Type 1 Diabetes and Glucose Monitoring

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This is the third in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, in Chicago, discussing aspects of type 1 diabetes and new approaches to glucose monitoring.

Aspects of type 1 diabetes

George King (Boston, MA) discussed the Joslin award for documented type 1 diabetes of at least 50 years duration. The program, which began in 1970, has awarded more than 2,100 medals so far, comprising 0.05% of individuals with type 1 diabetes in the U.S. Of the medalists, 14 have had diabetes for at least 75 years. The mean age is 71 years for males and 68 years for females, with diabetes for 58 and 57 years, respectively; mean ages of onset are 14 and 12 years, respectively. Their average A1C levels are 7% and 7.2% for men and women, and 45 and 48%, respectively, have no significant evidence of eye, kidney, or nerve disease. Of the 211 who were more closely evaluated, at mean age 67 years, age was 11 years at diagnosis, their mean BMI was 25 kg/m^2, and triglycerides 66, HDL 62, and LDL 84 mg/dl. Of this group, 44% have no to mild nonproliferative retinopathy, with <2 microaneurisms, 7% have moderate-to-severe nonproliferative retinopathy, and 49% have proliferative diabetic retinopathy. Complications did not correlate with C-peptide or HLA type, and A1C did not correlate with microvascular complications, although correlating with cardiovascular disease (CVD). King noted the evidence that individuals with long-standing diabetes may continue to produce insulin, with only modest decrease in insulin production with increasing disease duration (1). The C-peptide level in the Joslin patients showed no correlation with sex, age, insulin dose, or complications.

Mona Landin-Olsson (Lund, Sweden) described aspects of type 1 diabetes, noting that the disease affects 0.35% of the Swedish population below age 35 years, developing at relatively early age, with only 10% having a positive family history. Low BMI, young age, low C-peptide levels, and positive antibodies suggest type 1 diabetes or latent autoimmune diabetes of adults (LADA), which she defined empirically by onset at age >30 years with a positive autoimmune β-cell marker and insulin dependence for at least 6 months. The classification of diabetes may be useful for research, to consider future treatment needs, to avoid insulin deficiency with ketoacidosis, or, perhaps, to save remaining β-cells. The Diabetes Incidence Study in Sweden registry of all newly diagnosed individuals aged 15–35 years currently includes 782 individuals, 590 of whom have type 1 diabetes, with 93 of the remainder appearing to have LADA. Those with type 1 diabetes had a mean BMI of 20 kg/m^2, those with type 2 diabetes 30 kg/m^2, and those with LADA were intermediate. C-peptide levels in individuals with LADA were somewhat higher than those of individuals with type 1 diabetes, with one-half of type 1 diabetic individuals having no detectable C-peptide at 3 years. At follow-up, insulin was used for treatment of 25% of those with type 2 diabetes and 60% of those with LADA at disease onset and for 60 and 90%, respectively, at 3 years. At 4-year follow-up of antibody-positive patients, those only positive for islet cell antibody had the highest C-peptide levels, with GAD antibodies (GADAs) the most predictive of β-cell failure.

In a study in the Skåne region of Sweden, of 1,455 diabetic individuals aged 18–80 years, 16% had evidence of autoimmunity, a finding more common at younger ages, but type 1 diabetes developed at all ages. BMI was higher in younger individuals with type 2 diabetes, but after age 50 years, BMI was identical in individuals with type 1 and type 2 diabetes and with LADA. C-peptide levels increased with increasing age in all the diagnostic groups. Comparing individuals with type 1 diabetes and LADA, the Th2 subset of helper-inducer T-lymphocytes producing interleukin (IL)-4 and -5, and inducing IgG4 and IgE antibody production, were contrasted with the Th1 subset, producing IL-2 and -12, γ-interferon, tumor necrosis factor-α, and IL-12, leading to cytotoxicity and inflammation. Those with LADA principally produced IgG-1 and -4 forms of GADA, denoting the Th2 response, in contrast to the IgG-1 and -3 forms of GADA in type 1 diabetes (2). Three-year follow-up of GADA IgG subclasses in 40 individuals with type 1 diabetes and 43 with LADA showed IgG-1 and -3 levels to be similar, with decrease over time in type 1 diabetes and IgG-2 showing a slight increase in LADA and decrease in type 1 diabetes. IgG-4 was also higher initially in LADA and decreased to a greater extent in type 1 diabetes. Landin-Olsson concluded that in health Th1 and Th2, T-lymphocyte responses are balanced, while in type 1 diabetes there is overreactivity of the Th1 system, a phenomenon seen to a lesser extent in LADA. She suggested that in adults, antibody measurements are more useful for correct classification than are C-peptide and BMI, with GADA the most frequently found and hence most useful antibody and GADA IgG-1 the most frequently found subclass, suggesting that insulin treatment may be appropriate for all GADA-positive diabetic individuals and, perhaps,

