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Insulin resistance, exercise, and obesity

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This is the sixth of seven reports on the American Diabetes Association (ADA) 1998 Annual Meeting and Scientific Sessions held in Chicago in June. It covers insulin resistance, exercise, and several topics related to obesity.

INSULIN RESISTANCE — In the U.S., 70–80 million people have the insulin resistance syndrome, which becomes type 2 diabetes only when insulin deficiency is also present. In his Banting lecture, Jerold Olefsky, San Diego, CA, discussed this syndrome and its relationship to insulin action and type 2 diabetes. Most (80–90%) of insulin-mediated glucose uptake is by muscle, the major site of insulin resistance in patients with impaired glucose tolerance (IGT). Fasting glucose levels directly correlate with hepatic glucose output, which is normal in IGT and increases in both lean and obese patients with diabetes. Olefsky pointed out that the cause of β-cell failure is unknown, and noted that the insulin resistance of type 2 diabetes is more severe than that of the insulin resistance syndrome alone, suggesting that there is an acquired component to both arms of the diabetic state. Biochemically, the kinase activity of the insulin receptor is decreased in type 2 diabetes, and this also worsens as the fasting glucose level increases. Weight loss reduces fasting glucose and improves glucose disposal in association with normalization of receptor kinase activity, suggesting that hyperglycemia causes decreased kinase activity as a form of glucotoxicity. Potential cellular mechanisms of such glucotoxicity include protein kinase C activation and increased flux through the hexosamine pathway. The major abnormality in type 2 diabetes is decreased translocation of the insulin-sensitive GLUT4 glucose transporter to the cell membrane, perhaps because of an abnormality of the cell membrane in patients with diabetes. Olefsky also stressed that there are two different pathways of insulin action, the metabolic pathway and the mitogenic pathway, with some evidence of discordant abnormality in the two in the insulin resistance syndrome. Phosphatidylinositol (PI) kinase stimulation has a role in both pathways, and abnormalities of the G-protein regulatory compounds and of PI 3-kinase activity may be important in the abnormalities in glucose transport, but, ultimately, Olefsky pointed out that the mechanism of insulin resistance is unknown.

Interestingly, these pathways are also relevant to insulin secretion. Kulkarni et al. reported decreased insulin secretion and content of β-cell lines lacking insulin receptor substrate (IRS)-1 genes (abstract 219; abstract numbers refer to the Abstracts of the 58th Annual Meeting and Scientific Sessions of the ADA, *Diabetes* 47 [Suppl. 1]:1–A496). This suggests a role for IRS-1 in insulin synthesis or secretion as well as in the insulin receptor signaling pathway, where IRS-1 undergoes insulin-dependent tyrosine phosphorylation and association with other signaling proteins, such as PI 3-kinase, mediating peripheral biological actions of insulin. Gutierrez et al. (abstract 220) studied IRS-2–deficient mice, which display fasting hyperglycemia and threefold higher fasting insulin levels than wild-type animals but have reduced β-cell mass, also suggesting both peripheral insulin resistance and inadequate β-cell compensation. It is also interesting that Xu et al. (abstract 221) studied a β-cell line transfected with IRS-1 cDNA and observed that overexpression of IRS-1 led to a decrease in hyperglycemia-stimulated insulin biosynthesis.

Richard Bergman, Los Angeles, CA, discussed the interrelationships between β-cell defects and insulin resistance in the development of type 2 diabetes. Mild forms of insulin resistance are difficult to detect because of increased β-cell responsiveness to glucose. Clearly, insulin resistance alone is neither necessary nor sufficient for the development of type 2 diabetes. When insulin sensitivity decreases, compensatory increased secretion by the β-cell may further mask a tendency toward underlying insulin deficiency. Hence the need arises to assess β-cell function in patients matched for the degree of insulin resistance. This approach has shown on multiple occasions that individuals with normal glucose tolerance have greater levels of β-cell function than do those with IGT. Alternatively, mathematical modeling can normalize β-cell function for the degree of insulin resistance. This approach has been the basis of Bergman's "disposition index" studies. The ability of the β-cell to respond to glucose is a "closed loop gain system" where the product of insulin sensitivity multiplied by insulin secretion can be used as an index, with lower levels seen in individuals with IGT (1). The hyperbolic relationship between these parameters is seen in many populations and has been used in the Insulin Resistance Atherosclerosis Study (IRAS). Insulin sensitivity is 43% decreased in IGT and 67% decreased in type 2 diabetes, with 36% and 90% decreases in insulin secretion, respectively. The normal pancreas compensates for insulin resistance with increased insulin secretion. Based on estimates of such compensation, IGT is associated with 80% less β-cell function than would be expected, a line of reasoning that emphasizes the role of insulin defi-

