Diabetes Treatment and Measures of Glycemia

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

Incretin treatment

Visboll et al. (abstract 1465) studied 13 women with gestational diabetes mellitus during the third trimester and 2–3 months following delivery, showing almost a doubling of the insulin secretory effect of oral glucose over that of intravenous glucose, evidence of reversibility of the reduced incretin effect of type 2 diabetes with improvement in glycemia. Yokoo et al. (abstract 1597) identified a protein, CF266, expressed in the intestine, which increased glucose-stimulated islet insulin secretion and appeared to have β-cell trophic effects—perhaps a novel incretin. (Abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 57 [Suppl. 2], 2008).

A number of studies were presented of glucagon-like peptide-1 (GLP-1) receptor activators. Novel formulations are being explored. Asakura et al. (abstract 12) synthesized glycosylated GLP-1 by chemical and enzymatic modifications, showing resistance to degradation by dipeptidyl peptidase-4 with preservation of GLP-1 receptor binding and functional activity and with a 10- to 100-fold increase in duration of activity and glucose-lowering potency in *db/db* mice. Blase et al. (abstract 195) administered 60–1,800 μg intranasal exenatide in a formulation containing an absorption enhancer to 17 type 2 diabetic patients, finding therapeutic plasma levels and reduction in glycemia after a standardized meal. Although nausea, vomiting, and sneezing occurred in 6, 5, and 2 patients, respectively, this might be an effective therapeutic approach. Costello et al. (abstract 198) administered GLP-1 adsorbed to Technosphere microparticles by inhalation in 26 healthy individuals, with a rapid increase in plasma GLP-1 to levels >100 pmol/l at 1 and 1.5 mg doses, respectively, increasing insulin and reducing glucose levels. Nausea and vomiting were not reported, although cough and headache occurred. Drucker et al. (abstact 107) treated 295 type 2 diabetic patients with 10 μg exenatide twice daily or 2 mg exenatide long-acting release weekly for 30 weeks, finding A1C reductions of 1.5 vs. 1.9% and fasting glucose reductions of 42 vs. 25 mg/dl, respectively, with a mean weight loss of approximatel 4 kg in each group.

The currently available formulation of exenatide continues to be a subject of investigation. Brodows et al. (abstract 485) treated 233 drug-naïve type 2 diabetic patients with 5 or 10 mg exenatide or placebo, showing reduction in A1C from 7.8% by 0.7, 0.9, and 0.2%, respectively, with greater weight loss in the groups receiving exenatide. Kendall et al. (abstract 513) presented 2-year follow-up data of 457 type 2 diabetic patients receiving exenatide in combination with metformin, a sulfonylurea, and/or a thiazolidinedione. A total of 156 had early weight loss of 6 kg over the initial 26 weeks, and 210 had more gradual but similar weight loss over the 2-year period. Both groups showed a 1.3% A1C reduction at 2 years, while 91 patients with 1 kg weight gain, although initially having a 1.3% A1C reduction, showed a gradual increase in A1C after the initial 6 months. Recognizing this to be an open-label follow-up, one should presume that the actual rates of weight loss and A1C reduction in clinical practice might not be as favorable. Indeed, Yoon et al. (abstract 482) presented their 2-year follow-up of 192 patients with exenatide added to insulin: 78 discontinued—30 because of side effects, 13 because of a lack of insurance coverage, and 35 for lack of efficacy. A1C decreased 8% from baseline by 0.5–0.6%. Eleven stopped insulin, and another 11 stopped prandial insulin, with a mean 40% reduction in insulin dose at 6 months, although there was only a 20% reduction in insulin dose at 12–24 months. Loh and Clement (abstract 105) reported their 2-year experience with 30 type 2 diabetic patients treated with exenatide. Weight loss was 3.5 kg at 6 months, 2.1 kg at 1 year, and 1.5 kg at 2 years, and A1C was 7.6% at baseline and at 2 years. Only 11 patients remained on treatment at 2 years, although this group did continue to show improvement in A1C and in weight. Fabunmi et al. (abstract 1213) compared 3,262 patients beginning exenatide with 3,038 beginning insulin glargine in a health plan claim database, finding 68 and 58% adherence, respectively, based on refill rates, with 47 vs. 29% having >80% refill rates while 56 vs. 75% of patients had a >2 month gap between refills, suggesting exenatide to be associated with greater compliance and persistence. However, different sampling policies with the two medications might influence this conclusion because 10-μg exenatide samples are not offered. Bunck et al. (abstracts 104 and 109) randomized 69 metformin-treated type 2 diabetic patients to addition of exenatide vs. glargine for 12 months and found a 0.8 vs. 0.7% A1C reduction but 3.6 kg weight loss vs. 1 kg weight gain, respectively. The exenatide-treated group had greater arginine-stimulated C-peptide secretion during hyperglycemia at 52 weeks, but after a 4-week washout both groups returned to baseline. Postprandial excursions of both glucose and triglyceride after a standardized meal were reduced with exenatide to a greater degree than with glargine.

