Glycemic Treatment

Control of glycemia

ZACHARY T. BLOOMGARDEN, MD

This is the first of three articles dealing with the International Diabetes Federation meeting, which was held in Paris, 24–29 August 2003. Michael Stumvoll (Tübigen, Germany) gave the Minkowski lecture, discussing aspects of the control of glycemia, illustrating the "hyperbolic law of glucose control," depicting the inverse relationship between insulin secretion and insulin sensitivity. If one adds the 2-h glucose in a three-dimensional plot, however, as insulin resistance worsens there is a progressive increase in the 2-h glucose, so that one cannot consider insulin secretion to perfectly balance the degree of insulin resistance (1). Stumvoll gave an overview of the fascinating science involved in understanding glycemia, describing the products of six genes involved in glucose homeostasis. Adiponectin is a protein released by fat cells to an extent inversely related to total body fat mass. Treatment of insulin-resistant diabetic mice with adiponectin decreases glucose levels, and in humans there is an inverse relationship between the degree of insulin resistance and the adiponectin level. Stearoyl-CoA desaturase regulates tissue lipid synthesis and is involved in the metabolism of stearate to oleate. In liver, inhibition of this enzyme prevents hepatic steatosis in leptin-deficient animals, and the oleate-to-stearate ratio on liver biopsy is inversely related to the insulin sensitivity. The insulin receptor (IR) substrate (IRS)1 modulates insulin secretion, with β-cell overexpression of normal IRS1 increasing insulin secretion, whereas overexpression of an abnormal IRS1 decreases insulin secretion by these cells. In humans, those with the Gly972Arg IRS1 polymorphism have shown a decrease in both the first- and second-phase insulin secretory response to intravenous glucose (2). CEACAM1 (CEA-related cell adhesion molecule 1) regulates a pathway responsible for IR internalization, and abnormality causes diabetes. CEACAM1 causes receptor-mediated hepatic insulin endocytosis and degradation in a phosphorylation-dependent manner (3). The liver clears approximately half of the insulin molecules with each circulatory passage, a phenomenon negatively associated with free fatty acid (FFA) levels. Peroxisome proliferator–activated receptor (PPAR)γ2 is involved in transcriptional regulation of a host of processes. The Pro12Ala polymorphism affects insulin clearance, which is greatest with Ala/Ala homozygotes, which show the greatest insulin-induced suppression of lipolysis, further suggesting that release of fatty acids from adipose tissue modulates hepatic insulin degradation. The final gene product Stumvoll discussed is the IR, which has fascinating effects in the central nervous system. Mice that selectively do not express the IR in the central nervous system have evidence of overall insulin resistance. Using magnetoencephalography, it is possible to detect insulin effects in the human cerebral cortex during a hyperinsulinemic clamp, with specific analysis of the auditory cortex showing insulin action on the response to sound and attenuation of this response in persons with obesity.

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

Abbreviations: 11β-HSD, 11β-hydroxysteroid dehydrogenase; ACC, acetyl CoA carboxylase; AICAR, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside; AMPK, AMP-activated protein kinase; CVD, cardiovascular disease; DPP, dipeptidyl peptidase; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; FFA, free fatty acid; GLP, glucagon-like peptide; IGT, impaired glucose tolerance; IR, insulin receptor; IRS, IR substrate; K_{ATP}, ATP-sensitive potassium; PPAR, peroxisome proliferator–activated receptor; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

Type 2 diabetes treatment

At a symposium sponsored by the U.K. Prospective Diabetes Study (UKPDS), Bernard Zinman (Toronto, Canada) discussed the baseline findings of the ADOPT (A Diabetes Outcome Prospective Trial) study of 4,356 persons randomized from type 2 diabetes diagnosis to glyburide, rosiglitazone, and metformin treatment. The mean glucose at onset was ~150 mg/dl, ~80% had metabolic syndrome, which was either diagnosed based on the Adult Treatment Panel III or World Health Organization criteria, and patients from North America were somewhat younger and more obese. Of the subjects, 4.2% were GAD positive and similar in most measures to those who were negative, although with somewhat higher triglyceride and lower HDL, lower fasting insulin, and higher initial glucose, suggesting a greater degree of β-cell dysfunction, although similar when corrected for the degree of insulin sensitivity. Microalbuminuria was high in prevalence and associated with obesity and higher glucose and blood pressure levels. A number of presentations at the meeting addressed additional baseline findings. Zinman et al. (abstract 417) compared the 170 persons positive for GAD antibody with the 3,896 GAD-negative persons, reporting that the HbA_{1c} was 7.5 vs. 7.3%, with the former showing somewhat lower fasting and glucose-stimulated insulin, higher HDL cholesterol, and lower triglyceride levels, which is compatible with having a lesser degree of insulin resistance and features of type 1 diabetes. Viberti et al. (abstract 945) analyzed characteristics of the subjects with microalbuminuria (15.2%) in the cohort, showing 63 vs. 57% male sex and greater waist circumference (109 vs. 105 cm) and BMI (33 vs. 32 kg/m^2). The microalbuminuric persons had higher fasting glucose, HbA_{1c}, and blood pressure, and the urine microalbumin correlated with homeostasis model assessment of insulin resistance, C-reactive protein, fibrinogen, and white blood cell count.

