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Type 2 diabetes treatment

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This is the fifth of eight reports on the American Diabetes Association (ADA) Annual Meeting and Scientific Sessions held in San Diego in June. It covers topics related to the treatment of type 2 diabetes, most notably the use of pioglitazone, rosiglitazone, troglitazone, thiazolidinediones, and combination and alternative treatments.

Alan Garber, Dallas, TX, reviewed the benefits of glyrcemic control in type 2 diabetes in relation to the evidence of adverse effects of hypoglycemia. Swedish studies have shown that the risks associated with glyburide treatment include mortality exceeding that due to alic acidosis induced by treatment with metformin. Data from Tennen, a Medicaid reimbursement program in Tennessee with information on 33,000 patient-years of diabetes treatment, show that ~1 of every 1,000 patients has an emergency room visit or is hospitalized for hypoglycemia. In the U.K. Prospective Diabetes Study (UKPDS), hospitalizations for hypoglycemia occurred most frequently among patients treated with insulin, glyburide, and, to a lesser extent, chlorpropramide. Potential differences among insulin secretagogues are most apparent when comparing glyburide with repaglinide, the latter reducing the frequency of hypoglycemia by 50–80%. Thus, hypoglycemia may be a barrier to intensive treatment of type 2 diabetes, just as it is to treatment of type 1 diabetes.

Phillip Raskin, Dallas, TX, discussed algorithmic approaches to combination treatment of type 2 diabetes. He commented that the disease is caused by a combination of increased hepatic glucose production and decreased peripheral glucose disposal with a loss of insulin secretion in a setting of increased nutrient ingestion. In the UKPDS, HbA1c levels increased progressively, an effect attributable not to "sulfonylurea failure, but to progressive loss of β-cell function." Treatment goals for type 2 diabetic patients comprise clinical well-being, reduction of GHB values to the range of individuals without diabetes, establishment of normal lipid and blood pressure levels, and stabilization of body weight at a level as close to normal as possible. Combination approaches are used for synergistic improvement of glycyemic control while, ideally, slowing the progression of β-cell failure and deterring weight gain and dyslipidemia. Raskin discussed DeFronzo's study of glyburide and metformin in 632 patients. HbA1c concentration decreased by almost 2% when the patients were treated with a combination of the two agents versus either agent alone. Studies of troglitazone (TGZ) in combination with glyburide show a similar decrease (~1.5%) in HbA1c concentrations. Metformin with TGZ and rosiglitazone (RGZ), which, according to Rankin, "makes good pathophysiologic sense," leads to decreases in HbA1c concentrations of 1.2–1.3%.

Finally, studies of repaglinide in combination with metformin and TGZ are now available and show decreases in HbA1c concentrations of 1 and 1.5%.

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Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; CAP, cbl-associated protein; DPP, dipeptidyl peptidase; E-4, exendin-4; FFA, free fatty acids; GLP, glucagon-like peptide; HGO, hepatic glucose output; INS-1, o-chiro-inositol; KATP channel, ATP-sensitive potassium channel; MCP, monocyte chemotactic protein; PGZ, pioglitazone; PPAR, peroxisome proliferator-activated receptor; RGZ, rosiglitazone; RXR, retinoid X receptor; TGZ, troglitazone; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) Units and conversion factors for many substances.
sulfonylurea receptors and what Lebovitz characterized as “a unique receptor for repaglinide”; the former receptors have a “slow on and slow off” behavior, whereas the latter receptor has a short (~40 min) peak effect. Consequently, administration of repaglinide is required before each meal. Repaglinide shows excretion only in the liver. Therefore, it is safe to administer to individuals with renal insufficiency, but dose modification is required if the drug is administered to individuals with hepatic disease. “Drug naive” patients experience a decline in concentrations of HbA₁c of 1.8% after preprandial administration of repaglinide. Compared with sulfonylureas, repaglinide allows greater flexibility in treatment: hypoglycemia was seen in 24% of glyburide-treated patients, but it was absent in patients treated with repaglinide, and patients treated with repaglinide had a tendency to gain less weight.