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Abbreviations: ADA, American Diabetes Association; CGM, continuous glucose monitoring; CSCII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; GADA, GAD antibody; IL, interleukin; IMT, intima-media thickness; LADA, latent autoimmune diabetes of adults; MAGE, mean amplitude of glycemic excursion; PPG, postprandial glucose.

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that individuals with LADA are candidates for immunological intervention.

Eric Liu (Bethesda, MD) discussed a number of National Institutes of Health studies of β-cell function in type 1 diabetes. Initial studies of C-peptide showed measurable levels in 11–41% of type 1 diabetic individuals, with evidence from the Diabetes Control and Complications Trial (DCCT) (3) that good glycemic control preserves β-cell function. In 141 type 1 diabetic individuals screened for islet transplantation, 38 had C-peptide >0.5 nmol/l and, of the remainder, 16 had measurable C-peptide after arginine stimulation. Absence of C-peptide was weakly associated with disease duration, with Liu suggesting that islets may retain regenerative capacity, which perhaps is not evident because of the ongoing autoimmune process. Studies in type 1 diabetes have shown effects of immunosuppressant treatment on β-cell function. Liu reviewed a case report of a type 1 diabetic patient who, after combined pancreas-kidney transplantation, had biopsy of the native pancreas. β-Cells, some expressing both insulin and somatostatin, were present in the biopsy specimen, suggesting that the combination of control of hyperglycemia with immunosuppressive treatment allowed islet regrowth (4). Using portal vein sampling after arginine stimulation in three individuals 2–3 years after islet transplant, two showed evidence of native pancreas C-peptide production. After whole-pancreas transplantation, iliac vein sampling showed C-peptide production by the transplanted tissue, and hepatic vein C-peptide measurement was used to measure native pancreas β-cell insulin secretion. Great variability was found, with relatively little regeneration occurring, even a decade after transplantation. A study currently being performed with exenatide will assess this as a potential approach to increasing β-cell recovery. Caveats are that calcineurin inhibitor immunosuppression may adversely effect β-cell progenitor development, current immunosuppressive regimens may not fully suppress autoimmunity, and the euglycemia accompanied by supraphysiologic insulin levels seen in all patients after islet transplantation may hinder islet regeneration. At the present time, Liu concluded that there is no robust evidence that β-cell regeneration occurs in a clinically meaningful fashion.

Michael Steffes (Minneapolis, MN) reviewed C-peptide data from the 12-year follow-up DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) studies, noting that the primary prevention subgroup of the DCCT had the greatest number of C-peptide–positive individuals, with >90% followed long term. Of the original 1,441 individuals, 305 had stimulated C-peptide >0.2 but <0.5 nmol/l. Quarterly DCCT and yearly EDIC A1C values are available, as well as information about retinopathy, nephropathy, and severe hypoglycemia. Mixed-meal stimulation tests were done on all individuals at DCCT study entry, with C-peptide measurement after an overnight fast and 90 min after a test meal. Annual repeat stimulation tests were performed on all individuals with stimulated values >0.2 nmol/l for up to 6 years. C-peptide was less than 0.03 nmol/l in 44%, 20% had levels 0.03–0.1 nmol/l, 15% had levels 0.1–0.2 nmol/l, and 10% sustained levels above 0.2 nmol/l for at least 1 year. Postmeal C-peptide concentrations were higher with intensive treatment for 6 years (3), although Steffes pointed out that the remaining islets may have simply functioned at a higher level with intensive treatment rather than there being greater islet survival.

