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New approaches to insulin treatment and glucose monitoring

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This is the second of eight reports on the American Diabetes Association Annual Meeting and Scientific Sessions held in San Diego in June. It will cover topics related to a variety of current and potential approaches to type 1 diabetes treatment, such as gene therapy, insulin pump therapy, inhaled insulin, and home glucose monitoring. Some related presentations from the Mount Sinai Diabetes Conference are also covered.

Gene Therapy

In a lecture at the Mount Sinai Diabetes Conference on 1 April 1999, Robert MacEvoy, New York, NY, discussed the "promises and problems" of gene therapy for type 1 diabetes. The current goal is to provide a fasting level of insulin that is sufficient to avoid ketoacidosis and to help normalize glucose levels between meals while avoiding hypoglycemia from overexpression of insulin. MacEvoy characterized postprandial increases in insulin as "not achievable at present." Other than the insulin gene, there may be roles for transfer of the genes for glucagon, amylin, and lysozymal enzymes, which bind and remove advanced glycosylation endproducts from tissues and circulation to decrease complications, regardless of blood glucose levels.

A number of problems have been encountered with insulin gene therapy, one of which is the inability of hepatocytes to cleave proinsulin to insulin. A proposed strategy for overcoming this obstacle is to change the proinsulin sequence so that hepatic furin can cleave C-peptide, thereby leaving the A and B chains of insulin. One method of gene transfer has been to use early gene 1–deleted adenovirus (E1-ADV) as a vector, which allows high-titer virus production, although E1-ADV itself is incapable of entering cells. This method is susceptible to immune rejection, resulting in initial hyperinsulinemia and hypoglycemia, typically followed by recurrence of the diabetic state. However, gene transference with E1-ADV as a vector has been used as a model in immune-incompetent animals.

"Gutless" ADV particles, which lack many viral proteins, have been developed to decrease immunogenicity, but production of sufficient numbers of particles has been a problem, particularly when envisioning future therapeutic trials in which normal hepatocyte turnover and ongoing hepatic growth in children would necessitate readministration at relatively frequent intervals. Another approach involves the use of promoters in addition to E1-ADV to increase expression. The use of liposomally delivered DNA and of "naked DNA" and ex vivo tissue transfection have also been examined as possible approaches. At the ADA meeting, Abai et al. (abstract 51; abstract numbers refer to the Abstracts of the 59th Annual Meeting and Scientific Sessions of the American Diabetes Association, *Diabetes* 48 [Suppl. 1]:1–A550) showed expression of insulin after intramuscular injection of plasmid DNA expressing mature insulin in athymic nude mice with streptozotocin-induced diabetes. Tanaka et al. (abstract 423) showed effective glucose-lowering in streptozotocin diabetic mice by using an adeno-associated virus vector to transfect the insulin gene into skeletal muscle. In another interesting approach to developing gene therapy for insulin sensitization, Etgen et al. (abstract LB19) used an intramuscular adenoviral vector injection to deliver human protein kinase C-ζ. The injected muscle showed a 100–240% increase in basal and a 40–90% increase in insulin-stimulated glucose transport activity without change in total GLUT1 or GLUT4, suggesting a redistribution of existing transporters to the cell surface.

With current approaches to hepatic insulin gene delivery, approximately one-fifth of hepatocytes express insulin. Unfortunately, the dose-response curve is very steep and consequently renders a dose of 1×10^{11} E1-ADV particles ineffective and a dose of 2×10^{11} particles partially effective. A dose of 3×10^{11} particles results in profound hypoglycemia in a rat model with inbred genetically identical animals. MacEvoy pointed out that prediction of the required dose would be even more complex in a clinical setting. Retroviral delivery vectors potentially provide long-term insulin production, because they are permanently included in the host genome, although they are not transcribed in all cells. However, they require a 10-fold higher dose, and there is a greater possibility that excessive doses of retroviral delivery vectors may result in adverse effects. A possible solution for diabetic patients is to titrate the insulin level to that which does not cause fasting hypoglycemia, but the immune response to subsequent administration of viral particles precludes giving multiple doses. Different viral serotypes could be used for repeated gene delivery, or temporary immunosuppression could be used, although with potential toxicity. Inclusion of a "fail-safe" gene to abort insulin expression if necessary would be an important safety requirement. The *Herpes simplex* virus thymidine kinase has been widely used in cancer treatment trials to allow gancyclovir to be used as a safety requirement to abort insulin expression. Another approach is to induce NADPH reductase overexpression, which increases cytoxan sensitivity. However, in

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Abbreviations: BP, binding protein; CSII, continuous subcutaneous insulin infusion; E1-ADV, early gene 1–deleted adenovirus; NIR, near-infrared; rhIGF-1, recombinant human IGF-1; SC, subcutaneous.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

vivo experiments involving the addition of these elements have not been successful. In addition to the possibility of systemic overexpression of insulin, it is possible that insulin expression in some tissues may cause local adverse effects. For example, insulin expression in might cause accelerated atherosclerosis.

