

# Diabetes Treatment

ZACHARY T. BLOOMGARDEN, MD

This is the third of six articles based on presentations at the American Diabetes Association Scientific Sessions held 6–10 June 2008 in San Francisco, California.

## Type 2 diabetes treatment approaches

Ralph DeFronzo (San Antonio, TX) suggested an interesting set of approaches to the treatment of type 2 diabetes. DeFronzo noted that the natural history of type 2 diabetes involves a reduction in insulin sensitivity during the progression from lean to obese with normal tolerance, and that the subsequent progression to impaired glucose tolerance (IGT) is associated with a further decrease in insulin sensitivity and a relative deficiency in insulin secretory function. As IGT progresses to diabetes, insulin secretion decreases without a further worsening in insulin sensitivity. DeFronzo presented studies of normal glucose-tolerant, impaired glucose-tolerant, and type 2 diabetic individuals that demonstrated an increase in the absolute rate of glucose-induced insulin secretion during the progression from normal to varying degrees of IGT, with insulin secretion subsequently decreasing progressively with worsening degrees of diabetes. Examining the ratio of insulin secretion to insulin resistance (the disposition index), DeFronzo showed that the logarithm of insulin secretion/insulin resistance is inversely proportional to the log of the 2-h glucose, and that with advanced degrees of IGT, ~80% of insulin secretory capacity is lost, implying that insulin deficiency begins well before the onset of diabetes as currently defined. He cited an autopsy study showing that by the time elevations occur in fasting glucose, there is a 50% loss of  $\beta$ -cell mass, with a further decrease in  $\beta$ -cell volume with progression to diabetes (1).

The Diabetes Prevention Program further raises concern about the clinical implications of the term “pre-diabetes,” as

the program found a 7.9% prevalence of diabetic retinopathy among individuals with IGT. At the time of diabetes diagnosis, 12.6% had retinopathy, although the mean A1C was only 6.1%. Peripheral neuropathy also was seen in 5–10% of participants with IGT. DeFronzo concluded that individuals with IGT are near maximally insulin resistant, with decreased  $\beta$ -cell function and mass, and with appreciable prevalence of diabetic complications.

$\beta$ -cell failure occurs, DeFronzo said, in an age-related fashion and clusters in families. The transcription factor 7-like 2 gene (TCF7L2) polymorphism is associated with reduced insulin secretion, perhaps from reduced insulin responsiveness to glucagon-like peptide (GLP)-1. Carriers of the abnormal gene have a 60% increase in diabetes development. Deficiency of GLP-1 and resistance to glucose-dependent insulinotropic peptide (GIP) action also occur in type 2 diabetes. Lipotoxicity from increased plasma free fatty acids (FFAs) is another factor impairing insulin secretion. A 48-h infusion of heparin with triglyceride emulsion elevating FFAs in normal glucose tolerant offspring of two diabetic parents led to decreased insulin secretion. Increased glucose levels also impair insulin secretion, the phenomenon of glucotoxicity; DeFronzo's studies of phlorizin, which reduces glucose levels by increasing glycosuria, showed improvement in  $\beta$ -cell function. Increased amyloid polypeptide (IAPP) deposition is another factor leading to  $\beta$ -cell failure, with relative islet amyloid area increased in association with decreased insulin secretion and increased fasting glucose in a nonhuman primate study.

DeFronzo discussed insulin resistance in type 2 diabetes, noting potential differences between the fasting and insulin-stimulated states. In type 2 diabetic patients, elevation in basal hepatic glucose production correlates strongly with increase in fasting glucose, while in the

insulin-stimulated state the insulin resistance of type 2 diabetes is largely accounted for by skeletal muscle insulin resistance. Intramyocellular defects include impaired glucose transport and decreased glycogen synthesis. Insulin action begins with insulin receptor autophosphorylation, then causing phosphorylation of insulin receptor substrate (IRS)-1, leading to activation of a number of intracellular processes, with a decrease in the ability of the insulin receptor to tyrosine phosphorylate IRS-1 in insulin resistance. At the same time, the mitogenic insulin response pathway is relatively increased, with activation of proinflammatory pathways, abnormalities which only respond to pharmacologic intervention with thiazolidinediones (TZDs).

