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Thiazolidinediones, obesity, and related topics

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This is the second of four reports on the American Diabetes Association (ADA) 60th Scientific Sessions held in San Antonio, TX, in June 2000. It covers topics related to thiazolidinediones, insulin resistance, and obesity.

Prevention and Treatment of Type 2 Diabetes

At a debate at the meeting, Thomas A. Buchanan, Los Angeles, CA, spoke in favor of the use of thiazolidinediones (TZDs) for prevention of diabetes. He described a prevention trial in a mainly Hispanic group of patients who had previously had gestational diabetes mellitus (GDM) at ~30 years of age. Approximately 10% of such women have type 2 diabetes after pregnancy, and their ultimate diabetes risk approximates 50%. These women have decreased β-cell function and insulin resistance, both during and after pregnancy. Buchanan hypothesized that the β-cell defect is either caused or worsened by insulin resistance.

In 1994, given the hyperbolic relationship between insulin secretion and insulin resistance, his group adopted the strategy of increasing insulin sensitivity with troglitazone. The initial short-term study was of women who had been diagnosed with GDM within the past 4 years and impaired glucose tolerance (IGT), whose risk of developing type 2 diabetes is ~80%. Insulin sensitivity increased with treatment, and the insulin responses to oral and intravenous glucose and to intravenous tolbutamide, suggesting "afterload reduction for the β-cell." Based on these data, the Troglitazone in Prevention of Diabetes (TRIPOD) study was started in a group of women who had had GDM and who had an estimated 70% 5-year risk of developing diabetes; 121 received placebo and 114 troglitazone (400 mg daily), with 27 and 29 months of follow-up. There was no significant difference in weight gain or pregnancy rates. Intention-to-treat analysis showed a 60% reduction in diabetes, with a 12.4% annual risk in patients receiving placebo and 5.7% annual risk in those treated with troglitazone. Buchanan noted that approximately one-third of the intervention group did not have an improvement in insulin sensitivity with troglitazone. Their annual risk of diabetes was 9%, suggesting that it might be possible to develop targeted subgroup treatment.

When asked about the risk of weight gain, Buchanan agreed that weight gain was an important predictor of the risk of diabetes, which was also seen in his study. The weight gain, however, averaged 1.7 vs. 2.0 kg/year in the placebo versus troglitazone groups, so "based on what we have so far, the weight gain was not limiting." Furthermore, there is a greater increase in subcutaneous than in intra-abdominal fat with TZD treatment, which may be advantageous. Buchanan suggested that further studies of TZD should be carried out "in a clinical trial setting but not as standard clinical care." Carotid artery intima-medial thickness studies in the TRIPOD study showed an increase of 0.009 vs. 0.006 mm/year in the placebo versus troglitazone groups, suggesting another potential benefit.

Steven Kahn, Seattle, WA, argued against prophylaxis with TZDs, pointing out the critical importance of insulin secretion in normal glucose regulation. The pancreas, he said, is "making a comeback in its role in the pathogenesis of type 2 diabetes." Insulin increases muscle glucose uptake and decreases hepatic glucose production. Free fatty acids originating in adipose tissue counteract these effects. In type 2 diabetes, the acute insulin response to glucose is lost, and the question is what happens during the progression from normal to IGT to type 2 diabetes. Kahn measured insulin sensitivity and early insulin response to intravenous glucose in 93 healthy subjects, showing a hyperbolic relationship. Patients with type 2 diabetes have insulin resistance and decreased acute insulin response to glucose.

A number of groups have studied individuals with insulin resistance and have shown decreased insulin secretion to be the cause of glucose intolerance. A longitudinal study in Pima Indians compared 17 individuals progressing from normal glucose tolerance to diabetes, with 31 showing continuing normal glucose tolerance (1). The latter group showed a small decrease in insulin sensitivity, with a compensatory increase in insulin secretion, whereas those progressing to diabetes had somewhat more insulin resistance and evidence of β-cell dysfunction at baseline, with progressive worsening of β-cell function as they developed diabetes. Kahn presented an analysis of Buchanan's study of women with GDM followed postpartum, 14 of whom progressed to diabetes and 77 of whom did not (2). Those who progressed to diabetes had greater glucose intolerance with reduced acute insulin response to glucose at baseline, suggesting β-cell dysfunction as the cause of the diabetes.