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Abbreviations: ACC, acetyl-CoA carboxylase; CPT1, carnitine palmityl transferase 1; ICV, intracerebroventricular; IGT, impaired glucose tolerance; PFK, phosphofructokinase; PI, phosphatidylinositol; IRAS, Insulin Resistance Atherosclerosis Study; IRS, insulin receptor substrate; NPY, neuropeptide Y; TNF-α, tumor necrosis factor-α; UCP, uncoupling protein.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ciency in the development of type 2 diabetes. Studies addressing this in Pima Indian populations show that individuals with IGT and low disposition index have a 20-fold increase in risk of deterioration to type 2 diabetes.

Meigs et al. (abstract 599) studied 2,311 nondiabetic offspring in the Framingham Heart Study, 20% with one and 1% with two diabetic parents. Those with diabetic parents had increased BMI, 2-hour post-glucose insulin levels, and decreased insulin sensitivity. Mykkanen et al. (abstract 616) investigated the association of fasting intact proinsulin and fasting insulin with insulin sensitivity and insulin deficiency in 479 subjects with type 2 diabetes in the IRAS. As expected, both proinsulin and insulin levels decreased with increasing insulin sensitivity. The proinsulin-to-insulin ratio was not affected by changes in insulin sensitivity but decreased with increasing acute insulin response, suggesting that the proinsulin-to-insulin ratio is a marker of a defect in proinsulin processing or insulin secretion. A fascinating additional feature of insulin resistance was reported by Mayer-Davis et al. (abstract 1567): an inverse U-shaped relation between alcohol consumption and insulin sensitivity in 1,188 men and women without previously diagnosed diabetes from the IRAS. Those having 0.5–2 alcoholic drinks/day had ~20% higher insulin sensitivity than nondrinkers or those having ≥3 alcoholic drinks/day.

Mason et al. (abstract 180) used triglyceride and oleic acid infusion to chronically elevate free fatty acids in rats and showed decreased insulin secretory response to glucose. Cavaghan et al. (abstract 181) used triglyceride emulsion and heparin infusion to elevate free fatty acids in 12 obese patients with IGT and 8 with normal glucose tolerance. Insulin resistance and compensatory hypersecretion of insulin were seen in patients with IGT, while those with normal glucose tolerance showed decreased insulin response to glucose stimuli. Jucker et al. (abstract 1102) used ^{13}C and ^{31}P nuclear magnetic resonance measurements in safflower oil–fed rats to show muscle insulin resistance associated with increased intramuscular triglyceride and fat plus ketone oxidation. These results were in contrast to those in rats that were fed fish oil; in those animals, there was decreased triglyceride accumulation.

In other studies related to insulin resistance, Moises et al. (abstract 1079) showed that captopril increases early insulin-induced phosphorylation events in cultured myocytes, contributing to the increase in insulin sensitivity observed clinically. Breant et al. (abstract 1213) reported a decrease in β-cell mass in the head of the pancreas in adult rats subjected to maternal food restriction during late pregnancy, an observation that is perhaps relevant to the association of decreased birth weight with the development of the insulin resistance syndrome. Marks et al. (abstract 762) treated 16 nondiabetic women with ovarian hyperandrogenism with metformin at doses of 1.5–2.5 g daily or placebo for 9 weeks. In women receiving metformin, there were significant falls in estrogen and in dihydrotestosterone activity without change in fasting or stimulated insulin or in glucose tolerance. There are many complexities in the analysis of the relationship of hyperandrogenism to insulin resistance. Kitabchi et al. (abstract 1548) reported a significant relationship between insulin resistance and testosterone and androstenedione, androgens of gonadal origin, but not with adrenal androgens, in women of African-American ethnic background, but no relationship in women of Caucasian-American ethnic background.