Rury Holman (Oxford, U.K.) presented new results from the UKPDS (see

www.dtu.ox.ac.uk for UKPDS publications and Risk Engine) after 5 years post-study monitoring that was aimed at determining whether glycemic and blood pressure levels remained stable, whether risk reductions were maintained, and whether impact was maintained on macrovascular disease of glucose control, of metformin, and of metformin plus the sulfonylureas glyburide and chlorpropamide. A total of 5,102 persons with new-onset diabetes was recruited by 1991 at 23 clinical centers. The study end was in 1997, and all participating patients were informed of the results in 1998. Five-year monitoring was performed through 2002, and 10-year monitoring is in progress. The primary analysis compared diet as primary with sulfonylurea or insulin (with additional treatment only for fasting glucose >270 mg/dl) in 1,138, 1,573, and 1,156 persons, respectively. HbA_{1c} levels were 8.9 vs. 8.0% at study end, with levels similar in the two groups from 3 years on, and HbA_{1c} levels were 8.0% after 5 years. At 5 years, 58% were on insulin either alone or in addition to oral agents. The intervention decreased for total diabetes-related end points (12% at study end and 10% at 5-year follow-up; decrease remained significant). Diabetes-related death showed a trend to benefit at study end, and at 5-year follow-up, decreased significantly by 16%. Myocardial infarction decreased 16% ($P = 0.052$) at study end, and at 5-year follow-up, the decrease was 15% (statistically significant at $P = 0.042$). Microvascular disease decreased 25% at study end and 28% at 5-year follow-up. Thus, diabetes-related end points, myocardial infarction, and microvascular disease were significantly benefited by glycemic treatment. Holman raised the question of whether these results suggest a "legacy effect" of having received glucose-lowering therapies, even when glycemic levels had become similar. Metformin was used in obese persons, and diabetes-related death decreased significantly by 42% at study end and, perhaps because metformin treatment was added for those who had been in the control group, by 18% at 5 years. The reductions in risk were 39 and 18% at study end and 5-year follow-up, respectively, for myocardial infarction, and there was also a significant decrease at both time points for all-cause mortality. A peculiarity of the UKPDS was the apparent adverse effect of sulfonylurea plus metformin versus sulfonylurea alone in 537 normal-weight or overweight persons. The initial analysis at 6.6 years showed no significant difference in total diabetes-related end point but significant 60 and 96% increases in total and diabetes-related deaths. At 5-year follow-up, Holman reported, the increases in mortality were 29 and 37%, respectively, and were no longer statistically significant.

Steve Haffner (San Antonio, TX) discussed new strategies for prevention of type 2 diabetes and its complications, outlining the approach taken in the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study. A cardiovascular disease (CVD) intervention that has been shown to have glycemic benefit, valsartan, and a glycemic intervention with nateglinide are being applied in a 2×2 factorial study design for persons with impaired glucose tolerance (IGT). Haffner noted that IGT is common in a variety of populations that have both insulin deficiency and insulin resistance as risk factors. The use of a short-acting insulin secretagogue may limit postprandial glucose excursions, he stated, and thereby improve insulin resistance. Persons with IGT show a much steeper decline in acute insulin response than insulin sensitivity when developing diabetes, further suggesting benefit. Furthermore, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study showed increased 2-h glucose to be associated with adverse outcome (4). In the Japanese Funagata cohort, the 2-h, but not fasting, glucose level was similarly an important risk factor (5). The Captopril Prevention Project (6), HOPE (Heart Outcomes Prevention Evaluation) study (7), SOLVD (Studies Of Left Ventricular Dysfunction) trial (8), and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (9) show evidence that ACE inhibitors protect against diabetes, and the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study (10) shows similar protection with angiotensin receptor blocker treatment. In the NAVIGATOR study, the primary end point will be the development of diabetes and overall CVD. The secondary end points will include mortality and specific CVD events, and patients with CVD and CVD risk factors will be recruited to increase the power of the study to detect latter end points.

