Exploring Treatment Strategies for Type 2 Diabetes

ZACHARY T. BLOOMGARDEN, MD

Perspectives on the News commentaries are now part of a new, free monthly CME activity. The Mount Sinai School of Medicine, New York, New York, is designating this activity for 2.0 AMA PRA Category 1 credits. If you wish to participate, review this article and visit www.diabetes.procampus.net to complete a posttest and receive a certificate. The Mount Sinai School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This is the second in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions in June 2007, in Chicago, discussing approaches to the treatment of type 2 diabetes, contrasting the use of older therapies with the use of new agents to lower blood glucose levels.

At a symposium on the use of insulin in treatment of type 2 diabetes, Rury Holman (Oxford, U.K.) reviewed the findings of the UK Prospective Diabetes Study (UKPDS) and A Diabetes Outcome Progression Trial (ADOPT) in terms of the performance of metformin, sulfonylureas, thiazolidinediones, and insulin.

Among the newly diagnosed diabetic individuals entering the UKPDS, mean A1C fell from 9 to 7% with diet modification. At 1 year, mean A1C was 6% with insulin, sulfonylurea, and metformin treatment. After 3, 6, and 9 years in UKPDS, however, only ~40, 40, and 30% of individuals receiving insulin maintained A1C <7%. Among those on sulfonylurea monotherapy, 45% had A1C <7% at 3 years, but the proportions decreased to 30 and 20% at 6 and 9 years, respectively, with 45, 35, and 15% of those receiving metformin monotherapy maintaining A1C <7% at these times. Holman characterized this inexorable increase as one of the principal challenges of glycemic treatment of individuals with type 2 diabetes. Interestingly, the widely used sulfonylurea glyburide was less effective in maintaining glycemic control than the now much less commonly used sulfonylurea chlorpropamide (1). Using the homeostasis model assessment, sulfonylureas failed to improve insulin sensitivity, which improved by 10% with metformin (2). β-Cell function progressively decreased in all patients participating in the UKPDS—the improvement with sulfonylureas appearing to be only a temporary phenomenon. Among individuals randomized to insulin in the UKPDS, the required dose progressively increased; by 14 years, 58% of patients not randomized to insulin required this treatment to attain adequate control.

The greatest weight increase was with insulin, with lesser but still significant weight gain with sulfonylureas and with little weight change in patients receiving metformin or those randomized to conventional treatment (3). Holman reviewed a study of 2,220 patients in a research database in the U.K. who were receiving metformin as initial treatment and were subsequently given a sulfonylurea. There was a progressive rise in A1C with metformin, as in the UKPDS, with a 6-month period of improvement on sulfonylureas, after which the A1C began to increase at approximately the same rate (4). In the UKPDS 3-year acarbose substudy, among those treated patients who actually took the tablets, A1C fell by 0.5%, although a similar resumption of the upward A1C trend after the initial period occurred with this agent as well (5).

Holman suggested that ADOPT be considered a successor study to the UKPDS, comparing the thiazolidinedione rosiglitazone with metformin and glyburide (6). The study's objective was to compare the durability of glycemic control in 4,360 individuals with newly diagnosed diabetes having fasting glucose between 126 and 180 mg/dl followed for a median of 4 years. In the study, 1,456, 1,454, and 1,441 patients were treated, respectively, with rosiglitazone, at a maximal dose of 8 mg/day, metformin, at a maximal dose of 2,000 mg/day, and glyburide, at a maximal dose of 15 mg/day. The time to monotherapy failure (two consecutive fasting glucose levels >180 mg/dl—a standard that would not currently be considered adequate) was shortest with glyburide, then metformin, and rosiglitazone associated with the longest duration of glycemic control. A1C was 7.3% at baseline, showing the most rapid and greatest decrease with glyburide but subsequently having the greatest rate of increase with this agent—approximately twice that of metformin and three times that of rosiglitazone.

In ADOPT, insulin sensitivity and β-cell function were assessed using homeostasis model assessment, with the lowest insulin sensitivity seen with the sulfonylurea and the highest with rosiglitazone. β-Cell function pattern was similar to that in the UKPDS, with dramatic early improvement in individuals receiving glyburide but, interestingly, with a suggestion of greater maintenance of β-cell function in individuals receiving rosiglitazone. Weight decreased with metformin and increased with glyburide and rosiglitazone, although beginning at 1 year a greater increase was seen with rosiglitazone. Holman also commented that congestive heart failure rates were greater with rosiglitazone but that there was no significant increase in cardiovascular disease with this agent (7). Holman noted the "unexpected . . . increased fracture rate for women" treated with rosiglitazone. He concluded that achieving and maintaining optimal glycemic control is essential to decreasing complications but that progressively worsening hyperglycemia caused by declining β-cell function appears to be characteristic of type 2 diabetes, posing a major challenge. This process is not slowed by metformin, sulfonylureas, or acarbose but appears to be improved with thiazolidinedione treatment. In the ADOPT, however, rosiglita-

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.

Abbreviations: ADA, American Diabetes Association; ADOPT, A Diabetes Outcome Progression Trial; DPP, dipeptidyl peptidase; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; UKPDS, UK Prospective Diabetes Study.

DOI: 10.2337/dc07-zb10

zone was associated with a nonsignificant increase in cardiovascular events, with a significant increase in heart failure and with increased fractures in women—all of which must be taken into account in determining appropriate treatment approaches. The majority of type 2 diabetic individuals do appear to require insulin over time, but it is noteworthy that initial insulin treatment in the UKPDS was not more successful than use of oral agents. More modern approaches to use of insulin may offer improved glycemic control with less risk of hypoglycemia and weight gain.