Autoregulated or glucose-regulated insulin expression would be viable long-term options, but present technology cannot achieve such regulation, even in experimental models. The phosphoenol pyruvate carboxykinase promoter is stimulated by glucagon and inhibited by insulin whereas the glucokinase promoter is stimulated by insulin and inhibited by glucagon. Theoretically, these genes could be used to drive insulin and glucagon transcription. There are also glucose response elements that can be used to allow glucose feedback on insulin expression. Faradji et al. (abstract 244) transferred the insulin gene to intermediate lobe pituitary cells, which then secreted insulin at sufficient levels to cure diabetes in NOD mice while resisting immune attack. These investigators constructed recombinant adenoviruses containing GLUT2 and the islet isoform of glucokinase, and transduction of the pituitary cells with both viruses led to cells whose ATP generation from glucose increased from 3 to 20 mmol/l glucose and thereby offered the potential to confer glucose-sensing capabilities similar to those of islet cells. Potentially, additional structures could be added to create β-cell surrogates for the treatment of diabetes.

Several presentations at the ADA meeting assessed gene therapy approaches to decreasing the immune response to transplanted β-cells. Konkal-Matt et al. (abstract 248) developed a potential approach to gene therapy of pancreatic cells or β-cells that uses an adeno-associated virus vector for transferring a "reporter gene" to porcine islets, rat islets, and two β-cell lines. Yang et al. (abstract 247) transfected whole pancreas and islets in a type 1 diabetes rat model with the gene for uteroglobin, a uterine protein secreted only during pregnancy that acts as a tolerogenic and anti-inflammatory mediator. Transfected islets had normal insulin secretion in response to in vitro glucose stimulation and expressed the uteroglobulin gene; rejection was delayed from ~9 to 45 days for islets and from ~16 to >42 days for pancreas transplants, suggesting an approach that might allow decreased requirement for immunosuppression. In an interesting related study, Vasavada et al. (abstract 245) developed transgenic mice with islet cells expressing placental lactogen, a β-cell mitogen involved in islet proliferation during pregnancy. Circulating insulin levels, pancreatic insulin content, and glucose-stimulated insulin secretion of perifused islets increased, suggesting a method for increasing islet mass and endogenous insulin production. Leibowitz et al. (abstract 249) also addressed problems related to islet transplantation and showed that as many as three-quarters of human fetal islet cells are lost from apoptosis after collagenase digestion. Inhibition of this process by using caspase inhibitors or by infecting islet clusters with an adenoviral vector that expresses the BCL-2 gene doubles the number and insulin content of islets, which may allow for development of techniques to increase transplantable β-cell mass.