EXERCISE — David Wasserman, Nashville, TN, discussed the major hormonal effector of increased glucose production during exercise, the increase in glucagon and decrease in insulin levels, which is magnified by a 2-fold greater level of glucagon in the portal vein than in the systemic circulation. Increases in epinephrine levels are much less important, particularly because the gut extracts epinephrine so that portal vein levels are actually lower than those in the periphery. In the diabetic state norepinephrine may play a greater role, because there appears to be increased hepatic norepinephrine spillover. The regulation of muscle glucose uptake is mainly insulin independent and is partially related to increased blood flow. Free fatty acid flux is increased with moderate exercise, with decreased reesterification as well as increased lipolysis, reflecting decreased insulin levels and increased sympathetic output. With heavy exercise, however, reesterification increases, perhaps due to increased lactate levels.

Mechanisms for controlling muscle glucose uptake during exercise include brainstem "feedforward" signals as well as feedback from the mechanical signal of muscle contraction. Other important factors affecting glucose levels include an individual's fitness level, the temporal relationship of exercise to meals, and, in patients with diabetic complications, their metabolic control and the treatment used, including the site and method of insulin administration. Issues related to hormonal control include the different factors controlling heavy versus light exercise, because carbohydrate utilization increases, free fatty acid mobilization is suppressed, and catecholamine levels increase but glucagon decreases with increasing exercise intensity. In patients with diabetes, the degree of metabolic control is important, both during and in the days preceding the exercise. Normal subjects undergoing hypoglycemia show a blunted catecholamine response to exercise on the following day, which may have implications for the exercise tolerance of patients with diabetes who experience hypoglycemic episodes. There is an important sex difference in the response to exercise, with males showing a greater increase in catecholamine levels, both norepinephrine and epinephrine, although the free fatty acid increase is greater in females. Addressing this point, Davis et al. (abstract 297) reported that during aerobic exercise of moderate intensity by normal subjects, men have greater epinephrine and norepinephrine responses and carbohydrate oxidation, while women have higher free fatty acid and glycerol levels, suggesting a greater degree of lipolysis.

Neil Ruderman, Boston, MA, discussed cellular events and energy balance during exercise. There are two neurohumeral components involved in maintaining energy balance, an increase in hepatic glucose output and an increase in adipose tissue free fatty acid release. Intracellular events include changes in metabolism of both glucose and fatty acids. In skeletal muscle, insulin-stimulated glucose transport and incorporation into glycogen, as well as increased pyruvate metabolism, are paralleled by changes in fatty acid metabolism. Transport does not change but there is increased long-chain fatty acid–CoA conversion to triglycerides, particularly because of decreased carnitine palmityl transferase 1 (CPT1) activity, the rate-limiting step in fatty acid metabolism. CPT1 is inhibited by malonyl-CoA, an essential metabolite. Malonyl-CoA levels fall in the absence of insulin and glucose and increase with increasing glucose, particularly when insulin is added to in vitro systems. Malonyl-CoA is in turn regulated by acetyl-

CoA carboxylase (ACC), which is activated by phosphorylation, but although hepatic ACC increases after meals, muscle levels are not affected either by insulin or by glucose but are affected by citrate and malate. Ruderman hypothesized, as an extension of the concept of a "glucose–fatty acid cycle," that hyperglycemia increases citrate levels, in turn increasing ACC, which increases malonyl-CoA activity and decreases fatty acid oxidation.

With exercise the pattern is different. Increased intracellular adenine nucleotide levels stimulate phosphofructokinase (PFK), causing increased glycogenolysis and, via PFK, pyruvate production, which in turn stimulates the tricarboxylic acid cycle. There is a parallel effect on fatty acid metabolism, with CPT1 having a role similar to PFK. In exercising muscle, malonyl-CoA and ACC activity decrease within minutes, probably reflecting ACC phosphorylation. Malonyl-CoA, then, acts as a fuel-sensing mechanism, reflecting different effects of both exercise and of substrate availability. In certain animal models, increased malonyl-CoA levels are associated with insulin resistance, and the high respiratory quotient of "pre-obese" subjects suggests high malonyl-CoA levels, perhaps caused by decreased physical activity and by hyperinsulinemia. Ruderman noted that leptin increases fatty acid oxidation and decreases adipocyte ACC activity and that leptin administration decreases malonyl-CoA, suggesting an effect of abnormal leptin action in diabetes. Regardless of the mechanism, it is fascinating to note that the biochemistry predicts that exercise treatment would directly address many of the abnormalities seen in insulin resistance and in type 2 diabetes.