Combination oral hypoglycemic treatment approaches

Barry Goldstein (Philadelphia, PA) asked whether oral agents can "do the job." "We know that monotherapy is not going to be successful," he said, suggesting that the most meaningful clinical translation of ADOPT will be in the development of appropriate treatment combinations (8). Most organizations have suggested similar glycemic guidelines, aiming for A1C levels below 6.5–7%, with fasting glucose below 110 mg/dl. The traditional approach has been to initiate and then intensify oral agents, then to add oral agents in combination, then to add basal insulin, and finally to move to multiple insulin injections. "There's been a paradigm shift," however, with Goldstein commenting that in order to achieve more aggressive goals rapid intensification of treatment is required (9).

There are multiple targets and multiple therapeutic approaches that can be taken to improve insulin sensitivity, increase insulin secretion, and decrease inappropriate glucagon elevations in type 2 diabetes. Early comparisons of postprandial insulin and glucose curves in individuals with and without type 2 diabetes were interpreted to suggest that "there's lots of insulin" with insulin resistance (10). Metformin appears to target hepatic overproduction of glucose, largely via AMP kinase; thiazolidinediones' initial effect is on adipocytes, and insulin secretion enhancers and dipeptidyl peptidase (DPP)-4 inhibitors improve insulin secretion and suppress glucagon. Combination therapy allows complementary mechanisms to be used to achieve greater benefit, perhaps with lowering of side effects by reducing dosages of individual drugs, with glucose lowering also potentially preserving and improving function of β-cells. The use of a metformin-thiazolidinedione combination leads to decreased hepatic glucose uptake, insulin sensitization, and potential cardiovascular benefits. Although recognizing that outcome studies looking at the approach are ongoing, improvement in β-cell function and avoidance of hypoglycemia are potential benefits, allowing good glycemic control and ameliorating the weight gain seen with thiazolidinediones. These drugs are ineffective without sufficient endogenous insulin.

A number of clinical trials have explored this approach. In a study randomizing type 2 diabetic individuals to 1 g metformin with 8 mg rosiglitazone daily or to 2 g metformin daily alone, 28% of the former vs. 39% of the latter group experienced gastrointestinal side effects, and A1C fell 0.9 vs. 0.7%, although there was 1.8-kg weight gain vs. 1.8-kg weight loss in the respective groups (11). In a study comparing the addition of glyburide versus rosiglitazone to metformin, there was somewhat greater glycemic improvement with the former, with A1C decreasing from 8.4 to 6.9 vs. 7.3%, occurring at the expense of considerably greater hypoglycemia frequency of 38 vs. 1% (12). In a study of the approach of initial combination therapy comparing glyburide, metformin, or the combination, 5 mg glyburide decreased A1C 1.2% and 1,317 mg metformin decreased A1C 1%, but the combination in mean doses of 2.8/557 and 4/818 mg led to 1.5% falls in A1C (13). As expected, hypoglycemia occurred infrequently with metformin alone, and gastrointestinal side effects occurred more frequently with higher metformin doses. The development of combination approaches may allow improvement in specific side effects. In a 2-year study of glyburide versus nateglinide in combination with metformin, A1C fell similarly from 8.3 to 6.8 vs. 6.9%, with hypoglycemia prevalence 18 vs. 8% (14). The combination of rosiglitazone with metformin in mean doses of 7 and 1,800 mg daily, respectively, led to a 2.3% fall in A1C, while 8 mg rosiglitazone daily led to a 1.6% fall and 1,847 mg metformin daily to a 1.8% fall in A1C from baseline levels of 8.8% (15). Rosiglitazone increased adiponectin, with potential for anti-inflammatory and anti-atherosclerotic benefit, but was associated with more edema, while metformin led to more gastrointestinal side effects. In a study of glimepiride with rosiglitazone, at 28 weeks A1C fell from baseline levels of 9–9.2% by 1.7% with 4 mg glimepiride alone, by 1.8% with 8 mg rosiglitazone alone, and with the combination by 2.5% (16). The combination of pioglitazone with vildagliptin has also been studied: 30 mg pioglitazone daily reducing A1C from 8.7% by 1.4%, 100 mg vildagliptin daily from 8.6% by 1.1%, and the combination decreasing A1C from 8.8% by 1.9% at 24 weeks (17). Similarly, in a 24-week study, 100 mg sitagliptin daily decreased A1C from 8.9% by 0.7%; 1,000 and 2,000 mg metformin daily decreased A1C from 8.9% and 8.7% by 1% and 1.3%, respectively; and the combination of 100 mg sitagliptin with 1,000 and 2,000 mg metformin daily decreased A1C from 8.8% by 1.6% and 2.1%, respectively (18). Thus, a variety of combinations can effectively reduce A1C, with Goldstein pointing out that more than one-half of individuals starting at baseline A1C of 8–9% can attain the glycemic goal of A1C <7% with these approaches.

Insulin for treatment of type 2 diabetes: pro

David Nathan discussed a different tactic: the use of insulin early in the treatment of individuals with type 2 diabetes. There are currently, he noted, 21 million individuals in the U.S. with diabetes, of whom ~1 million have type 1 diabetes. All the latter and ~4 million individuals with type 2 diabetes use insulin, the impetus being the goals of glycemic control of below 7% for all, with each person aiming for a level as close to 6% as achievable. This consensus approach (19), Nathan suggested, can be "used as kind of a launching point," based on A1C goals with titration considered reasonable at 3- to 6-month intervals by measuring A1C levels. Interventions may be based on glucose-lowering effectiveness, as well as on safety, side effects, tolerability/patient acceptance, and other patient factors such as weight, cardiovascular disease risk factors, potential β-cell preservation, and cost. Although not showing supporting data, Nathan termed insulin the most potent glucose-lowering agent, and metformin and sulfonylureas/metiglinides "the next most potent, ironically the two oldest." He considered less-effective agents to be exenatide, pramlintide, DPP-4 inhibitors, and α-glucosidase inhibitors—in order of most to least potent. He cited a number of studies of combinations with metformin, with insulin reducing A1C 2.5%, sulfonylureas 1.7%, thiazolidinediones 1.2%, and exenatide and DPP4 inhibitors 0.8%, although he failed to show initial and final A1C levels,

leading one to suspect that the comparisons may have been such that apparently more effective agents were studied in individuals with worse initial glycemic control.