DeFronzo showed fascinating differences between the effects of oral and parenteral glucose. The latter only increases hepatic glucose uptake when plasma glucose levels increase, even during hyperinsulinemia. Oral glucose, in contrast, markedly increases hepatic glucose uptake in normal individuals, acting to a lesser extent in type 2 diabetic patients, which suggests an abnormality of a gut factor. Increased FFAs may play a role in inhibiting muscle glucose uptake, increasing hepatic glucose production, and decreasing insulin secretion. The use of lipid plus heparin infusion to elevate FFA in normal individuals decreases hepatic and muscle insulin signaling via a number of tyrosine phosphorylation steps and results in a doubling of muscle lipid content. Pioglitazone increases the expression of peroxisome proliferators-activated receptor (PPAR)- $\gamma$  coactivator (PGC)-1, thereby reducing intramyocellular lipid and fatty acylCoA content, an effect similar to that with administration of the nicotinic acid derivative acipimox to reduce circulating FFAs. Decreased incretin effect is another factor in the pathogenesis of type 2 diabetes. A 2-week course of exenatide in type 2 diabetic patients showed beneficial effects, including an improved ratio of insulin secretion to 2-h glucose and increased splanchnic glucose uptake. Abnormalities of  $\alpha$ -cell function may be another factor in the pathogenesis of type 2 diabetes. Marking another benefit of incretin treatment approaches, glucagon secretion is increased and correlates with

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

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increased fasting glucose levels, and this further improves after administration of somatostatin. In addition, there are central nervous system effects on glycemia, and the hyperinsulinemia of obesity may involve central insulin resistance, with evidence of altered hypothalamic function in obese individuals after glucose ingestion.

Given the variety of pathogenic abnormalities in type 2 diabetes, its treatment requires multiple drugs in combination. Metformin and TZDs act on the liver, and TZDs act on muscle, the adipocyte, and the  $\beta$ -cell, suggesting to DeFronzo that these agents are preferable to metformin and to sulfonylureas. All long-term TZD studies, he said, including PERISCOPE, CHICAGO, ADOPT, and the UKPDS, show that sulfonylureas do not give durable glycemic benefit, while long-term glucose-lowering is seen with TZDs in type 2 diabetic patients and in prevention studies such as the DPP, TRIPOD, PIPOD, DREAM, and ACT-NOW. "The TZDs and the GLP-1 analogs," DeFronzo concluded, "offer a new therapeutic approach." This is, he said, preferable to the stepwise approach of typically using metformin followed a sulfonylurea recommended by ADA, which he characterized as "nonphysiological." He recommended a "pathophysiologic-based algorithm" of initial treatment with lifestyle, TZDs, metformin, and exenatide, with an A1C goal  $<6\%$ , suggesting that this would be durable, would result in  $\beta$ -cell preservation, and would not cause hypoglycemia or weight gain.

These and many additional approaches to treatment of type 2 diabetes were explored in studies presented at the ADA meeting.

### Metformin

Foretz et al. (abstract 1507) investigated the relationship between metformin's activation of AMP-activated protein kinase (AMPK) and its inhibition of gluconeogenesis, finding that although hepatocytes from mice not expressing AMPK had a 30% reduction in gluconeogenesis, both in the basal state and in response to cyclic AMP, metformin reduced glucose production to a greater extent in the knockout hepatocytes than in those from wild-type animals. Mice overexpressing PGC-1 $\alpha$ , which is distal to AMPK in activation of gluconeogenesis, continued to respond to metformin. The authors found that metformin reduced intracellular ATP, suggesting that this rather than its

effect on AMPK might explain its effect on gluconeogenesis. (Abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 57 [Suppl. 2], 2008).

This work was supported by Baverel et al. (abstract 38), who found a dose-dependent inhibition by metformin of gluconeogenesis from lactate in liver slices from Zucker diabetic fatty rats and a reduction of cellular ATP levels and of CO<sub>2</sub> production from lactate, while lactate production and ketogenesis nearly doubled with increased  $\beta$ -hydroxybutyrate-acetoacetate ratio, reflecting the mitochondrial redox state. Schaefer et al. (abstract 97) treated 19 nondiabetic obese adults with 850 mg metformin daily for one week, then twice daily for three more weeks, showing a reduction in 24-h energy expenditure by 3% with carbohydrate and fat oxidation increasing 17% and decreasing 33%, respectively.