Hertzel Gerstein (Hamilton, Canada) discussed the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study of 5,269 persons, 86% with IGT and 43% with impaired fasting glucose (IFG), in which ramipril and rosiglitazone are being given, and in a similar 2×2 factorial design. He pointed out that the study is predicated on the belief that prevention of diabetes will "treat the pre-diabetes conditions" and lead to a decrease in end points "because in the end diabetes is just a surrogate marker for diseases down the line." The results of a number of trials have confirmed that it is possible to prevent diabetes with a variety of glucose-oriented interventions. The STOP-NIDDM also showed 49% decreased CVD end points with acarbose treatment (11). ACE inhibitors decrease vasoconstriction, increase pancreatic blood flow, decrease potassium loss, decrease catecholamines, decrease lipolysis and FFA levels, decrease hepatic glucose output, and increase bradykinin; have potential direct vasodilatory effects on skeletal blood flow; increase insulin-mediated vasodilation and glucose uptake; and have possible inflammatory effects. A number of studies suggest that thiazolidinediones (TZDs) decrease insulin resistance and may also improve β-cell function, with supporting clinical data in the TRIPOD study (12) and recent subanalysis of 585 persons with IGT randomized to troglitazone in the U.S. Diabetes Prevention Program showing a 75% decrease in diabetes vs. 58 and 31% reported with lifestyle and metformin, respectively. A carotid ultrasound substudy will involve ~1,000 persons, and the Epi-DREAM study will follow ~25,000 persons who had glucose tolerance testing in the screening studies for DREAM.

Insulin sensitizer treatment

Jim McCormack (Oxford, U.K.) discussed new approaches to the treatment of insulin resistance at a symposium on new treatments, noting that this would not simply lead to diabetes treatment, but would have many CVD benefits. Causes of insulin resistance include central adiposity, elevations in FFA and resistin levels (13), lowering of adiponectin, and lowering of hyperinsulinemia itself, the latter consideration leading to the devel-

opment of agents that decrease insulin secretion by opening the ATP-sensitive potassium (K_{ATP}) channel. PPARγ is a specific molecular target; it's activation leads to a host of effects, including increased adipose tissue mass with change in distribution, increased HDL and LDL particles, decreased small dense LDL levels, and decreased triglyceride, FFA, and prothrombotic factors. A number of dual PPARα and -γ agents have been or are in development, including rivoglitazone (Sankyo), farglitazar (GlaxoSmithKline), ragaglitazar (Novo Nordisk), KRP-297 (Kyorin/Merck), tesaglitazar (AstraZeneca), and BMS-298585 (Bristol-Myers Squibb). Side effects such as edema and weight gain, however, have led many of these agents to be withdrawn before or during clinical trials.

Other signaling pathways of insulin action are being explored. Insulin-mimetic agents and drugs stimulating IR phosphorylation may be further targets. L-783281 is such an agent. It is a small fungal metabolite that shows strong selectivity for the IR rather than receptors of other growth factors, and there is evidence for stimulation of glucose uptake (14). As this agent works at an early step, in principle it could, however, lead to greater decrease in insulin sensitivity. Potential therapeutic targets include enzymes involved in the mitogenic pathway of insulin action, such as the inositol polyphosphate 5-phosphatase SHIP2 (15) and the mitogen-activated protein kinase pathway intermediary protein tyrosine phosphatase-1β. Animals that do not express this gene show increased insulin sensitivity with resistance to obesity and hypertriglyceridemia in type 2 diabetic models (16), although selective inhibitors have not been developed. McCormack noted that part of the insulin-mimetic effect of vanadate may involve this pathway, and he suggested that this is "a very attractive target." Glycogen synthase kinase-3 inhibition, which can be produced with lithium, has been thought of as another target. This is an important negative regulator of insulin-stimulated glycogen metabolism, with levels increased in type 2 diabetes, perhaps playing a role in serine phosphorylation of IRS1 and hence in causing insulin resistance.

Another potential target is 11β-hydroxysteroid dehydrogenase (11β-HSD) 1, which converts cortisone to cortisol, with increased levels of production in visceral fat cells. Overexpression of 11β-HSD produces a phenotype resembling the metabolic syndrome (17), while animals not expressing the gene show a lowering of glucose levels and decreased phosphoenolpyruvate carboxykinase (18). PPARγ agonists decrease 11β-HSD, and a selective inhibitor has been described as showing antidiabetic action (19), although mutations decreasing 11β-HSD activity in humans have been found to be associated with adrenocorticotropin-mediated androgen excess and a phenotype resembling polycystic ovary syndrome (20).

R. Yelchuri et al. (abstract 104) randomized 213 persons with IGT to a control group, a lifestyle modification group, and a lifestyle group additionally treated with 4 mg rosiglitazone daily. Follow-up at 18 months showed 32, 15, and 6% diabetes conversion in the respective groups, suggesting 53 and 81% efficacy of the lifestyle and lifestyle plus TZD interventions. Both coffee and alcohol were also reported as being of benefit. A. Hilding et al. (abstract 416) reported that among 3,128 and 4,821 Swedish men and women, respectively, aged 35–56 years, consumption of more than five cups of coffee daily decreased the likelihood of developing type 2 diabetes by 55 and 72% and IGT by 37 and 51%, respectively. G. Pacini et al. (abstract 1,700) performed frequently sampled intravenous glucose tests with and without administration of 40 g vodka, showing 178 and 55% improvement in insulin sensitivity in eight persons with and eight without type 2 diabetes, respectively, due to ethanol. Circulating FFAs decreased 17 and 23% in the nondiabetic and diabetic subjects, respectively, with ethanol, suggesting this to mediate the improvement of insulin sensitivity and to be relevant to its cardioprotective effect.