A number of studies have shown the relationship between obesity and risk of diabetes. Kahn showed data suggesting that lean insulin-sensitive patients, lean insulin-resistant patients, and obese insulin-resistant patients all show a relationship between insulin resistance and body weight, with some lean individuals having the same degree of insulin resistance as obese

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Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; apo, apolipoprotein; AST, aspartate aminotransferase; CDKI, cyclin-dependent kinase inhibitor; GDM, gestational diabetes mellitus; IGFBP, IGF binding protein; IGT, impaired glucose tolerance; IL, interleukin; IRS, insulin receptor substrate; MMP, matrix metaloproteinase; PPAR, peroxisome proliferator–activated receptor; TRIPOD, Troglitazone in Prevention of Diabetes; TZD, thiazolidinedione; VCAM-1, vascular cell adhesion molecule-1.

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

patients. He suggested that intra-abdominal fat is the actual mediator of insulin resistance. 26 older individuals who had a 10% weight loss over a 6-month period showed a significant decrease in intra-abdominal fat in association with improved insulin sensitivity. A study that followed patients after a 6-month nutrition and exercise intervention showed that weight remained below control levels through 5 years, with a fall in 2-h glucose throughout this period (3). In the Da Qing study, 68% of control patients developed diabetes over the 6-year follow-up period, but in the groups treated with nutrition and/or exercise, 41–46% developed diabetes (4). The potential effect of nutrition and exercise in preventing type 2 diabetes is being tested by the Diabetes Prevention Program.

When asked by the moderator of the debate, Nir Barzilai, New York, NY, whether we are "preventing diabetes or treating diabetes in its early stages," Kahn outlined potential outcomes of diabetes prevention studies. Any approach would lower fasting and postprandial glucose, hence reducing IGT and diabetes rates. Baseline levels might decrease, with treated and placebo groups then increasing in parallel (which could be considered treatment), or there could be a change in the fundamental pathophysiology (prevention). Kahn pointed out that either effect could be beneficial. He noted that there are morphological as well as functional changes in β-cells in the progression to type 2 diabetes. These changes are seen with IGT and early diabetes in monkey studies, and they presumably occur in humans as well. Buchanan pointed out that the glycemic response to a glucose load did not improve with troglitazone in the TRIPOD study, suggesting a real preventive effect. Furthermore, 25-year follow-up studies of individuals who have had intravenous glucose tolerance testing show that those who are insulin sensitive have a very low risk of diabetes, suggesting that there may be a level of insulin responsiveness above which "the β-cell will not fail."

Hepatic Safety

At a symposium on TZD treatment, James H. Lewis, Washington, DC, discussed the question of hepatic safety of the TZDs pioglitazone and rosiglitazone. He recalled that Hans Popper termed drug-induced liver disease "a penalty for progress" more than three decades ago. More than 600 chemicals and pharmaceutical drugs cause clinical liver disease, accounting for 20–40% of episodes of fulminant hepatitis and 10% of acute hepatitis hospitalizations for patients >50 years of age. Acetaminophen is responsible for most of these episodes. To diagnose drug-induced liver disease, there should be a temporal association (usually with a latency period of weeks to months), response to withdrawal of the agent, and exclusion of other causes, the latter being the most difficult criterion.

Hepatocellular injury tends to be associated with greater elevation of alanine aminotransferase (ALT) than of aspartate aminotransferase (AST), with necrosis and steatosis seen on biopsy; jaundice is uncommon, although it is an important sign of greater severity. In contrast, with alcoholic liver disease, AST levels are usually higher. Cholestatic hepatitis is due to interruption of bile flow, usually with elevations in alkaline phosphatase, γ-glutamyl transpeptidase, and 5′-nucleotidase; jaundice is not characteristically seen, and the prognosis is usually good. Hypersensitivity injury is usually seen within weeks after exposure, with fever, rash, and eosinophilia typically present. In contrast, aberrant metabolism injury usually occurs over a period of months and is associated only with the manifestations of liver injury. Risk factors include alcohol and acetaminophen use, malnutrition, and increasing age. The dose used and duration of treatment are typically not related to the degree of hepatotoxicity, with the notable exception of acetaminophen. The genetic predisposition that leads to drug-induced injury is currently not measurable, leading to a classic risk-benefit dilemma, although it may be possible to assess this more accurately in the future.