A number of other agents may regulate pathways similar to those affected by metformin. Van Poelje et al. (abstract 350) found a reduction in glucose production from lactate in human hepatocytes with the fructose-1,6-bisphosphatase inhibitor MB07803. In diabetic rodents and nonhuman primates, glucose decreased without any change in blood lactate. Motoshima et al. (abstract 351) found that the protein kinase C $\delta$  inhibitor rottlerin decreased AMPK phosphorylation in adipocytes, myocytes, and hepatocytes and increased cellular glucose consumption; the latter effect is not observed with overexpression of dominant-negative AMPK, which suggests this phenomenon to mediate the glucose-lowering effect observed in animal models in vivo.

### PPAR $\gamma$ agonists

A number of studies at the ADA meeting contributed to the endeavor to unravel cardiovascular (CV) risks versus benefits of the TZDs. Bilik et al. (abstract 300) compared 8,739 type 2 diabetic patients who were followed from 1999 to 2003 and either received or did not receive a TZD. Mortality among the patients was 5 vs. 7%, and major CV events occurred in 11 vs. 10%, respectively. A total of 817 took just rosiglitazone and 724 just pioglitazone, with major CV events in 9 and 10%, respectively. However, Wang et al. (abstracts 590 and 604) analyzed 11,283 type 2 diabetic patients receiving either metformin or a sulfonylurea alone at baseline. They found a 23% greater likelihood of a CV event among patients receiving add-on rosiglitazone than among

those receiving combined sulfonylurea-metformin treatment. Spanheimer et al. (abstract 299) reported that 33% of patients in the PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) were treated with insulin, 39% with a nitrate, and 70% with an angiotensin-directed agent, with no evidence of these treatments increasing risk of stroke, myocardial infarction, or mortality. Seung Jin Han et al. (abstract 435) administered pioglitazone versus placebo to 75 nondiabetic renal allograft recipients for 12 months, and found a significant increase versus decrease in insulin sensitivity and a decrease versus increase in carotid intima-media thickness. Bao et al. (abstract 441) studied outcome among 3,713 diabetic patients treated with metformin alone for at least 12 months; 29 and 71% of the patients subsequently took rosiglitazone and a sulfonylurea, respectively. On average, the latter group was 2 years older; the patient groups had a similar sex distribution and prevalence of hypertension and CVD, and baseline resource utilization was similar. Comparing those adding rosiglitazone versus sulfonylurea, 74 vs. 69% were adherent to glucose-lowering therapy, 23 vs. 27% experienced hospitalizations, 26 vs. 29% had ER visits, and 54 vs. 58% had outpatient visits. There was a 40% greater adjusted likelihood of adherence to rosiglitazone, and rates of both hospitalizations and ER visits were 20% lower among those who added rosiglitazone.

Tint et al. (abstract 303) administered rosiglitazone for 16 weeks to 14 type 2 diabetic patients of Chinese and Asian Indian ethnicity. Euglycemic-hyperinsulinemic clamp insulin sensitivity increased 52 vs. 120%, respectively, with somewhat more weight gain in those of Asian Indian ethnicity. Kritchevsky et al. (abstract 1736) administered 30 mg pioglitazone daily versus placebo to 88 nondiabetic adults who had a BMI  $>27$  kg/m<sup>2</sup> and were on a calorie-restricted diet for 4 months; weight loss did not differ between the pioglitazone and placebo groups, but men receiving pioglitazone had 3% reduction in percent body fat, while there was a 2% reduction in the placebo group; there was a greater reduction in visceral fat among pioglitazone-treated men.

Chou et al. (abstract 304) compared a new TZD, rivoglitazone, at 1, 2, and 3 mg doses, with pioglitazone 45 mg daily and with placebo in a study of 441 type 2 diabetic patients. A1C decreased by 0, 0.4, 0.5, and 0% and increased 0.6%, re-

spectively. Triglyceride decreased 10, 15, and 21% with the 1, 2, and 3 mg doses and 8% with pioglitazone, while HDL cholesterol increased 11, 10, 14, and 8%, respectively. Peripheral edema, however, occurred in 14, 17, 24, and 11%, respectively, and weight gain was also more likely to occur at the 2 and 3 mg doses. Truitt et al. (abstract 437) studied 426 patients receiving 0.5, 2, and 5 mg rivoglitazone, 30 mg pioglitazone, and placebo. The 2 and 5 mg doses had more potent glycemic effects than pioglitazone, although edema occurred in 6 and 16% of those receiving the 2 and 5 mg doses but in only 0–1% of those receiving pioglitazone. There was also greater weight gain with the higher rivoglitazone doses. An interesting implication is that activation of PPAR $\gamma$  is submaximal with existing TZDs at recommended dosages, with additional glucose lowering possible, although the greater risks of fluid retention and weight gain may make the more potent agents not clinically viable.