In a study addressing the relationship between in utero growth retardation, obesity, and insulin resistance, N.S. Levitt et al. (abstract 1722) measured insulin sensitivity in 72 persons at age 25 years, with birth weight either below the 10th percentile or between the 25th and 75th percentiles. Those with BMI below the median at age 25 and normal birth weight had an insulin sensitivity (glucose uptake during a hyperinsulinemic-euglycemic clamp) of 6.02, while those below median BMI at age 25 with low birth weight had an insulin sensitivity of 6.78. Those whose BMI was above the median at age 25 had insulin sensitivities of 4.54 and 3.91, respectively, however, suggesting that the insulin resistance of low birth weight is dependent, to a large extent, on attained body mass.

A number of studies presented at the meeting compared metformin with TZDs. R.M. Lautamäki et al. (abstract 172) randomized 30 newly diagnosed persons with type 2 diabetes to 2 g metformin daily, 8 mg rosiglitazone daily, or placebo for 26 weeks, showing a decrease with both active treatments in fasting glucose and increase in insulin-mediated visceral fat but not subcutaneous fat glucose uptake measured with positron emission tomography using [18F]-2-fluoro-2-deoxyglucose. Increases in hepatic and visceral fat insulin-mediated glucose uptake were correlated. M.E. Cleasby et al. (abstract 860) compared the effects of rosiglitazone with metformin in lipid-infused rats and showed improvements in insulin sensitivity, with relatively greater peripheral effects of rosiglitazone in association with a 62% increase in systemic fatty acid clearance and a doubling of adipose tissue fatty acid uptake while decreasing liver fatty acid uptake by 40%. In contrast, liver AMP-activated protein kinase (AMPK) activity increased 3.8-fold with metformin and 2.3-fold with rosiglitazone, suggesting acute lipid-induced hepatic insulin resistance to be ameliorated by metformin and rosiglitazone via distinct mechanisms. In a clinical study, S. Lenton et al. (abstract 828) compared 1,199 drug-naïve persons with type 2 diabetes randomized to metformin versus pioglitazone, showing similar decrease in HbA_{1c} at 52 weeks, from 8.7% to 7.2 vs. 7.3%. R. Urquhart et al. (abstract 832) presented an interesting analysis of HbA_{1c} in studies of drug-naïve patients treated with pioglitazone versus metformin (n = 597 in each group) and pioglitazone versus gliclazide (n = 626 vs. 624) monotherapy, showing that the percentage increase in HbA_{1c} per year, based on regression lines from weeks 24, 32, 42, and 52, was 0.057 vs. 0.291% for pioglitazone versus metformin and 0.25 vs. 0.85% for pioglitazone versus gliclazide, suggesting the TZD effect to be more durable. In a 24-week study comparing the addition of rosiglitazone versus glyburide to metformin monotherapy in 69 vs. 72 persons with type 2 diabetes, A. Cobitz et al. (ab-

stract 835) reported that fasting glucose decreased from 178 to 140 mg/dl and from 174 to 133 mg/dl, respectively, with ~78% less hypoglycemia and 83% less diarrhea in the former group. C. Lee et al. (abstract 169) compared 639 sulfonylurea-treated patients randomized to addition of metformin versus pioglitazone, showing a decrease in HbA_{1c} of 1.36 vs. 1.21%, with 14 vs. 11% incidence of hypoglycemia, 13 vs. 3% diarrhea, 1 kg weight loss vs. 3 kg weight gain, and 7 vs. 2% peripheral edema. L.J. Maher randomized 630 persons treated with metformin to also receive pioglitazone or sulfonylurea gliclazide. There was a 1% decrease in HbA_{1c} in both groups at 1 year, with 6 vs. 2% incidence of peripheral edema and 1 vs. 11% developing hypoglycemia. C. Lambert et al. (abstract 188) compared weight changes during a 1-year treatment of type 2 diabetes with pioglitazone (up to 45 mg), metformin (up to 1,550 mg), or the sulfonylurea gliclazide (up to 320 mg) daily. In a study of 597 persons receiving pioglitazone vs. 597 with metformin, 65 vs. 23% gained weight (mean weight change +1.9 vs. −2.5 kg). In a comparison of 646 persons treated with pioglitazone vs. 626 with gliclazide, 72 vs. 67% gained weight (mean weight gain 2.8 vs. 1.9 kg). In combination therapy, 319 persons receiving gliclazide plus pioglitazone were compared with 320 receiving gliclazide plus metformin (weight change +2.8 vs. −1 kg), with 69 vs. 31% gaining weight, and 317 persons receiving metformin plus pioglitazone were compared with 320 receiving metformin plus gliclazide (weight gain 1.5 vs. 1.3 kg), with 60 vs. 61% gaining weight. The authors concluded that with particular attention to weight control, it is possible to lessen the potential weight-increasing effect seen with both sulfonylureas and TZDs.