**New treatments: human studies**

Schwartz (abstract 427) used the Ergoset formulation of bromocromine (Ergo Science, Boston, MA) in doses of 0.8-4.8 mg daily to treat 32 type 2 diabetic patients who were on insulin therapy. During the 12-week treatment period, HbA₁c concentration rose from 9.2 to 9.3% in the group given placebo, but it decreased from 9.5 to 8.8% in the group given bromocromine; there was a decrease in 9-point glucose day-profile of 29 mg/dl and a decrease in insulin dose of 8% in the treated group. Because deficiency of D-chiro-inositol (INS-1) and methyl-D-chiro-inositol (pinitol) may contribute to the insulin resistance syndrome, Okike et al. (abstract 1582) studied metabolism of these insulinimimetic molecules in 12 patients with type 2 diabetes and 19 patients with type 1 diabetes. INS-1 and pinitol are abundant in dietary legumes, particularly soy. Pinitol in doses of 20 mg·kg⁻¹·day⁻¹ increased both inositols 10- to 50-fold, and plasma INS-1 correlated negatively with triglyceride and positively with HDL cholesterol levels in the patients with type 1 diabetes. Kessler and Allain (late-breaking abstract 2) administered INS-1 versus placebo to 110 patients with type 2 diabetes who were not receiving other forms of hypoglycemic treatment. Of these patients, 27 with elevated levels of free fatty acids (FFAs) showed a decrease of 27% in levels of FFAs and a decrease of 48 mg/dl in 2-h glucose levels on an oral glucose tolerance test. Similarly, 37 newly diagnosed individuals experienced a decrease in total and LDL cholesterol levels. Baron et al. (abstract 123) reported findings of the Early Diabetes Intervention Program (EDIP), which was designed to study the effects of controlling postprandial hyperglycemia with an α-glucosidase inhibitor in patients with fasting glucose levels <126 mg/dl and 2-h post-oral glucose levels >200 mg/dl on 2-h postprandial glucose, β-cell function, and the progression of diabetic complications. Of the 81 patients who were enrolled in the study, 10% had microalbuminuria or retinopathy. Meal glucose testing showed near-normal levels of 122 and 169 mg/dl before and after breakfast, respectively, and 111 and 132 mg/dl before and after lunch. These data suggest that hypoglycemia after the first meal of the day may be sufficient to cause diabetes-related complications. Bahadori et al. (abstract 1526) treated 16 type 2 diabetic patients taking sulfonylureas and metformin with 500 µg chromium picolinate twice a day for 4 months. Fasting insulin levels decreased, and there was no change in HbA₁c concentration or insulin sensitivity. Tayek and Chhibber (abstract 418) administered low-dose oral arginine during infusion of [6-³⁵⁰H]glucose. Glucose production decreased 12% in normal individuals and 18% in patients with type 2 diabetes, and there was a 25 mg/dl decrease in blood glucose levels in the latter group without change in C-peptide or insulin concentrations, which suggests a direct hepatic effect. Gabbay et al. (abstract 49) administered recombinant human IGF-1 to two patients with the type B syndrome of severe insulin resistance, which is characterized by the presence of anti-insulin receptor antibodies in the setting of lupus erythematosis. HbA₁c concentration decreased from 14.9 to 10.4% and from 10.4 to 7.6% in the two patients, the latter of whom had a 30% decrease in insulin dose requirement over 1 month, after which treatment was discontinued because of persistent myalgia; the former patient had a 72% decrease over the course of 1 year. Ryan (abstract 353) surveyed 403 individuals with and 85 individuals without diabetes to assess the use of prescribed and nonprescribed medications. Of those patients with diabetes, 25% relied on alternative therapies, most commonly garlic (8%), echinacea (5.2%), herb mixtures (4%), chromium (3.7%), and glucosamine sulfate (3.5%), with an average monthly cost of $14.50, which exceeded the $10.32 cost of conventional vitamin and mineral supplements. Combined, these costs were close to the $26.91 per month spent on prescribed medications.

**New treatments: animal studies**

van Poelje et al. (abstract 436) studied GP3034, which inhibits fructose 1,6-bisphosphatase, a key regulatory enzyme of gluconeogenesis. GP3034 in orally administered doses of 250 mg/kg resulted in increased levels of hepatic fructose biphosphate and decreased levels of blood glucose by 50% at 6 h with elevation of levels of blood lactate in normal but not in type 1 and type 2 diabetic rat models. Komori et al. (abstract 464) reported that metformin increased phosphorylinoisol 3-kinase-dependent translocation of GLUT1 from the low-density microsome to the plasma membrane fraction with increased glucose transport in cultured human myotubes, suggesting a mechanism of action. Reed et al. (abstract 476) evaluated harunganan, an extract of the plant Harungana madagascariensis, which is used to treat type 2 diabetes in West Africa. In rats given streptozotocin, harunganan decreased levels of blood glucose from 418 to 248 mg/dl with a 25–50% decrease in triglyceride levels. Nag et al. (abstract 485), Dey et al. (abstract 512), and Nag et al. (abstract 1552) studied CLX-0100, an 18-amino acid peptide, and CLX-0900/CLX-0901, which were isolated from plants that are used in traditional medicine for treatment of diabetes. After oral and parenteral administration of the former agent, streptozotocin-induced diabetic rats and NOD mice with undetectable insulin levels showed decreased glucose responses. Unlike insulin, CLX-0100 did not induce hypoglycemia in normal animals, and it resulted in decreased levels of serum triglycerides, FFAs, and cholesterol in a type 2 diabetes animal model; the latter agent acted as an insulin sensitizer. Another compound, CLX-030, modulates activated macrophages by blocking the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-12, and by inducing COX-II. Administration of CLX-030 was shown to decrease serum glucose levels in an insulin-deficient diabetes model and to decrease levels of cholesterol, FFAs, triglycerides, and serum insulin in a type 2 diabetes model. Tran and Robertson (abstract 1017) showed that long-term exposure to interleukin-1β decreased islet insulin secretion with reversal by a cyclooxygenase-2 inhibitor and duplication by addition of...
Thiazolidinediones