Dunn et al. (abstract 499) administered the non-TZD partial PPAR $\gamma$  agonist INT131 to 69 type 2 diabetic patients not receiving a glucose-lowering agent. Fasting glucose increased from 165 by 8 mg/dl with placebo and decreased from 163 and from 184 by 22 and 46 mg/dl with 1 mg and 10 mg doses, respectively. Guha et al. (abstract 1478) studied the effect of the PPAR $\delta$  agonist KD3010, which exhibits >1,000-fold selectivity over human PPAR $\alpha$  and  $-\gamma$  and has been associated with weight loss, in diabetic *db/db* mice. A1C, fasting insulin, and postload glycemia decreased. Multani et al. (abstract 569) administered this agent to normal and obese volunteers, improving peripheral insulin resistance and reducing fasting insulin levels; no weight gain or signs of fluid retention or other toxicity were exhibited. Marita (abstract 196) studied a non-TZD, P1736-05, that does not activate human PPAR $\gamma$  or  $-\alpha$  receptors but increases adipocyte glucose uptake via a process involving phosphatidylinositol-3 kinase and thereby induces translocation of GLUT4 transporter to the plasma membrane. In a type 2 diabetic model, this process reduces glucose and triglyceride levels and improves muscle insulin-induced glucose uptake without increasing plasma volume at 60-fold the effective dose.

### Bile acid sequestrants in type 2 diabetes

Schwartz et al. (abstract 440) randomized 35 type 2 diabetic patients to 3.75 g

colesevelam daily versus placebo for 8 weeks, finding no effect on the glucose response to a standardized meal tolerance test. This finding suggests the effect of the agent is not mediated by altered glucose absorption. Jialal et al. (abstract 459) analyzed the pooled effect of the bile acid binding resin colesevelam in 1,081 type 2 diabetic patients receiving insulin, metformin, or a sulfonylurea, and found a 0.5% placebo-adjusted reduction in A1C, a 15 mg/dl reduction in fasting glucose, and a 15% reduction in LDL cholesterol but a 7% reduction in non-HDL cholesterol, reflecting a 15% increase in triglyceride levels. Guha et al. (abstract 439) administered an agonist of the gut bile acid receptor TGR5 in type 2 diabetic animal models, showing an improvement in glycemia and insulin sensitivity and increased active GLP-1 levels in portal and systemic circulation. Brufau et al. (abstract 1553) reported the cholic acid synthesis rate to be increased by 70% in type 2 diabetic patients, with a consequent increase in deoxycholic acid synthesis, pool size, and total bile acid synthesis. As bile acids are ligands for nuclear FXR and cell membrane TGR5 receptors, this may be related to abnormal glycemia in diabetes and to the beneficial effect of bile acid-binding resins.

### Sodium-glucose cotransporter 2 inhibitors

The kidney filters 160 g glucose daily, with 90% reabsorbed by sodium-glucose cotransporter 2 (SGLT2) and 10% by SGLT1 in the renal tubules. Interestingly, in animal models of diabetes and in diabetic patients, the maximal renal tubular reabsorptive capacity is increased. Wancewicz et al. (abstract 334) administered ISIS 388626, an SGLT2 antisense oligonucleotide designed to specifically distribute to the kidney, in canine and rodent diabetic models. Administration of ISIS 388626 resulted in improved glucose levels and may be an effective treatment modality. List et al. (abstracts 329 and 461) administered 2.5–50 mg of the renal SGLT2 inhibitor dapagliflozin daily, 1,500 mg metformin daily, or placebo to 389 treatment-naïve type 2 diabetic patients for 12 weeks, and found dose-related 52–85 g/day glycosuria with dapagliflozin. There was no change in serum sodium, potassium, or creatinine or in serum or urinary calcium. Magnesium increased 0.1–0.2 mEq/l, urate decreased 1 mg/dl, and serum phosphate increased 0.2 mg/dl at the highest doses. At base-

line, A1C was 7.7–8% and decreased by 0.7–0.9% with dapagliflozin, 0.7% with metformin, and 0.2% with placebo, and there were 2.7–3.4, 1.7, and 1.2% weight losses, respectively. Adverse events with dapagliflozin included urinary tract infection, nausea, dizziness, headache, fatigue, back pain, and nasopharyngitis. Chaudhury et al. (abstract 729), however, in an effort to address the question of whether glycosuria is associated with renal tubular damage in 106 newly diagnosed untreated type 2 diabetic individuals, showed the degree of glycosuria to correlate with a marker of proximal tubular damage. A1C was an independent predictor, raising the question of whether a therapeutic approach to increasing glycosuria might have adverse renal effects.

