Gestational Diabetes Mellitus and Obesity

ZACHARY T. BLOOMGARDEN, MD

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Gestational diabetes mellitus

In a symposium on advances in the understanding of obesity and weight gain during pregnancy, Teresa A. Hillier (Portland, OR) discussed the implications that pregnancy weight gain in gestational diabetes mellitus (GDM) has for the fetus. Much of the discussion following her lecture and those of the other speakers concerned the May 2009 guidelines of the Institute of Medicine (IOM) for weight gain during pregnancy (www.iom.edu/pregnancyweightgain), which suggest that recommendations to patients be based on prepregnancy BMI. For BMI levels <18.5, 18.5–24.9, 25–29.9, and >30 kg/m^2, weight gain ranges are suggested at 28–40, 25–35, 15–25, and 11–20 pounds, respectively, and the recommended rates of weight gain are 1–1.3, 0.8–1, 0.5–0.7, and 0.4–0.6 pounds/week.

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Hillier noted the lack of consensus on screening and diagnostic criteria for GDM. In the U.S. two steps are used, a 1-h 50-g glucose challenge followed by a 75- or 100-g oral glucose tolerance test (OGTT); outside the U.S., a 2-h 75-g OGTT is recommended. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study of providers blinded to GDM status reported correlations between fasting, 1-h, and 2-h glucose levels and adverse outcomes, including Caesarian section (1). The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) was a randomized controlled trial of 1,000 women with normal fasting glucose not having GDM by World Health Organization criteria (2-h glucose 140–199 mg/dl) assigned to treatment with dietary advice, self-monitoring, and insulin as required or to routine care (2). There was gestational weight gain of 8.1 vs. 9.8 kg, and adverse fetal outcomes occurred in 7 of 506 infants in the intervention group versus 23 of 524 infants in the routine care group; incidences of large for gestational age (LGA) status and macrosomia were reduced, and those was no increased risk of small for gestational age (SGA) status. Similar findings were reported in the National Institute of Child Health and Human Development (NICHD) maternal fetal study (3). (I have criticized what I consider lack of "clinical equipoise" in the design of this study, in which the women in the control group [and their caregivers] were deliberately not informed of the results of their OGTTs [4], despite our extensive knowledge of benefit of treatment of GDM summarized above and elsewhere [5].) Hillier also pointed out that macrosomia increases the risk of metabolic syndrome developing in the children at age 6–11 years (6).

In an observational study of outcomes associated with gestational weight gain among ~30,000 women with GDM, greater weight gain increased the likelihood of need for insulin, of preterm delivery, and of macrosomia, although it reduced the likelihood of low birth weight (7). When stratified by weight gain before versus after diagnosis of GDM, both were associated with an increase in the need for insulin, while preterm delivery rates increased only with weight gain that occurred prior to GDM diagnosis. Thus, weight gain prior to onset of GDM is important. (Studies presented at the ADA meeting further addressing this topic are discussed below.) Hillier described her study of ~40,000 mother-child pairs, in which women with increasingly abnormal levels of glucose tolerance had greater risk of adverse outcome with greater weight gain (8). Follow-up observations of weight at age 5–7 years of 9,439 children from this study showed that abnormal maternal glucose tolerance increased the likelihood of the child's weight being >95th percentile, suggesting GDM to be a modifiable risk factor, particularly in nonmacrosomic-at-birth children (9). Thus, excess weight gain increases LGA risk, risk of preterm delivery, and risk of childhood metabolic syndrome and obesity, and excessive maternal weight gain is a risk factor across all ranges of glucose intolerance; one cannot "just think about the glucose."

Ellen A. Nohr (Aarhus, Denmark) discussed risks associated with pregnancy weight gain in terms of outcomes for the mother and child. An issue with the IOM guidelines is the assessment of whether optimal weight gain for the infant is optimal for the mother. She addressed this in an analysis of 60,892 pregnancies in the Danish National Birth Cohort (10). Mothers were categorized by prepregnancy BMI, and gestational weight gain was subdivided at <10 kg (13%), 10–15 kg (45%), 16–19 kg (21%), and >20 kg (21%). Outcomes studied included infants who were SGA and LGA, delivered by Caesarean section, and maternal weight retention of ≥5 kg 6 months postpartum. SGA risk was markedly increased with low weight gain only in the underweight group, although its frequency was somewhat greater with low gain in all baseline weight groups. LGA and Caesarean section risks showed similar patterns, occurring most often in the overweight and obese groups with greatest weight gain. The weight retention 6 months postpartum was greatest with greater pregnancy weight gain in all groups, but was of greatest consequence in those with greater baseline weight. Nohr concluded that ideal weight gain varies with baseline weight and appears to be 20 kg in underweight, 16–19 kg in normal weight, 10–15 kg in overweight, and <10 kg in obese women.