Stephen Schneider, New Brunswick, NJ, discussed "what kinds of benefit you can really expect" with exercise in individuals with type 2 diabetes. He pointed out the highly sedentary habits of most patients, who have decreased aerobic exercise capacity, even below that of the notoriously inactive "average" North American adult. Although physical training benefits patients with diabetes, they appear to have a defect in their potential exercise capacity, a feature also present in nondiabetic relatives. The proposed benefits of exercise include the potential for improved glycemic control, prevention of the progression of metabolic abnormality, weight loss, decreased risk of atherosclerosis, and, perhaps, prevention of sudden death. A 0.5–1.5% improvement in HbA_{1c} levels, similar to that seen with most oral agents, is seen with institution of three-times-weekly exercise programs in patients with type 2 diabetes, although not in patients with type 1 diabetes. Most of the improvement appears to be due to increased insulin sensitivity. Schneider reviewed a study of 187 patients with mild type 2 diabetes who showed a modest weight loss but a 30 mg/dl fall in fasting glucose levels with stable insulin. He commented that the duration of exercise is not as important as the need to exercise at least three times per week. Avoidance of exercise for as little as three days can worsen insulin sensitivity.

The effects of exercise on cardiovascular risk factors are important. The increase in coronary hear disease risk in patients with IGT is similar to that with mild type 2 diabetes. Schneider suggested that glycemic control alone is not the only benefit of exercise, and pointed out that typically a 5- to 10-mmHg fall in blood pressure is seen in insulin-resistant hypertensive patients. There is often a substantial fall in triglyceride, with a more modest fall in LDL and rise in HDL cholesterol levels. All of these are relatively acute effects of exercise and may return to baseline after >3 days without exercise. There is also evidence that the hypercoagulable state improves with regular physical activity. Exercise may even have benefit in the prevention of type 2 diabetes. There is evidence that decreased aerobic capacity is a risk factor. The Malmo study (2) showed 10 vs. 28% progression to type 2 diabetes from IGT with versus without exercise, and the Da Qing study of a population with somewhat more advanced hyperglycemia (3) showed a 45 vs. 65% progression. Wing et al. (4) showed a less impressive reduction with a shorter (2 year) study. Schneider concluded that "it is worthwhile — we can do it if we devote a modest amount of resources."

Other studies of the effects of exercise include that of Weinstock et al. (abstract 1210), who reported a 13.8-kg 16-week weight loss in 45 obese patients with a 48-week supervised diet program, without additional benefit of either aerobic or strength training exercise. Johnston et al. (abstract 1500) assessed daily physical activity in 72 African-American women with type 2 diabetes, whose mean age was 59 years, mean weight 93 kg, and mean BMI 35 kg/m^2. Activity was assessed with the use of a lightweight electronic device to measure daily body movement. The mean energy expenditure was 1,798 metabolic equivalents · min^{-1} · day^{-1}, only 25% greater than a resting metabolic equivalent of sitting in a chair, suggesting that physical inactivity is a major impediment to optimal diabetic control. Yamakita et al. (abstract 625) assigned 10 sedentary patients with type 2 diabetes to aerobic exercise training, 5–7 h/week for 4–6 weeks, and 12 patients to a control group. Initial serum leptin levels were strongly correlated with fat mass and showed a greater decrease during the study in the exercise group, to about two-thirds the levels of the sedentary patients, standardized for fat mass. Rabasa-Lhoret et al. (abstract 630) studied six patients with type 1 diabetes who exercised for 90 min postprandially and took either regular or lispro insulin or a half-dose of lispro insulin preprandially. The full-dose lispro led to a lower postprandial glycemic rise than seen with regular insulin, and both led to a similar glycemic drop during exercise. The half-dose lispro also led to a decreased postprandial glycemic rise while lessening the glycemic drop during exercise, reducing the risk of hypoglycemia.