Although acknowledging that no one agent can be recommended over the others in all cases, the guideline recommended that at diagnosis of diabetes metformin be given at the time of initiation of lifestyle treatment, with consideration to relatively early use of insulin, an approach that he termed "usually more effective and cost-effective than three oral agents." He reviewed a study comparing the combination of insulin plus metformin with that of a sulfonylurea, metformin, and a thiazolidinedione, noting that both groups attained mean A1C of 7.6% from a baseline of 9.6%, with greater reduction in triglyceride and cholesterol levels and projected cost of insulin with metformin one-third that of the triple oral hypoglycemic agent approach (20). A further approach would be to administer a thiazolidinedione and metformin with insulin. This approach of early insulin administration contrasts with that typically used, however, with Nathan reviewing a survey of 6,424 individuals with type 2 diabetes treated at his health center, 55% of those on monotherapy receiving metformin, with sulfonylureas next most frequently used, while >60% of those on combination treatment received metformin with a sulfonylurea. When three agents were used, thiazolidinediones and insulin were administered equally, to approximately one-third of patients. There is the potential for particular benefit of insulin, with an implanted pump study in patients with type 2 diabetes showing partial restoration of the acute insulin secretory response to glucose (21), suggesting that "if we lower glycemia, we can rescue these β-cells that are wounded."

Aggressive insulin treatment, then, is crucial. There is some experimental data suggesting that intensive insulin treatment early in the course of type 2 diabetes may lead to remission (22). In a Veterans' Administration cooperative study of 153 men with type 2 diabetes, comparing standard with intensive insulin treatment, the former began on ~20 units daily, increasing to ~50 units daily, while the latter began with ~30 and increased to ~80 units daily, with A1C remaining around 9.5% in the former group while decreasing to <7% in the intensive group (23). Similarly, a study with aggressive administration of NPH insulin at bedtime reduced A1C from 9.5 to 7.2%, at a mean daily dose of 85 units (24). Reviewing a large group of studies of the efficacy of insulin in type 2 diabetic patients, Nathan showed that A1C levels around 7% are relatively readily achieved, typically with insulin doses of 0.6–0.9 units/kg body wt daily, although Nathan noted that in the Kumamoto Study, carried out in Japan, 0.44 units · kg^{-1} · day^{-1} was required, suggesting the importance of ethnic differences. The risk of severe hypoglycemia was ~3%, a level considerably lower than that in type 1 diabetes. The Diabetes Control and Complications Trial showed that with intensive and conventional insulin treatment, there were 61 and 19 major hypoglycemic events per 100 person-years of treatment of type 1 diabetes (25).

Nathan reviewed the initial comparisons of glargine with NPH insulin (26) and suggested that, on balance, "the A1Cs achieved [with different insulin preparations] are generally about the same . . . I'm not sure that it makes that much of a difference." A number of different approaches can be taken. Combination of insulin with metformin has been compared with administration of NPH insulin twice daily, with administration of insulin with glyburide, and with administration of insulin with both glyburide and metformin, with bedtime NPH insulin added to metformin alone giving similar glycemic benefit to the other approaches, with lesser degree of weight gain (27). In a study of type 2 diabetic individuals failing to achieve goal with two oral hypoglycemic agents alone, both insulin glargine and NPH showed convincing benefit (28). There has been interest in inhaled insulin (29). In a study of the addition of inhaled insulin to the combination of a sensitizer with a secretagogue oral agent, hypoglycemia occurred considerably more frequently but was not severe, with evidence of improvement in glycemic control (30). Nathan concluded that multiple factors lead to inadequate therapy of type 2 diabetes, with limited time for treatment adjustment, therapeutic inertia, inadequate resources for teaching and for care intervention, fear of injections, and inadequate health care insurance often leading to slow adoption of effective interventions, particularly of insulin, as well as to failure to use adequate doses and to adjust doses in a sufficiently timely fashion.

Insulin for treatment of type 2 diabetes: con

Robert Henry (San Diego, CA) discussed what he termed "the cons of insulin therapy." He reviewed Nathan's consensus algorithm of type 2 diabetes treatment approaches, agreeing that the initial steps of lifestyle modification and metformin are inexpensive and offer a number of benefits but fail for many individuals to offer sufficient glucose-lowering efficacy. He commented, however, that many individuals are unable to tolerate metformin, particularly in full dose. Additional treatments considered "step 2" are insulin and sulfonylureas, which are considered to be inexpensive, although associated with weight gain and risk of hypoglycemia, and thiazolidinediones, characterized as expensive and associated with fluid retention, although with some lipid benefits. The algorithm excludes as overly expensive α-glucosidase inhibitors, which have gastrointestinal side effects; exenatide, which requires injections and also has gastrointestinal side effects; meglitinides, requiring three times daily dosing; pramlintide, requiring three times daily dosing and also causing gastrointestinal side effects; and the DPP-4 inhibitors. Barriers to insulin are, Henry suggested, to a large extent those of patient resistance, with many individuals "trying to do anything to get away from insulin," considering it to require increased self-care efforts and to be associated with more frequent adverse effects such as hypoglycemia, leading many diabetic individuals to feel there to be a stigma associated with its use. Furthermore, the initiation of insulin treatment may increase the overall complexity of treatment for a given diabetic patient.