An important consideration in the assessment of liver dysfunction in patients with diabetes is the entity of nonalcoholic steatohepatitis. When hepatitis C, hemochromatosis, and drugs (including sulfonylureas, acarbose, and TZDs) have been excluded as causes, this should be strongly considered. A recent analysis of a large U.K. general practice database reported evidence of hepatitis in ~1% of patients with diabetes, of which ~5% was caused by diabetes treatment and 5% by other medications. Another important cause of liver disease in patients with diabetes is the combination of hypoxia and ischemia referred to as "shock liver," which is usually caused by an identifiable acute illness with sepsis or another cause of acute hypotension.

Troglitazone was reported to be associated with >75 fatal or transplant-requiring cases of liver failure, with its use restricted in 1999 and withdrawn in 2000 because of the availability of safer alternatives. There was a 2:1 female-to-male ratio, the hepatotoxicity was not dose-related, there was usually a latency period of 3–6 months, and injury patterns were predominantly hepatocellular, with peak ALT levels of ~2,000. Lewis pointed out that this may have been predictable because of the ALT elevations seen in clinical trials. Levels >3 times the upper limit of normal were seen in 1.9% of patients, >5 times the upper limit of normal in 1.7%, >8 times in 0.9%, and >20 times in 0.2%. Furthermore, preclinical animal toxicity studies showed hepatic injury in all species tested. However, others have argued that the severe hepatotoxicity was not predictable because in all ALT elevations resolved in the clinical trials, there was no identified toxic metabolite or sign of drug allergy, and jaundice was not seen.

Because a quinone metabolite is the cause of acetaminophen hepatotoxicity, there is speculation that the quinone metabolite of troglitazone is the cause of troglitazone hepatotoxicity as well. Neither rosiglitazone nor pioglitazone have such a metabolite, and they are mainly excreted intact. In clinical trials, neither has shown an increased risk of abnormal liver function, with ALT >3 times the upper limit of normal in 0.25% of patients treated with rosiglitazone, 0.26% treated with pioglitazone, 0.24% treated with sulfonylureas or metformin, and 0.18–0.25% treated with placebo. Nevertheless, liver enzyme monitoring is currently recommended for patients treated with either agent. Pretreatment enzyme levels must be <2.5 times the upper limit of normal, and the drugs should not be given to individuals who developed jaundice with troglitazone. Semi-monthly testing, as well as testing of patients who have symptoms of hepatitis, is recommended for the first year of treatment, with the drug to be discontinued if levels are >3 times the upper limit of normal or if jaundice develops.

Peroxisome Proliferator–Activated Receptors

Willa Hsueh, Los Angeles, CA, discussed the relationship of insulin resistance to atherogenesis, and the relationship of insulin resistance and atherogenesis to a new understanding of the function of peroxisome proliferator–activated receptor (PPAR)-γ and retinoid X receptors in the vasculature. Both receptors are present in

the endothelium of many vascular sites and in arterial wall lesions involving vascular smooth muscle cell proliferation and macrophage infiltration. Activation of PPAR-γ ligands inhibits migration and growth of coronary artery smooth muscle cells in a dose-related fashion. Hsueh discussed a model of postangioplasty restenosis in which neointimal proliferation is markedly inhibited by troglitazone pretreatment in animal and human studies. An interesting ongoing study of arteriovenous dialysis shunts is being carried out with rosiglitazone to see whether the development of atherosclerotic lesions in arterialized veins at these sites can be prevented.

Cellular growth processes, particularly during the progression from the G_1 to the S phase, are regulated by cyclin-dependent kinase inhibitors (CDKIs). Troglitazone and rosiglitazone inhibit both platelet-derived growth factor and insulin-stimulated G_1 to S progression in rat vascular smooth muscle cells, acting by inhibition of mitogen-induced degradation of CDKIs. Monocyte/macrophage entry into the arterial wall is controlled by injury with subsequent production of chemoattractants. PPAR-γ agonists inhibit monocyte migration, and in vivo studies show that troglitazone inhibits atherosclerotic lesion formation in LDL-receptor knockout mice on a high-fat diet independent of effects on lipids. Troglitazone and rosiglitazone also inhibit retinal endothelial proliferation and migration in a dose-dependent fashion. Thus, a variety of factors, including hyperinsulinemia, hyperglycemia, and angiotensin II, appear to act as activators in the setting of vascular injury, with PPAR-γ agonists inhibiting the nuclear effects of these factors and decreasing the atherosclerotic process.