Barry Forman, Duarte, CA, discussed the discovery of hormonal ligands, discrete sources of transcription regulation, such as those associated with steroid and thyroid hormones. Intermediary metabolites also play roles in regulating transcription, but their nuclear ligands are less readily determined. PPARs are transcription factors: PPAR-\(\alpha\) is associated with the oxidation of fatty acids; PPAR-\(\gamma\) is associated with the storage of fat in adipocytes and the increase in levels of leptin and other adipocytokine-derived factors. Long-chain fatty acids, particularly if polyunsaturated, bind to PPAR-\(\alpha\), inducing their \(\beta\) oxidation to medium- and short-chain fatty acids and acetyl-CoA. Fibrates also bind to PPAR-\(\alpha\), which explains at least part of the action of these drugs. Arachidonic acid binds weakly and 15-deoxy-\(\Delta\)12-14 prostaglandin J, and TZD bind more strongly to PPAR-\(\gamma\). A decrease in endogenous PPAR-\(\gamma\) ligands may be related to the development of the insulin-resistant state, although there is presently no explanation of the relationship between PPAR-\(\gamma\) action in fat and insulin sensitization in muscle. Forman questioned whether the hepatic side effects of TZG are intrinsic to TZD action in general. The action of high-affinity PPAR-\(\gamma\) ligands are currently being studied to address this issue. Up to 500 mg/day of cholesterol is degraded in the liver to bile acids, which has a tremendous effect on the overall lipid balance, but we have little information on the control of this process. Interruption of the enterohepatic circulation increases bile acid formation, suggesting that bile acids may act through another nuclear receptor. Forman showed data that FXR, a receptor that is expressed in liver, gut, and kidney, is activated by bile acids, chenodeoxycholic acid and, to a lesser extent, deoxycholic acid being the most potent endogenous ligands. The use of transporters increases the activity of a variety of other bile acids. Another nuclear receptor, LXR, is a direct regulator of cytochrome P7a, the rate-limiting enzyme in cholesterol degradation, and is activated by FXR, suggesting a similarity to fatty acid metabolism via the PPAR.

David Moller, Rahway, NJ, discussed studies of the molecular mechanism of PPAR-\(\gamma\) activation, the role of its ligand-binding domain, and data pertaining to non-TZD PPAR-\(\gamma\) ligands and to insulin signaling in the liver. PPAR-\(\gamma\) and retinoid X receptor (RXR) bind to a nuclear receptor site after activation by either PPAR-\(\gamma\) or RXR ligands, which leads to a conformational change in the nuclear binding domain and consequently initiates transcription. By use of a fluorescein-based assay, the relative potency of different compounds can be determined, and partial versus complete agonists can be characterized. The TZDs cause conformational changes in PPAR-\(\gamma\): partial changes are seen with weaker agonists. In vivo, insulin sensitiza-tion by TZD via PPAR-\(\gamma\) involves decreased levels of FFA, triglycerides, and hepatic glucose output (HGO) with increased insulin-stimulated glucose disposal. Cellular actions include increased phosphoenolpyruvate carboxy kinase and fatty acid transport protein levels. The use of a new group of PPAR-\(\alpha\)/\(\gamma\) agonists to study adipogenesis reveals that neither PPAR-\(\alpha\) nor PPAR-\(\gamma\) plays a role in this process, which is affected solely by PPAR-\(\gamma\). Similarly, only PPAR-\(\alpha\)/\(\gamma\) agonists appear to have glucose-lowering actions, whereas both PPAR-\(\alpha\) and PPAR-\(\gamma\) lower triglyceride levels. The FFA-lowering effect of PPAR-\(\alpha\)/\(\gamma\) occurs much more rapidly than its triglyceride-lowering effect, which, in turn, is seen earlier than the effect on glucose by PPAR-\(\alpha\)/\(\gamma\); these observations suggest that the effect on FFA levels is the primary effect. Furthermore, the effects on glucose uptake in white adipose tissue are seen early, whereas those on glucose uptake in skeletal muscle occur after \(\sim\)7 days in models in vivo. Thus, the effects on glucose homeostasis appear to be indirect. Interestingly, insulin-mediated suppression of HGO is seen after 2 days with TZD treatment in this model, which is earlier than the effect on peripheral glucose disposal, and enhanced insulin-induced IRS-1 tyrosine phosphorylation \(<24\) h after TZD exposure. Thus, more data are now available about the cellular effects of TZD.

Alan Saltiel, Ann Arbor, MI, presented additional information regarding PPAR-\(\gamma\) and insulin action. The accepted hypothesis is that TZD effects are secondary to improvement in lipid metabolism; but some studies show profound increases in insulin action without change in lipid homeostasis. Insulin action is complex and requires a variety of mechanisms, including translocation of GLUT4, protein synthesis, gene expression, and cellular growth. Saltiel discussed the concept that both signaling and signal reception are compartmentalized, perhaps to specific plasma membrane domains, and that such compartmentalization contributes to specificity. Many insulin-sensitive cells contain small invaginations in the cell membrane, the caveolae, which appear to act as signaling organelles. Tyrosine phosphorylation of caveolin, a protein specific to these structures, is correlated with the metabolic sensitivity of these cells to insulin, even though the insulin receptor is not present in the caveolar fraction. Thus, there appears to be an insulin-responsive protein that is phosphorylated and rapidly transferred to the caveolae. In an adipocyte cell line, the c-cbl proto-oncogene product appears to function in the same fashion as an insulin-responsive protein, but it requires a cbl-associated protein (CAP), an adaptor protein. CAP has sequence homology to a protein secreted by the gastrointestinal tract, sorbin, and to another protein, flotillin, which is present in caveolae and possibly offers a site of attachment for the CAP-Cbl complex when it is released from the insulin receptor. Insulin causes dissociation of CAP from the insulin receptor, which presumably leads to the movement of phosphorylated CAP to the caveolae. Saltiel showed that CAP is induced by TZD in vitro and in vivo and that its presence correlates with the increase in insulin action. In addition, TZD increases c-cbl tyrosine phosphorylation, whereas other signaling pathways appear to show decreased phosphorylation. The CAP promoter contains a PPAR-response element that binds the PPAR-RXR heterodimer. Thus, a gene involved in insulin action that is responsive to PPAR-\(\gamma\) may be responsible for the effect of TZD on glucose homeostasis. Isolated expression of the sorbin domain of CAP does not affect the ability of the insulin receptor to activate the mitogen-activated protein kinase pathway but blocks insulin-induced glycogen synthetase and glucose transport, giving additional support to the concept that the CAP-Cbl complex represents a spatially compartmentalized signal of insulin action.