X. Li et al. (abstract 171) studied 12 GAD antibody–positive patients with fasting C-peptide ≥300 pmol · l^{-1} · l^{-1}, fulfilling criteria for latent autoimmune diabetes in adults treated with insulin alone or insulin plus rosiglitazone. After 1 year, HbA_{1c} was similar in both groups. Fasting and postprandial C-peptide decreased with insulin alone from 620 to 360 and from 1,401 to 782 pmol · l^{-1} · l^{-1}, respectively, with an increase in daily insulin dose from 19 to 25 units, while C-peptide was stable with insulin plus rosiglitazone, with the daily insulin dose decreasing from 17 to 13 units/day. F. Ovalle and D.S.H. Bell (abstract 2267) randomized 17 persons treated with glimepiride plus metformin with HbA_{1c} >8% to rosiglitazone 8 mg daily or insulin for 6 months, reporting improvement in the acute insulin response to glucose in a frequently sampled intravenous glucose tolerance test with rosiglitazone but not with insulin, similarly suggesting recovery of pancreatic β-cell function.

Glucagon-like peptide-1

Jens Holst (Copenhagen, Denmark) discussed glucagon-like peptide (GLP)-1 analogs, pointing out that the proglucagon gene produces GLP-1 in the gut. GLP-1 potentiates glucose-induced insulin secretion; therefore, in principle, it does not produce hypoglycemia. It increases insulin biosynthesis, upregulates insulin gene expression and expression of other β-cell genes producing insulin, stimulates β-cell proliferation and differentiation of progenitor cells in the ductular epithelium, and inhibits β-cell apoptosis—trophic effects that are similar to those of other endocrine stimulatory hormones. GLP-1 also inhibits glucagon secretion and decreases gastrointestinal secretion and mortality, as well as inhibits appetite and food intake, and so might be termed "the diabetologist's dream," as it deceases glucose with little risk of hypoglycemia, decreases appetite and body weight, lowers FFA levels, improves insulin sensitivity, and increases β-cell secretion.

Initial studies of GLP-1 were reported in 1993 (21), with evidence of benefit in persons with poorly controlled diabetes in subsequent reports (22). Continuous subcutaneous administration of GLP-1 to persons with type 2 diabetes for 6 weeks demonstrates the potential therapeutic effect of the agent, showing 4.3 and 5.5 mmol · l^{-1} · l^{-1} decreases in fasting and mean glucose and a 1.3% decrease in HbA_{1c}, with weight loss occurring gradually without nausea and evidence of improvement in β-cell function based on C-peptide levels (23). Native GLP-1 is rapidly degraded with a very short-circulating half-life by dipeptidyl peptidase (DPP)-IV (24) and has extensive renal extraction, one-quarter from glomerular filtration and the remainder from tubular secretion, with similar elimination rates of GLP-1 in persons with and without type 2 diabetes (25). Strategies being pursued include development of resistant analogs and the inhibition of GLP-1 degradation. Use of analogs or GLP-1 receptor activators resistant to DPP-IV may be promising therapeutic approaches, although it will be important to reduce the rapid 50–70% renal elimination rate. Fast absorption from the injection site can be addressed with delayed absorption approaches.

The natural GLP-1 receptor agonist exendin-4, found in the saliva of the Gila monster (*Heloderma suspectum*), has possible endocrine function related to metabolic control in this lizard. Interestingly, the animal has its own GLP-1 with high homology to human GLP-1. Exendin-4 is a full agonist to the GLP-1 receptor and is cleared mainly by glomerular filtration but not by tubular uptake, with a biological effect for ~12 h following administration. In a 4-week study, AC2993 (Synthetic Exendin-4) led to a significant decrease in postprandial glucose and a 1.1% decrease in HbA_{1c} (26). Nausea, which is seen early in treatment and is relatively mild, occurred in 31% and hypoglycemia in 15% of patients, although only with sulfonylurea administration. Amylin Pharmaceuticals has reported a 6-month phase 3 study with 336 patients inadequately responding to metformin, with doses of 5–10 μg twice daily, and the higher dose was associated with a decrease in HbA_{1c} from 8.2 to 7.3% (27). Several albumin-based GLP-1 analogs are being developed. A Novo Nordisk agent, liraglutide (NN2211), has a 12-h half-life. After a single dose at bedtime in persons with type 2 diabetes, the glucose-lowering effect can be demonstrated the next morning (28). Like GLP-1, the agent improves β-cell sensitivity to glucose in humans, and increases β-cell mass in animal models, with evidence of decreased cytokine-induced β-cell apoptosis. In a 12-week phase 2 study, an effect similar to glimepiride has been reported in reducing HbA_{1c}, with decreased body weight in comparison to the sulfonylurea treatment and hypoglycemia in 0.7% vs 15%, with nausea seen during the first few weeks of treatment. Holst commented that tacchyphylaxis appears to occur to nausea but not to glycemic effects. Neurologic side effects are seen in rodent models, and increased blood pressure is seen at high doses, but this does not occur in human studies, and antibody production has not been seen at this point. Albugon from Human Genome