### G protein-coupled receptor

Fyfe et al. (abstract 297) studied PSN821, an agonist of G protein-coupled receptor (GPR) 119 expressed in pancreas and gut, and showed stimulation of both  $\beta$ -cell insulin and gut GLP-1 secretion in vitro and improved glucose tolerance in type 2 prediabetic and diabetic animal models. A1C was lower in the latter, and weight was reduced in a dietary obesity model. Tremblay et al. (abstract 1489) evaluated mice not expressing GPR-39, which is normally expressed in the gastrointestinal tract, adipose tissue, liver, and pancreatic islets. The researchers found reduced serum insulin and elevated glucose levels associated with a high-fat diet or aging, which suggests that agonists of GPR-39 might have glucose-lowering effects. Zhou et al. (abstract 541) studied activators of GPR-40 (which is expressed in pancreatic  $\beta$ -cells) and found enhanced glucose-dependent insulin secretion in vitro and improved glucose tolerance in type 2 diabetic models.

### Glucokinase activators

Glucokinase (GK) has glucose affinity in the physiologic range of 5–12 mmol/l, allowing it to function as a glucose sensor. The diabetes variant MODY2 is caused by decreased hepatic GK activity, while activating GK mutations cause hyperinsulinemic hypoglycemia of infancy. GK acts in the  $\beta$ -cell to form glucose-6-phosphate and increase intracellular ATP, closing the ATP-sensitive potassium channel, depolarizing the cell, and opening a calcium channel, thereby leading to insulin secretion. As such, there has been interest in GK activators as insulin secretagogues. In the liver, GK is the rate-limiting step for

## NEWS FROM THE FOOD AND DRUG ADMINISTRATION

*From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.*

An interview with Dr. David Orloff, former director of the division of metabolism and endocrinology products at the FDA, reviewed the recent FDA cardiovascular risk assessment guidelines for diabetes drugs, pointing out that the guidelines would increase the cost and time of developing a diabetes drug and suggesting that several companies are likely to discontinue development of their diabetes drugs (interview downloaded January 26, 2009, from <http://www.closeconcerns.com/>). To understand this, it may be useful to review the guidelines, which state, "For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA), sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8" (<http://www.fda.gov/cder/guidance/8576fnl.pdf>).

Consider drugs that are completely neutral with regard to cardiovascular outcome. Say that drug A from company A is tested in a population of 2,000 patients, with 2,000 control subjects, in whom the cardiovascular event rate is 1%. If both groups have precisely 20 cardiovascular events, the relative risk (RR) ratio is, of course, 1.0. The 95% CI, however, would be 0.5397-1.8528. Now, say company B performed the same studies, but in their case there were 20 events among the 2,000 patients receiving drug B but 21 events among the 2,000 control subjects. The relative risk is now 0.95, with a 95% CI of 0.5179-1.7514 (CIs for RRs and odds ratios calculated with a statistical calculator downloaded 25 January 2009 from [vl.academicdirect.org/applied\\_statistics/binomial\\_distribution/ref/CI\\_calculator.xls](http://vl.academicdirect.org/applied_statistics/binomial_distribution/ref/CI_calculator.xls), according to the methods described in the following source: Armitage P, Berry G: *Statistical Methods in Medical Research*. 3rd ed. London, Blackwell, 1994, p. 131). Certainly, drug A and drug B have indistinguishable cardiovascular risk. Yet, the language of the FDA document states clearly that company A, but not company B, will need to undertake a postmarketing trial "to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3." Company A now needs to study a total of 12,000 patients in each group to show that, with 1% cardiovascular event rates, the same RR of 1.0 has a 95% CI of 0.7774-1.2863. It appears, then, that arbitrary and statistically meaningless differences may lead some companies to abandon the development of potentially promising new therapies for diabetes—certainly an undesirable and hopefully an unintended result of the FDA guidance.