Some 27–28% of diabetic individuals in the U.S. take insulin, with the percentage stable from 1988 to 2003, although many more use it now in combination with oral agents (31). Approximately one-third of patients experience anxiety about injections, with at least one-half of those experiencing such anxiety declining to initiate insulin treatment (32). It is not widely recognized that, presumably for these reasons, more than one-quarter of the 496 individuals in the UKPDS randomized to insulin refused this treatment (33). Henry described a survey of 767 diabetic individuals, with 28% stating they would not be willing to take insulin if prescribed, a survey of 99 diabetic individuals finding that 76% had "negative feelings" about insulin treatment, and an-

other study of 708 type 2 diabetic individuals found multiple barriers to insulin use (34). Furthermore, physicians are resistant to initiation of insulin treatment, and many are not familiar with its use. In the UKPDS, there was no clear proof of greater efficacy of insulin over other treatment approaches (3). Henry acknowledged that hypoglycemia is less severe among type 2 diabetic patients receiving insulin but pointed out that it remains an issue both for patients and physicians. In the UKPDS, total and severe hypoglycemia occurred in ~35% and 2.5% of individuals receiving insulin, respectively, both in the overall population and in the overweight subgroup; both figures are considerably greater than with sulfonylureas and metformin (3,35). Similarly, in the "Treat To Target" Study with glargine or NPH insulin added to treatment of individuals failing oral agents and with weekly forced titration for 24 weeks, severe hypoglycemia occurred five to six times per 100 person-years with both agents, although there was more nocturnal hypoglycemia with bedtime NPH than glargine (28). Henry did cite recent evidence that with both type 2 and type 1 diabetes, the frequency of hypoglycemia is decreasing (36).

Another problem with intensive insulin treatment is weight gain. In the UKPDS, patients gained 4–5 kg after 10 years with insulin treatment, and in the Diabetes Control and Complications Trial similar weight gain was reported in the intensive treatment group. Henry reviewed his study of intensive insulin treatment in type 2 diabetes, in which patients required ~100 units daily, with an 8.7-kg 1-year weight gain, although he was able to reduceA1C nearly to 6% (37). A study of glyburide-treated type 2 diabetic patients randomized to the addition of metformin, of NPH at bedtime, or of insulin lispro before meals showed similar glycemic control with the two insulin approaches but greater weight gain with the single long-acting insulin dose (38), although Henry noted that metformin may reduce the weight gain seen in such regimens (28,39). Other approaches should, however, be considered in such settings, such as the use of exenatide, which in comparison with glargine insulin led to weight loss rather than gain, with similar improvement in glycemia (40).

Henry concluded that current approaches to intensive insulin use require very regular patient contact and that alternative approaches teaching patients self-titration are "not simple, not necessarily straightforward, and many folks simply do not have the resources." He suggested that "it is doubtful whether most recent-onset type 2 diabetic patients can follow the directions and procedures necessary to implement intensive insulin therapy."

A number of studies relevant to the use of insulin in type 2 diabetic patients were presented at the American Diabetes Association (ADA) meeting. Huizinga et al. (abstract 30) compared weight change over 2 years among 164 type 2 diabetic individuals with baseline A1C 6.7%; 88 patients using insulin had baseline BMI 35 kg/m^2 and gained 1.3 lb, while those not using insulin had baseline BMI 33 kg/m^2 and gained 7.3 lb, despite there being no difference in use of thiazolidinediones, exenatide, or pramlintide between the groups (abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007). This suggests that under appropriate settings, weight gain is not an inevitable consequence of insulin treatment. Mullins et al. (abstract 603) presented a meta-analysis of six studies of 3,175 type 2 diabetic individuals randomized to NPH versus insulin glargine, showing the latter to be associated with 32% lower frequency of hypoglycemic events confirmed by 65 mg/dl glucose, 33% lower frequency of nocturnal hypoglycemia, and 51% lower frequency of severe hypoglycemia. At A1C 9%, hypoglycemia rates with NPH vs. glargine would be ~1 vs. 0.6 per patient-year, while at A1C 7%, the respective rates would be 1.4 vs. 1 per patient-year.

Philis-Tsimikas et al. (abstract 487) compared 168 vs. 163 type 2 diabetic individuals receiving at least one oral agent randomized to insulin detemir vs. NPH given at bedtime, in mean dose 0.4 units/kg. At 20 weeks, A1C decreased from 8.9% by 1.6% vs. from 9.2% by 1.7%, with weight gain significantly different at 0.7 vs. 1.6 kg. Weight gain was similar at ~1.7 kg with both insulin preparations at baseline BMI 25 kg/m^2, but at baseline BMI 35 kg/m^2 there was ~0.4 vs. 2.1-kg weight gain. Hermansen et al. (abstract 489) and Le Floch et al. (abstract 546) similarly reported evidence of less weight gain in randomized controlled studies comparing detemir versus NPH. Sreenan et al. (abstract 549) reported an observational study of individuals receiving sulfonylureas or thiazolidinediones treated with detemir, showing that whether or not these agents were continued, A1C decreased from ~9 to 7.9% but that significant weight loss was only seen when these oral agents were discontinued at the time of detemir initiation.

Incretin mimetics for type 2 diabetes

A second symposium discussed two approaches to the treatment of type 2 diabetes based on the glucose-lowering effect of gut peptides, contrasting DPP-4 inhibitors with incretin mimetics. Ralph DeFronzo (San Antonio, TX) discussed incretin mimetics with emphasis on exenatide, pointing out their relative advantages, although noting that "both of these classes of drugs are very good drugs." The pathogenesis of type 2 diabetes involves genetic susceptibility to insulin resistance, both in muscle and liver, with the latter causing fasting hyperglycemia and the former postprandial hyperglycemia. Over time, β-cell failure ensues in a progressively worsening fashion. There is also adipocyte insulin resistance, leading to increased lipolysis with elevated free fatty acid taken up by liver and muscle, as well as the β-cell contributing to the abnormalities of function of these organs. The gut also plays an important role in the progressive hormonal dysfunction leading to diabetes, with abnormal incretin secretion a major cause of the hyperglucagonemia of type 2 diabetes. Central nervous system abnormalities appear to contribute to dysregulation of appetite and of neural input to the liver, muscle, and the β-cell, playing a direct role in diabetes pathogenesis.