Insulin Pump Therapy

Bode et al. (abstract 264) noted industry estimates of a threefold increase in usage of insulin pump therapy in the U.S. over the last 5 years to ~60,000 type 1 patients at the end of 1998. For 389 patients with average age 33 ±12 years and average duration of diabetes 15 ± 10 years who were started on insulin pumps, the initial insulin dosage (48 ± 18 U) decreased by 26% within 15 days and remained 15 and 11% below baseline at 6 and 18 months, respectively, with lower dose requirements of lispro than regular insulin. HbA_{1c} decreased from 8.3 to 7.4% at 6 and at 18 months, respectively. Garg et al. (abstract 977) reported on 62 pump-treated patients who used buffered human regular insulin for 20.1 months versus lispro for 19.7 months. HbA_{1c} values were 7.9 vs. 7.4% with insulin requirement 0.65 vs. 0.61 U/kg body wt, respectively. Hypoglycemic episodes were similar in the two groups. Crawford et al. (abstract 1499) reported on 19 patients who were beginning insulin pump treatment. Total daily dose of insulin decreased from 0.66 ± 0.05 to 0.53 ± 0.04 U/kg. HbA_{1c} levels were reduced from 8.36 to 7.67%. Before pump use, the ratio of regular to NPH insulin was 0.6; at follow-up, the pump bolus-to-basal ratio was 1.02. Rembert et al. (abstract 1548) studied 59 patients using continuous subcutaneous insulin infusion (CSII) therapy. Those patients in the upper quartile of HbA_{1c} were characterized by less frequent glucose monitoring (3.3 vs. 4.6 times/day in the lower quartile) and higher daily insulin dose (0.45 vs. 0.6 $U \cdot kg^{-1} \cdot day^{-1}$). Bouhanick et al. (abstract 1839) reported that costs for 50 adults treated with CSII for 1 year added up to 3,168.65 euros per patient: 1,364.77 were allotted for hospitalization; 243.16 for insulin; 426.86 for pumps; 967.92 for pump supplies; and 165.94 for health care worker charges. Almost one-third (31%) of hospital costs were for inpatient pump initiation for 13 patients. Kaufman et al. (abstract 50) administered insulin injections of lispro and NPH in the morning and insulin pump therapy at dinner and night to 10 children aged 7–10 years with type 1 diabetes whose HbA_{1c} levels were 7.6 ± 0.09. Mean blood glucose and fructosamine levels in this group decreased during treatment but increased in a comparable group assigned to three injections each day.

Inhaled Insulin

Weiss et al. (abstract 48) studied 69 patients with type 2 diabetes with HbA_{1c} levels >8% on monotherapy with sulfonylurea or metformin. Preprandial inhalation of insulin by means of a dry powder aerosol delivery system lowered mean HbA_{1c} levels from 9.8 to 7.5%, but levels did not change for those patients who were treated with placebo plus sulfonylurea or metformin. Pulmonary function remained stable over 12 weeks, and there was only one episode of severe hypoglycemia. Gerber et al. (abstract 53) studied 72 patients with type 1 diabetes treated with either preprandial inhaled insulin in addition to bedtime ultralente injection or SC insulin for 3 months. The mean percentage improvement in overall patient satisfaction score with inhaled insulin (35%) was higher than that with SC insulin (12%). Patients cited "convenience/ease of use" of insulin therapy to explain 66% of the improvement and the absence of "social stigma" to explain 20% of the improvement in overall satisfaction. Kipnes et al. (abstract 410) showed glucose increments after a standard liquid meal with the AERx hand-held aerosol insulin delivery device (Acadigm, Hayward, CA) and with SC insulin in 20 type 1 diabetic patients. Heinemann et al. (abstract 466 reported that inhaled insulin had a biopotency of 12% of SC insulin, although the effect was greater from 0–2 h. The variability of action of inhaled insulin was similar to that of SC insulin.

Lispro

Chase et al. (abstract 429) analyzed data from 9,579 clinic visits between 1993 and 1998 by 696 subjects with type 1 diabetes.

After the Diabetes Control and Complications Trial report of 1993, a change to intensive insulin therapy (>2 injections/day) lowered HbA_{1c} levels fell from 9.4 to 8.5%, but average occurrence of severe hypoglycemia increased from 0.31 to 0.5 episodes · patient^{-1} · year^{-1}. After 1996, when there was a change from regular to lispro insulin, HbA_{1c} levels fell further from 8.4 and 8.1 in 1997 and 1998, and average incidence of severe hypoglycemia decreased in 1998 to 0.4 episodes · patients^{-1} · year^{-1}. Valle and Santoro (abstract 437) described a 3-month open-label parallel study involving 1,184 type 1 diabetic patients who were administered 1–3 doses/day of human regular or lispro insulin before meals with NPH. Post-breakfast and -lunch glucose levels were 166 mg/dl with regular insulin vs. 150 mg/dl with lispro, and post-dinner glucose levels were 183 vs. 170 mg/dl, respectively. HbA_{1c} levels were 8.2 with regular insulin vs. 8.1% with lispro, and severe hypoglycemia was respectively seen in 19 vs. 13% of patients. Ferguson et al. (abstract 526) studied 33 patients with type 1 diabetes complicated by hypoglycemia unawareness who were treated in a crossover study with lispro and regular insulin for 6 months. HbA_{1c} levels were 9.1 with lispro vs. 9.3% with regular insulin, and severe hypoglycemia occurred 49 vs. 83 times, while nocturnal episodes occurred 18 vs. 42 times, resulting in 41 and 57% reductions, respectively. Sun et al. (abstract 507) pointed out that 57–73% of patients in clinical lispro trials did not experience nocturnal hypoglycemia. Calculation of mean ± SD rates will be skewed by this "zero-inflated data." A rank sum test revealed a significant 40–50% lower frequency of nocturnal hypoglycemia during treatment with lispro and NPL mixtures compared with human insulin and NPH mixtures.