The FDA issued a Public Health Advisory to alert consumers, patients, health care professionals, and caregivers about potentially serious and life-threatening side effects from the improper use of skin-numbing products such as lidocaine, which may be administered to patients with painful diabetic neuropathy. Noting that application under occlusion or when skin temperature is increased may lead to systemic absorption, the advisory stated that the agents may be associated with arrhythmia, seizures, respiratory difficulty, or decreased mental status.

glucose metabolism and it increases glycogen formation, so that GK activators could also increase hepatic insulin action. Archer et al. (abstract 465) studied the small molecule GK activator ARRY-588, which is capable of increasing glucose-induced  $\beta$ -cell insulin secretion as well as that of GIP and GLP-1, and of reducing glucose levels in type 2 diabetic models,

without hyperinsulinemia or weight gain. In addition to the liver, the  $\beta$ -cell, and gut L- and K-cells, GK is expressed in  $\alpha$ -cells and in hypothalamic neurons involved in physiologic glucose-sensing. Nakamura et al. (abstract 493) showed that a small molecule GK activator increased glucose-stimulated insulin secretion in islets from mice with and without  $\beta$ -cell-specific

haploinsufficiency of the GK gene. In high-fat-fed mice, glucose tolerance improved with the agent, again with and without deletion of one copy of the GK gene. Bodvarsdottir et al. (abstract 328) studied the liver-specific GK activator TTP355, showing increases in vitro in hepatocyte glucose metabolism, without effect on insulin secretion, and showing improvement in glycemia in a type 2 diabetic animal model. Bonadonna et al. (abstract 322) reported improved glucose levels and increased insulin secretion in 15 mild type 2 diabetic patients receiving another GK activator, RO4389620.

### Dipeptidyl peptidase-4 inhibitor treatment

Hjollund et al. (abstract 1464) measured portal vein active GLP-1 levels in pigs, finding an increase from 6.6 to 45.1 pmol/l after administration of bombesin (neuromedin C). After dipeptidyl peptidase-4 (DPP-4) inhibition with vildagliptin, GLP-1 increased from 16.3 to 90.3 pmol/l. Portal levels were two to three times greater than peripheral blood levels, potentially acting on the liver and on vagal afferents, which the authors suggest might explain the comparable glycemic effect of DPP-4 inhibitors to those of GLP-1 receptor activators. Peripheral blood GLP-1 receptor activation appears to be much lower with DPP-4 inhibition, but portal levels may be comparable. Auling et al. (abstracts 1,545 and 1,551) reported that although neither GLP-1 nor vildagliptin reduced food intake given separately in a rat feeding model, combined administration was effective. Exenatide showed a more potent and longer-lasting anorexic effect and, interestingly, the combination of exenatide with vildagliptin suppressed food intake to an even greater extent, suggesting a potential clinical benefit of combined treatment of overweight patients with diabetes. Two interesting studies suggest that some of the effects of  $\alpha$ -glucosidase inhibition may be mediated by changes in incretin secretion. Narita et al. (abstract 447) reported effects of miglitol on GLP-1 and GIP responses to a mixed meal in nine type 2 diabetic patients, finding a modest increase in GLP-1 concentrations by approximately one-third at 60 and 120 min, but a marked reduction in GIP by 60% at 30 and 60 min, with a 3-h integrated increase in GLP-1 and decrease in GIP by 14 and 47%, respectively. Goto et al. (abstract 470) administered miglitol and the DPP-4 inhibitor SK-0403 in combination

in a rat model, showing that after a mixed meal the combination increased GLP-1 levels to a greater extent than the DPP-4 inhibitor alone. Miglitol alone did not change GLP-1 levels, and curiously the GLP-1 response to oral sucrose was less with the combination than with SK-0403 alone. As in the human study, GIP levels after the mixed meal were reduced by administration of miglitol.

Williams-Herman et al. (abstract 495) and Katzefz et al. (abstract 496) found, adjusting for baseline A1C, a greater placebo-controlled reduction in A1C by use of sitagliptin among individuals in the highest proinsulin/insulin tertile and in the lowest HOMA- $\beta$  tertile in four randomized controlled trials of 1,691 type 2 diabetic patients. Lower  $\beta$ -cell function may be associated with greater response to sitagliptin. There was no differential effect by age, sex, or BMI group. Chapell et al. (abstract 512; disclosure: ZB was a coauthor) compared the glucose-lowering effects of sitagliptin, pioglitazone, and rosiglitazone in a meta-regression analysis of 23 randomized controlled studies, finding weighted mean reduction in A1C of 0.7, 0.9, and 0.5%, respectively. Differences in baseline A1C explained most of the apparent difference between the agents, with strong correlation between baseline A1C and change in A1C across studies.