A follow-up study (11) compared findings among ~27,000 primiparous and ~32,000 multiparous women in the overall dataset. Among the latter, the risk of SGA was lower, perhaps justifying lower weight gain recommendations in this group of 10–15 kg for underweight, 5–9 kg for normal weight, and, perhaps, <5 kg both for overweight and obese multiparous women. "These suggestions

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.
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[…] are meant to start a good discussion," she noted, rather than be definitive. Regardless of parity, the risk of postpartum weight retention was greater with increasing weight gain, and the highest risk of LGA was in obese women.

Michael C. Lu (Los Angeles, CA), who participated in the committee to reexamine IOM pregnancy weight guidelines, reviewed the rationale for reexamining weight gain recommendations. In 1990, he explained, the primary concern was preventing low birth weight, but now the obesity epidemic has become a much greater concern (12), not only in the general population, but also, in particular, among women prior to pregnancy (13). Excessive weight gain during pregnancy has become more common over the past four decades, particularly among women who are overweight and obese, and "the more weight gain during pregnancy, the more weight retained after pregnancy," so that women who gain excessive weight during pregnancy "never get back to their prepregnancy weight," while obese women who gain weight within the guidelines often are able to maintain lower weight after the pregnancy, suggesting that pregnancy weight gain may be a driver of the obesity epidemic.

Consequences of gestational weight gain, as discussed by the previous speakers, include increased risk of Caesarean delivery and increased risk of postpartum weight retention, with maternal prepregnancy weight status an important predictor of health outcomes. The IOM group identified 11 studies of gestational weight gain. Four reported that weight gain above guideline levels was associated with abnormal glucose tolerance, but three reported that less weight gain was associated with higher rates of GDM, and four studies reported no association, so that the direction of causality of negative studies was uncertain. The group found no studies of the effect of gestational weight gain on development of metabolic disorders later in the woman's life. Studies of the relationship between gestational weight gain and hypertensive disorders of pregnancy also reported inconsistent findings. There is definite evidence of association of gestational weight gain with LGA, and there is weaker evidence of an increased likelihood of preterm birth, with potential mechanisms including activation of the maternal-fetal hypothalamic-pituitary-adrenal axis, amniochorionic-decidual or systemic inflammation, uteroplacental ischemia or thrombosis, and pathologic distension of myometrium. Gestational weight gain is also associated with childhood obesity (14,15), as well as with higher blood pressure (16).

Lu explained that the new IOM guidelines suggest new different cutoffs for prepregnancy BMI, a new weight recommendation of 5–9 kg (11–20 pounds) weight gain for obese women, raising the possibility that <5 kg weight gain might be associated with even more favorable outcomes, particularly in those with a BMI >35 kg/m^2. He noted, however, that there is an obligatory weight gain of 5–9 kg based on fetal and placental weight and that restrictive weight guidelines could lead to ketonemia, which in turn might lead to an adverse outcome.

Naomi E. Stotland (San Francisco, CA) further reviewed the new IOM guidelines, from the perspective that existing interventions are insufficient in helping women gain appropriate amounts of weight during pregnancy. Certainly, women should be informed of the importance of optimizing preconception BMI, and prenatal care should include counseling on diet and physical activities.

In a population-based sample in 2004–2005, 45.9% of obese women gained >25 pounds during pregnancy; weight gain for overweight and obese women is above the new guidelines for more than half (17). Pregnancy might be considered "a teachable moment" for women to learn appropriate lifestyle behaviors, and studies of prenatal advice do show benefit (18,19), although approximately one-third of women state they are not given such advice during pregnancy. Studies have shown that interventions are effective when applied. A study of 160 obese pregnant women showed 2.6 kg less weight gain during pregnancy in participants (20), with evidence that exercise plus diet advice may be particularly helpful (21). Such interventions may also improve glucose tolerance (22). Additional approaches include giving women scales, pedometers, and graphic tools to follow their ongoing progress.