A1C was lower in the intensive treatment group in the DCCT in C-peptide–positive patients, although in control group patients A1C levels were not affected by C-peptide. Retinopathy less frequently occurred in C-peptide–positive intensive treatment patients in the DCCT, with a trend for conventional group patients with positive C-peptide to have less retinopathy as well. At year 10 in the EDIC study, C-peptide responders continued to show a trend to less retinopathy. Microalbuminuria development in the DCCT was also less frequent among intensively treated individuals who had C-peptide reactivity, although this was not demonstrable at years 11–12 in the EDIC, and C-peptide responders did not show a reduction in development of macroalbuminuria. Intensively treated patients in the DCCT with positive C-peptide had fewer episodes of severe hypoglycemia, with trends for this to occur in the conventionally treated group as well, although, curiously, in EDIC, severe hypoglycemia occurred more commonly in the previous intensive group with measurable C-peptide. Loss of β-cell function, then, may occur early in type 1 diabetes, with greater loss associated to some extent with higher A1C and with increased risk of complications, as well as predisposition to hypoglycemia perhaps reflecting elimination of glucagon's effect in raising glucose levels. Intensive treatment prolonged β-cell function, although whether regeneration occurred cannot be established. The β-cell function effect was not found in EDIC.

A number of presentations at the meetings explored further aspects of the natural history of type 1 diabetes. LeCaire et al. (abstracts 940 and 941) presented studies of 152 type 1 diabetic individuals with mean age 26 years and diabetes duration 15 years, with nondiabetic matched control subjects, showing only a 3% greater carotid intima-media thickness (IMT) in the diabetic group (abstract numbers refer to the American Diabetes Association [ADA] Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007). They speculated that this unexpectedly similar carotid IMT was related to the recent trend to improved treatment. LDL cholesterol, LDL particle concentration, and triglyceride levels correlated with IMT both in case and control subjects, with blood pressure, A1C, and urinary albumin as additional factors in the diabetic patients. Costacou and Orchard (abstract 1033) studied correlates of early menopause among 325 women with type 1 diabetes, 14 having menopause at age ≥50 years, 17 between ages 40–49 years, and 34 before age 40 years. Menopause before age 40 years was associated with higher A1C, higher non-HDL and lower HDL cholesterol, higher albumin, and greater risk of cardiovascular disease, suggesting that this is a risk factor worth considering.

Nathan et al. (abstract 996) reviewed the natural history of type 1 diabetes as reflected in complications of 730 control group participants in the DCCT/EDIC, with 96% of survivors followed for a mean 18.5 years, 59% having no serious complications, 21% requiring retinal laser therapy, 16% with >300 mg/day proteinuria or renal failure, and 3% having myocardial infarction, stroke, or cardiovascular death. Secrest and Orchard (abstract 992) studied 7,650 type 1 diabetic individuals from Finland, Japan, or the U.S., diagnosed between 1965 and 1979. Of 377 deaths before 1995, in 85% diabetes was considered either the direct cause of death (this was particularly common with death before age 30 years) or a significant contributory factor. Diabetes, however, contributed to fewer deaths among those diagnosed after 1970, also suggesting improvement in outcome. Cara studied 935 deaths among type 1 diabetic individuals registered at the Bucharest Antidiabetic Centre between

1943 and 2004. From 1942 to 1955, disease duration averaged 5 years and age averaged 35 years, with these values increasing to 23 and 54 years, respectively, between 1995 and 2004; death from infection decreased 29-fold, while death from cardiovascular disease increased 5-fold and that from end-stage renal disease doubled. Skrivarhaug et al. (abstract 949) analyzed the 24 deaths among all 3,137 type 1 diabetic Norwegians with onset below age 15 years developing the disease between 1989 and 2003. Compared with the general population, mortality was 2.9-fold greater, with male subjects having mortality 1.4 times that of females. Mortality was twice as great among those developing diabetes between ages 10 and 14 years compared with those developing diabetes before age 10 years. Orchard and Costacou (abstract 1917) addressed diabetes characteristics related to age of onset, comparing 161 type 1 diabetic individuals over age 18 years who were diagnosed before age 6 years with 291 diagnosed between ages 6 and 11 years and 140 diagnosed at age 12 years or greater. Adult heights were 165, 167, and 169 cm; hematocrit 44.8, 44.1, and 43.9 g/dl; and insulin dose 0.79, 0.77, and 0.70 units/kg, respectively; the relationship between these differences and differences in complications is uncertain.

Glucose variability

At a debate held at the ADA meeting, Louis Monnier (Montpellier, France) took the position that glucose variability is important in the development of complications of diabetes. Dysglycemia can be thought of as involving abnormality of fasting glucose and postprandial glucose (PPG) or as the set of glucose fluctuations from peaks to nadirs—the former two contributing to chronic hyperglycemia and the latter two to glycemic variability—so that PPG may be considered to include both aspects of hyperglycemia. PPG has two components: duration contributing to the degree of chronic hyperglycemia and absolute magnitude contributing to acute glucose fluctuations. Monnier suggested that PPG, as a contributor to glycemic variability, may be associated with increased oxidative stress.