Two new DPP-4 inhibitors are undergoing clinical testing. Rosenstock et al. (abstract 517) administered the DPP-4 inhibitor saxagliptin (2.5, 5 and 10 mg daily) to 401 drug-naïve type 2 diabetic patients for 24 weeks. The researchers found a placebo-adjusted reduction in fasting glucose of 21, 15, and 23 mg/dl and in A1C of 0.6, 0.6, and 0.7%, respectively. Adverse events occurring in at least 5% of patients included respiratory infection, headache, nasopharyngitis, and sinusitis, presumably an overlapping complex of diagnoses, and urinary infection. Karim et al. (abstract 538) administered the DPP-4 inhibitor alogliptin (50 mg) to six individuals with a creatinine clearance of 51–80 ml/min, six individuals with a creatinine clearance of 30–50 ml/min, six individuals with a creatinine clearance of <30 ml/min (but not on dialysis), and six individuals with end-stage renal insufficiency. The researchers found a 1.7-, 2.1-, 3.2-, and 3.8-fold increased plasma exposure over 5 days when compared with six healthy individuals with normal renal function. The authors suggested that the dose should be reduced to

one-half and one-quarter with glomerular filtration rates <50 and <30 ml/min, respectively, although there is a presumable overlap between the 1.7- and 2.1-fold increases; therefore, the dose might also be reduced in the 51–80 ml/min group. Fleck et al. (abstract 479) administered alogliptin 6.25, 12.5, 25, 50, or 100 mg daily or placebo for 12 weeks to 265 type 2 diabetic patients not receiving pharmacologic treatment. The researchers found placebo-adjusted A1C reductions of 0.2, 0.5, 0.6, 0.4, and 0.5%, respectively, from baseline levels of 8–8.2%. Pratley et al. (abstract 478) added alogliptin 12.5 or 25 mg or placebo for 26 weeks in 493 type 2 diabetic patients receiving pioglitazone; some of the patients were also receiving metformin or a sulfonylurea. A1C decreased 0.7% and 0.8% with 12.5 and 25 mg alogliptin and 0.2% with placebo, exhibiting a greater reduction with a higher baseline A1C level. Nauck et al. (abstract 477) administered alogliptin 12.5 or 25 mg or placebo for 26 weeks in 527 type 2 diabetic patients receiving metformin, finding 0.6%, 0.6%, and 0.1% reduction in A1C and 19, 17, and 0 mg/dl falls in fasting glucose. DeFronzo et al. (abstract 446) administered alogliptin 12.5 or 25 mg or placebo for 26 weeks to 329 type 2 diabetic patients not receiving pharmacologic treatment, finding 0.6%, 0.6%, and no reduction in A1C and a 10 and 16 mg/dl reduction and an 11 mg/dl increase in fasting glucose, respectively. Pratley et al. (abstract 445) added 12.5 or 25 mg alogliptin or placebo for 26 weeks to 500 type 2 diabetic patients receiving glyburide, finding 0.4%, 0.5%, and no reduction in A1C with 5 and 8 mg/dl decreases and a 2 mg/dl increase in fasting glucose, respectively. Rosenstock et al. (abstract 444) added 12.5 or 25 mg alogliptin or placebo for 26 weeks to 390 type 2 diabetic patients receiving insulin, alone or with metformin, with 0.6%, 0.7%, and 0.1% reductions in A1C and a 2 mg/dl increase, a 12 mg/dl decrease, and a 6 mg/dl increase in fasting glucose, respectively.

### Protein tyrosine phosphatase inhibitors

Brian Kennedy (Merck Frosst Centre for Therapeutic Research, Pointe-Claire-Dorval, PQ, Canada) discussed protein tyrosine phosphatase (PTP)-1B, insulin sensitivity, and weight control. Insulin receptor (IR) signal transduction involves its autophosphorylation. PTP dephosphorylates the IR, returning it to the inac-