The important incretins glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP) affect many of these pathogenic mechanisms. In 1930, La Barre described the greater effect of oral than parenteral glucose in increasing insulin secretion. Creutzfeld and Nauck performed a classic experiment demonstrating this two decades ago, with a graded glucose infusion to give identical plasma glucose levels to that seen with oral glucose leading to an insulin response only one-quarter as great (41). GLP-1, secreted by the L-cells of the distal small bowel, and GIP, secreted by the K-cells of the proximal gut—both more in response to neural input than as direct responses to ingested nutrients—account for ~90% of the incretin effect. GLP-1 also has an appetite-suppressing effect, although this is not the case for GIP. GLP-1 but not GIP slows gastric emptying, reversing the more rapid gastric emptying associated with early diabetes. Both have short half-lives and are

degraded by DPP-4. Both DPP-4 inhibitors and GLP-1 replacement have been shown effective in the treatment of type 2 diabetes.

There is a progressive decline in the GLP-1 response to an oral glucose load as glucose tolerance worsens, from individuals with normal glucose tolerance, to impaired glucose tolerance, to type 2 diabetes. There is, however, a paradoxically high GIP level in type 2 diabetes, suggesting resistance to its effect in this condition, with comparison of the insulin-secretory responses to infusion of GLP-1 and GIP in type 2 diabetes showing considerably greater response to the former. DeFronzo reviewed an elegant and important presentation at the ADA meeting (Højberg et al., abstract 1,455) studying release of GLP-1 and GIP in type 2 diabetes, finding that GIP responsiveness normalized with intensive insulin treatment. The eight type 2 diabetic patients studied began with mean A1C 8.9% and achieved mean glucose 126 mg/dl during a 4-week period of intensive insulin therapy with reduction in A1C to 7.1%. Comparing hyperglycemic clamps before and after the 4-week intensive treatment period, the insulin response to GIP increased 2.7-fold, that to GLP-1 increased 2.4-fold, and that to hyperglycemia alone increased 1.8-fold, with GLP-1 but not GIP increasing insulin secretion before intensive treatment but both hormones increasing insulin secretion after restoration of near euglycemia, suggesting that what has been considered an abnormality of β-cell responsiveness to GIP in type 2 diabetes may actually be a feature of poor glycemic control.

Normalization of glycemia in type 2 diabetes may be achieved with infusion of GLP-1, but its short half-life makes this not a useful therapeutic agent. This has been addressed by the use of the GLP-1 receptor agonist exenatide, derived from the venom of the Gila monster, showing high homology to GLP-1 and similar metabolic effect but without susceptibility to degradation by DPP-4.

Exenatide shows a dose-response effect in stimulating insulin and inhibiting glucagon to improve glucose homeostasis in type 2 diabetic individuals. Exenatide reverses the abnormality in first-phase insulin secretion in type 2 diabetes, suggesting it to be a physiologic approach to insulin replacement. Its administration is not associated with hypoglycemia, however, as its insulin secretory effect is attenuated as glucose levels fall toward normal. In DeFronzo's study of 336 metformin-treated type 2 diabetic individuals with baseline A1C 8.2% who were treated with 5 or 10 μg placebo or exenatide twice daily for 28 weeks, there was a 1–1.2% decrease in A1C at the higher dose, with dose-dependent weight loss averaging 8 lb (42), with further weight loss over time in open-label extension studies lasting up to 3 years. Examining postprandial glucose and insulin responses in treated patients, glucose levels are lower with improvement in insulin secretion. In open-label extension studies at 82 weeks, one-quarter of patients had no weight loss, with a 0.7% fall in A1C, while the highest quartile had weight loss of ~11 kg with an A1C fall of 1.7%—both weight loss and direct action of the drug presumably contributing to the degree of glycemic improvement, with the latter group also showing a fall in triglyceride and elevation in HDL cholesterol levels. In a clinical experience summary of 160 individuals treated with exenatide, Oyer et al. (abstract 585) reported that A1C decreased from 7.4 to 7%. The drug was relatively well tolerated, but 13 patients stopped within the first week and 34 stopped after 1 month, mainly for gastrointestinal intolerance. Mean weight loss was 5% of body weight and was greater with 10 μg than with 5 mcg doses. Among individuals treated with thiazolidinediones at baseline, those discontinuing this treatment had greater weight loss but a mean increase in A1C of 0.5%.

Another GLP-1 receptor agonist, liraglutide, gives placebo-subtracted improvement in A1C by 1.2–1.6% (with placebo increases of 0.3%, so the absolute fall was ~0.9%) (43). This agent is given once daily rather than twice daily with exenatide and appears to cause greater reductions in fasting glucose than seen with exenatide. In a 14-week Japanese study of 226 type 2 diabetic individuals not receiving other treatment, Seino et al. (abstract 520) administered liraglutide 0.1, 0.3, 0.6, and 0.9 mg daily, showing placebo-adjusted A1C fall from baseline of 8.3% by 0.8, 1.2, 1.6, and 1.9%, respectively, with dose-related reductions in 2-h postprandial glucose approximately twice as great as those in fasting glucose. A long-acting form of exenatide given weekly is in development, with 15-week falls in A1C of 1.4–1.7% compared with a rise in A1C of 0.4% in the placebo group, suggesting that this drug could also be a potentially highly effective agent in type 2 diabetes treatment (44). In a study presented at the ADA meeting, Wang et al. (abstract 498) administered CJC-1134-PC, a modified exendin-4 analog conjugated to recombinant human albumin, to 42 type 2 diabetic patients, showing glucose-lowering effect lasting for at least 1 week, with evidence of weight loss. The use of these agents, then, reduces A1C, promotes weight loss, stimulates insulin, and suppresses glucagon. DeFronzo pointed out that in animal models, there is increased islet cell replication with neogenesis from pancreatic ductal cells and with decreased apoptosis.