OBESITY

Pharmacological induction of weight loss

At a symposium on weight management in diabetes, Jay Skyler, Miami, FL, pointed out that one-third of all individuals over 20 years of age in the U.S. are obese and that the prevalence is expected to increase by 10% over the next decade. Because a BMI over 30 kg/m^2 is associated with a 10- to 20-fold increase in diabetes prevalence, and because 90% of patients with type 2 diabetes are obese, treatment of this condition is extremely important. Interestingly, the costs of medical care for patients with type 2 diabetes increase with the degree of obesity, and there are data suggesting that these costs may decrease with weight loss. Thus, such treatment may be cost-effective. Barbara Hansen, Baltimore, MD, spoke further about the benefits of moderate weight loss in type 2 diabetes. A weight loss of 10 kg is associated with a 1% decrease in HbA_{1c}, a loss of 5 kg is associated with a 12-mmHg fall in blood pressure, and a loss of 1 kg is associated with a 2-mg/dl fall in cholesterol levels. In studies of rhesus monkeys, where diabetes develops in about one-third of animals on an ad lib diet, diabetes and IGT can be prevented with a weight-stabilizing

diet, which also lowers mortality. Studies in women with diabetes similarly suggest decreased mortality with weight loss. Hansen noted that the average fashion model has a BMI of 16, an unrealistic goal to which many women aspire and one that overweight patients may simply feel makes success at dieting impossible. Hansen suggested that, instead, a goal BMI of 27 is realistic, particularly in individuals with risk factors such as diabetes and dyslipidemia, and that for a patient with BMI >30, aggressive treatment is warranted. She suggested that "we are right at the brink of effective long-term mechanisms of treating obesity" and stressed the need for close follow up of these patients.

Julio Rosenstock, Dallas, TX, spoke on the pharmacological treatment of obesity. Orlistat may be effective, with a 9% weight loss reported, although placebo patients had a 6% weight loss in these studies. The best-studied agent currently available is sibutramine, which inhibits reuptake of both serotonin and norepinephrine without causing their release, which may have contributed to higher local serotonin levels with fenfluramine treatment. More than 4,000 patients have been studied, with the only side effect being a 1- to 3-mmHg increase in blood pressure, with no evidence of increased valvular heart disease risk. Over 6 months, patients treated with 5, 10, and 15 mg daily experience weight loss of ~5, 10, and 15 lb. In a 24-week study of patients with diabetes and HbA_{1c} averaging 8.1%, Rosenstock observed a 4–5% weight loss with sibutramine at a dose of 20 mg. Fasting glucose levels fell by >20 mg/dl from 8 weeks on, although there was no significant fall in HbA_{1c}, and there was a fall in triglyceride and a trend to increased HDL levels. Day et al. (abstract 1218) showed that chronic administration of sibutramine reduced weight gain by 12%, decreased hyperinsulinemia 53%, and increased the rate of insulin-induced plasma glucose disappearance by 10% in *ob*/*ob* mice. Bates et al. (abstract 1219) showed evidence of a direct effect of the active primary amine metabolite of sibutramine in improving insulin sensitivity in muscle in vitro.

Khan et al. (1204) presented echocardiographic findings on fenfluramine- and dexfenfluramine-related valvulopathy in obese diabetic and nondiabetic patients. Of 185 subjects without treatment and without diabetes and of 20 patients without treatment and with diabetes, 1% and none had echocardiographic evidence of valvular disease. In contrast, 26% and 20% of 230 and 30 nondiabetic and diabetic patients treated with fenfluramine or dexfenfluramine showed valvulopathy. Bantle et al. (abstract 405) presented a randomized trial in obese patients with type 2 diabetes of fenfluramine at a dose of 20 mg three times daily and phentermine at a dose of 37.5 mg daily (n = 23) or dual placebos (n = 21), which was stopped in September 1997 when fenfluramine was withdrawn from the U.S. market. Treatment patients showed a sustained 8–10 kg weight loss vs. 1–2 kg with placebo, with a 70-mg/dl fall in fasting glucose and 1.7% fall in HbA_{1c}, which were sustained through 6 months, with 13 subjects in each group, but waned at 12 months, with 8 subjects in each group.