A number of studies presented at the ADA meetings discussed other aspects of GDM. Kim et al. (abstract 82) analyzed birth certificate data from seven states, finding GDM in 4%; for BMI 25.1–29.9, 30–34.9, and >35 kg/m^2, the risk was 2.2-, 2.4-, and 4.5-fold greater than that with normal weight, with these groups accounting for 15.7, 9.7, and 18.7% of GDM, respectively, so that lifestyle intervention could in principle eliminate 44% of cases. (Abstract numbers refer to the Abstracts of the 69th Scientific Sessions of the American Diabetes Association, *Diabetes*, Vol. 58, Supplement 1, 2009.) Hedderson and Ferrara (abstract 83) compared 345 women with GDM with 800 control subjects, and found that women who gained 0.27–0.4 and >0.4 kg/week had a 1.5- and 1.6-fold increase in the likelihood of GDM, thus offering a way of identifying and intervening for women at particular risk. Yeung et al. (abstract 84) analyzed 21,632 women from the Nurses' Health Study II with at least one singleton pregnancy between 1989 and 2001, 1,405 with GDM, with weight gain from age 18 years, and prepregnancy waist circumference associated with increased risk; particularly high risk was seen in women with a birth weight <5.5 pounds and high prepregnancy BMI. Qvigstad et al. (abstract 99-LB) performed OGTTs in 1,032 pregnant Scandinavian women, comparing 2002–2005 versus 2005–2008. Although BMI at weeks 14–16 was lower, at 24.9 vs. 24.1 kg/m^2, there was similar weight gain of 10.6 vs. 10.4 kg during pregnancy, and the prevalence of GDM at weeks 30–32 actually increased somewhat, from 10.6 to 12.5%.

Owens et al. (abstract 320) studied 1,441 women with normal glucose tolerance at 24–28 weeks of pregnancy, finding that overweight women had greater rates of macrosomia and were more likely to have miscarriage and Caesarian section and had higher birth weight. Crume et al. (abstract 259) studied 250 children age 6–13 years, 46 of whom were exposed to maternal diabetes in utero. After adjustment for age, sex, and race/ethnicity, Owens et al. found that abdominal subcutaneous adipose tissue was greater in the latter group, while there was no difference in BMI or visceral fat. Gunderson et al. (abstract 314) presented information on 1,390 initially nulliparous women aged 18–30 years without metabolic syndrome in 1985–1986, and reexamined 7, 10, 15, and/or 20 years later with 9,993 person-years of observation. A total of 704 had one or more singleton pregnancies; 120 developed metabolic syndrome, with incidence rates (independent of weight gain and lifestyle) decreasing as lactation duration increased from 0 to 1 month to >9 months. The protective effect was particularly noteworthy among the 84 women who had had GDM.

Chen et al. (abstract 939) reported that, among 13,475 women who reported

at least one singleton pregnancy between 1991 and 2001 in the Nurses' Health Study II, cumulative average intake of sugar-sweetened beverages was associated with risk of GDM. Those who consumed >4 servings per month had a 22% greater risk than those who consumed <1 serving per month. Sugar-sweetened cola, but not other sugar-sweetened carbonated beverages or fruit punch, was associated with particular risk. Retnakaran et al. (abstract 1,007) found that adiponectin levels among 487 women tested in the second and third trimesters of pregnancy were associated not only with GDM, but also with postpartum levels of fasting glucose and with insulin sensitivity and β-cell function. Chamarthi et al. (abstract 321) reported that among 56 pregnancies with pregestational diabetes, maternal microalbuminuria was associated with lower birth weight.