Bart Staels, Lille, France, discussed vascular effects of PPARs and the metabolic syndrome. PPARs are nutritional ligand-activated transcriptional factors regulating gene expression. PPAR-α is expressed in liver, muscle, heart, and other tissues involved in fatty acid oxidation, and it regulates peroxisome proliferation, fatty acid oxidation, and lipoprotein metabolism. PPAR-γ is involved in adipocyte differentiation and proliferation, leading to fatty acid storage as adipocyte triglyceride. PPARs are activated by polyunsaturated fats, such as arachadonic and linoleic acids, and by their lipoxygenase and cycloxygenase derivatives. Fibrates, including fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil, are pharmacological PPAR-α agonists that lower triglycerides. They act in the liver, starting a cascade that leads to increased mitochondrial fatty acid β-oxidation, resulting in a fall in triglyceride production and consequent decrease in secretion of apolipoprotein (apo)C3. Because apoC3 blocks lipoprotein lipase, decreasing its production leads to an increase in triglyceride clearance, further lowering triglyceride levels as well as decreasing small dense LDL levels and increasing HDL levels. There is threefold variability in PPAR-α mRNA levels in different individuals, with low expression predisposing to dyslipidemia and increased cardiovascular risk. PPARs also play a role in macrophage lipid metabolism. Both PPAR-α and PPAR-γ activators induce macrophage apoA1 receptors, which tends to lead to cholesterol efflux and should potentiate reverse cholesterol transport. PPAR-α is expressed in aortic smooth muscle and in vascular monocytes and endothelial cells. It appears to have an antiatherosclerotic role, inhibiting interleukin (IL)-1 induction of IL-6 secretion. Fenofibrate treatment of patients with dyslipidemia decreases IL-6 production. PPAR-γ also decreases induction of the IL-6 gene promoter by nuclear factor kappa B. PPAR-γ agonists inhibit expression of tissue factor, a membrane-activated glycoprotein involved in the thrombogenicity of the ruptured atherosclerotic plaque. Both PPAR-α and PPAR-γ inhibit endothelial cell expression of endothelin induced by thrombin and thus have anti-inflammatory effects.

Jorge Plutzky, Boston, MA, considered direct vascular effects of PPARs via target genes expressed in the vessel wall, showing a number of lines of investigation that suggest that PPAR-γ and, to a lesser extent, PPAR-α agonists are antiatherosclerotic. In human atherosclerotic carotid artery lesions, PPAR-γ is present in monocytes and macrophages and, to a lesser extent, in vascular smooth muscle. Potential therapeutic targets for atherogenesis are endothelial adhesion molecule expression and foam cell formation. Molecular targets include chemoattractants, adhesion molecules, matrix metaloproteinase (MMP), and tissue factor. Chemoattractant cytokines (chemokines) influence a large number of target cell types, interacting with specific receptors. γ-Interferon induces chemokines involved in atherogenesis, with partial inhibition by PPAR-γ agonist pretreatment. Leukocyte chemotaxis is inhibited by the endogenous PPAR-γ agonist 15-deoxy-prostaglandin-J2 and to a lesser extent by TZDs. PPAR-γ agonists also decrease monocyte chemokines, further decreasing inflammation. Plaque rupture involves a decrease in matrix synthesis and an increase in matrix degradation, the latter caused by MMP. Both endogenous PPAR-γ ligands and TZDs inhibit MMP expression and may decrease plaque rupture. PPAR-α is expressed in the endothelium. Vascular cell adhesion molecule-1 (VCAM-1) allows monocyte adherence to the endothelium. Expression of VCAM-1 after incubation with tumor necrosis factor-α is inhibited by a number of PPAR-α agonists acting to decrease transcription by a decrease in expression of the VCAM-1 promoter and leading to a functionally significant decrease in monocyte entry into the vessel wall.