Luo et al. (abstract 306) administered the dopamine D_2 receptor agonist bromocryptine to glucose-intolerant Syrian hamsters for 14 days. The effects of peripheral administration of 800 µg/day bromocryptine were duplicated by intracerebroventricular administration of 1 µg/day, with similar prevention of weight gain, fall in fasting plasma insulin, and decrease in glucose and insulin excursions after oral glucose. Cincotta et al. (abstract 1230) and Cincotta et al. (abstract 1383), from the same group, showed that in high fat–fed Syrian hamsters, the effects of bromocryptine and metformin were additive in reducing body weight, glucose intolerance, and hyperinsulinemia. They also found that dopamine receptor antagonists decreased body weight, plasma leptin, and glucose and insulin levels in lethal yellow (A^y/a) mice, which have a defect in central proopiomelanocortin signaling associated with obesity and insulin resistance.

Robbins, for the Orlistat investigators (abstract 362), reported the rates of development of diabetes and IGT among obese patients randomly assigned to receive orlistat at a dose of 120 mg three times daily or placebo for 2 years. Of these subjects, 855 had normal glucose tolerance initially, with 2.4 and 2.2% deteriorating to IGT at 1 and 2 years with orlistat, but 3.8 and 7.5% deteriorating in the placebo group. Among those in the study were 63 subjects with IGT, with 4.7 and 4.3% deteriorating to diabetes at 1 and 2 years with orlistat, but 25 and 25% deteriorating in the placebo group. There were also 44 diabetic subjects, with 32.3 and 46.7% improving to IGT at 1 and 2 years with orlistat, but only 7.7 and 11.1% improving in the placebo group. Davidson (abstract 1039) analyzed the change in lipid status in 1,561 obese individuals treated with orlistat compared with 1,119 receiving placebo in five large, multicenter, randomized U.S. and European clinical trials. Weight decreased 8.9 vs. 5.6%, LDL cholesterol decreased 4.2% vs. a 4.8% increase with placebo, and apolipoprotein B decreased 13% vs. an increase of 72%.

Epidemiologic factors in obesity and diabetes

Resnick et al. (abstract 575) used ~10 years of follow-up data from 1,918 nondiabetic individuals with baseline obesity from the National Health and Nutrition Examination Survey. The average weight gain was 0.1 kg/year for the overall group but was 0.5 kg/year in the 248 individuals who developed diabetes. Each kilogram of weight gained over the first 10 years of the study was associated with a 50% increase in the risk of developing diabetes. Williamson et al. (abstract 593) analyzed data on 1,644 men aged 40–64 years with BMI ≥27 who reported they had diabetes in 1960. There had been 696 deaths by 1972. Compared to 555 men who reported no change in weight, 151 men who intentionally lost 1–19 lb had a 10% reduction in total mortality, and 479 men who intentionally lost ≥20 lb had a 32% reduction in total mortality. Among 235 subjects with unintentional weight loss there was an 11% reduction in mortality, while 27 with unintentional weight gain had an 18% increase in mortality. Sakurai et al. (abstract 603) studied 1,664 Japanese men without serious past medical history and with ≥10 years of available data. Suggesting an adverse effect of weight cycling, those whose weight increased at least 5 kg during a 5-year interval and decreased at least 5 kg during another 5-year interval had ~fourfold age- and BMI-adjusted risk of type 2 diabetes. Lakka et al. (abstract 1646) found a J-shaped association of obesity with mortality among 1,347 men followed for 8.2 years, adjusting for age, examination years, smoking, alcohol consumption, socioeconomic status, serum leukocytes, conditioning physical activity, and maximal oxygen uptake. The mortality risk for men with BMI <24.3 was 1.90-fold greater than for men with BMI 24.4–26.1, while the risks for men with BMI 26.2–28.6 and ≥28.7 were 2.70-fold and 2.80-fold greater than those of men with BMI 24.4–26.1. Blood

pressure, hyperinsulinemia, overall obesity, and the waist-to-hip ratio appeared to mediate this phenomenon.

Thompson et al. (abstract 1651) estimated lifetime costs of type 2 diabetes management for the U.S. population for men and women aged 55–64 years according to degree of obesity. Based on BMI cutoff levels of 22.5, 27.5, 32.5, and 37.5 kg/m^2, costs were $2,770, $4,330, $6,530, and $9,390 respectively, for men, and $5,150, $7,520, $10,700, and $14,710, for women.