Sciences has a 3-day half-life, with human studies pending, and a GLP-1–albumin conjugate with a 10- to 12-day half-life in humans, CJC-1131, has been reported by Conjuchem. "What we do with GLP-1," Holst concluded, "is to substitute something that is missing in the diabetic patient."

J.J. Meier et al. (abstract 825) infused GLP-1 in eight persons with type 2 diabetes following major surgery, showing an increase in insulin levels and glucose-lowering effect without development of hypoglycemia, suggesting a potential alternative to insulin treatment in glycemic control for hospitalized persons. M.E. Trautmann et al. (abstract 174) administered the Lilly GLP-1 analog LY307161-SR once daily for 12 weeks to 182 persons with type 2 diabetes, showing a decrease in preprandial to maximal postprandial glucose increment by 4, 8, 22, 30, and 35 mg/dl with 0, 0.5, 1.0, 2.0, and 3.0 mg doses, respectively. Of patients, 69%, however, had injection site reactions with the preparation. K.B. Degn et al. (abstract 822), A.M. Chang et al. (abstract 823), and M.A. Nauck et al. (abstract 824) presented studies of NN2211 in 13, 10, and 11 persons with type 2 diabetes, respectively, showing improvement in glycemia, with increased insulin secretion showing suppression by hypoglycemia. Raun et al. (abstract 1772) reported a >60% reduction in food intake with NN2211 over a 7-week period in the minipig animal model of obesity. K. Taylor et al. (abstract 2344) described a study of persons with type 2 diabetes given exendin-4 twice daily before meals in addition to metformin, sulfonylurea, or both, with 3-month data on 38 persons showing a 1.5% fall in HbA_{1c} and with <5% withdrawal because of nausea and development of low-titer anti–exendin-4 antibody without effect on glycemic effect. J. Dupre et al. (abstract 1771) administered GLP-1, exendin-4, or placebo to eight subjects with type 1 diabetes, showing a decrease in postprandial glucose increase that may be due to delay of gastric emptying or to glucagon suppression.

E. Mannucci et al. (abstract 1778) measured levels of DPP-IV activity, responsible for GLP-1 inactivation, in 115 persons with and 85 without type 2 diabetes, showing 16% higher levels in the diabetic patients and an association between change in HbA_{1c} over a 3-month period and change in DPP-IV activity, suggesting that hyperglycemia partially mediates the lower GLP-1 in diabetic persons. C.M. Rotella et al. (abstract 1945) from the same group showed that in vitro incubation of endothelial cells with hyperosmolar medium, either with 22 or 5.5 mmol/l glucose plus 16.5 mmol/l mannitol, increased DPP-IV activity, although it did not affect DPP-IV mRNA expression. E.T. Wargent et al. (abstract 482) reported on an inhibitor of DPP-IV increasing the biological half-life of GLP-1, which when administered orally decreased food intake and diabetes development in Zucker diabetic fatty rats.

In a related presentation, Sergei Zaitsev (Moscow, Russia) discussed imidazolines as novel insulinotropic compounds. Glucose induces insulin secretion via metabolism in order to increase ATP, closing the K_{ATP} channel, leading to increases in the intracellular calcium concentration. ATP, and perhaps other glucose metabolites, also has direct effect on insulin exocytosis. Zaitsev's group has studied organic compounds possessing activity similar to GLP-1, which can be administered orally. Phentolamine, an α-adrenergic blocker with an imidazoline ring, stimulates insulin secretion. Another insulinotropic imidazoline, RX871024, a close analog without adrenergic blocking effect, increases islet insulin secretion. In vitro, it inhibits the K_{ATP} channel, and in vitro, it increases islet insulin secretion in a glucose-dependent manner. It also has a direct (K_{ATP} channel–independent) effect in increasing insulin secretion at high- but not low-glucose levels, but only in diazoxide-treated depolarized cells and in "permeabliized" islet cells with membrane defects. The K_{ATP}-independent effect depends on protein kinases A and C. RX871024 stimulates increase in diacylglycerol levels in a fashion additive to that of the cholinergic agonist carbachol. A new generation of imidazolines with pure glucose-dependent insulinotropic activity includes BL11282. This potentiates glucose-induced insulin secretion without effect at low-glucose concentration, not acting on the K_{ATP} channel, with effect seen both under depolarized and permeabilized conditions, in K_{ATP}-deficient mice, and acting on protein kinases A and C. Zaitsev concluded that the new generation of imidazolines potentiate glucose-induced insulin secretion and promote insulin exocytosis independently from blocking K_{ATP} channel, directly stimulating exocytosis via diacylglycerol, with positive in vivo studies in animal models.