Charles Burant, Ann Arbor, MI, discussed differences in the mechanisms among TZDs at the ADA Annual Meeting and expanded on the topic in his lecture at the Mount Sinai School of Medicine, New York, NY, on 11 November 1999. PPAR-\(\gamma\) mediates their action with highest concentration in adipocytes but with effects on glucose homeostasis, fluid retention, and lipid metabolism. TGZ activates PPAR-\(\gamma\) associated with the 3, M12-14 prostaglandin J, and is involved in decreasement, may be responsible for the effect of ligands and to insulin...
less than RGZ does, with TGZ being less potent in binding cofactors to PPAR-γ and acting as a partial antagonist to inhibit the effect of RGZ in adipocyte models, although there may be differential sensitivity in other tissues. Compared with RGZ, TGZ is not as efficient in stimulating adipocyte differentiation, which suggests that TGZ may activate only a subset of the genes activated by RGZ. By drawing a parallel to selective estrogen-receptor modulators, such as tamoxifen, one could describe selective PPAR modulators that activate distinct gene subsets. By using arrays of test chips, each in effect performing several thousand separate Northern blot analyses, one can screen simultaneously for expression of thousands of genes. Burant described studies that have used such an approach in differentiated adipocytes in tissue culture and in mice of the actions of TGZ and RGZ. Interestingly, only a small degree of overlap was found between genes whose expression was increased or decreased by the two agents, suggesting that TGZ and RGZ may not change the conformation of the same set of coactivators and corepressors of the PPAR-γ RXR heterodimer. Only a small number of genes was changed in skeletal muscle. Burant pointed out, however, that experiments in mice that lacked adipose tissue and showed severe insulin resistance have found marked improvement with TGZ, which indicates that the agent may affect the ability of skeletal muscle to metabolize fatty acids, their major substrate. He hypothesized that the mechanism of their effect on glucose homeostasis may involve a decrease in skeletal muscle fatty acid metabolism, which leads to an increase in glucose utilization with a subsequent increase in peripheral glucose uptake. It is worth noting that although the ratio of muscle PPAR-γ levels to total muscle protein levels is small, because of very high contractile protein levels, correcting PPAR-γ for total muscle DNA may be a more appropriate approach and would result in levels of the same order of magnitude as those in adipose tissue. The increase in adipocyte differentiation and triglyceride deposition with these agents may not then be inextricably linked to their beneficial effect in type 2 diabetes. In the liver, gene chip studies do show a number of effects of TZD and, particularly, TGZ.

Burant also discussed RXR agonists, which may show some benefit in glycemia, but appear to decrease levels of lipoprotein lipase and consequently lead to hypertriglyceridemia, which is in contrast to the triglyceride-lowering effects induced by PPAR-γ agonists. RXR agonists may also potentiate thyroid hormone action and thereby lower thyrotropin and thyroxin levels. Because PPAR-γ regulates the expression of its target genes as an obligate heterodimer with the RXR, Ogilvie et al. (abstract 24) compared TZD treatment with RXR agonist insulin sensitizer treatment in an insulin-resistant rodent model. Both agents decreased insulin levels, but body fat increased with TZD and decreased with increased adipocyte apoptosis with RXR agonist treatment. These findings suggest that the use of this class of insulin sensitizers in the treatment of type 2 diabetes is beneficial. Ligands of PPAR-γ increase insulin sensitivity, and activation of the retinoic acid receptor opposes the binding of PPAR-γ to its hormone-response element.

Studies presented at the ADA meetings addressed various aspects of PPAR action. Tanaka et al. (abstract 128) showed that TGZ, PGZ, and 15-deoxy-Δ12,14-prostaglandin, an endogenous ligand of PPAR-γ, inhibited monocyte-macrophage cell proliferation and migration under stimulation by monocyte chemotactic protein (MCP)-1, and Murao et al. (abstract 548) showed TZD-inhibition of MCP-1 production by vascular endothelial cells, which could potentially decrease the risk of atherosclerosis. Smith et al. (abstract 1156) showed that RGZ did not affect macrophage differentiation, but decreased metalloproteinase-9, an enzyme involved in atherosclerotic plaque rupture. Doi et al. (abstract 138) have shown endothelial cell production of C-type natriuretic peptide, which acts as a vasodilator and a growth inhibitor of vascular smooth muscle cells, with decreased concentration in diabetic patients with macroangiopathy. They showed that both TGZ and PGZ increased human aortic endothelial cell growth and natriuretic peptide levels while decreasing production of the vasoconstrictor endothelin. These findings suggest a mechanism of direct benefit of TZD in diabetic vascular disease. Collins et al. (abstract 129) showed that TGZ attenuates atherosclerosis in an LDL receptor knockout mouse model, regardless of changes in glucose, triglyceride, or HDL cholesterol levels. Araki et al. (abstract 597) showed effects of TGZ (but not of RGZ) in decreasing albuminuria and cataract formation in insulin-resistant rats that had blood glucose levels >700 mg/dl. The rats failed to show glycemic response to either agent, which suggests a direct effect of TGZ.