Pathophysiology of obesity

Barzilai et al. (abstract 1216) subjected moderately obese Sprague-Dawley rats to surgical removal of epididymal and perinephric, but not mesenteric, fat pads, or to a sham operation. After 3 weeks, insulin sensitivity improved more than 2-fold in animals from which fat pads had been removed, to levels similar to those of lean young rats. This suggests a direct causal relationship between visceral fat and insulin resistance. Snitker et al. (abstract 49) studied subcutaneous abdominal adipose tissue biopsies from 119 healthy nondiabetic male Pima Indians. Basal in vitro lipolysis correlated negatively with the annual rate of weight gain independent of initial weight; sensitivity to the antilipolytic effect of insulin correlated positively. These observations suggest that fat storage in adipocytes rather than fat oxidation in skeletal muscle increases the risk of type 2 diabetes.

Kelley et al. (abstract 106) performed leg-balance studies in 31 obese, glucose-tolerant subjects and 9 type 2 diabetes patients before and after 4 months of a behavior modification program aimed at reducing weight, without increasing exercise. Fasting blood glucose and insulin-stimulated glucose metabolism improved by 30–40% following weight loss. Muscle free fatty acid uptake did not increase, which may predispose patients to regain body weight.

Willi et al. (abstract 50) measured levels of protein and mRNA for uncoupling protein (UCP)2, which is ubiquitous, and UCP3, which is expressed primarily in skeletal muscle, in skeletal muscle biopsies from 20 nondiabetic subjects and 12 type 2 diabetic subjects undergoing indirect calorimetry and a euglycemic hyperinsulinemic clamp. UCP2 and UCP3 mRNA and protein levels were positively correlated with one another but showed no relation to total energy expenditure, either resting metabolic rate or insulin-induced thermogenesis. Both UCP2 and UCP3 were positively associated with carbohydrate oxidation and negatively associated with lipid oxidation in women; they were positively associated with insulin-mediated glucose uptake in men. In men and in women, UCP2 (but not UCP3) was negatively correlated with BMI and the proportion of body fat. Thus, UCP may regulate body weight via effects on fuel partitioning and insulin sensitivity.

The β_3-adrenergic receptor is expressed in visceral adipose tissue and regulates the resting metabolic rate and lipolysis. A mutation in the gene encoding the receptor is associated with an early onset of type 2 diabetes and increased capacity to gain weight. Addressing a potential therapy, Akiyama (abstract 1667) administered a traditional Japanese herbal medicine that activates thermogenesis, Bofu-Tsusho-San (TJ62), to 11 obese subjects with a mutation in the β_3-adrenergic receptor gene and to 12 without the mutation. TJ62 treatment was associated with 0.3 vs. 0.5 kg greater weight loss than placebo in the two groups, with similar improvement in insulin resistance and decrease in visceral fat, suggesting a role for TJ62 in the treatment of obesity. Weyer et al. (abstract 379) reported the effects of a selective β_3-adrenoceptor agonist, CL 316.243, in 14 healthy men. After 4 weeks of treatment, a 45% increase in total body glucose utilization and 82% increase in nonoxidative glucose disposal were noted, without change in splanchnic glucose production. After 8 weeks, however, these effects were greatly diminished, possibly due to downregulation of β_3-adrenoceptors. Fasting insulin did not change during the study.

The inflammatory cytokine tumor necrosis factor (TNF)-α may play an important paracrine role in the insulin-resistance syndrome. Ree et al. (25) used a viral gene transfer system of a TNF-inhibitor gene in obese Zucker rats. Peripheral glucose disposal increased 2.4-fold over control levels and there was increased skeletal muscle (but not hepatic) insulin receptor tyrosine phosphorylation, suggesting a role of TNF-α in the insulin resistance of obesity. Medina et al. (abstract 217) showed that incubation of isolated rat adipocytes with TNF-α inhibits leptin secretion in a concentration-dependent fashion, suggesting that a previously reported stimulatory effect on leptin secretion in vivo is indirect. Pipek et al. (abstract 1336) reported an increase in plasma TNF-α in 71 Mexican-American patients with type 2 diabetes, and a significant, although weak, correlation with the degree of insulin resistance when compared with 54 control subjects and 22 patients with IGT. Trajanoski et al. (abstract 1198), however, reported that while adipose tissue interstitial fluid as well as plasma leptin levels were increased in obese women, TNF-α levels were similar to those in lean women, implying that TNF-α may not have an important paracrine role in the adipose tissue insulin resistance of obesity.