He described an assessment of oxidative stress with measurement of urinary isoprostanes, metabolites of arachadonic acid via a nonenzymatic pathway alternative to the eicosanoid pathways leading to prostaglandin and leucotrien production. Monnier has found diabetes to be associated with a doubling of urinary isoprostanes (5) with particular effect of increased glycemic variability. Similar studies have shown nitrotyrosine to be another measure indicative of PPG-induced oxidative stress (6). In Monnier's studies, the contribution of PPG to glucose fluctuations was assessed from the mean amplitude of glycemic excursions (MAGEs), based on continuous glucose monitoring (CGM), MAGE, and, to a lesser extent, the area under the PPG curve correlating significantly with urinary isoprostane levels, which failed to show significant association with A1C, mean daily glucose, BMI, cholesterol, triglycerides, HDL, or LDL cholesterol in multivariate analysis. Thus, chronic hyperglycemia appears to activate oxidative stress, but this is importantly associated with glycemic fluctuation, leading Monnier to conclude that glycemic variability should be considered an important component of diabetic dysglycemia.

Monnier discussed several tools for assessing glycemic variability. The SD of the mean glucose value perhaps most appropriate from statistical point of view, although MAGE might be pathophysiologically more important. The SD may, however, minimize effect of sudden very large changes in individuals with overall modest glycemic fluctuation. A problem with both approaches is that large swings may not be detected if relatively long time intervals separate glucose measurements. MAGE may be particularly elevated in unstable type 1 diabetic patients, while the SD shows a less marked abnormality in this setting. In tracking urinary isoprostane levels, MAGE was more strongly associated than the SD, leading Monnier to suggest that new approaches to assessing glycemic variability will be important.

It is important, however, to assess the association of glycemic variability with complications to determine whether this is a useful endeavor. In 11-year follow-up of a study of more than 1,100 type 2 diabetic individuals, PPG showed a stronger correlation than fasting blood glucose with overall cardiovascular risk and with myocardial infarction (7), and Monnier reviewed another study suggesting association of lower PPG with lower rates of CVD development. Although controversial, the Study to Prevent NIDDM of 1,429 individuals with impaired glucose tolerance randomized to acarbose versus placebo showed this drug, which acts predominantly on PPG, to be associated with reduced CVD (8). On balance, he suggested, it is uncertain whether glycemic variability is of importance in the genesis of diabetes complications.

This led Monnier to a final question of whether measurements of glycemic variability should be included in the clinical testing of antidiabetes agents. He reviewed a study with CGM showing that abnormality of PPG is the most characteristic finding with worsening of type 2 diabetes, noting that after A1C exceeds 8% the degree of glycemic variability no longer increases (9). He observed that no studies of glucagon-like peptide-1 receptor activators or dipeptidyl peptidase-4 inhibitors have reported glycemic variability, although a number of studies do report PPG and multiple point glycemic profiles, suggesting that such information is available. He described a study of individuals receiving metformin plus glimepiride, showing decreased A1C and mean glucose but a lack of significant decreases in MAGEs, while metformin plus rosiglitazone led to similar decreases in A1C and mean glucose, as well as to significant decreases in MAGEs, suggesting greater benefit in glycemic variability, perhaps an important difference.

Eric Kilpatrick (Hull, U.K.) argued that glucose variability is not related to outcome, quoting T.H. Huxley to state that he would be "slaying . . . a beautiful hypothesis with ugly fact," and saying to Monnier, "I am too much of a skeptic to deny the possibility of anything . . . but I don't see my way to your conclusion." He showed his analysis of the DCCT database of 247,717 laboratory glucose measurements comprising 7-point glucose profiles measured quarterly with ~72,000 accompanying A1C measurements. Microvascular complications were associated with A1C, but Kilpatrick showed no difference in the association of A1C with mean glucose between individuals having higher versus lower variability of glucose, suggesting that variability did not importantly contribute to risk. He did point out that in the intensively treated group, those individuals with A1C levels of 9% had lower retinopathy risk than the conventionally treated group at A1C 9%, and as the conventionally treated group had greater variability, this might explain their greater complication risk. He suggested an alternative explanation, however, that individuals in the intensively treated group with A1C 9% might actually have had lower mean glucose than those in the conventional group with A1C 9%, given the person-to-person differences in he-