Liraglutide is a new GLP-1 analog not degraded by dipeptidyl peptidase-4. Noyan-Ashraf et al. (abstract 190) administered liraglutide to mice in a myocardial infarction model, finding reduction in infarct size and improved survival, with increased expression of protective genes, reduction in matrix metalloproteinase 9 expression, and a cardioprotective effect in an isolated heart model. Shimoda et al. (abstract 9) reported a 60% increase in

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pancreatic β-cell mass in diabetic mice with liraglutide administration, with evidence of reduced oxidative or endoplasmic reticulum stress.

Liraglutide has been the subject of extensive clinical trials. Marre et al. (abstract 12) reported effects of 0.6, 1.2, or 1.8 mg liraglutide daily, 4 mg rosiglitazone, or placebo added to 2–4 mg glimepiride daily in 1,041 type 2 diabetic patients. A1C decreased 0.6, 1.1, 1.1, and 0.4% and increased 0.2%, respectively, from baseline levels of 8.4–8.6%. Weight increased by 0.7 and 0.3 kg with the 0.6- and 1.2-mg doses, decreased 0.2 kg with the 1.8-mg dose, and increased 2.1 kg with rosiglitazone. Nauck et al. (abstract 504) randomized 1,091 metformin-treated type 2 diabetic patients to 0.6, 1.2, or 1.8 mg liraglutide daily or 2–4 mg glimepiride daily for 26 weeks, finding 1% A1C reductions from 8.5% with the two higher liraglutide doses and with glimepiride but with 2.6–2.8 kg weight loss vs. 0.9 kg weight gain. Russell-Jones et al. (abstract 536) randomized 581 type 2 diabetic patients receiving 1 g metformin twice daily plus 2–4 mg glimepiride daily to 1.8 mg liraglutide daily, liraglutide placebo, or open-label insulin glargine for 26 weeks, with an A1C decrease from 8.3% by 1.3, 0.2, and 1.1% and weight decreasing 1.8 and 0.4 kg and increasing 1.6 kg, respectively. Jendle et al. (abstract 106) administered 0.6, 1.2, or 1.8 mg liraglutide daily; glimepiride; or placebo to 160 metformin-treated type 2 diabetic patients for 26 weeks. Dual-energy X-ray absorptiometry showed an increase in both fat and lean body mass with addition of glimepiride, while there was progressively greater reduction in fat, particularly visceral fat, with increasing liraglutide doses. Matthews et al. (abstract 505) analyzed β-cell function effects of liraglutide in three trials including 2,613 type 2 diabetic patients with baseline A1C 8.2–8.4%, finding ~10% reduction in proinsulin-to-insulin ratio and 28–34% improvement in homeostasis model assessment of β-cell function. Colagiuri et al. (abstract 554) reported that mean systolic blood pressure decreased 3–5 mmHg in three trials, with a trend to increase in pulse. Flint et al. (abstracts 555 and 556) performed a standardized meal test on 18 type 2 diabetic patients receiving 1.8 mg liraglutide daily vs. placebo, finding lower preprandial glucose and lesser glucose increments after a standardized meal, with higher fasting and postload insulin levels and evidence of delayed gastric emptying based on acetaminophen absorption kinetics. Hunger levels were lower in the postprandial period, with a 204-kcal-lower intake during a subsequent meal.