Ronald Law, Los Angeles, CA, further discussed the effects of PPAR-γ ligands in several mouse models of atherosclerosis. Two different types of coronary lesions are seen: type 1, which involve mainly smooth muscle cells, and type 2, with macrophage infiltration. The latter have increased PPAR-γ activity. All cell types in the vessel wall express PPAR-γ. PPAR-γ ligands inhibit vascular macrophage proinflammatory effects and decrease vascular smooth muscle proliferation and migration, as well as act systemically to improve lipids and decrease insulin resistance. PPAR-γ inhibits expression of endothelial VCAM-1, MMP, and inflammatory cytokines. Troglitazone inhibits atherosclerosis in the LDL-receptor knockout mouse on a high-fat diet, and both troglitazone and rosiglitazone inhibit monocyte migration in response to MMP-1.

Lipids, Leptin, and Insulin Resistance

In a symposium on lipids, leptin, and PPARs, J. Dennis McGarry, Dallas, TX, suggested abnormal lipid homeostasis to be the fundamental basis of insulin resistance. Type 2 diabetes and obesity are characterized by insulin resistance, with hyperinsulinemia, hypertension, elevated free fatty acids, and a variety of related findings. "One of the difficulties," McGarry commented, "is to try to understand the order in which these arise."

Thus, the conventional view is that insulin resistance leads to compensatory hyperinsulinemia, causing eventual β-cell failure. Alternatively, there may be a primary defect that leads to both insulin deficiency and insulin resistance, or there may

be primary hyperinsulinemia that leads to insulin resistance.

McGarry asked what causes the insulin resistance and why β-cells subsequently fail. He noted that leptin increases sympathetic nervous system activity with either systemic or intracerebroventricular administration in association with decreasing body fat levels. Therefore, the insulin resistance syndrome could originate in a leptin signaling defect that leads to decreased sympathetic outflow with a consequent decrease in muscle capacity to oxidize fatty acids, leading to accumulation of muscle acyl-CoA and triglyceride, interfering with glucose uptake, and causing the clinical manifestations of insulin resistance. In the β-cell, the decrease in sympathetic tone causes an increase in insulin secretion to levels appropriate for the muscle but not the liver. This leads to an increase in esterification rather than oxidation of fat, causing an increase in adipose tissue stores, further causing more insulin secretion and more increase in triglyceride both in liver and in muscle. In support of this hypothesis, McGarry pointed out that denervation of rat skeletal muscle increases malonyl-CoA levels and causes insulin resistance and that both rodent models of obesity and studies of Pima Indian populations have shown decreased sympathetic tone.

Daniel Stein, Bronx, NY, spoke on the role of intramyocellular triglyceride in insulin resistance. He reviewed McGarry's hypothesis that in the prediabetic state, increasing levels of insulin and nutrients increase intracellular malonyl-CoA, inhibiting carnitine palmitate transferase-1 and consequently decreasing fatty acid oxidation. This leads to increased myocellular triglyceride, which is in equilibrium with long-chain fatty acid–CoA and in turn can inhibit insulin action.

Contamination of muscle biopsy specimens with surrounding adipocytes has been a problem in assessment of muscle metabolism. Nuclear magnetic resonance spectroscopy can be used to measure concentrations and composition of skeletal muscle triglyceride noninvasively, with deconvolution analysis allowing separation of adipose tissue and muscle fat. Biopsy studies in animals have confirmed the quantitative accuracy of this approach, and studies of patients with congenital generalized lipodystrophy further verify the distinction between muscle and adipocyte triglyceride. In this extremely insulin-resistant group entirely lacking adipocyte tissue, muscle triglyceride stores are increased to more than twice normal levels.

In individuals without diabetes, there is a wide range of insulin sensitivity. Intramyocellular fat shows a similar great degree of variability and is by far the strongest predictor of insulin sensitivity. In individuals with diabetes, intramyocellular lipid is increased, with a suggestion of a threshold above which insulin sensitivity no longer worsens. There is a parallel increase in intrahepatic triglyceride in insulin-resistant normal subjects and individuals with diabetes. Predictors of intramyocellular lipid are basal insulin and basal free fatty acid levels, with BMI, 24-h average glucose, percentage of body fat, and a variety of other measures not showing a significant association in multivariate analysis.