The liver plays a central role in the development of fasting hyperglycemia in diabetes, related to low insulin and elevated glucagon levels. De Fronzo noted that oral glucose augments hepatic glucose uptake, while this is not readily observed following parenteral glucose administration. He reviewed a study of the mechanisms of action of GLP-1 in which 10 individuals with type 2 diabetes treated with metformin or a sulfonylurea underwent a 6-h C^{14}-labeled meal tolerance test before and 2 weeks after exenatide treatment, showing falls both in fasting and in postprandial glucose (without administration of exenatide on the morning of the study and with acetaminophen used to show that gastric emptying was similar before and after treatment). Exentatide decreased entry of labeled glucose into circulation, suggesting increased hepatic glucose uptake. De Fronzo recalled his article speculating almost three decades ago that a gut factor is necessary for normalization of hepatic glucose production in individuals with type 2 diabetes (45), which suggests that GLP-1 is the long-sought factor. Thus, GLP-1 has effects on appetite centers of the brain, on β-cell and α-cell insulin, and glucagon secretion, perhaps increasing β-cell neogenesis, with potential evidence of cardiovascular benefits as well. When asked about nonresponders, he acknowledged that there is large variability in weight loss but suggested that the glycemic response is fairly consistent.

DPP-4 inhibitors for type 2 diabetes

Richard Pratley (Burlington, VT) discussed the role of DPP-4 inhibitors in the treatment of diabetes. He reviewed the effects of GLP-1 and GIP and their potential treatment of islet dysfunction, illustrating the dual defect of insulin resistance as well as decreased insulin response—the latter playing a crucial role in the development of diabetes. In addition to insulin

secretory defects, type 2 diabetes is associated with elevations in glucagon secretion, particularly after meals. Pratley further discussed the effects of GLP-1 and GIP and pointed out that both have the amino acid alanine in the second NH_2-terminal position, allowing inactivation by DPP-4. The two have overlapping physiological effects, with GLP-1 having protective effects on the neurologic and cardiovascular systems, potentially playing therapeutic roles, while GIP increases both first-phase and, to a greater extent than GLP-1, second-phase insulin secretion. In experimental animals, both improve β-cell survival. GLP-1, but not GIP, slows gastric emptying and inhibits glucagon secretion.

Interestingly, >50% of secreted GLP-1 is degraded by local DPP-4 before absorption into plasma. Clearly, then, the glucose-lowering effect of endogenous GLP-1 is limited by its short half-life. The initial studies of DPP-4 inhibition with the nonspecific inhibitor valine pyrrolidide showed increased active GLP-1 levels following GLP-1 administration in animal models, leading to increased insulin secretion. The DPP-4 serine protease family includes fibroblast activation protein and DPP-8 and -9. In vitro substrates of DPP-4 include GLP-1, GLP-2, GIP, enterostatin, gastrin releasing peptide, neuropeptide Y, peptide YY, insulin-like growth factor-1, and inflammatory peptides including RANTES (regulated on activation, normal T-cell expressed and secreted); monocyte chemotactic protein-1, -2, and -3; eotaxin; and interleukin-1β and -2.

There were 55 abstracts studying 12 different DPP-4 inhibitors at the current meeting; thus, Pratley noted, "so we are going to be seeing even more . . . in the coming months." The most long-term clinical data are available for sitagliptin and vildagliptin. Both are given once daily, reach their maximal effect after 2–3 h, and can be taken with or without meals. Sitagliptin is not metabolized, and vildagliptin is metabolized by hydrolysis, with neither showing potential for interaction with other medications. Sitagliptin shows a >1,000-fold greater specificity for DPP-4 than for other related peptidases. Duration of DPP-4 inhibition is dose dependent, with 85% effect at 12 h and 40% effect at 24 h after a 100-mg vildagliptin dose. In a 28-day study with this agent, both GLP-1 and GIP levels were increased throughout the day. Glucagon levels decreased by one-half, with a robust decrease in the glucose response to a standard meal. Insulin levels showed no change, but, given the lower blood glucose levels, the glucose-insulin dose-response curve was shifted to greater insulin response. Insulin secretion was increased, with evidence of increased insulin sensitivity as well. In drug-naïve patients, a 12-week course of vildagliptin increased firs-phase insulin secretion, with some residual increase 2 weeks after drug washout and with evidence of increased insulin sensitivity. In animal studies with sitagliptin, β-cell apoptosis decreased with increased islet neogenesis, suggesting potential structural benefit (46).

In monotherapy, both vildagliptin and sitagliptin decreased A1C by ~0.8% from a baseline of 8%, due to both improvement in fasting and, to a greater extent, in postprandial glucose (47). In a comparative study of rosiglitazone with vildagliptin, both led to similar reductions in A1C, both showing greater A1C lowering at higher baseline levels (48). In a 104-week trial comparing vildagliptin with metformin, both had sustained glucose-lowering effects, metformin showing somewhat greater effect at 52 weeks but not at the end of the 2-year study. In a study by Migoya et al. (abstract 286) in nondiabetic individuals, postprandial active GLP-1 levels were 1.95-fold greater after 2 days of treatment with 100 mg sitagliptin daily, 1.75-fold greater with 500 mg metformin twice daily, and 4.12-fold greater when both agents were administered; metformin appeared to increase total GLP-1 secretion, while sitagliptin decreased GLP-1 metabolism, suggesting that the combination may be particularly useful. Indeed, sitagliptin has been studied in combination with metformin (49) and pioglitazone (50), showing additive effect. Furthermore, a comparison of adding glipizide and sitagliptin to metformin showed identical glucose-lowering effects, with similar increasing effects at increasing baseline glucose levels, although with greater hypoglycemic frequency and weight gain in patients treated with the sulfonylurea (51). In insulin-treated type 2 diabetic patients, addition of vildagliptin led to greater fall in A1C with less hypoglycemia, suggesting an additional potential for this agent (52). When the combination of sitagliptin with metformin is studied as initial treatment, the agents alone decreased A1C by 0.8 and 1.3%, respectively, while the combination decreased A1C by 2%, starting at a level of 8.8%. Similarly, initial combination of vildagliptin with pioglitazone decreased A1C ~2% (17).