Garg et al. (abstract 261) compared maternal and fetal outcomes in 35 type 1 diabetic women treated with human regular with 25 type 1 diabetic women treated with lispro during pregnancy. HbA_{1c} levels were similar before pregnancy but were 6.8% in those treated with human regular insulin during pregnancy vs. 6.2% in those treated with lispro during pregnancy. Retinopathy, toxemia of pregnancy, and premature labor were similar in frequency. Fetal abnormalities consisted of one heart defect, one craniosynostosis, and one sudden infant death in the group treated with regular insulin and one partial deafness and one cleft lip and palate in the group treated with lispro. Treatment with lispro during pregnancy appeared safe in that it resulted in better glycemic control and no increase in adverse effects. Browdos et al. (abstract 450) studied 131 patients treated with sulfonylureas with HbA_{1c} >8.5% before and 6 months after adding preprandial lispro, metformin, or bedtime NPH. HbA_{1c} levels decreased from 10–10.4% to 7.6, 8.3, and 8.5% with fasting glucose 10.6, 9.7, and 8.5 mmol/l, respectively. The postprandial glucose increment was 0.6, 1.4, and 2.3 mmol/l in the three groups. From the same group, Robertson et al. (abstract 518) reported similar treatment satisfaction with lispro and metformin, suggesting these treatments to be reasonable approaches for patients with diabetes who are failing to respond to sulfonylurea monotherapy. Petkova and Angelova (abstract 1536) reported smaller postprandial glucose increments in 20 patients with type 1 diabetes whose treatment was changed from regular to lispro insulin. The antioxidative status of the plasma, measured by thiobarbituric acid–reacting substances, superoxide dismutase activity, and total antioxidant capacity, improved, suggesting that lispro reduced free radical production during the test meal.

Insulin Aspart

Brunner et al. (abstract 425) studied postprandial glycemia in 20 patients with type 1 diabetes after administration of insulin aspart, another analog with rapid onset of action. The maximum glucose levels after aspart at 0 and +15 min and after regular insulin at −15 and 0 min were 209, 243, 243, and 262 mg/dl, respectively. Halberg et al. (abstract 448) compared separate or mixed injection of insulin aspart with NPH insulin, showing the two regimens to be equivalent. Jacobsen et al. (abstract 465) compared the pharmacokinetics and pharmacodynamics of a premixed 30:70 formulation of soluble and protamine-retarded insulin aspart with a similar premix of human insulin. The time to maximal insulin concentration was 60 vs. 110 min, respectively, with the insulin aspart mixture having an earlier glucose-lowering effect. Rosenfalck et al. (abstract 499) reported that maximal glucose levels after insulin aspart was given immediately before a meal were 194 vs. 200 and 216 mg/dl, respectively, when regular insulin was given immediately before or 30 minutes before a meal in 25 insulin-treated type 2 diabetic patients. Uwe et al. (abstract 481) randomized 283 type 1 diabetic patients to treatment with insulin aspart and 141 to regular insulin with NPH as basal insulin. Treatment satisfaction and quality-of-life with respect to nutritional restrictions improved. Patients who felt at risk of hypoglycemia and those wishing to increase their physical strength were most likely to achieve benefit. Home et al. (abstract 1567) compared 707 type 1 diabetic patients who were treated with insulin aspart with 358 type 1 diabetic patients who were treated with regular insulin preprandially and with NPH one to two times daily. HbA_{1c} levels declined by 0.1%, and postprandial glucose increment was 1.2 mmol/l. Treatment satisfaction was greater with insulin aspart, and there was a trend to decreased hypoglycemia. Raskin et al. (abstract 496) randomized 884 patients with type 1 diabetes to insulin aspart versus regular insulin for 6 months. HbA_{1c} levels were 7.8 vs. 7.9%, and glucose levels after breakfast, lunch, and dinner and before lunch were respectively 156, 137, 153, and 126 mg/dl vs. 185, 162, 168, and 138 mg dl. With insulin aspart,16% of hypoglycemic episodes occurred from midnight to 6:00 A.M. vs. 34% with regular insulin.