K_{ATP} openers

Interestingly and somewhat surprisingly, a number of studies are being performed that suggest benefit of agents that open rather than close the K_{ATP} channel. Early administration of the nonselective potassium channel opener diazoxide may preserve residual β-cell function in patients with recent-onset type 1 diabetes. K. Lyby et al. (abstract 2345) described a 10-day study of the Novo Nordisk agent NN414, a β-cell selective potassium channel opener, in 24 nondiabetic male subjects, showing increased glucose and decreased insulin 24-h patterns, without evidence of adverse effect, suggesting a potential for clinical "β-cell rest." R.A. Ritzel et al. (abstract 1644) described decreased in vitro β-cell apoptosis induced by incubation with islet amyloid polypeptide during coincubation with NN414. T.B. Bφdvarsdóttir et al. (abstract 357) studied *Psammomys obesus*, a desert gerbil that spontaneously develops diabetes when fed a high-energy diet. NN414 and vehicle were administered to animals after development of hyperglycemia and with resumption of a low-energy diet, with glucose 5.7 vs. 14.2 mmol/l after 4 weeks of treatment. K. Skak et al. (abstract 176) studied a type 1 diabetes animal model, demonstrating that 54% of treated rats, but 18% of those receiving either vehicle or diazoxide, showed minimal levels of islitis after 3 weeks, suggesting the potential for improved β-cell survival.

Metformin

David Moller (Rahway, NJ) discussed the molecular mechanism of action of metformin, pointing out that the medieval herbal treatment, French Lilac, was the original agent in this family. Metformin decreases gluconeogenesis (29) and has variable lipid-lowering effects, including actions on VLDL triglycerides and FFAs. There is evidence of a decrease in CVD mortality (30) and of protection against progression to diabetes (31).

Potential effects of metformin might involve the IR, the glucagon receptor, glucose transporters, and AMPK. There have also been studies suggesting that metformin decreases the activity of DPP-IV (32), and there is evidence that metformin potentiates the effect of infused GLP-1 (33), although no direct effect of met-

formin on DPP-IV has been demonstrated in vivo. Gastrointestinal absorption of glucose may be another potential site of action, although less well characterized.

Metformin decreases gluconeogenesis in hepatocytes, increases insulin action in myocytes (34), and may inhibit mitochondrial oxidative phosphorylation (35). All of these could involve AMPK, which is activated by AMP or adenosine nucleotides and has a variety of actions, including effects on fatty acid synthesis via acetyl CoA carboxylase (ACC) and on lipid synthesis, on muscle glucose uptake, and on nuclear transcription. In Moller's studies, both 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) and metformin activate AMPK, with the metformin effect occurring at levels seen with pharmacologic administration and appearing to operate via a different mechanism than that of AICAR (36). The effect of metformin on AMPK appears to be indirect, as it is not seen in cell-free systems. In rodents, metformin decreases liver and muscle ACC activity (37). Skeletal muscle biopsy studies in humans show increased AMPK activity with metformin treatment, and in rat hepatocyte studies, the effects of metformin can be reversed with an AMPK inhibitor, further suggesting this as an important mechanism. The inhibitory effects of metformin on ACC lead to increased oxidation and decreased synthesis of fatty acids, which may explain the decreases in circulating FFA and triglyceride levels seen with treatment, as well as antiobesity actions. Activation of AMPK by metformin suppresses the lipogenic transcription factor sterol regulatory element-binding protein-1 (38), perhaps contributing to the lipid-lowering effects and to the reported benefit of metformin in nonalcoholic fatty liver disease (39,40). Studies using a microarray system showing ~20,000 genes show considerable overlap of metformin with AICAR, including the downregulation of lipogenic factors, such as sterol regulatory element-binding protein-1 and fatty acid synthase, and of gluconeogenic genes, including phosphoenolpyruvate carboxykinase and glucose-6 phosphatase. Muller concluded that AMPK appears to be an important drug target "to produce a better metformin," particularly as the effect of metformin on AMPK may be indirect, via its effect on oxidative phosphorylation, so that a direct activator of AMPK might lack the adverse potential to cause lactic acidosis. S. Del Guerra et al. (abstract 481) incubated islets isolated from organ donors with type 2 diabetes, showing 35% decreased insulin content, 28% decreased glucose-induced insulin secretion, and doubling of apoptosis in comparison to islets from persons without diabetes. Islet AMPK mRNA expression was decreased 60%. A 24-h incubation with metformin increased insulin content and release and normalized AMPK levels, suggesting direct islet effects of the agent.