Several additional GLP-1 analogs are undergoing clinical testing. Kapitza et al. (abstract 506) administered 1, 8, or 30 mg of the GLP-1 analog R1583 or placebo to 48 type 2 diabetic patients receiving metformin, finding weight loss and reduction in 24-h glycemia with the 30-mg dose over 14 days. Ratner et al. (abstract 10) administered 20–40 mg R1583 weekly for 8 weeks to 133 metformin-treated diabetic patients, finding a 29–41 mg/dl reduction in fasting glucose; placebo-treated patients had an 11 mg/dl fasting glucose decrease. Balena et al. (abstract 108) administered R1583 to 306 patients for 8 weeks at doses of 5, 10, or 20 mg weekly or 10 or 20 mg every two weeks, finding A1C reduction by 1–1.2% in all groups, while a placebo group had a 0.2% A1C reduction. The 10 and 20 mg weekly and 20 mg every other week group had 2, 2.8, and 1.9 kg weight loss, respectively. Distiller and Ruus (abstract 520) administered 5 μg of GLP-1 receptor activator AVE0010 daily or twice daily, increasing the dose as tolerated to 20 μg daily or twice daily, to 64 type 2 diabetic patients for 28 days, finding 20 and 25 mg/dl reductions in fasting and 48 and 56 mg/dl reductions in mean daily glucose with the once and twice daily dosing regimens, respectively. Ratner et al. (abstract 433) administered 5, 10, 20, or 30 μg AVE0010 daily or the same doses twice daily to 542 metformin-treated type 2 diabetic patients with a baseline A1C of 7.5%, showing decreases of 0.3, 0.3, 0.5, 0.6, 0.5, 0.6, 0.6, and 0.7%, respectively and a 2-kg placebo-adjusted weight loss at the higher doses. Stewart et al. (abstract 519) administered another GLP-1 receptor activator, albiglutide, to type 2 diabetic individuals, showing 22–35 and 41–53 mg/dl reductions in fasting and mean postprandial glucose at 3 days after a 64 mg dose, with a half-life of 4–6 days.

Insulin treatment

Yang et al. (abstract 349) treated 10 newly diagnosed type 2 diabetes patients with continuous subcutaneous insulin infusion for 2 weeks, showing a 9.2-fold increase in the acute insulin response to a glucose load, with a 3.6-fold-greater glucose infusion requirement to maintain euglycemia during a hyperinsulinemic clamp—suggesting improvement in β-cell function as well as in insulin sensitivity, both of which could contribute to the diabetes remission that has been reported with this approach. Wolfe et al. (abstract 202) treated 29 type 2 diabetic individuals with glargine insulin at bedtime with various combinations of oral agents and exenatide, reducing glucose levels on continuous monitoring to a mean of 98 mg/dl from midnight to 6:00 A.M.; postmeal glycemia consistently exceeded 140 mg/dl, however, suggesting that premeal rapid-acting insulin is needed to optimize control. Henriksen et al. (abstract 456) randomized 371 patients to NPH insulin at bedtime or insulin aspart before meals and to placebo, metformin, rosiglitazone, or both. Weight gain was found with all regimens (less with metformin and more with rosiglitazone), as was improved glycemic control in those receiving both sensitizers. Ahmann et al. (abstracts 490 and 2042) and Colon et al. (abstract 480) randomized 374 type 2 diabetic individuals with mean A1C 8.8% on insulin glargine plus oral agents to a 1:1 lispro-protamine lispro suspension three times daily vs. glargine at bedtime plus lispro three times daily, with a weekly dose adjustment to achieve premeal glucose <110 mg/dl, achieving a similar mean A1C of <7% with similar weight gain and hypoglycemia frequency; older age and lower baseline BMI increased risk of hypoglycemia. Miyashita et al. (abstract 982) randomized 42 type 2 diabetic patients with A1C averaging >9% on sulfonylurea treatment to preprandial aspart plus basal insulin vs. biphasic insulin analog twice daily for 6 months, finding that A1C decreased similarly from 9.1 to 6.9% vs. from 9.7 to 7.7%, with similar patterns of BMI, carotid intima-media thickness, and adiponectin levels. With less rigorous approaches, then, biphasic insulin may offer benefits similar to those of a basal-bolus regimen. Swan et al. (abstract 1812) noted that many pediatric clinics allow patients to mix aspart and detemir insulins but presented euglycemic clamp data showing that such mixing may not be well-advised. When combined in a 1:2 ratio, the peak glucose infusion requirement at 90 minutes was lost, with a flat glucose infusion requirement from 60 through 300 minutes; the use of biphasic insulin would probably be preferable to allowing mixing of detemir with a rapid-acting analog.