Insulin Glargine

Lepore et al. (abstract 416) studied the pharmacokinetics/dynamics of the long-acting insulin glargine (HOE 901) versus NPH in 20 patients with type 1 diabetes over 24 h. The onset of action was 1.1 vs. 0.71 h, and mean duration was 22.8 vs. 13.8 h, respectively. With insulin glargine, plasma free insulin was maintained at 9–11 μU/ml for 24 h. With NPH, plasma free insulin peaked at 19 μU/ml at 6 h and fell below therapeutic levels, which resulted in discontinuation before 24 h. Plasma glucose levels at 0, 6, 12, 18, and 24 h were 129, 129, 134, 140, and 140 mg/dl with insulin glargine, respectively, vs. 130, 137, 140, and 178 mg/dl through 18 h with NPH, respectively. Intersubject coefficient of variation of the integrated free insulin was 19% with insulin glargine vs. 31% with NPH, suggesting the former to have more prolonged and peakless activity and more reproducible pharmacokinetics than NPH. Luzio et al. (abstract 480) compared absorption characteristics of ^{125}I-labeled glargine and NPH insulin after SC injection into the abdomens of 14 type 2 diabetic patients. The median disappearance time of 25% of radioactivity was 15.0 vs. 6.5 h; mean residual radioactivity after 24 h was 54.4 vs. 27.9%. A comparable study in nondiabetic subjects by Linkeschowa et al.

(abstract 417) showed that insulin glargine showed an even time-action profile as opposed to the "peak" with NPH at 4–7 h.

Two large clinical studies of glargine were reported. Rosenstock et al. (abstract 432) reported the results of treatment of 518 patients with type 2 diabetes with insulin glargine at bedtime versus NPH once or twice daily with preprandial regular insulin as required. Glycohemoglobin decreased 0.4% in both groups with a 0.9 vs. 3.1 lb weight gain and 31.3 vs. 40.2% frequency of nocturnal hypoglycemia. Ratneret al. (abstract 516) compared insulin glargine with NPH for 28 weeks in 534 patients with type 1 diabetes. HbA_{1c} levels decreased 0.2% in both groups with a fall in fasting glucose of 1.7 mmol/l in the group treated with insulin glargine vs. 0.3 mmol/l in the group treated with NPH. There were 201 vs. 345 total, 65 vs. 101 nocturnal, and 25 vs. 38 severe hypoglycemic episodes per 100 patient-years, respectively.

Other Insulin and Related Peptide Preparations

Meyerhoff et al. (abstract 452) described a study of hexyl insulin with oral doses of 0.3, 0.6, 1.2, and 2.4 mg/kg in 18 normal volunteers, who showed increase in serum insulin with hypoglycemic action. Allaudeen et al. (abstract 453) tested hexyl insulin for oral activity in pancreatectomized dogs and showed particular activity of one of the subfractions of the preparation. Brunner et al. (abstract 440) reported pharmacokinetic and pharmacodynamic properties of the insulin analog NN304 (ε-LysB29-myristoyl, des-[B30] human insulin), a long-acting insulin analog that is acylated with a 14-C–fatty acid chain and exhibits prolonged action due to reversible binding to albumin (with ~2% in the unbound fraction) rather than to slow absorption. Integrated insulin absorption areas were greater, but bioactivity was ~70% lower with NN304 than with NPH in 10 nondiabetic subjects. Strange et al. (abstract 444) showed that intrapatient pharmacokinetic variability of NN304 was ~50% that of NPH in 16 nondiabetic subjects. Mudaliar et al. (abstract 462) reported that 85:15 premixed insulin showed intermediate action compared to NPH and 70:30 premixed insulin in 36 nondiabetic subjects. Moses et al. (abstract 401) reported on the use of combination recombinant human IGF-1 (rhIGF-1) and IGF binding protein (BP) 3, given the observation that poorly controlled type 1 diabetes is associated with increased growth hormone and IGF-BP1 but decreased total and free IGF-1. A total of 12 patients treated with the mixture showed a 49% decrease in insulin requirement and a 23% decline in mean home glucose levels. No edema, jaw pains, headaches, or other adverse effects were noted. Kolterman et al. (abstract 451) S treated 480 type 1 diabetic patients with insulin and pramlintide, a synthetic analog of the human β-cell hormone amylin. HbA_{1c} levels fell 0.4% in those patients treated with pramlintide and insulin vs. 0.2% in those patients treated with insulin alone. Mild nausea was a common side effect during the initial 8 weeks of treatment. Of the patients treated with pramlintide and insulin, 44% had HbA_{1c} reductions >0.5% at 4 weeks and maintained mean reductions >0.7% throughout the study and a 1-year open-label extension. Fineman et al. (abstract 489), from the same group, reported that after a 6-month study of 586 patients with type 1 diabetes, those treated with placebo experienced an increase of HbA_{1c} levels of 0.1%; those treated with 60 μg pramlintide three times daily had a decrease in HbA_{1c} levels of 0.2%; those treated with 90 μg three times daily had an increase in HbA_{1c} levels of 0.1%; and those treated with 90 μg twice daily showed a decrease in HbA_{1c} levels of 0.1%. Nausea was again seen during the first 8 weeks of treatment, and there was a tendency to weight loss.