Because long-chain fatty acid–CoA can be considered the "bad actor" with triglyceride "just a marker" of this elevation, it is noteworthy that muscle biopsy shows long-chain fatty acid–CoA to have a similar negative correlation with insulin sensitivity. In addition, intramyocellular lipid increases acutely with infusion of lipid emulsion plus heparin, whereas exercise decreases muscle lipid, with insulin sensitivity decreasing with the former and increasing with the latter. Furthermore, leptin acts both directly on muscle in vitro and indirectly when administered intracerebroventricularly to decrease muscle lipid. Thus, a plausible hypothesis has intracellular lipid as the central cause of dysfunction of muscle in type 2 diabetes, as in the liver and β-cell. Exercise, leptin, and PPAR-γ agonists may ameliorate this.

Stephen O'Reilly, Cambridge, U.K., spoke on his investigations of genetic syndromes with defects in insulin action. In individuals with these syndromes, insulin resistance is primary, with compensatory hyperinsulinemia causing secondary effects, including acanthosis nigricans and ovarian hyperandrogenism. A number of subtypes have been described, including insulin receptor mutations, lipodystrophy, and several syndromes that have not been as well characterized. O'Reilly pointed out that study of these rare diseases allows insight into normal insulin action and the common clinical illnesses associated with abnormal insulin action. He has studied 83 patients with acanthosis nigricans and either extreme hyperinsulinemia or diabetes with very high insulin requirements, excluding individuals with morbid obesity. Some of these patients have evidence of insulin receptor, insulin receptor substrate (IRS)-1, or phosphatidylinositol-3 kinase defects. PPAR-γ is an important candidate gene in view of the serendipitous finding that the TZDs are agonists. O'Reilly found 2 of the 83 patients to have mutations of PPAR-γ—one a woman whose son shares the mutation and the abnormal phenotype. All three had early and severe hypertension, suggesting a role of PPAR-γ in blood pressure regulation. Six other PPAR-γ mutations have been defined. There is a common PPAR-γ mutation with normal phenotype, which recently has been shown to lead to a decrease in insulin sensitivity with an increase in the ingested polyunsaturated-to-saturated fat ratio. A mutation in the NH_2-terminus leads to an increase in PPAR-γ activity with obesity but without insulin resistance. A somatic mutation has been described in association with malignancy of the gastrointestinal tract. Three PPAR-γ knockout rodent mutations have been developed, all showing fetal wastage in the homozygous form, whereas heterozygotes paradoxically show increased insulin sensitivity. Thus, at present, we have the peculiar finding that insulin sensitivity is lowest without PPAR-γ, possibly higher with one PPAR-γ gene, lower with two functional PPAR-γ genes, and highest with activating PPAR-γ mutations. Further study will be required to fully understand the relationship between PPAR-γ and insulin sensitivity.

Insulin Resistance Syndrome

A number of studies presented at the ADA meeting analyzed aspects of the insulin resistance syndrome. In a pediatric study, Sinha et al. (abstract 168) reported IGT, associated with elevations in circulating insulin and triglyceride levels, in 6 of 24 prepubertal and 13 of 61 pubertal children seen in an obesity clinic. Delamater et al. (abstract 344) studied 110 Hispanic children between 5 and 9 years of age, finding that 40% had BMI >95th percentile, and 52% had a positive family history of type 2 diabetes. Obesity, but not the family history of diabetes, was associated with expected trends toward abnormality of lipids, blood pressure, and insulin and glucose levels.

Karter et al. (abstract 765) reported no relationship between baseline BMI and the change in insulin sensitivity, but in the 591 individuals from the Insulin Resistance Atherosclerosis Study followed for 5 years, the baseline waist circumference showed weak correlation with the change in insulin sensitivity in nonobese individuals. Pascot

et al. (abstract 55) assessed dyslipidemia in 35 women with IGT, shown by a blood glucose between 7.8 and 11.1 mmol/l 2 h after a 75-g oral glucose load, and 293 women with normal glucose tolerance. Multivariate adjustment for visceral adipose tissue, measured by computed tomography, explained the higher levels of LDL cholesterol, apoB, and total–to–HDL cholesterol ratio and the lower HDL cholesterol levels with IGT, but did not explain the higher levels of triglycerides, insulin, and glucose. Visceral adiposity may be more strongly related to atherogenic dyslipidemia than to abnormalities of glycemia.

