (abstract 344) reported the effect of the 5-hydroxy-tryptophane $(5HT)_{2C}$ agonist APD356 in 469 individuals with BMI 29–46 kg/m^2. At 12 weeks, without caloric restriction, weight decreased from 100 kg by 0.3, 1.8, 2.6, and 3.6 kg with 0-, 10-, 15-, and 20-mg daily doses, respectively, with 2, 13, 20, and 31% losing at least 5% of initial weight. Side effects of headache, nausea, and dizziness were reported in 5–10% more individuals receiving active treatment compared with placebo, without evidence of adverse effect on echocardiogram. Kopelman et al. (abstract 1,711) compared a new lipase inhibitor, cetilistat (ATL-962), with orlistat and with placebo in 612 obese metformin-treated type 2 diabetic individuals, showing similar 4-kg weight loss and 0.5% reduction in A1C (from baseline values of 7.2%), with 2 vs. 12% withdrawal rates, respectively, suggesting the new agent may be preferable to orlistat with similar therapeutic benefit. Galitz et al. (abstract 1,705) reported a 14-day study of cetilistat in 80 obese individuals, finding greater tolerability than in those receiving orlistat, with gastrointestinal side effects of pain, nausea, abnormal feces, and flatulence occurring in ≤5% of treated individuals.

Martínez-Abundis et al. (abstract 1,716) randomized 27 obese individuals to sibutramine, metformin, or both, finding a 3-month fall in BMI of 9, 5, and 11% in association with decrease in fat mass measured with electric bioimpedance only in the sibutramine-treated individuals. Greenway et al. (abstract 1,706) noted that naltrexone and bupropion synergistically block β-endorphin inhibition of the proopiomelanocortin system and administered 300 mg bupropion, 50 mg naltrexone, placebo, or bupropion with naltrexone daily to 206 individuals with BMI 30–40 kg/m^2, finding 24-week weight loss of 3.8, 2.2, 0.9, and 6.6%, respectively, suggesting the two agents to be synergistic in producing weight loss, although nausea, insomnia, dizziness, and diarrhea occurred in >10% of treated individuals. Wing et al. (abstract 1,724) administered the β3-agonist KRP-204/N-5984 at doses of 6, 3, or 1 mg twice daily or placebo to 89 obese type 2 diabetic individuals for 12 weeks, finding 2, 2, 1, and 1% weight loss, respectively, with 10, 5, and 5% decreases, and a 5% increase, respectively, in visceral fat area measured on a single-slice magnetic resonance imaging scan. Ludvik et al. (abstract 1,714) studied 24 obese type 2 diabetic individuals with laparoscopically implanted bipolar gastric electrodes stimulating gastric contraction on detection of food intake. At 5 months, 18 individuals showed a decrease in fasting glucose from 183 to 140 mg/dl and in A1C from 8 to 7.3%. Weight loss was 1.3 kg/month over 9 months of follow-up.

Yu et al. (abstract 1,164) analyzed economic effects of weight change in 266 type 2 diabetic individuals using an HMO claims database, finding each 1% 6-month weight loss among obese individuals to be associated with a 10% decrease in health care cost, while there was no significant increase in health care cost associated with weight gain. Wu et al. (abstract 1,163) further analyzed this database, finding associations of weight gain with high baseline A1C and with insulin use (2% more weight gain) and thiazolidinedione use (3% more weight gain). Huizinga et al. (abstract 1,707), however, reported that over 24 months of observation of 91 individuals participating in a program aimed to sustain glycemic control, those taking insulin (57% at baseline and 58% at 24 months) lost 1 lb, while those not taking insulin gained 7 lb, leading them to distinguish weight gain upon initiation of insulin treatment from the weight change in well-controlled patients continuing to take insulin. Park et al. (abstract 296) reported data from a 5-year study of 2,930 older adults, 2,375 nondiabetic, 448 with known diabetes, and 107 developing fasting glucose over 125 mg/dl during the course of the study. Rather than diabetes being associated with weight gain, in this community-based study, body mass decreased 219, 305, and 601 g/year, with lean body mass decreasing 207, 228, and 401 g/year and fat mass increased to 8 but decreasing 70 and 169 g/year in the respective groups; the newly diagnosed group being at particularly high risk for loss of lean and fat mass.

Formoso et al. (abstract 1,704) enrolled 10 individuals with BMI 34 kg/m^2 in a lifestyle program. After 5% weight loss, the improvement in insulin sensitivity {using the quantitative insulin sensitivity check index 1/[log(fasting insulin) + log(fasting glucose)]}, tumor necrosis factor-α, and interleukin-6 correlated with an *r* value of 0.6–0.7 with the decrease in visceral adipose tissue but not with the change in subcutaneous adipose tissue measured with magnetic resonance imaging. McLaughlin et al. (abstract 1,718) reported a 30-month follow-up of 57 individuals completing a 4-month dietary weight loss program. Of 50 contacted, half had maintained weight loss, with this group showing continued improvement in insulin sensitivity measured from the

steady-state plasma glucose, as well as in fasting triglyceride levels.