Home Glucose Monitoring

Ryan and Ragsdal (abstract 1517) compared meter information with patient recall in 132 patients provided with meters and test strips without charge. On average, patients tested glucose levels only 46 times but received 162 strips during the prior 6 months. Comparison of patient logs with meters showed that 51% of patients overreported testing frequency by >20%. Nadeau et al. (abstract 1520) assessed the accuracy of home glucose monitor reporting by 15 adults with intensively managed type 1 diabetes and 45 adults with type 2 diabetes provided with memory-equipped glucose meters. "Phantom values" comprised 9.2 and 20.5% of reports for the type 1 and type 2 patients, while "modified values" (by >15%) comprised 9 and 3% of reported readings. In this study, 13 and 18% of the two groups showed ~50% of readings to be inaccurate.

A symposium on microdialysis and noninvasive approaches to glucose sensing opened with Lutz Heinemann, Düsseldorf, Germany, pointing out that the use of home glucose monitoring began in 1978 and that "from the patient's point of view, very little has happened in the past 20 years. Now, for the first time, we have commercially available glucose sensor technology." Urban Unger, Stockholm, Sweden, discussed the principles of microdialysis monitoring. "It is a simple way," he said, "of trying to replicate the function of a capillary in a tissue." A semipermeable SC catheter is placed, and fluid is infused, withdrawn, and analyzed with adjustment made for catheter length and infusate flow and diffusion rates. The advantage of this approach is that blood samples are not required and that nearly continuous monitoring becomes possible, allowing the observation of glycemic excursions that would otherwise not be appreciated. In a research setting, this approach can be used to measure lactate, pyruvate, and glycerol in addition to glucose. Unger noted that SC glucose may decrease more rapidly than blood glucose after insulin levels rise, particularly in the postprandial period, so that disagreement between blood and tissue measurements need not indicate errors in the new approach. Furthermore, SC catheters in different locations may reveal regional differences in tissue glucose levels. Similarly, SC lactate tends to increase after insulin administration, presumably reflecting glucose metabolism, again diverging from blood lactate levels. Measurement of tissue glycerol allows assessment of lipolysis and, indirectly, gives a measure of catecholamine effects.

Theodor Koschinsky, Düsseldorf, Germany, showed a continuous SC glucose measurement system that consists of a base unit, a system unit, and a microdialysis probe. The base unit contains an integrated glucose meter for calibration (required of all existing systems) and allows storage of data for several weeks. The sensor unit measures glucose levels with a glucose oxidase method. Drawbacks to the system include difficulty with calibration, and, common to many of these systems, a lagtime of 20–30 min between tissue sampling and glucose measurement at the sensor because of the length of the tubing and the very slow flow-rate used. Thomas Pieber, Graz, Austria, discussed an open-flow microperfusion system that is designed to be minimally invasive (comparable to SC insulin infusion pumps), with measurement stability decreasing the required frequency of calibration. The system uses a double-lumen catheter with microholes that allow open exchange of large and small molecules, and

an ionic reference method that measures conductivity, mainly from sodium, and does not require calibration. The perfusate is recycled with glucose readings averaging 60–70% of the simultaneous blood glucose level; however, these levels significantly decrease after administration of glucose loads (which presumably increase insulin as well). Moreover, this system, which is clearly not yet ready for clinical use, requires that the infusate reservoir be at the same height as the catheter insertion site to match inflow and outflow.