Hsia (abstract 201) compared NPH at bedtime to insulin glargine in 80 type 2 diabetic individuals with mean A1C 9.3%, finding a 2.1 vs. 0.9% A1C improvement with glargine in the morning vs. at bedtime and more frequent hypoglycemia on fasting glucose determination with NPH. King and Armstrong (abstract 436) treated 35 type 2 diabetic individuals receiving basal but not bolus insulin with insulin glargine at bedtime for one week using continuous glucose monitoring (CGM), titrating to midnight–6:00 A.M. glucose <120 mg/dl with <5% of readings <70 mg/dl. Titration required on average 3.7 days, and glycemic patterns were similar with the two insulin preparations. Wernsing et al. (abstract 200) compared glulisine and lispro insulin after a standard meal in 21 obese type 2 diabetic patients maintained at 100 mg/dl glucose overnight with intravenous regular insulin, showing identical postprandial glucose patterns.

Smith et al. (abstract 309) described a study of a transdermal insulin-delivery device based on the proprietary PassPort System (Altea Therapeutics) in eight C-peptide–negative type 1 diabetic individuals with a mean A1C of 9%, reporting stable insulin levels and glucose infusion requirements after a 4-h equilibration period, with stable insulin levels during the subsequent 8 h. Strange et al. (abstract 197) treated 6 type 2 diabetic individuals who had received glargine with or without oral agents using the V-Go device (Valeritas, Parsipanny, NJ) for insulin delivery as a preset basal rate plus intermittent boluses. With the same total daily insulin dose, the approach led to lower daytime glucose levels without an increase in nocturnal or morning levels on CGM.

Schwartz et al. (abstract 417) described studies of orally administered liposomally entrapped 1% encapsulated insulin containing a hepatocyte-targeting molecule in its bilipid layer administered to 30 type 1 diabetic patients receiving insulin glargine. They found a reduction in the mean of daily seven-point (pre- and postmeal and at bedtime) blood glucose levels compared with those seen with preprandial subcutaneous human insulin. Kidron et al. (abstract 425) administered another oral insulin formulation (Swiss Caps), demonstrating a significant glucose-lowering effect in nondiabetic individuals. Brandt et al. (abstract 424) presented a study of five type 2 diabetic patients with A1C <8% and fasting glucose <140 mg/dl treated with insulin aspart vs. a new intranasal insulin formulation preprandially and showing a 35 vs. 54% reduction, respectively, in the degree of postprandial glucose increase, with four vs. one patient developing hypoglycemia during titration. The authors attribute the better results with the intranasal formulation to rapid (<20 min) development of peak insulin concentration with this approach. Staiger et al. (abstract 1379) reported less adipocyte differentiation in vitro with insulin detemir than with human insulin, which is a potential mechanism for lesser weight gain reported with this agent.