A number of studies addressed ethnic and genetic factors associated with GDM. Lawrence et al. (abstract 87) found that, among women of Asian ancestry, compared to those born outside North America, GDM occurred more commonly with Japanese and Southeast Asian and less commonly with Chinese and Filipina ancestry. Freathy et al. (abstract 80) studied 5,528 Asian and Europid women at 28 weeks of pregnancy. Allelic variants in *GCK* were associated with elevated fasting and 1-h glucose level, as well as with elevated cord C-peptide levels and birth weight, while variants in *TCF7L2* were more strongly associated with 1- and 2-h than with fasting glucose elevations, and not with fetal differences. Sathananthan et al. (abstract 220), however, studied 190 nondiabetic persons (fasting glucose <7 mmol/l/l), finding the diabetes-associated (T) allele at rs7903146 of *TCF7L2* was associated with a 35–44% reduction in insulin sensitivity rather than with impaired insulin secretion. Hayes et al. (abstract 187) found a polymorphism encoding threonine to isoleucine change in exon 4 of the *HNF4A* gene to be associated with fetal size, particularly with head circumference.

Obesity

Rudolph Leibel (New York, NY) discussed leptin biology in the context of weight perturbation and its relevance to the treatment of obesity. In a study of body weight changes induced in rodents by under- or overfeeding, energy requirements deviated in a compensatory fashion (23). Leptin is a hormone secreted by adipose tissue in proportion to the adipose tissue mass, acting as a signal primarily in the arcuate nucleus of the brainstem to regulate energy intake and expenditure, with neuropeptide (NP) Y/Aguoti-related protein (AgRP) neurons orexogenic, driving food intake, while pro-opiomelanocortin (POMC)-containing neurons produce α-melanocyte stimulating hormone (MSH) to reduce food intake (24). Leptin suppresses NPY/AgRP and increases POMC, while its withdrawal has the opposite effects. Leptin action may be considered as exhibiting threshold effects, with the setting of the thresholds related to genetic, developmental, and other influences, so that obese individuals have higher set-points than do lean individuals. When the leptin concentration exceeds the threshold, food intake decreases, while at lower levels the individual behaves as though leptin-deficient. In studies of persons maintained on liquid diets, initially at a stable basal weight and then reducing body weight by 10%, total energy expenditure decreased by 450 kcal, of which 350 was from nonresting and 100 from resting energy expenditure, without change in the thermic effect of food. Examining these persons on a bicycle ergometer, at low energy expenditure a large fraction of the change in nonresting energy expenditure was accounted for by an increase in the mechanical efficiency of exercising skeletal muscle (25). In animal studies, starvation causes NPY and AgRP to increase and POMC to decrease, with reversal by administration of leptin (26). When low-dose leptin was administered to persons weight-stabilized at a lower body weight to restore prior circulating concentrations, the energy expenditure reduction was rectified, and the improved exercise efficiency also returned to its prior level (27). Muscle biopsy studies showed that leptin increased phosphofructokinase and decreased cycloxygenase, leading to reversal of the fatty acid–preferring muscle metabolism in individuals after weight loss (28). Leptin also led to reversal of the decrease in sympathetic tone seen in the weight loss state, with increased epinephrine excretion, and there was low T3 and T4 in the weight-reduced state, which also was normalized by leptin. Thus, the bioenergetics of reduced body weight are such that weight loss reduces the caloric requirement for weight maintenance, and this is restored by leptin administration in these studies. The reduction in energy expenditure with weight loss does not appear to be transitory, but Leibel's studies have demonstrated it to remain after 3–5 years (29).

The hypothalamus must have upward signaling actions to change learning and behavior, and indeed effects of leptin are seen at such levels (30). In persons with congenital leptin deficiency, functional magnetic resonance imaging (fMRI) shows reduction in the activity of specific brain regions that increase food intake behavior with leptin treatment (31). In such studies, the medial and lateral hippocampus and caudate nucleus, which dampen the hedonic impact of food, show decreased fMRI activity with weight loss, and the insular cortex, which mediates food/taste sensibility, shows increased activity with weight loss; these changes are reversed by administration of leptin. Hunger increases and satiety decreases with weight loss, and leptin normalizes these effects.