Clinical TZD treatment

Several studies at the ADA meeting presented new clinical information regarding PGZ, RGZ, and TGZ. Mathisen et al. (abstract 441) reported the effects of administering PGZ 30 mg daily vs. placebo in 193 patients with type 2 diabetes whose mean fasting glucose level and HbA1c concentration were 270 mg/dl and 10.3%, respectively. Administration of PGZ decreased the mean fasting glucose level and HbA1c concentration by 50 mg/dl and 0.6%, whereas administration of placebo increased them by 8 mg/dl and 0.76%, respectively. Compared with placebo, PGZ decreased the mean triglyceride level by 85 mg/dl and increased the mean HDL cholesterol level by 5 mg/dl; there was no change in the mean LDL cholesterol level. Schneider et al.
(abstract 469) showed results of treatment with 0, 7.5, 15, 30, and 45 mg PGZ in 408 patients with type 2 diabetes. Previously treated patients were withdrawn from hypoglycemic treatment for 8 weeks. There was a dose-related decrease and a placebo-adjusted decrease in HbA1c levels in 127 previously untreated patients of 0.62, 1.41, 1.26, and 2.55% and in 281 previously treated patients of 0.5, 1.0, 0.9, and 1.4% from baseline levels of 9–11%. Mathiesen et al. (abstract 457) and Schneider et al. (abstract 458) reported the effects of PGZ 15 and 30 mg daily vs. placebo in 560 patients with type 2 diabetes whose HbA1c concentration was >8% on sulfonylureas. In comparison with placebo, PGZ decreased HbA1c concentrations by 0.8 and 1.2%, respectively, and fasting glucose levels by 34 and 52 mg/dl. Moreover, there were 14 and 15% decreases in triglyceride levels from the baseline of 260 mg/dl and 3 and 10% increases in HDL cholesterol levels from the baseline of 42 mg/dl. Egan et al. (abstracts 459 and 504) reported the effects of adding PGZ 30 mg daily to metformin therapy in 328 patients whose HbA1c concentrations were >8%. With PGZ and metformin, mean HbA1c concentration decreased by 0.6 from 9.9% at baseline, whereas it increased by 0.2% with metformin and placebo. Mean triglyceride levels decreased by 63 vs. 20 mg/dl, respectively, from a baseline of 300 mg/dl, but the mean HDL cholesterol level increased by 3 mg/dl vs. no change from a baseline of 42 mg/dl, and the LDL cholesterol level increased by 7 vs. 3 mg/dl from a baseline of 119 mg/dl. Rubin et al. (abstract 474) studied 566 patients whose mean HbA1c concentration was >8%. The patients were treated with >30 U insulin combined with doses of PGZ of 0, 15, or 30 mg daily. Administration of insulin combined with the respective PGZ doses decreased the mean HbA1c concentrations by 0.3, 1.0, and 1.3% from a baseline concentration of 9.8%; mean fasting glucose levels decreased by 0, 35, and 48 mg/dl from baseline levels of 221–229 mg/dl. In all of the PGZ studies, incidences of weight increase, hypoglycemia, and edema were more frequent with active treatment.