Russell Potts, Redwood City, CA, described the GlucoWatch Biographer, a product now being released that extracts glucose transdermally by a reverse iontophoresis method. A 200-amp current that moves ions through the skin is applied and glucose is measured by electro-osmosis at a flow rate of ~10 ng/(3 min) (1); the current localizes at the cathode, while urate, ascorbate, and most other potentially interfering molecules localize at the anode. High–molecular weight substances are not extracted. An in situ glucose oxidase sensor measures glucose over a 7-min period with two consecutive measurements averaged. Four feasibility studies have been performed that have assessed the unit's accuracy in a laboratory environment with simultaneous Hemocue (Hemocue AB, Ängelholm, Sweden) glucose measurements and have assessed home use in comparison to capillary glucose measurements with One Touch meters (LifeScan, Milpitas, CA). The mean average error was 7–23 and 6–25% in the laboratory and home studies with average accuracy of 15.6 and 18.7%, respectively. The unit gives acceptable results from 40 to 400 mg/dl but causes some degree of local skin irritation and cannot be used during periods of increased sweating. Garg et al. (abstract 262) described the correlation of GlucoWatch with Hemocue glucose values in 39 young patients with type 1 diabetes. Of the readings, 97% were in the clinically acceptable A and B regions of the error grid with a mean error of 14.5%.

Jack Aronowitz, Pompano Beach, FL, discussed clinical trial results with another transdermal approach, in which a "patch" is placed on the forearm for 5 min, after which a meter is placed in the tabbed area of the patch to take the glucose reading. The meter does not require patient calibration and includes an alarm system for readings up to six times daily and memory for 120 days of results, which can be downloaded to a computer. Aronowitz stated, "It will be competitively priced to fingerstick meters and strips." Kruger et al. (abstract 263) reported the results of a study of 28 patients with diabetes who measured capillary glucose levels with the AtLast, a combined blood sampling and glucose-testing meter that obtains and measures capillary blood from nonfingertip sites. Measurements of capillary glucose at all sites were correlated with measurements of venous glucose.

G. Reach, Fontainbleau, France, discussed the problem of calibrating SC glucose sensor electrodes. Because there is sufficient linearity of response, two calibration points are sufficient. When the regression line goes through the origin, one calibration point gives valid results. A potential problem is inaccurate measurement of the calibration value, which may affect many subsequent values. He showed data from eight patients with 3- and 7-day implanted glucose sensors. The sensors of seven patients could be calibrated with one glucose measurement twice daily. Andreas Pfuetzner, Mainz, Germany, presented results of a multicenter study of 132 patients who used an implanted microdialysis glucose measurement method recently approved by the Food and Drug Administration. The lagtime was 7 min with glucose readings every 5 min. Patients were tested with 5–10 sensors for 15–20 days and performed glucose meter readings 11 times daily, before meals, 1 and 2 h after meals, at bedtime, and during the night. The sensor was inserted subcutaneously by patients and physicians. In the U.S., 62 patients furnished 315,347 glucose readings, averaging 69 h of use with no deterioration in results during this period. Seven patients noted local irritation or bleeding; local skin redness such as that seen with insulin infusions was common. Mechanical problems were infrequent. Calibration was performed once daily with results in close agreement with the capillary glucose readings over the 40–400 mg/dl range. Gabriely et al. (abstract 426) described the performance of a NIR transcutaneous glucose monitor (BioNIR, New York) that assesses the absorbance spectra at the thumb in the hypoglycemic and euglycemic ranges. A total of 1,697 spectra representing >95% of tests showed significant correlation with blood glucose. Of 183 masked values in the range of 52–136 mg/dl, >98% were in a clinically acceptable range on the error grid. Crothall et al. (abstract 454) and Crothall et al. (abstract 470) discussed an implantable NIR spectroscopic blood glucose sensor that was used in dog studies and studies of whole blood. Lutz Heinemann, Düsseldorf, Germany, discussed optical detection glucose measurements based on the principle that when glucose levels increase, then light scattered back from the skin decreases. Heinemann et al. (abstract 1573) showed the correlation between glucose measurement by means of the scattering coefficient of human skin and venous glucose levels in diabetic patients and nondiabetic subjects. Although measurements could not be performed in 20–40% of patients with existing methods, the studies showed that "in principle physiological changes in blood glucose can be monitored by registration of scattering coefficient changes." A variety of factors, such as skin temperature, must be closely controlled, and although experimental measurements can be performed, Heinemann commented that "it will take years until we reach an acceptable performance under real-life conditions."

References

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