Hospital insulin treatment strategies were explored by several groups. Garg et al. (abstract 71) randomized 24 nondiabetic individuals after cardiac surgery to standard treatment with or without administration of 0.15 units/kg insulin glargine daily for 3 days, finding mean glucose 126 vs. 133 mg/dl with intravenous insulin infusion for 8 vs. 15 h, respectively. Newton et al. (abstract 76) randomized 98 medical intensive care unit patients with blood glucose >140 mg/dl to a computer-guided (Glucommander) vs. a column-based paper protocol insulin infusion algorithm. From initial glucose levels averaging 198 vs. 188 mg/dl, glucose 80–120 mg/dl was achieved in 5 vs. 8 h, respectively, with mean glucose values 103 vs. 120 mg/dl, using insulin infusion rates of 0.67 vs. 0.48 units $\cdot$ kg^{-1} $\cdot$ day^{-1}. Glucose <60 mg/dl was seen in 2.6 vs. 1.4% of tests, while levels >200 mg/dl occurred at some point in 5 vs. 15 patients. Dukatz et al. (abstract 78) compared three preoperative insulin glargine dosing strategies in 165 insulin-treated type 2 diabetic patients the evening prior to a surgical procedure: *1*) taking 80% of the usual dose; *2*) not using rapid-acting insulin and taking 50% if the usual self-reported fasting glucose was 150 mg/dl (otherwise 80%) or using rapid-acting insulin but omitting this on the morning of the procedure and taking 80 or 100% of the usual glargine the evening before based on usual fasting glucose more or less than 150 mg/dl, or *3*) consulting their private physician. On arrival to the hospital, mean fasting glucose was 134, 132, and 128 mg/dl for those not taking rapid-acting insulin and 155, 134, and 149 mg/dl for those taking rapid-acting insulin in the three groups, with 5, 3, and 8% and 6, 4, and 9% having fasting glucose <80 mg/dl and with 3, 0, and 6% and 14, 2, and 6% having fasting glucose >250 mg/dl, respectively. None of the differences were statistically significant, leading the authors to suggest that simply taking 80% of the usual glargine dose appeared as effective as more complex dosing schemes.

Approaches to glucose monitoring

Voelme et al. (abstract 223) compared capillary glucose monitoring during pregnancy in type 1 diabetic women performing vs. not performing CGM; 13 patients used DexCom or Medtronic CGM, and there were 13 age-, duration of diabetes–, ethnicity-, and albuminuria-matched control subjects. From a similar baseline A1C of 6.8%, A1C decreased to 5.8 vs. 6.3%, without an increase in hypoglycemia, suggesting that under appropriate circumstances this may be a useful approach. In an observational study, Zoupas et al. (abstract 405) used the Medtronic insulin pump combined with CGM in 10 type 1 diabetic patients treated for 12 months, noting a fall in A1C from 8.4 to 6.8% and reduction in insulin dose from 56 to 48 units daily without increasing the frequency of hypoglycemia. Mc Namara et al. (abstract 231) used the DexCom CGM in 20 type 1 diabetic children age 11.6 years for 5.6 days on average. Sixty percent of patients developed hypoglycemia, which occurred on 17% of nights. Garg et al. (abstract 221) used a DexCom CGM adopted for 10-day use per sensor in 30 type 1 diabetic patients, finding absolute relative differences from laboratory glucose of 13, 13, and 14% on days 2, 7, and 10, respectively. Meneghini et al. (abstract 403) analyzed 700 three-day CGM profiles in 325 type 1 diabetic patients with 1,952 technically valid nights. Morning fasting glucose >200 mg/dl occurred after 43% of nights, and these patients had a mean A1C level of 8.7 vs. 7.7% in those with lower morning glucose. Persistent nocturnal hypoglycemia was found in 63% of patients, and 25% of patients had unrecognized nocturnal hypoglycemia.

Mazze et al. (abstract 45) studied 62 individuals with mean A1C 6.4%, capillary glucose 133 mg/dl, and an average of 3,214 CGM and 92 capillary glucose results per person, finding correlations of capillary glucose and CGM with A1C of 0.81 and 0.86, respectively. They noted that neither A1C nor mean glucose correlated with hypoglycemia, suggesting the need for CGM for understanding overall daily glucose patterns for clinical decision making. Hudson et al. (abstract 43) de-

scribed use of a Medtronic CGM in 12 adult type 2 diabetic patients following cardiac surgery having hourly glucose testing and intravenous insulin. The 310 pairs of CGM-meter glucose readings in this study showed a lower correlation coefficient of 0.72, with absolute difference 23 mg/dl (relative difference 16%). The authors stated that 25% of pairs would lead to minor insulin dosing changes and 2% to major changes, although the authors believed no error had potential for serious harm.