Raskin and Rappaport (abstract 409) reported the effects of administering RIZ in doses of 2, 4, and 6 mg twice a day in 303 patients with type 2 diabetes. The mean fasting glucose level increased 19 mg/dl from 229 mg/dl in a group administered placebo, whereas it decreased 36, 43, and 46 mg/dl, respectively, in the three active RIZ groups. Nolan et al. (abstract 478) treated 369 type 2 diabetic patients with RIZ in doses of 4, 8, and 12 mg once daily. Administration of placebo resulted in an average increase of 7 mg/dl from 185 mg/dl, whereas active treatment with RIZ resulted in average decreases of 28, 52, and 55 mg/dl, respectively. Grunberger et al. (abstract 439) studied a cohort of 959 type 2 diabetic patients and compared treatment with placebo with treatment with RIZ in doses of 4 mg daily, 2 mg twice a day, 8 mg daily, and 4 mg twice a day. The baseline HbA1c concentration was 8.9%, which increased by 0.8% with placebo and decreased by 0, 0.1, 0.3, and 0.7%, respectively, in the four active treatment groups. Gomis et al. (abstract 266) studied 574 patients with type 2 diabetes who were treated with RIZ in doses of 0, 2, or 4 mg daily in two divided doses that were added to sulfonylurea treatment. The mean HbA1c concentration was 9.2% at baseline. In the group administered placebo, HbA1c increased by 0.2%, and the mean fasting glucose level increased by 6 mg/dl from a baseline level of 207 mg/dl. In the active treatment groups, HbA1c decreased by 0.5 and 0.9%, and fasting glucose decreased by 17 and 38 mg/dl. Raskin et al. (abstract 404) reported on 391 patients with an HbA1c concentration >7.5% who were treated with insulin twice a day. The patients were randomly assigned to additional treatment with placebo or RIZ 2 or 4 mg twice a day. The mean HbA1c concentration in patients who received placebo increased by 0.1 from 8.9% at baseline, and the mean fasting glucose level increased by 10 from 195 mg/dl. In the groups who received additional RIZ treatment, HbA1c decreased by 0.6 and 1.2%, and fasting glucose decreased by 42 and 44 mg/dl. Fonseca et al. (abstract 431) treated 348 patients with type 2 diabetes with metformin 2.5 g daily in combination with placebo or RIZ in doses of 4 or 8 mg once daily. The average baseline glucose and HbA1c values were 214 mg/dl and 8.6%. In the group administered placebo, the mean glucose level increased by 6 mg/dl, and the mean HbA1c concentration increased by 0.5%. In the groups administered RIZ, the glucose values decreased by 33 and 48 mg/dl, and the HbA1c concentrations decreased by 0.6 and 0.8%. Salzman et al. (abstract 408) reported that RIZ therapy is not associated with hepatotoxicity. Of 3,455 type 2 diabetic patients who were treated with RIZ, 0.17% showed transaminase values more than three times the upper limit of the normal range, as compared with 0.18% of 561 patients treated with placebo and 0.48% of 828 patients treated with sulfonylurea and metformin. Beebe et al. (abstract 479) reported that among 832 patients aged >65 years who were treated with RIZ, adverse-event frequency was similar to that in 197 patients who were treated with placebo, except for that of edema (7.5 vs. 1.7%, respectively).

To determine whether TID can be used for prevention of glucocorticoid-induced hyperglycemia, Willi et al. (abstract 324) administered dexamethasone 4 mg daily for 3–4 days to six individuals with normal glucose tolerance before and after a 4- to 5-week course of TID in doses of 400 mg daily. Administration of TID prevented the impaired glucose tolerance that developed as a result of administration of dexamethasone in five of the study subjects, and it increased insulin levels two- to fourfold. Levels of muscle glucose uptake, which were assessed by use of a hyperinsulinemic clamp, decreased by 40% on average during the courses of dexamethasone; however, this effect also was blocked by administration of TID. Morita et al. (abstract 402) similarly studied five healthy subjects who were treated with dexamethasone 4 mg daily for 3 days before and after 14-day courses of TID in doses of 400 mg daily and metformin in doses of 500 mg daily. TID, but not the (subtherapeutic) metformin, returned glucose and insulin levels to baseline. Petersen et al. (abstract 399) used nuclear magnetic resonance spectroscopy with 13C to measure the rate of muscle glycogen synthesis and 31P measurement of intramuscular glucose-6-phosphate to assess glucose metabolism in seven patients with type 2 diabetes before and after 3 months of treatment with TID 400 mg daily. The patients' mean level of fasting glucose decreased from 10.9 to 8.6 mmol/l. Insulin-stimulated whole-body glucose uptake increased by 60%, glucose oxidation increased by 70%, and muscle glycogen synthesis increased 10-fold with increased glucose transport and phosphorylation. These findings indicate that TID improves skeletal muscle insulin responsiveness in patients with type 2 diabetes by increasing insulin-stimulated muscle glycogen synthesis through reversal of an underlying defect in insulin-stimulated glucose transport and/or phosphorylation. Yokoyama et al. (abstract 421) used skele-
tal muscle positron emission tomography imaging to assess the effects of TGZ on skeletal muscle glucose utilization in 15 patients with type 2 diabetes. Skeletal muscle glucose uptake in the type 2 diabetic patients was significantly lower than that of the control subjects (0.44 vs. 1.96 mg·min⁻¹·kg⁻¹), and it doubled with treatment. Maher and Mirza (abstract 366) reported on two cases of 80-year-old patients with type 2 diabetes who were treated with TGZ for new-onset ataxia; one of the patients also suffered from memory loss, urinary incontinence, and the inability to perform complex cognitive tasks. The ataxia resolved in 2–3 days and 2 weeks after TGZ withdrawal; it recurred in one patient upon readministration of the drug.

Arioglu et al. (abstract 403) administered TGZ to 14 patients with lipodystrophic diabetes, which is characterized by extreme insulin resistance and partial or total absence of adipose tissue. HbA₁c concentration decreased from 9.7 to 7.4%, levels of fasting FFAs decreased from 862 to 577 µEq/l, and triglyceride levels decreased from 602 to 358 mg/dl with a small increase in total body fat. Kamada et al. (abstract 406) reported a decrease in visceral fat with increased subcutaneous and muscle fat in 11 patients with type 2 diabetes who were treated with TGZ 200–400 mg daily for 12 months. The increase in muscle fat was associated with worsening HbA₁c levels during the latter 6 months of treatment. Gomez-Perez et al. (abstract 428) compared the effects of 400 and 600 mg/dl TGZ for 24 weeks on the metabolic and lipid profile of 96 patients with type 2 diabetes whose fasting glucose levels were between 140 and 200 mg/dl. Glucose levels decreased from 172 to 131 mg/dl and from 167 to 130 mg/dl, and levels of HbA₁c, C-peptide, proinsulin, insulin, and FFAs also changed similarly. There were no changes in weight, total, LDL, or HDL cholesterol levels; lipoprotein(a); or fibrinogen. Serum triglyceride levels decreased with the 600 mg-but not with the 400-mg dose. Schwartz et al. (late-breaking abstract 1) reported on the HbA₁c and alanine transaminase (ALT) values in 630 patients who were treated with TGZ over a 4-year period. The mean HbA₁c concentration was 8.8% before treatment and 7.4% at least 3 months after starting TGZ. Of the patients, 2.2% had ALT levels more than three times the upper limit of normal before and after TGZ was started.