Aspects of dietary treatment

Stark and Gary (abstract 971) reviewed a diet recall survey of 8,844 adults in the National Health and Nutrition Examination Survey 1999–2002 showing that only 21 and 32%, respectively, consumed two or more servings of fruit and three or more servings of vegetables, and only 8% met both the fruit and vegetable recommendations, with Mexican Americans, those aged ≥60 years and those with higher education and income, somewhat more likely to follow these dietary recommendations. A number of studies compared the benefits of diets of varying macronutrient compositions given to diabetic individuals. McLaughlin et al. (abstract 332) randomized 29 obese diet-controlled diabetic individuals to hypocaloric 60 vs. 40% dietary carbohydrate diets, finding similar weight loss, improvement in insulin sensitivity measured with steady-state plasma glucose, and fall in blood pressure and triglyceride. Westman et al. (abstract 32) treated 57 individuals with either a low-calorie, low–glycemic index diet or a low-carbohydrate ketogenic diet, with falls in A1C from 8 to 7.5% and from 8.7 to 7.1% and with 5.6 and 8.3-kg weight loss, respectively, with the majority of both groups reducing diabetes medication. Barnard et al. (abstract 33) compared a low-fat vegan diet with a diet following ADA guidelines in 99 type 2 diabetic individuals, finding 6.5- vs. 3.1-kg weight loss, 0.96 vs. 0.38% reduction in A1C, 21 vs. 9% reduction in LDL cholesterol, and 16 vs. 11 mg/24-h reduction in urine microalbumin, respectively. Daly et al. (abstract 34) reported the effect of 6 months of carbohydrate restriction versus energy-deficit diets in 206 type 2 diabetic individuals, finding 3.8- vs. 1.3-kg weight loss, with 4.4- vs. 0.8-cm decrease in waist circumference, although with similar improvement in A1C, urine albumin, blood pressure, and lipids. Brehm et al. (abstract 1,650) treated 80 overweight type 2 diabetic individuals with high monounsaturated fat versus high carbohydrate hypocaloric diets, with 68 vs. 75% adherence at 12 months, respectively, finding similar 4.0- vs. 3.3-kg weight loss and similar improvement in blood pressure, HDL cholesterol, and A1C. In a study of male vervet monkeys, Kavanagh et al. (abstract 328) fed monounsaturated cis versus trans-fatty acids comprising 8% of calories for 5 years, finding that the trans-fat diet was associated with 7 vs. 2% weight gain, 214 vs. 168 mmol/l fructosamine, and evidence of postreceptor abnormality in insulin action in fat and muscle biopsy specimens.

A number of nutritional supplements may have glycemic effects. Stirban et al. (abstract 333) treated 16 type 2 diabetic individuals with a high – versus low–advanced glycation end product meal, with or without benfotiamine, finding that adiponectin decreased following the high-AGE meal, while befotiamine increased levels, as well as decreasing oxidative stress and serum AGE levels. Pins et al. (abstract 31) treated 155 healthy adults whose baseline LDL cholesterol was 130–190 (mean 152) mg/dl with low – and high–molecular weight barley β-glucan concentrate preparations, showing reductions in LDL cholesterol to 127–139 mg/dl, in triglyceride from 185 to 150–162 mg/dl, and in C-reactive protein from 2.8 to 1.6 mg/l, with reductions in postprandial free fatty acid and glucose levels, suggesting this to be a potentially effective intervention for individuals with metabolic syndrome. Pittas et al. (abstract 327) treated 231 nondiabetic individuals aged ≥65 years with 700 IU vitamin D3 and 500 mg calcium versus placebo daily for 3 years, finding that those whose baseline serum 25-hydroxy vitamin D was <50 nmol/l and who had low calcium intake had 0.3 vs. 9 mg/dl increase in fasting glucose, respectively, without difference among individuals with normal baseline vitamin D level. Van Dam et al. (abstract 1,672), however, studied a prospective cohort study of 41,306 U.S. black women, finding that although the highest quintile of calcium intake was associated with a 31% lower risk of diabetes than the lowest quintile, the improvement was largely explained by adjustment for their greater degree of physical activity, higher fiber intake, and lower cigarette use, red meat intake, and sugar-sweetened beverage intake. Ma et al. (abstract 330) analyzed data on ginseng and ginkgo supplement use among 5,504 adults in the Multi-Ethnic Study of Atherosclerosis, finding that 64% took supplements, 6% ginseng, and 7% ginkgo, the former with evidence of lower fasting insulin levels. Lee et al. (abstract 1,660) administered Korean Red Ginseng in a pre-diabetic rat model, showing reduction in body weight and peritoneal fat mass with reductions in glucose, lipids, and CRP but increased adiponectin. Albarracin et al. (abstract 1,649) treated 24 individuals with chromium picolinate plus biotin for 9 months, reporting a 1.1% reduction in A1C. Chow et al. (abstract 1,651) compared a guar gum-containing food bar with a commercial nutrition bar designed for people with diabetes in 99 individuals, finding the former to be associated with enhanced fullness and reduced hunger and subsequent food consumption. Similarly, Flammang et al. (abstract 1,657) administered a crispy snack bar containing viscous guar gum to 52 individuals with type 2 diabetes, finding lower glycemic response than with a control food product. Williams et al. (abstract 1,675) studied the effects of extracts of a traditional Indian herbal medicine, salacia oblonga, an α-glucosidase inhibitor, showing dose-related 14–22% reductions in glucose and insulin levels in 66 individuals with type 2 diabetes after a high-carbohydrate meal.