Other glycemic treatment

H. Schlebusch et al. (abstract 1941) perfused human placenta in vitro, with repaglinide showing significant transplacental passage, although concentrations fivefold higher than therapeutic levels were utilized. C. Weyer et al. (abstract 852) reported the effect on body weight of pramlintide in 292 insulin-treated persons with type 2 diabetes, showing a significant 1.8-kg weight loss and a 0.4% decrease in HbA_{1c} from baseline 9.1% in comparison to 284 placebo- and insulin-treated patients. T. Burrell et al. reported acetaminophen absorption studies in 24 persons with type 2 diabetes treated with pramlintide, suggesting a 36–41% decrease in gastric emptying. F.A. Van De Laar et al. (abstract 2341) presented a Cochrane review meta-analysis of the effect of acarbose in the treatment of type 2 diabetes, reporting on 38 studies selected from 852 papers analyzed. Compared with placebo, acarbose decreased HbA_{1c} 0.71% and fasting and postprandial glucose 20 and 34 mg/dl, respectively, with a decrease in postprandial insulin levels. Compared with sulfonylureas, however, HbA_{1c} was 0.6% and fasting glucose 20 mg/dl higher with acarbose. Gastrointestinal side effects were three to four times more likely with acarbose than with either placebo or sulfonylurea. M. Hanefeld et al. (abstract 1099) presented a meta-analysis of the effect of acarbose on CVD in seven studies performed between 1987 and 1999 with a minimum duration of 52 weeks of 1,248 persons with type 2 diabetes, showing a 41% decrease in total CVD events and a 68% decrease in myocardial infarction, with significant effect controlling for weight, triglyceride, and blood pressure levels, suggesting that control of postprandial hyperglycemia may contribute to prevention of macroangiopathy.

Obesity treatment

A number of interesting reports addressed aspects of action with the lipase inhibitor orlistat. S. Yang et al. (abstract 506) noted that in vitro orlistat, by inhibiting islet lipase activity, as demonstrated by reduction in glycerol release, inhibits insulin secretion, suggesting that β-cell lipase activity is involved in glucose-stimulated insulin secretion. Although presumably this is not important in therapy as the drug is absorbed only to a low extent, M. Horowitz et al. (abstract 851) reported that gastric emptying following a glucose-containing olive oil and water mixture was more rapid with administration of orlistat in seven persons with type 2 diabetes, with 2-h gastric retention of oil decreased from 60 to 19% and that of glucose decreased from 81 to 34%. Plasma GLP-1 was decreased from 51 to 14 pmol $\cdot l^{-1} \cdot l^{-1}$, and blood glucose increased from 155 to 256 mg/dl, suggesting a potential clinical caution. The overall effect of the agent is, however, beneficial in persons with type 2 diabetes. Q. Huang et al. (abstract 850) reported that in 33 previously untreated persons with type 2 diabetes receiving orlistat for 24 weeks, weight loss and improved glycemia were seen in association with an increase in adiponectin levels. T.P. Didangelos et al. (abstract 1891) randomized 97 persons with type 2 diabetes to orlistat versus hypocaloric diet alone, with expected improvement in body weight and waist circumference, and showed 6-month glucose decreasing from 181 to 135 mg/dl and HbA_{1c} from 8.2 to 6.4% with orlistat vs. 175 to 181 mg/dl and 7.9 to 7.2% with diet alone. V.V. Bogomolov et al. (abstract 1901) compared 51 persons with type 2 diabetes randomized to orlistat versus metformin 500–1,500 mg daily, showing 9 vs. 5% weight loss, with a decrease in HbA_{1c} from 9.1 to 7.8% vs. from 8.8 to 8.7% and in LDL cholesterol from 165 to 137 vs. from 180 to 138 mg/dl.

K. Stenlof et al. (abstract 1896) randomized 541 persons with type 2 diabetes not requiring pharmacologic glucose-lowering treatment, with BMI between 27 and 50 kg/m^2, to placebo versus topiramate 96 or 192 mg daily for 60 weeks, with 40-week data available for 229 persons. Twenty four, 57, and 77% had lost >5% of initial weight; HbA_{1c} decreased by 0.2, 0.6, and 0.7% (from 6.8%); and significantly greater benefits were seen in the topiramate groups. Adverse events in-

cluded paresthesia in 46 vs. 12%, fatigue in 26 vs. 23%, hypoesthesia in 15 vs. 4%, dry mouth in 9 vs. 4%, concentration difficulty in 9 vs. 3%, and vertigo in 5 vs. 2% of persons receiving topiramate versus placebo, respectively. Efforts to reformulate the agent are now proceeding to lower these side effects.

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