tive state, with inhibition of IR-PTP prolonging the insulin signal. Mice not expressing this enzyme display remarkable tissue specificity of insulin sensitivity, with a reduction in fed blood glucose, a 50% lowering of insulin levels, and increased tyrosine phosphorylation of the IR in muscle and liver, without effect in adipose tissue, leading to resistance to diet-induced obesity (2). Hormone signaling in adipocytes involves both insulin and  $\beta$ -adrenergic pathways. Insulin leads to phosphodiesterase 3b phosphorylation and increases GLUT4 translocation to the cell surface, while in the absence of insulin, cAMP levels increase thereby leading to activation of protein kinase A (PKA); in mice not expressing PTP-1B, PKA activity is increased in white and brown fat and in muscle but not in liver, but there is adipocyte insulin resistance, suggesting that in adipocyte PTP-1B is a positive regulator of insulin signaling. IR substrate (IRS)-1 levels are reduced 40% in mice not expressing PTP-1B, and IRS-1 phosphorylation is decreased, appearing to involve the mTOR pathway. A number of small-molecule PTP-1B inhibitors are being studied, with evidence of improved glycemia in a variety of obese rodent models. Interestingly, PTP-1B is overexpressed in breast cancer, and reduced carcinogenesis has been shown in some animal models with PTP-1B inhibitors.

### Further therapeutic approaches

Santilli et al. (abstract 395) administered 100 mg acarbose three times daily versus placebo for 20 weeks to 48 type 2 diabetic patients with A1C <7%, finding fasting and 2-h post-test meal glucose to decrease from 126 to 117 mg/dl and from 171 to 139 mg/dl, respectively, with a fall in A1C from 6.7 to 6.3%. Urinary 11-dehydrothromboxane-B2 and 8-iso-prostaglandin-F2a, markers of platelet activation and oxidant stress, decreased 40 and 30%, respectively, and correlated with the reduction in postprandial rather than in fasting glucose, potential cardioprotective effects. Hawkins et al. (abstract 344) administered INCB013739, a selective inhibitor of 11 $\beta$ -hydroxysteroid dehydrogenase type 1, to 30 type 2 diabetic individuals for 28 days, finding a reduction in hepatic glucose production during hyperinsulinemic, euglycemic, pancreatic clamp studies, with improved peripheral glucose uptake. Fasting glucose decreased 18 mg/dl and LDL cholesterol 20 mg/dl. Plasma ACTH increased 12 pg/ml, although morning plasma cortisol lev-

els were unchanged. Huyen et al. (abstract 508) studied *Gynostemma pentaphyllum*, also called jiaogulan or southern ginseng tea, a traditional Vietnamese herbal treatment. The researchers administered 6 g *Gynostemma pentaphyllum* twice daily to 24 type 2 diabetic patients, with a placebo-adjusted 43 mg/dl reduction in fasting glucose (baseline 180 mg/dl) and a 1.8% reduction in A1C, with evidence of improvement in insulin sensitivity. Luo et al. (abstract 333) noted that mice not expressing thyrotropin-releasing hormone (TRH) are hyperglycemic, and thyroxin does not improve this effect. In a streptozotocin-diabetic model, TRH administration markedly reduced the degree of hyperglycemia and maintained normal insulin levels. Normal animals receiving TRH alone had mild hyperinsulinemia without hypoglycemia.

Several treatment approaches may combine glycemic with cardiovascular benefit. Scranton et al. (abstract 331) administered a rapidly absorbed formulation of bromocryptine to increase early morning dopaminergic activity versus placebo for 52 weeks to 3,070 type 2 diabetic patients in the Cycloset Safety Trial (ClinicalTrials.gov Identifier NCT00377676), showing a 42% reduction in the combination of myocardial infarction, stroke, coro-

nary revascularization, and hospitalization for angina or congestive heart failure ( $P = 0.036$ ) and a 55% reduction in the combination of myocardial infarction, stroke, or death, with benefit seen in subgroups stratified by A1C ( $\leq 7$  vs.  $> 7\%$ ), age, sex, or race. Chisholm et al. (abstract 528) randomized 727 type 2 diabetic patients to the anti-angina agent ranolazine versus placebo, and found an A1C reduction with active treatment which correlated with baseline glucose; there was no relationship between glucose and change in A1C in those receiving placebo. Klug et al. (abstract 443) and Tardif (abstract 335) treated 6,144 patients with acute coronary syndrome with succinobucol, with a 19% decrease in the prespecified secondary end point of cardiovascular death, cardiac arrest, myocardial infarction, and stroke. Of the 2,271 type 2 diabetic patients, 1,952 had evaluated A1C data, showing a reduction from 7.2% by 0.5%, without an increase in weight, waist circumference, or edema. Of those not having diabetes, 82 of 1,950 who received placebo versus 30 of 1,923 who received succinobucol developed diabetes during the period of observation. There was a trend to increased hospitalization for heart failure, a significant increase in atrial fibrillation, and the occurrence of hepato-

toxicity, with one patient developing liver failure.

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