Kuenen et al. (abstract 848) analyzed average glucose and A1C from 262 type 1 and 158 type 2 diabetic patients and from 80 nondiabetic control subjects with ~2,700 CGM values over 12 weeks. Average glucose correlated with A1C with a correlation coefficient of 0.91. Dunn (abstract 404) analyzed CGM data from the FreeStyle Navigator system from 37 type 1 diabetic patients, finding a correlation of both premeal and postmeal glucose with A1C. Meals preceeded by glucose falling >0.5 mg $\cdot$ dl^{-1} $\cdot$ min^{-1}, intermediate, or rising by this amount were associated with progressively higher pre- and postmeal glucose levels, suggesting a role of premeal CGM patterns (rather than simply using single premeal measurements) in adjusting prandial insulin dosing. Mehra et al. (abstract 393) performed a study of another factor influencing glycemia, comparing postdinner glycemia after two lunches: one with one-quarter vs. another with one-half of the usual daily caloric intake, with intravenous insulin during lunch maintaining similar glycemic control after both lunch meals. Despite identical suppers and pre-supper glucose levels of 127 vs. 122 mg/dl, 2-hr postdinner glucose levels were 143 vs. 197 mg/dl.

A number of studies explored approaches to premeal insulin bolus calculation. Peterson et al. (abstract 1695) treated 6 type 1 diabetic patients using the Medtronic CGM sensor, recommending insulin adjustment based on premeal glucose, and found no effect of consumption of high–glycemic index foods on mean glucose levels, albeit with three of the patients not showing excellent glycemic control. Bishop et al. (abstract 1788) asked 48 adolescent type 1 diabetic patients to estimate carbohydrate content (grams) of 32 commonly consumed foods. For daily carbohydrate intake, 11 were accurate within 10 g and the estimate for an additional 4 patients was within 11–20 g. Those who were accurate within 10 g for dinner had A1C 7.7%, while those who overestimated and underestimated by >10 g had A1C 8.5 and 7.9%, respectively. Carbohydrate contents of syrup, hash browns, rice, spaghetti, and chips were overestimated by >5 g/serving, while those of cereal, French fries, and soda were underestimated by >5 g/serving. This level of accuracy needs to be considered in planning prandial insulin schedules based on carbohydrate content. Mehta et al. (abstract 1787) performed a similar study of parents' CHO estimates for 67 type 1 diabetic children ages 2–12 years. Again, underestimators had similar glycemic control, while overestimators had children with A1C 0.8% higher than those with greater precision. Swan et al. (abstract 46) analyzed prandial insulin requirements in 17 type 1 diabetic patients receiving insulin based on a proportional-integrative-derivative algorithm, finding prandial carbohydrate-to-insulin ratios of 5.6, 7.7, and 7.1 at breakfast, lunch, and dinner but with plasma insulin levels approximately two-thirds as great before breakfast, suggesting that the lower insulin requirements for lunch and dinner may in part reflect residual insulin from the prior meal bolus rather than just reflecting lower insulin sensitivity in the morning.

Bohanon et al. (abstract 220) studied 90 type 1 diabetic adults using the FreeStyle Navigator CGM for 90 days. A total of 22 patients had 59 episodes of insertion-site bleeding. A1C levels decreased by 0.6 and 0.2% with baseline A1C ≤8 and >8%, respectively. There was no significant A1C change in those viewing the monitor <8 times daily, while those viewing it 8–12 times and, in 73% of patients, >12 times daily had decreases in A1C of 0.2 and 0.3%. Similarly, Ellis et al. (abstract 219) reported 75 type 1 diabetic patients using either the Dexcom or Medtronic CGM, finding no change in A1C in those using the sensor <15 days monthly but a 0.4% reduction in those using it more frequently. Overall and severe hypoglycemia decreased 27 and 68%, respectively, over 3 months. Garg et al. (abstract 43) compared Dexcom sensor insertion sites in the abdomen, proximal lower extremity, and proximal upper extremity, showing all to perform similarly.