Leibel described the compensatory process as "the perfect storm for weight regain" after weight loss, since energy intake is not adjusted to maintain lower weight, but, by reducing leptin levels, there is both increased food intake and decreased energy expenditure. The threshold idea has a number of implications. In rat models, ventromedial hypothalamus lesions lead to chronic weight increase, which may mimic effects of neuronal loss of aging, while lateral hypothalamic lesions lead to chronic reduction in body weight, as seen in anorexia nervosa and in cachectic illness. The defense against gain of body fat appears to be much weaker than that against weight loss, and it appears possible that with chronic weight gain the threshold may gradually increase. In animal studies with high-fat feeding to increase weight for long periods followed by weight reduction, energy expenditure is reduced, suggesting that, in contrast to the effect of weight loss, weight gain may lead to a persistently changed set-point. A number of molecular effects might determine the plasticity of this threshold: changes in gene transcription, in neuronal connectivity, or in growth of new neuronal cell bodies or in migration of circulating monocytes to form new glial elements. In vitro studies show leptin to increase arcuate neuronal density. Thus, responses to weight loss may involve endocrine/paracrine change, while weight gain may engender structural changes. There is a great deal of resistance to weight loss, Leibel summarized, which leads to develop-

ment of a hypometabolic, physiologically stressed state, whereas the goal should be the restoration of normal physiology.

Louis J. Aronne (New York, NY) reviewed obesity pharmacotherapy, focusing on combination therapy approaches. He extended the discussion of "why it is so hard to lose weight," noting the large number of central factors stimulating food intake (NPY, AgRP, galanin, orexin-A, dynorphin, and endocannabinoids), as well as those reducing food intake (α-MSH, CRH, GLP-1, CART, norepinephrine, and 5-HT), with myriad afferent signals from the gut and liver (ghrelin, GLP-1, CCK, vagal input), the pancreas (amylin, insulin), the adipocyte (leptin), and the adrenal cortex, and with CNS signals having a variety of effects mediated by the autonomic nervous system in changing food intake and energy expenditure (32,33). This appears to explain the plateauing phenomenon caused by lack of leptin, which leads to a reduction in energy expenditure and an increase in hunger seen with buproprion, sibutramine, phentermine, and the majority of pharmacologic approaches to reduction in appetite. Similarly, in the Swedish Obese Subjects (SOS) Study, with a variety of bariatric surgery approaches, there was a rather abrupt cessation in weight loss once a certain level had been reached (34).

How, Aronne asked, may one overcome this? It is surely incorrect to blame the patient and to say, "You do not want to lose weight!" Patients prefer banding procedures, which involve lesser surgery, leading Aronne to wonder whether combinations of surgery with pharmacotherapy might allow greater weight reduction with such approaches. In an animal study, the combination of sibutramine with replacement-dose leptin led to greater weight loss than with either agent alone (35), suggesting such a synergistic approach. Although such results have not been seen consistently seen in humans, it may be that the correct doses and forms of administration of leptin and other agents have not yet been studied.

A number of novel combination obesity treatments are being investigated in clinical trials: phentermine plus topiramate (Qnexa) by Vivus, bupropion plus naltrexone (Contrave) and bupropion plus zonisamide (Empatic) from Orexigen, and pramlintide plus leptin from Amylin. Naltrexone, which is used in the treatment of alcoholism, is not associated with weight loss, and buproprion is associated with modest weight loss, but the combination clearly leads to greater effect. Intent-to-treat analyses, however, show less effect, as some 40–50% of patients drop out, leading Arone to suggest that completer analyses are preferable in understanding the clinical effects of weight loss medications. Similar effects were seen with the combination of the anticonvulsant zonisamide with bupropion. With the combination of the anticonvulsant topiramate and phentermine (the latter approved in 1959) in doses one-quarter to one-half of those typically used with both agents, weight loss again was seen, with acceptable although definite side effects, including paresthesia in 16–23% vs. 3% of those on placebo and dry mouth in 13 and 19% versus none on placebo. An increase in depression and other psychiatric issues were not reported, although there was insomnia in 10–12% vs. 6%. In a 24-week study, 3% weight loss was seen with pramlintide alone, but 11% weight loss was seen when given in combination with either sibutramine or phentermine; increased blood pressure was seen with sibutramine and, to a lesser extent, with phentermine, and both were associated with tachycardia, insomnia, and dry mouth, leading Aronne to suggest that further studies are needed with even lower doses of the agents. Animal models show that the combination of leptin and amylin increases weight loss. A human study of the combination of pramlintide (in a 360 μg twice daily dose, exceeding the 15–120 μg three times daily usually used in diabetes) and meterleptin 5 mg twice daily showed that the agents alone result in a 7% weight loss, but the combination of the two results in a 13% weight loss in completers at 20 weeks (36). In an animal model, peptide YY (3–36), leptin, and amylin led to weight loss comparable to that seen with Roux-en-Y bypass surgery. "This is the future," Aronne concluded, looking ahead to a better understanding of appropriate targets, treatments using rational combinations of drugs, and effective combinations of drugs with surgery.