In regard to studying combination treatment with TZD, Raskin et al. (abstract 463) discussed the effect of repaglinide 2 mg before meals, TGZ 400 mg daily, and the combination of the two agents in 186 patients with type 2 diabetes. The mean HbA₁c concentration decreased from 8.9 to 7.9% and increased from 8.6 to 8.7%, and decreased from 8.6 to 7.3% in the three groups, respectively, over a 14-week period. Leiter et al. (abstract 495) administered TGZ in doses of 200 mg that were increased to 400 mg or placebo to 539 patients with type 2 diabetes inadequately controlled on insulin. In patients with HbA₁c concentrations of 6.6–8.4%, levels decreased by 0.9% on average; in patients with HbA₁c concentrations >8.4%, levels decreased by 1.4% as compared with placebo changes. Yale et al. (abstract 510) added TGZ 400 mg vs. placebo to treatment for 101 and 99 patients treated with sulfonylureas and metformin, respectively. Mean baseline concentration of HbA₁c at 9.7% decreased by 1.3%, and the mean level of fasting glucose at 232 mg/dl decreased by 43 mg/dl in the TGZ-treated group. In the placebo-treated group, HbA₁c increased by 0.1%, and the fasting glucose level increased by 5 mg/dl. The mean ALT level was 1.5–3 times the upper limit of normal in 13 vs. 14 patients, respectively.

Sulfonylureas and related agents

In pancreatic β-cells, KATP channels are comprised of the inwardly rectifying potassium channel subunit, K₆.2, and the high-affinity sulfonylurea receptor, SUR-1, which binds ATP. Closure of KATP Channels depolarizes the β-cell and consequently activates calcium channels with oscillations of cytoplasmic Ca²⁺ levels that stimulate insulin secretion. Seghers et al. (abstract 145) studied SUR-1 knockout mice that showed normal glucose levels and body weight after closure of the KATP channels. These findings indicate the activation of compensatory mechanisms that suppress insulin secretion and are in contrast to the situation in patients with the recessive form of persistent hyperinsulinaemic hypoglycaemia of infancy.

Dunning et al. (abstract 446) showed insulin secretion stimulation in insulin resistant Cynomolgus monkeys from 0.5 to 3.5 h after administration of repaglinide, but from 10 min to 1 h after administration of nateglinide, an amino acid derivative insulin secretagogue. Although glucose levels were similar after administration of each agent, the levels of insulin secretion stimulation suggest that nateglinide is more beneficial. Kabag et al. (abstract 456) compared 14 healthy individuals who were given placebo, repaglinide 0.5 or 2 mg, or nateglinide 120 mg before a standard breakfast. The data showed persistent insulin elevation at 1.5–4 h with repaglinide but not with nateglinide. Hirschberg et al. (abstract 430) compared daily glycemic profiles after 0, 30, 60, or 120 mg nateglinide in 10 patients with type 2 diabetes 10 min before meals three times a day for 7 days. No hypoglycemia was seen, and postprandial glucose increments decreased while insulin increased. Frandsen et al. (abstract 487) compared 138 patients who were treated with placebo with 270 patients who were treated with repaglinide 0.5 or 1.0 mg prandially. Of the patients, 25% chose two meals and 6% chose four meals daily. There was no change in the efficacy of lowering HbA₁c concentrations, which showed an average decrease from 7.6 to 7.4% with placebo and from 7.8 to 6.6% with active treatment. Only minor hypoglycemic episodes were noted. Testa et al. (abstract 502) assessed patient self-reports to compare the impacts on health care management of administering glipizide gastrointestinal therapeutic system (GITS) versus metformin. Testa et al. reasoned that physician assessment may underestimate the actual health care resources required to manage related-patient visits and telephone calls, because the management of side effects related to oral hypoglycemic agents requires detailed information from the patients' versus the physicians' perspectives. A total of 91 patients were randomized to one of the agents for 24 weeks with similar glycemic control. Glipizide increased hunger in 48 vs. 21% and weight in 33 vs. 8% of the patients, whereas metformin caused nausea in 47 vs. 14%, anorexia in 24 vs. 5%, diarrhea in 42 vs. 12%, abdominal pain in 29 vs. 3%, foot cramps and pain in 59 vs. 29%, and lethargy in 58 vs. 31%. The overall "distress impact" was 2.4 times greater for metformin. Cefalu et al. (abstract 344) treated 46 patients with type 2 diabetes with either glipizide GITS (up to 20 mg daily) or metformin (up to 2,500 mg daily) for 6 weeks, followed by a 3-month period of combination treatment. Levels of fasting blood glucose and HbA₁c fell similarly with the two agents separately and by 120–146 mg/dl and 2–3% with combination treatment. Magnetic resonance imaging assessments of abdominal fat distribution demonstrated no significant treatment difference for either monotherapy or combination therapy.
Insulin