Garg et al. (abstract 40) randomized 123 adult type 1 diabetic patients to control vs. insulin guidance software treatment, with reduction in A1C by 0.4 vs. 0.6%. The group using the software, however, despite more frequent capillary glucose testing, experienced more severe hypoglycemia. Davies et al. (abstract 39) performed CGM with a Medtronic system on 112 of the 708 individuals participating in the Treating to Target in Type 2 Diabetes trial (4-T), comparing biphasic aspart 70/30 insulin twice daily, insulin aspart three times daily before meals plus insulin detemir once or twice daily, and insulin detemir once or twice daily and finding hypoglycemia 5.5, 6.3, and 3.5 times weekly, respectively, and glucose levels within target (72–99 mg/dl before meals and 72–126 mg/dl during the 3 h after meals) on 25, 33, and 25% of readings. Algorithms designed to reduce hypoglycemia frequency are receiving attention. Dassau et al. (abstract 42) described a hypoglycemia prediction system based on a "vote" of five algorithms based on prior glucose patterns, all described in signal processing system theories: *1*) a linear glucose profile extrapolation; *2*) a Kalman filter recursive estimator using the estimate from the previous glucose and the current measurement to estimate rate of change, *3*) an adaptive Infinite Impulse Response filter, *4*) statistical linear prediction, and *5*) a numerical logical algorithm predicting hypoglycemia based on rate-of-change estimation. When this approach was applied to a CGM database of 21 type 1 diabetic patients with hypoglycemia caused by gradual increase in the insulin infusion rate, 94% of blood glucose levels <70 mg/dl were predicted at a mean of 34 minutes prior to the event. Buckingham et al. (abstract 230) increased the basal infusion rate to reduce blood glucose to ≤60 mg/dl in 18 of 22 type 1 diabetic patients using insulin pump treatment. On a second occasion, a predictive algorithm was used to suspend insulin infusion for 90 minutes. Hypoglycemia then occurred in just nine of the patients. Although three had transient ketonemia <1.0 mm/l during or following pump suspension, none had rebound hyperglycemia, and all showed recovery during a subsequent 2-h observation period, suggesting that it may be possible to develop partial closed-loop algorithms to suspend insulin treatment based on CGM results. Cengiz et al. (abstract 229) used a proportional-integrative-derivative algorithm in 17 adolescent type 1 diabetic patients to alter insulin delivery based on CGM glucose level and rate of change, observing 18 automatic pump suspensions for a mean of 1.5 h in 8 of the patients during a 36-h period. During the suspen-

sions to avoid predicted hypoglycemia, mean sensor and reference plasma glucose values fell from 170 and 177 to 92 and 96 mg/dl, respectively.