A number of studies at the ADA meeting addressed further aspects of obesity and its treatment. Prabhakar et al. (abstract 33) studied polymorphisms of perilipin, which controls lipid storage and metabolism in adipocytes and steroid-producing cells, finding that different variants were associated with greater or lesser weight loss on high– or low–glycemic load calorie-restricted diets. Hammarstedt et al. (abstract 148) described in vitro studies of WISP-2, secreted by adipose tissue with increased expression in obesity and associated with decreased insulin action. WISP-2 prevents differentiation of preadipocytes into adipocytes by maintaining Wnt-signaling pathway activation and inhibiting peroxisome proliferator–activated receptor (PPAR)-γ in a fashion counteracted by PPAR-γ ligands. WISP-2 induced proliferation, inflammation, and expression of macrophage attractants in preadipocytes, and increased adhesion of monocytes to endothelial cells, suggesting a role in adipocyte dysfunction in obesity, as well as a potential therapeutic target.

Campos et al. (abstract 34) compared Roux-en-Y gastric bypass, gastric banding, and calorie restriction without surgery in 18 patients with a mean BMI 48.8 kg/m^2. Fasting insulin and the glucose infusion rate during a euglycemic insulin clamp were comparable in the two groups, although there was greater insulin clearance in the bypass group. Postprandial insulin and GLP-1 levels increased in the bypass group, but not with caloric restriction. Salehi et al. (abstract 150) compared 11 individuals who had hypoglycemia after gastric bypass with 10 individuals who did not. The researchers showed a similar insulin secretion in response to parenteral glucose, as well as an enhanced incretin effect of insulin secretion in response to a liquid mixed meal; there was a similar reduction in this effect by ~50% with the GLP-1 antagonist exendin (9-39) in both groups in comparison to nonsurgical control subjects. Gastric bypass does then increase incretin response, with GLP-1 accounting for half of this effect, but hypoglycemia appeared to have no relationship to these changes. McEwen et al. (abstract 179) calculated cost-utility of bariatric surgery at approximately $15,000 per quality-adjusted life-year gained among 221 persons having procedures between 2001 and 2005; BMI decreased from 51 to 31 kg/m^2 in women and from 59 to 35 kg/m^2 in men. Sensitivity analyses showed it to be more cost-effective in older patients, women, whites, more obese patients, nondiabetic patients, and when performed laparoscopically.

Wadden et al. (abstracts 37 and 1,731) and Klein et al. (abstract 1,730) administered naltrexone 32 mg plus bupropion 360 mg daily versus placebo to 793 overweight persons. Fifty-eight per-

cent of the participants completed the 56-week study; those administered naltrexone plus bupropion experienced a 9.3% weight loss, as compared to 5.1% weight loss among those on placebo. Side effects were nausea in 34% vs. 11%, headache in 24% vs. 18%, constipation in 24% vs. 14%, insomnia in 9% vs. 6%, and anxiety in 5% vs. 4%. Depression occurred in 2% vs. 4%, the lower level in the active arm concordant with the known antidepressant effect of bupropion, and confirmed with a standardized depression score instrument. Two patients developed cholecystitis during rapid weight loss. Aronne et al. (abstract 119) administered placebo versus phentermine plus topiramate to 756 nondiabetic persons for 6 months, showing ~2% vs. 9% weight loss. Smith et al. (abstract 96-LB) administered the 5-hydroxytriptophan2C antagonist lorcaserin 10 mg twice daily versus placebo to 3,182 persons. Of these, 54% vs. 45% completed 1 year, and of these, 74% and 73% completed 2 years of the study, respectively. There was a 5.8 vs. 2.2 kg weight loss at 1 year, and less weight regain at 2 years. McElroy et al. (abstract 325) administered the peripherally selective, non—brain-penetrating cannabinoid-1 receptor antagonist JD-5006 to high-fat fed mice, showing similar improvement in glucose tolerance to that occurring with rimonabant, while not associated with weight loss. Garvey et al. (abstract 361) studied the effect of VI-0521, a combination of phentermine 15 mg and topiramate 92 mg daily, or placebo, in 130 type 2 diabetic individuals, showing reduction in A1C by 1.6% vs. 1.1% and weight loss of 9.4% vs. 2.7%. Bray et al. (abstract 286) reported effects of metformin in the 10-year open-label extension of the Diabetes Prevention Program, finding that among those assigned to treatment with metformin, there was a sustained 4 kg weight loss with consistent adherence, lesser weight loss with lesser degrees of adherence, and stable weight followed after 5 years by weight gain in those not using the agent, concordant with Aronne's discussion above of his preference that completer analyses be used in ascertaining the effect of various treatments on weight loss.