Tavintharan et al. (abstract 363) studied 148 patients >64 years of age (mean 74) who were treated with an average dose of 43 U insulin a day. Of the patients, 91% received two insulin doses a day, two-thirds used syringes, and one-third used pen-injectors. HbA1c concentrations were <8% in 56% of the patients, and 18% experienced hypoglycemia; there were five hospitalizations. Koenen et al. (abstract 356) compared 46 obese patients with type 2 diabetes who were treated with regular insulin before each meal with 58 patients who received “conventional insulin” treatment. The HbA1c concentration decreased by 2.4 vs. 2.1%, respectively; cholesterol levels decreased by 83 vs. 90 mg/dl, and triglyceride levels decreased by 40 vs. 79 mg/dl. However, there was a 1.1 decrease vs. a 1.3 kg/m² increase in BMI, which suggests that administration of preprandial regular insulin may be a superior approach. Similarly, Browdos et al. (abstract 450) studied 131 patients with HbA1c concentrations >8.5% who were receiving sulfonylurea treatment and were randomized for additional treatment with preprandial insulin lispro treatment and metformin, or bedtime NPH for 3 months. On average, there were 1.1, 0.7, and 0.6 hypoglycemic events per patient per month, respectively; weight gain was 3.4, 1.0, and 2.3 kg; and the mean concentration of HbA1c decreased from 10.0–10.4% by 3.3, 1.9, and 1.9%, although the fasting glucose levels were 190, 175, and 153 mg/dl in the three groups. Ponssen and Elte (abstract 364) administered metformin 1,700 mg daily versus placebo for 5 months each to 30 insulin-treated patients with type 2 diabetes whose mean HbA1c concentrations were 7.3 vs. 8.0%, whose mean insulin-dose requirements were 42 vs. 51 U/day, and whose mean cholesterol levels were 5.7 vs. 6.1 mmol/l. In the patients treated with metformin, levels of fasting C-peptide increased by 166 µmol/l, which suggests improvement in endogenous insulin and insulin sensitivity. Ryysy et al. (abstract 413) reported that liver fat content and lesser degrees of insulin absorption, the latter of which correlated with greater BMI, were significant independent determinants of bedtime NPH insulin requirements in 20 patients who were treated with NPH and metformin.

Glucagon-like peptide-1

Toft-Nielsen et al. (abstract 93) reported a 30% decrease in meal-related glucagon-like peptide (GLP)-1 response that was inversely related to BMI and positively related to serum glucagon levels in patients with type 2 diabetes. Parkes et al. (abstract 89), Kolterman et al. (abstract 861), and Gedulin et al. (abstract 864) reported that exendin-4 (E-4) increased plasma insulin levels and decreased plasma glucose and plasma glucagon levels in human subjects. E-4 is a 39–amino acid peptide that was first isolated from the salivary secretions of the Gila monster. It shares an approximate 50% sequence homology with and shows action similar to GLP-1. The insulintropic actions of E-4 during an intravenous glucose challenge in rats were greater than those of GLP-1. Bonner-Weir (abstract 86) reported evidence that a 10-day course of E-4 after a 90% pancreatectomy in rats increased β-cell mass by 40%, which explains the improvement in glucose tolerance observed 4 weeks after surgery. Sham-operated rats showed a 54% increase in β-cell mass with improved glucose tolerance. Rocca et al. (abstract 91) administered truncated E-4(9-39), a GLP-1 antagonist, with a diet enriched in monounsaturated fatty acids, which has been shown to stimulate GLP-1, and demonstrated that the improvement in glycemia seen with olive oil is mediated by its GLP-1-stimulating action. However, Kiel et al. (abstract 87) showed that E-4(9-39) has partial (~10%) agonist activity at the human GLP-1 receptor. Brand et al. (abstract 1186) reported that chronic administration of valine pyrrolidide, a selective inhibitor of dipeptidyl peptidase (DPP)-IV, the enzyme responsible for inactivation of GLP-1, improves glucose tolerance with increased insulin response in an insulin-resistant rodent model and does not alter food intake or body weight. Hughes et al. (abstract 90) reported that administration of NVP-DPP728, an orally active inhibitor of human and rat DPP-IV, prolongs the half-life of the active GLP-1(7-36) and decreases levels of the cleaved antagonist GLP-1(9-36) metabolite in rats. Joseph et al. (abstract 870) reported on oral delivery of a therapeutic microsphere-encapsulated GLP-1 analog that is resistant to DPP-IV degradation. In a mouse model of type 2 diabetes, basal and prandial glucose levels decreased. These findings demonstrate the efficacy of the analog to deliver therapeutic levels of GLP-1 over an 8-h period. Interestingly, Mannucci et al. (abstract 508) reported a 50% increase in postprandial GLP-1 levels without change in insulin concentrations in eight obese patients after 14 days of treatment with metformin 1,750 mg daily. These findings suggest that GLP-1 may mediate part of the action of metformin.