A number of noninvasive approaches to assessment of hypoglycemia were presented at the American Diabetes Association meeting. Caduff et al. (abstract 413) described a noninvasive multisensor device using dielectric spectroscopy, optical, sweat/moisture, and temperature measurement to predict glucose levels in 10 type 1 diabetic patients. Oral glucose–induced hyperglycemia changed these parameters in such a fashion that glucose levels could be predicted with a regression coefficient of 0.82. Nguyen et al. (abstracts 400 and 408) studied the HypoMon device (AIMedics), which similarly measures skin impedance, heart rate, rate-corrected QT interval, and their rates of change, transmitted from a set of four skin-surface biosensor electrodes on a chest-belt transmitter to a wireless handheld computer unit. Sixteen type 1 diabetic children monitored overnight showed significant correlation of predicted with actual glucose levels. Interestingly, the QT interval increased both with spontaneous and with insulin infusion-induced hypoglycemia, but the heart rate only increased after insulin infusion, suggesting the former to be a particularly useful physiologic parameter. Turner et al. (abstract 407) and Walton et al. (abstract 44) measured changes in volatile organic compounds excreted across the skin and in exhaled breath in eight type 1 diabetic patients during insulin-induced hypoglycemia and found a fall in acetone along with that in blood glucose, suggesting another approach to noninvasive measurement of blood glucose. Juhl et al. (abstract 574) placed subcutaneous electrodes at the second and third cervical vertebral areas to record electroencephalogram signals in 15 type 1 diabetic patients during induced hypoglycemia. Changes were detected by an automated algorithm beginning 29 min before development of "obvious" cognitive dysfunction and, in 13 of the patients, before any loss of cognition on standardized testing. Mattu et al. (abstract 222) studied a near-infrared diffuse reflectance spectroscopy noninvasive glucose-measurement method not requiring an arm-guide system and with an instrument head able to automatically determine the measurement site on 16 individuals with 989 data points for analysis, finding glucose levels with a mean absolute error of 12.4% and 98% of points in regions A and B of the Clarke error grid over the range 50–350 mg/d.

Mueller et al. (abstract 41) implanted a subconjunctival hydrogel in 5 diabetic patients. The substance, previously tested in a rabbit model, contained a glucose-binding lectin and a competitive binding fluorophore displaced by glucose, causing fluorescence, which was measured by the patients using a small fluorophotometer. After insulin administration to produce hypoglycemia followed by oral glucose–induced hyperglycemia, the correlation coefficient with blood glucose was 0.96 with a lag time averaging 5.4 minutes.

A1C versus glucose

My colleagues and I have recently commented on various aspects of the imperfect overlap between A1C and other measures of glycemia (1). Choi et al. (abstract 401) pooled data from 621 insulin-treated type 2 diabetic individuals to analyze the relationship between A1C and capillary glucose, finding that among the 235 with a fasting A1C <7%, mean 2-h postmeal glucose levels were <100 and 140 mg/dl in 19 and 42%, respectively, while among the 95 with fasting glucose <100 mg/dl, 46% had A1C <7%. They concluded that A1C and fasting and postmeal glucose "provide distinct information that should be used together to assess individual patients and optimize insulin therapy." In a study of 88 type 1 diabetic individuals followed for 90 days, Dunn et al. (abstract 414) analyzed the relationships of mean capillary and FreeStyle Navigator CGM, comprising 33,464 and 752,571 observations, with A1C at the end of the observation period. For every 1% increase in A1C, mean capillary and CGM glucose levels increased by 19.0 and 20.5 mg/dl, with squared correlation coefficients of 0.38 and 0.52, respectively. The modest degree to which the variance in glucose is explained by A1C suggested to the authors "that individual differences in rates of protein glycation at a given blood glucose concentration may be an important factor when addressing glycemic control." Pani et al. (abstract 927) analyzed the relationships between age and A1C in 5,743 individuals and found that A1C increased by 0.10–0.14% per decade, with mean A1C increasing 0.5% from age <40 to >70 years among those with normal glucose tolerance. The authors wondered whether "current [A1C] goals may be too stringent for older subjects with diabetes." Ziemer et al. (abstract 983) measured A1C in 1,434 individuals having random, fasting, and 1- and 2-h post–75-g oral glucose determinations. After adjustment for age, sex, and glucose levels, A1C levels were 0.2, 0.3, and 0.4% higher in blacks than in whites with normal glucose tolerance, impaired fasting glucose or glucose tolerance, or diabetes, respectively; ethnicity and, presumably, a number of other factors, are thus important in interpreting A1C levels. A1C is certainly, of course, an important clinical measure. Kilpatrick et al. (abstract 817) analyzed data from the Diabetes Control and Complications Trial and found that for every 1% increase in the SD for A1C there were 54 and 42% increases in development or progression of retinopathy and nephropathy, respectively, suggesting that those with intermittent periods of greater hyperglycemia had a worse outcome than those with stable glycemic control.

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