Diabetes and exercise

A number of studies examined effects of exercise in type 2 diabetes. Molskness et al. (abstract 21-LB) measured fat oxidation during exercise in seven untrained type 2 diabetic individuals before and after a 10-day period of daily exercise at 70% of maximal O_2 consumption for 60 min/day, finding a decrease in the respiratory exchange ratio and a 36% increase in fat oxidation at a 15-W workload, and a doubling of maximal O_2 consumption, indicating that the ability to oxidize lipid during exercise can readily be enhanced following a short training period. Bajepyi et al. (abstract 22-LB) studied 30 sedentary overweight individuals randomized to walking 12 miles/week, jogging 12 miles/week, or jogging 20 miles/week for 6 months, finding improvement in insulin sensitivity in all groups without change in biopsy measures of intramyocellular lipid.

Rana et al. (abstract 298) studied 68,971 initially nondiabetic women in the Nurses' Health Study. The effects of obesity and physical inactivity contributed independently to type 2 diabetes risk. Compared with those with BMI <25 kg/m^2 and exercising >21.8 MET hours/week, those with BMI >30 kg/m^2 who exercised <2.1 MET hours/week had a 16.7-fold increase in risk, those who were active but obese had a 10.8-fold increase, and those inactive with BMI <25 kg/m^2 had a 2.1-fold increase.

In a study by Sato et al. (abstract 961) of 9,205 initially nondiabetic Japanese

men aged 40–55 years followed for 4 years, 920 developed diabetes, based on fasting glucose ≥126 mg/dl and/or administration of diabetes medications. Compared with individuals walking ≤10 min to work, there was a 15% reduction in diabetes risk among those walking 11–20 min and a 28% reduction among those walking ≥20 min, with those in the latter group also reporting physical activity at least once per week having a 48% reduction in likelihood of diabetes. Hayashi et al. (abstract 907) found that in analysis of this database, those with white blood cell (WBC) count in the highest tertile (≥5,900/μl) had a 1.9-fold increase in likelihood of diabetes among nonsmokers and 1.45-fold increase among smokers, while smoking was associated with 1.45-fold increase in diabetes risk in those with WBC count <5,900/μl but was not a significant contributor to diabetes risk among those with WBC count ≥5,900/μl.

Boulé et al. (abstract 1,006) studied 158 sedentary nondiabetic individuals aged 20–65 years wearing a pedometer for 7 consecutive days, finding the first through fourth quartiles to take <3,366, 3,380–4,775, 4,776–5,942, and >5,970 steps/day, respectively, with respective metabolic syndrome prevalence decreasing significantly from 60 to 49% to 41 to 28%. Metcalf et al. (abstract 1,013) used an accelerometer (Manufacturing Technologies) to estimate physical activity in 212 children aged 5–8 years, finding that only 42% of boys and 11% of girls achieved the recommended guideline of >60 min/day at ≥3 METs, equivalent to walking 4 km/h. Boys meeting the guidelines were less likely to show an increase in a composite metabolic risk based on insulin, triglyceride, cholesterol/HDL, and blood pressure levels, while girls meeting the guidelines were less likely to have increased adiposity, based on BMI, waist circumference, and skinfold thicknesses. Storm et al. (abstract 1,015) estimated physical activity by questionnaires in 248 type 1 diabetic individuals in the Pittsburgh Epidemiology of Diabetes Complications study, finding increasing levels of physical activity to correlate negatively with the degree of coronary artery calcification in women, although not in men. Yassine et al. (abstract 1,017) studied 24 individuals with metabolic syndrome undergoing a 12-week supervised exercise program with or without caloric restriction, showing weight loss 6.8 vs. 3.7 kg, respectively, but similar effect on blood pressure, waist circumference, glucose, and triglyceride levels, suggesting the exercise program to give many of the benefits attributed to diet alone.

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