Nyholm et al. (abstract 1250) measured visceral and overall obesity in 20 first-degree relatives of patients with type 2 diabetes. Compared with 14 control subjects with matched BMI and waist-to-hip ratio, relatives had 37% lower glucose disposal during hyperinsulinemic clamp and 64% greater visceral obesity using dual-energy X-ray absorptometry and computed tomography scans. Kawasaki et al. (abstract 368) showed lesser correlation of hepatic fat than of visceral fat with insulin resistance estimated by the homeostasis model assessment in 93 Japanese subjects and suggested that liver adiposity is related more to whole-body adiposity than to insulin resistance. He et al. (abstract 1136) reported a reduction in skeletal muscle oxidative enzyme activity across all fiber types in patients with obesity and diabetes, presumably contributing to increased lipid content, which in turn is related to insulin resistance.

Weisnagel et al. (abstract 822) reported that 85 individuals heterozygotic for the Gly972Arg variant of IRS-1 had fat mass of 20.4 kg, whereas 541 individuals with normal IRS-1 had fat mass of 17.6 kg. Younger carriers also had higher BMI and waist circumference, suggesting a role of the IRS-1 gene in the development of obesity. Bruning et al. (abstract 1161) created mice with the neuron-specific disruption of the insulin receptor, showing no impact on brain development, neuronal survival, or neuropsychological performance, but development of obesity with insulin resistance and hypertriglyceridemia, suggesting a role of central insulin signaling in appetite regulation.

Treatment of Dyslipidemia and Obesity

Several studies were relevant to treatment of dyslipidemia. Rissanen et al. (abstract 1123) reported that obese diabetic patients treated with sibutramine (15–20 mg daily) showed falls in triglyceride of 0.24, 0.27, and 0.04 mmol/l at 12, 24, and 52 weeks, respectively, whereas placebo-treated patients showed rises of 0.21, 0.21, and 0.31 mmol/l at the same time points. No difference was seen in total or LDL cholesterol, which rose in sibutramine as well as placebo groups, and there was a modest although significant increase in HDL cholesterol at 52 weeks. Guldstrand et al. (abstract 1314) studied eight patients whose BMI decreased from 45 to 31 kg/m^2 after vertical banded gastroplasty. The fasting cortisol and cortisol response to hypoglycemia decreased by 21 and 67%, whereas leptin levels decreased by 70%.

Sleeman et al. (abstract 172) reported a decrease in food intake and body weight with administration of a modified form of ciliary neurotrophic factor in an obese mouse model of diabetes, with evidence of improved sensitivity of both hypothalamic and peripheral response to insulin. In view of the evidence that heterozygous PPAR-γ–deficient mice are protected from high-fat diet–induced adipocyte hypertrophy, obesity, and insulin resistance, Yamauchi et al. (abstract 156) administered a retinoid X receptor antagonist in an obese mouse model, reducing the size of adipocytes both by inducing adipocyte differentiation and by promoting apoptosis of large size adipocytes, similar to the effects of PPAR-γ agonist administration. Hyperglycemia and hyperinsulinemia decreased with both treatments. However, the PPAR-γ agonist induced adipocyte differentiation more potently than it did apoptosis, increasing the number of adipocytes, total fat mass, and body weight, whereas retinoid X receptor agonist treatment caused more apoptosis than adipocyte differentiation, decreasing the number of large adipocytes, total fat mass, and body weight. Kunitomi et al. (abstract 1313) reported a negative correlation of total IGF-I levels with visceral fat measured by computed tomography scanning.

Heald et al. (abstract 565) reported that IGF binding protein (IGFBP)-1 levels were 49 vs. 80 μg/l in patients with type 2 diabetes with versus without vascular disease or hypertension, showing negative correlation with BMI, waist-to-hip ratio, blood pressure, and triglyceride levels. Ricart et al. (abstract 1261) reported similarly that IGFBP-1 was significantly lower in 24 obese individuals than in 19 lean subjects, with failure of free IGF-I to be suppressed by insulin in the obese group. The IGF system may contribute to abnormalities of glucose homeostasis in insulin resistance and to the development of vascular disease. Corominola et al. (abstract 832) used mRNA differential display of RNA isolated from omental adipose tissue of four lean, four obese, and four diabetic patients, showing 30 cDNA fragments that were differentially expressed. Further analysis showed that five of those genes, encoding plasma retinol binding protein and complement c3 along with three unknown genes, were confirmed to be upregulated in diabetes and/or obesity, offering potential therapeutic targets.

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