Liu et al. (abstract 88-LB) studied a β-cell–specific knockout of protein tyrosine phophatase (PTP)-1B, a physiological regulator of insulin signaling that opposes the effect of tyrosine kinases in other tissues, finding reduced in vivo and in vitro glucose-stimulated insulin secretion, in keeping with short-loop feedback inhibition by insulin of β-cell function. Ruiz-White et al. (abstract 556) administered the PTP-1B inhibitor trodusquemine in a rodent model, finding improvement in glycemia in association with weight loss.

Ellis et al. (abstract 35) studied prevalence and effects of obesity in a clinic seeing >1,000 type 1 diabetic patients annually. From 2000 to 2005, the prevalence of BMI >30 kg/m^2 increased from 10.4% to 15.7%. Systolic blood pressure was 119 mmHg in nonobese versus 130 mmHg in obese persons, although A1C was similar at 8.4% vs. 8.1%.

Diet

Powers et al. (abstract 179) performed continuous glucose monitoring in 14 type 2 diabetic persons treated with metformin during two moderate and two high-carbohydrate lunches, showing a higher 4-h area under the glucose curve, mean glucose, peak glucose, and longer time to return to preprandial glucose levels with the high-carbohydrate lunch.

Stanhope et al. (abstract 176) compared low–glycemic index diets containing fructose- or glucose-sweetened beverages in 32 overweight persons. Postprandial glucose and insulin levels were greater with glucose, but postprandial triglyceride, apoB, LDL cholesterol, small-dense LDL, and oxidized LDL increased and insulin sensitivity decreased with the fructose-supplemented diet. Page et al. (abstract 80-LB) used functional magnetic resonance imaging (fMRI) to compare regional brain activation, finding greater cortical blood flow in the hypothalamus, amygala, hippocampus, and striatum with lesser increment in plasma glucose, insulin, and GLP-1 after ingesting 75 g fructose than glucose, potentially increasing appetite.

Neelima et al. (abstract 172) randomized 89 type 2 diabetic persons in Hyderabad, India, to low-fat versus control diet, with monthly education sessions for 3 years. There was no effect on weight or lipid levels, but A1C at baseline, 1, 2, and 3 years was 7.8, 7.0, 7.6, and 8.1% in the intervention group and 8.8, 8.3, 9.3, and 8.7%, respectively, in the control group.

Sato et al. (abstract 962) studied 8,567 nondiabetic Japanese men aged 40–55 years who were followed for 4 years; 878 developed diabetes. Among those who consumed alcohol >3 days weekly, light (0.1–23 g ethanol) and moderate (23.1–46 g) alcohol per drinking day were associated with 25–30% reduction in diabetes development over that in those not consuming alcohol, adjusted for age, BMI, fasting plasma glucose, cigarette smoking, family history of diabetes, walking to work, and regular leisure-time physical activity. The protective association was not seen among those consuming alcohol <3 days weekly.

Wang et al. studied diet characteristics among 146 Indian Americans living in the U.S., 28% of who had type 2 diabetes. Comparing tertiles of protein intake adjusted for dietary calories, age, sex, hypertension, and waist circumference, those in the middle and highest tertiles were 3.0- and 4.2-fold more likely to have diabetes than those in the lowest tertile.

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