Leptin

Much research has been focused on the role of leptin in obesity. Hawkins et al. (abstract 51) reported the results of intracerebroventricular (ICV) leptin administration in rats, with somatostatin to prevent variation in insulin and glucagon secretion and under conditions of hyperinsulinemia. Hepatic glucose production and peripheral glucose utilization were unchanged, but hepatic gluconeogenesis increased with decreased glycogenolysis. Wang et al. (abstract 107), in further studies from this group, showed that peripheral leptin administration in the presence of basal insulin similarly increased hepatic glycogen storage and gluconeogenesis, without affecting overall glucose production. Hepatic malonyl-CoA, acetyl-CoA, and triglyceride levels were markedly diminished following leptin administration for ≥3 days. Shi et al. (abstract 212), however, showed that long periods of ICV leptin administration increased insulin sensitivity, decreased glucose production, and increased systemic glucose utilization in rats. Turner et al. (abstract 1081) studied two mouse models of leptin deficiency, *ob*/*ob* and fasting. In both, hepatic glucose production was decreased with leptin administration by decreasing glycogenolysis and gluconeogenesis. Chinookoswong et al. (abstract 279) reported that in streptozotocin-induced diabetic rats, over a 7-day period ICV leptin normalized fasting blood glucose, perhaps by decreasing gluconeogenic precursors, including glycerol and lactate, and lowered triglyceride and β-hydroxybutyrate. Williams et al. (abstract 284) reported that leptin increased both basal and insulin-stimulated glucose uptake into isolated human subcutaneous adipocytes. Dobbins et al. (abstract 1084) found that a 10-day ICV leptin infusion decreased lean body mass and muscle triglyceride, as well as completely ablating

adipocyte triglyceride, in normal rats. Combatsiaris and Charron (abstract 1238) reported that acute leptin administration parenterally or ICV decreases white adipose tissue UCP2 mRNA and skeletal muscle UCP3 mRNA, suggesting that there is a centrally mediated action to increase peripheral tissue high-energy phosphate reserves.

The anorexic effect of leptin involves inhibition of transcription of neuropeptide Y (NPY). Fasting both lowers leptin levels and increases NPY transcription, and Baskin et al. (abstract 54) reported that fasting increases the number of NPY neurons in the arcuate nucleus that coexpresses leptin receptor, without affecting the number of neurons producing proopiomelanocortin, a precursor of α-melanocyte stimulating hormone, which causes anorexia. Satoh et al. (abstract 53) reported that ICV leptin decreased food intake and that an antagonist of α-melanocyte stimulating hormone, which had no effect administered alone, reversed this. ICV NPY increased food intake, an effect that was partially reversed by leptin.

McNeely et al. (abstract 99) reported that baseline leptin levels, which correlate strongly with total adipose tissue, were 6.0 ng/ml in 23 men who developed diabetes over the subsequent 5 years vs. 3.8 ng/ml in 212 who did not. Leptin levels are higher in women than men. In 17 women who developed diabetes, levels were 12.3 ng/ml, similar to levels of 11.6 ng/ml in 158 women who remained nondiabetic. Carantoni et al. (abstract 214) reported that the decrease in fasting leptin concentration seen with weight loss correlates with decreases in the insulin responses to meals rather than with changes in weight or body fat mass. Marco et al. (abstract 314) increased caloric intake of six young, physically active subjects, leading to a 4-lb weight gain with increase in body fat from 17 to 21% of total weight. Leptin increased from 4 to 6 ng/ml, but surprisingly there was a small improvement in insulin sensitivity. Fischer et al. (abstract 764) showed positive correlations of serum leptin with fat mass and insulin levels and negative correlations with insulin sensitivity and fasting blood glucose in 21 men with type 2 diabetes. Havel et al. (abstract 216) reported that high-carbohydrate meals increased leptin levels, while isocaloric high-fat meals did not, perhaps explaining the weight-reducing effects of high-carbohydrate diets. However, Larsson et al. (abstract 1661) reported a negative correlation of serum leptin with habitual dietary intake of total calories and of both carbohydrate and fat in 64 healthy postmenopausal women.

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