moglobin glycation; thus, rather than explaining their lower retinopathy rates by less glycemic variability, he attributed it to a direct effect of hyperglycemia, with hemoglobin glycation itself an epiphenomenon useful in assessing mean glycemia but not directly related to complications. Indeed, a study from the DCCT dataset shows that individuals with a 9% A1C ranged in mean plasma glucose from ~180 to 300 mg/dl (10). When the association between mean glucose and A1C is calculated separately for individuals in the intensively treated and control groups, at A1C of 7 and 11%, there were differences in mean glucose of 30 and 50 mg/dl, respectively (11). In Kilpatrick's analysis of the DCCT data, although both mean and SD of the plasma glucose were associated with retinopathy risk, in multivariate analysis mean glucose was highly predictive but the SD was not significant (12). Similar conclusions have been reached using MAGEs and mean glucose from the DCCT (13). He further observed that in the DCCT, A1C was not predictive of CVD, and the association between prior intensive treatment and reduction in CVD was not demonstrated until the EDIC data became available many years later (14). Using the original DCCT data, however, Kilpatrick showed that mean glucose was strongly predictive of CVD. Based on these analyses of micro- and macrovascular complications, he concluded that "it is the mean glucose that determines diabetic complications, no matter how that mean is arrived at."

A number of studies presented at the ADA meeting showed related information regarding A1C and glycemic variability. Cohen et al. (abstract 436) measured erythrocyte survival and in vivo A1C synthesis in six diabetic individuals and four nondiabetic control subjects. They calculated the glycation gap as the difference between actual A1C and the A1C predicted from the serum fructosamine, a measure of glycated albumin. Erythrocyte lifespan ranged from 77 to 104 days and explained 66% of the variance in glycation gap, controlling for diabetes status, suggesting that this may be an important factor—one not usually clinically recognized as contributing to variability of A1C. Kanehara et al. (abstract 396) presented data illustrating this phenomenon, showing lower A1C than that predicted from mean plasma glucose levels among diabetic and nondiabetic individuals with chronic active hepatitis and cirrhosis, with markers of disease severity such as thrombocytopenia particularly associated with A1C lowering; correction with glycated albumin gave a more accurate index of glycemia. Kumeda et al. (abstract 428) similarly found that among 538 diabetic individuals undergoing hemodialysis, A1C levels were lower than predicted from plasma glucose and glycated albumin, with erythropoietin doses showing modest negative correlation with A1C. Interestingly, Kishimoto et al. (abstract 834) studied 145 diabetic individuals followed in their institution for a mean of 23 years, showing that the coefficient of variability of A1C, calculated from at least four values, significantly predicted progression of retinopathy in multivariate analysis including mean A1C. In a study of a potential approach to the assessment of PPG, Akutsu et al. (abstract 423) studied levels of 1,5-anhydroglucitol. This is a monosaccharide similar to glucose, ingested in the diet. Its tubular reabsorption is prevented by glycosuria, decreasing circulating levels. In 36 relatively well-controlled type 2 diabetic individuals, with mean A1C 6.5%, the sum of PPG levels exceeding 180 mg/dl and mean PPG showed negative correlation with 1,5-anhydroglucitol, while there was no correlation with A1C or glycated albumin.

CMG

Jay Skyler (Miami, FL) introduced a symposium on CGM, recalling that home capillary glucose monitoring in the early 1970s used devices such as the Ames Eyetone meter, which was initially thought to be inaccurate and unlikely to achieve widespread use. "I think we're at the same place with CGM right now," he said, suggesting that in "a few years" this approach will be considerably more widely used. Intravascular glucose monitors are now feasible for clinical use. Most attention has, however, focused on subcutaneous tissue glucose measurement. The MiniMed (now Medtronic) system was initially developed in the late 1990s as a downloadable device that was used to give a 72-h glucose profile. The Glucowatch Biographer "took too long to warm up, was too inaccurate, and disappeared," Skyler said, as did the Pendragon Medical device, which was not used "for lack of effectiveness."

Several CGM devices are currently available and are in clinical use. The A. Menarini Diagnostics Research, GlucoDay S device, Skyler said, "works quite well." The Medtronic Guardian telemetered glucose monitoring system is comprised of a subcutaneously placed sensor connected wirelessly to a remote standalone reader or to a reader included in the Paradigm insulin pump. The DexCom continuous glucose sensor (15,16) now gives 7-day glucose data fairly accurately, with high and low glucose alarms and software for data analysis. The Abbot Navigator continuous glucose monitor (17,18) also appears to be an accurate and useful instrument. These sensors all have similar characteristics, with 22- to 25-gauge insertion devices, 6–13 mm in length, inserted at 45–90° angles, with sensors lasting ~7 days for the DexCom, 5 days for the Abbott, and 3 days for the Medtronic devices. The OrSense NBM-100G noninvasive continuous glucose monitoring system uses a ring-shaped probe placed around the patient's finger, intermittently occluding blood flow and allowing a red/near infrared measurement of light transmitted through the finger to assess blood glucose concentration.