Other effects are similar with vildagliptin and sitagliptin. Overall, there is some degree of decrease in weight, particularly among patients obese at baseline. There are minimal but beneficial changes in fasting lipid levels, with evidence of greater decrease in postprandial triglyceride levels. Side effects are relatively few. In a pooled analysis of 5,141 patients treated for 24–104 weeks with sitagliptin presented at the ADA meeting by Stein et al. (abstract 534), hypoglycemia and weight gain occurred less frequently than with comparators, while nasopharyngitis occurred 12 vs. 9 times, contact dermatitis 1 vs. 0.4 times, and osteoarthritis 2 vs. 1 times per 100 patient-years for sitagliptin- vs. comparator-treated individuals, respectively. Pratley commented that the efficacy of DPP-4 inhibitors may be somewhat greater among individuals with BMI <30 kg/m^2 and in older rather than younger individuals. Sitagliptin is principally metabolized by the kidneys. A 12-week study of 91 individuals with creatinine clearance 30–50 ml/min treated with 50 mg sitagliptin daily and with creatinine clearance <30 ml/min treated with 25 mg daily showed a 0.12 mg/dl increase in serum creatinine in those receiving sitagliptin and a 0.7 mg/dl increase in control subjects.

A number of presentations at the ADA meeting gave information pertaining to the newer DPP-4 inhibitors in development, as well as giving additional details pertaining to the actions of sitagliptin and vildagliptin. Christopher et al. (abstracts 495 and 499) studied 36 healthy men receiving alogliptin 25, 50, 100, 200, 400, or 800 mg, showing ~90, 80, and 70% DPP-4 inhibition at 24, 48, and 72 h after the 100-mg dose, with nearly 50% inhibition at 72 h after the 25 mg dose, suggesting somewhat greater potency and duration of action than that seen with previously studied agents. In 55 otherwise untreated type 2 diabetic individuals receiving 25, 100, and 400 mg alogliptin daily for 14 days, similar DPP-4 inhibition was found, with 4-h postprandial glucose showing placebo-corrected decreases of 40, 49, and 68 mg/dl, respectively. DeFronzo et al. (abstract 285) treated 743 type 2 diabetic individuals with A1C 8% on 1,500–2,550 mg/day metformin with 2.5, 5, or 10 mg saxagliptin daily, or placebo, for 24 weeks, finding a 0.7–0.8% reduction in A1C without weight change.

Other DPP-4 inhibitors described at the ADA meeting included ARI2243 (Sanford et al., abstract 604), PF-00734200 (Dai et al., abstract 506), SK-0403 (Sunami et al., abstract 482), ABT-279 (Zhu et al., abstract 562), BI-1356 (Huettner et al., abstract 586; Heise et al., abstract 588; and Forst et al., abstract 594).

He et al. (abstract 493) studied type 2 diabetic individuals receiving 100 mg vildagliptin daily for 28 days, showing the agent to be similarly effective whether given before the morning or the evening meal. Woerle et al. (abstract 500) treated 18 type 2 diabetic individuals with 100 mg vildagliptin, showing an acute reduction in gastric emptying, potentially playing a role in the reduction of postprandial glycemia. Garber et al. (abstract 501) treated 132 type 2 diabetic individuals with 50 mg vildagliptin once or twice daily in addition to 4 mg glimepiride daily, showing a 0.7% fall in A1C from baseline 8.5%, without difference between the once- and twice-daily vildagliptin regimens. Scherbaum et al. (abstract 503) treated 306 drug-naïve type 2 diabetic individuals with baseline A1C 6.2–7.5% (mean 6.7) with 50 mg vildagliptin daily versus placebo, finding a placebo-adjusted A1C fall of 0.3%. Rosenstock et al. (abstract 505) treated 179 individuals with impaired glucose tolerance with 50 mg vildagliptin daily versus placebo for 12 weeks, finding increased prandial GLP-1 and GIP, decreased glucagon, and increased insulin secretion, with consequent 22% reduction in peak postprandial glucose levels. Utzschneider et al. (abstract 515) administered 100 mg vildagliptin daily for 6 weeks to 22 individuals with impaired fasting glucose, showing evidence of improvement both in insulin sensitivity and in the acute insulin secretory response to glucose, using minimal model analysis of the response to intravenous glucose administration.

Karasik et al. (abstract 523) administered 100 mg sitagliptin daily versus 5–15 mg glipizide daily for 54 weeks in 544 type 2 diabetic individuals receiving metformin, finding 0.7 vs. 0.9% fall in A1C from a baseline of 7.9%, with hypoglycemia seen in <1 vs. 18% and a 0.9-kg weight loss vs. 1.5-kg weight gain. Hermansen et al. (abstract 535) administered 100 mg sitagliptin daily versus placebo to 441 type 2 diabetic individuals receiving glimepiride alone, finding a 0.6% fall in A1C, or glimepiride with metformin, finding a 0.9% A1C decline. The administration of sitagliptin with glimepiride was, however, associated with 12% hypoglycemia rate, while only 2% of individuals receiving placebo with glimepiride experienced hypoglycemia.

These presentations extend Pratley's observations on the use of DPP-4 inhibitors for treatment of type 2 diabetes. Pratley concluded that both vildagliptin and sitagliptin appear effective, lowering postprandial glucose to a greater extent than fasting levels, with evidence supporting their use in monotherapy and in combination with most oral agents and perhaps with insulin. Safety appears excellent, with the agents appropriate for the elderly, for individuals with renal insufficiency, and for individuals with coronary insufficiency and with heart failure. Open questions include the relative importance of their effects on GLP-1 versus GIP, whether their efficacy be sustained, whether they are weight neutral or associated with weight loss, and their effects on cardiovascular risk factors. The effects on other DPP-4 substrates may lead to adverse consequence, and need assessment, and differences between agents in DPP-4 selectivity may be of consequence. Full 24-h inhibition does, he suggested, lead to "a more robust effect on fasting glucose," another potential difference between agents. When asked about the Food and Drug Administration concerns with vildagliptin, Pratley noted that there was animal toxicity not seen in human studies but noted that the need for additional studies "will be a significant delay." Comparing the DPP-4 inhibitors with GLP-1 receptor agonists, their additional effect on GIP may increase glucose lowering, but they are limited by endogenous secretion, and Pratley considers them as effective as exenatide but perhaps not as effective as longer-acting agents now in development. DPP-4 inhibitors are better tolerated and are oral rather than injected, suggesting a particular role in early treatment and, perhaps, as suggested by the presentations of Rosenstock et al. and Utzschneider et al., in prevention of diabetes.

References

1. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC: UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years: UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 15:297–303, 1998
2. U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease: UK Prospective Diabetes Study Group. *Diabetes* 44:1249–1258, 1995
3. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
4. Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR: Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. *Diabetes Care* 28:995–1000, 2005
5. Holman RR, Cull CA, Turner RC: A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care* 22: 960–964, 1999
6. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355: 2427–2443, 2006
7. Krall RL: Cardiovascular safety of rosiglitazone. *Lancet* 369:1995–1996, 2007
8. Goldstein BJ: Clinical translation of "a diabetes outcome progression trial": ADOPT appropriate combination oral therapies in type 2 diabetes. *J Clin Endocrinol Metab* 92:1226–1228, 2007
9. Del Prato S, Felton AM, Munro N, Nesto R, Zimmet P, Zinman B; Global Partnership for Effective Diabetes Management: Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. *Int J Clin Pract* 59:1345–1355, 2005
10. Hofeldt FD, Lufkin EG, Hagler L, Block MB, Dippe SE, Davis JW, Levin SR, Forsham PH, Herman RH: Are abnormalities in insulin secretion responsible for reactive hypoglycemia? *Diabetes* 23:589–596, 1974
11. Weissman P, Goldstein BJ, Rosenstock J, Waterhouse B, Cobitz AR, Wooddell MJ, Strow LJ: Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. *Curr Med Res Opin* 21:2029–2035, 2005
12. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P: Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Diabetes Obes Metab* 8:156–163, 2006
13. Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D; Glyburide/Metformin Initial Therapy Study Group: Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab* 4:201–208,

2002
14. Gerich J, Raskin P, Jean-Louis L, Purkayastha D, Baron MA: PRESERVE-β: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. *Diabetes Care* 28:2093–2099, 2005
15. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A: Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab* 8:650–660, 2006
16. Chou HS, Palmer JP, Jones AR, Waterhouse B, Ferreira-Cornwell C, Krebs J, Goldstein BJ: Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. *Diabetes Obes Metab*. 2007 Jul 21; [Epub ahead of print]
17. Rosenstock J, Baron MA, Camisasca RP, Cressier F, Couturier A, Dejager S: Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab* 9:175–185, 2007
18. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE: Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 30:1979–1987, 2007
19. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006
20. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P; INS-2061 Study Team: Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. *Diabetes Care* 26:2238–2243, 2003
21. Blackshear PJ, Shulman GI, Roussell AM, Nathan DM, Minaker KL, Rowe JW, Robbins DC, Cohen AM: Metabolic response to three years of continuous, basal rate intravenous insulin infusion in type II diabetic patients. *J Clin Endocrinol Metab* 61:753–760, 1985
22. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β-cell function. *Diabetes Care* 27:2597–2602, 2004
23. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, Emanuele NV, Levin SR, Henderson W, Lee HS: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM): results of the feasibility trial: Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care* 18:1113–1123, 1995
24. Cusi K, Cunningham GR, Comstock JP: Safety and efficacy of normalizing fasting glucose with bedtime NPH insulin alone in NIDDM. *Diabetes Care* 18:843–851, 1995
25. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
26. Heinemann L, Richter B. Clinical pharmacology of human insulin. *Diabetes Care* 16 (Suppl. 3):90–100, 1993
27. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M: Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 130:389–396, 1999
28. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators: The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086, 2003
29. Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA; Inhaled Insulin Study Group: Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med* 134:203–207, 2001
30. Rosenstock J, Zinman B, Murphy LJ, Clement SC, Moore P, Bowering CK, Hendler R, Lan SP, Cefalu WT: Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 143: 549–558, 2005
31. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO: Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care* 27:17–20, 2004
32. Zambanini A, Newson RB, Maisey M, Feher MD: Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract* 46:239–246, 1999
33. United Kingdom Prospective Diabetes Study (UKPDS). 13. Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 310:83–88, 1995
34. Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV: Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. *Diabetes Care* 28:2543–2545, 2005
35. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
36. UK Hypoglycaemia Study Group: Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 50:1140–1147, 2007
37. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS: Intensive conventional insulin therapy for type II diabetes: metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 16:21–31, 1993
38. Bastyr EJ 3rd, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}: IOEZ Study Group. *Diabetes Care* 23:1236–1241, 2000
39. Aviles-Santa L, Sinding J, Raskin P: Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 131:182–188, 1999
40. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group: Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 143:559–569, 2005
41. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W: Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 29:46–52, 1986
42. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092–1100, 2005
43. Vilsboll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courreges JP, Verhoeven R, Buganova I, Madsbad S: Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* 30: 1608–1610, 2007
44. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M, Taylor K: Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 30:1487–1493, 2007
45. DeFronzo F, Ferrannini E, Wahren J, Felig P: Lack of a gastrointestinal mediator of insulin action in maturity-onset diabetes. *Lancet* 2:1077–1079, 1978
46. Mu J, Woods J, Zhou YP, Roy RS, Li Z, Zycband E, Feng Y, Zhu L, Li C, Howard AD, Moller DE, Thornberry NA, Zhang BB: Chronic inhibition of dipeptidyl pep-

tidase-4 with a sitagliptin analog preserves pancreatic β-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 55:1695–1704, 2006
47. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 49: 2564–2571, 2006
48. Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A: Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabetes Care* 30:217–223, 2007
49. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 29: 2638–2643, 2006
50. Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 28:1556–1568, 2006
51. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 9:194–205, 2007
52. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S: Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 50:1148–1155, 2007