To understand and make use of these approaches, one must recognize that interstitial glucose levels are "a little bit slower in equilibrating," lower than simultaneous blood glucose when levels are increasing, and higher when levels are decreasing. An important caveat, then, is that calibration should be performed at a time when blood glucose levels (from capillary sampling) are stable. The lag in glucose readings occurs with all subcutaneous tissue glucose sensors and can delay recognition of hypoglycemia and of recovery from hypoglycemia; thus, changes in glucose and absolute levels must be taken into account. The use of these devices allows understanding of the relationship between insulin administration and meals (17,19), with patients using the approach able to improve glycemia (15), particularly those with higher A1C (16). Skyler reviewed a study of 28 children using CGM for 3 months, showing a reduction in the likelihood of hypoglycemia, and those patients using CGM more frequently appear to have greater improvement in glycemia (20). The next step is to use CGM sensor-augmented insulin pumps for insulin delivery, with studies suggesting feasibility of such an approach with improvement in glycemia (21). Skyler concluded that the approach seems highly worthwhile, although noting that "it still is requiring lots of letter writing . . . I've been 50% successful with private insurers."

Howard A. Wolpert (Boston, MA)

further reviewed the use of CGM, suggesting that the challenge is in learning to use the data obtained, which offers patients the potential to detect and prevent hypoglycemia, with potential quality-of-life benefits. Furthermore, CGM can help diabetic patients modify inappropriate lifestyle behaviors and offers the potential to become a bridge to the development of hybrid "closed-loop" systems. Wolpert echoed Skyler's observations that capillary and interstitial glucose levels do not always correspond, with a delay between 5 and 30 min in equilibration; thus, postprandial hyperglycemia may not be readily recognized, and, further, the user must calibrate the CGM device when in a steady state. As an example, if capillary glucose measurement is performed after a meal, the "correct" CGM glucose would be ~30 mg/dl lower, and if this pair of observations is used for recalibration the device setting would be incorrect, so that users must "realize that some of these discrepancies are part of the physiology." However, in addition to the physiologic lag, there is also a lag due to duration of data processing, and improvement in this should be possible. The lag causes CGM to underestimate the rate of decline in glucose when falling, as may occur with exercise, and patient education to understand this limitation is crucial. Patient education needs to focus on the rate of change in glucose as well as to the CGM glucose level at a given time. Given these provisions, the use of CGM to recognize hypoglycemia, Wolpert said, it offers "real potential . . . as a tool for patients to fine tune and improve their glucose control." He suggested that patients confirm CGM glucose elevation after meals with capillary glucose testing. It is important to avoid hypoglycemia by giving overly frequent insulin boluses, realizing that insulin analogs act for up to 6 h and taking into account the glycemic index of ingested meals. After low glycemic index foods, if glucose levels are elevated, additional insulin may be required, whereas this might not be the case after high glycemic index foods. Wolpert noted that women who overfocus on weight loss may omit insulin doses (22) and that, conversely, those with frequent hypoglycemia may overeat with consequent weight gain. CGM is potentially useful in both settings and for all insulin-treated patients for whom hypoglycemia is an issue.

Boris P. Kovatchev (Charlottesville, VA) described some of the complexity of mathematical models for what he termed "proactive" and "reactive" interpretation of CGM, with potential applications to feedback control. Since the interstitial glucose compartment rather than the blood glucose compartment is being measured, analysis must include a model of the transfer of glucose between the two compartments. CGM data form a time series that provides analytical advantages in smoothing and artifact rejection, assessment of trends and real-time forecast of events, and analysis of temporal variability and system dynamics to ultimately enable closed-loop control. Developing a control algorithm for closed loop needs to recognize a variety of sensor inaccuracies, although Kovatchev noted that close-in-time readings are highly interdependent, and standard statistics may lead to inaccurate conclusions. He noted that measures of temporal glucose variability, such as SD and coefficient of variation, are designed to reflect symmetric deviations around a mean, and as glucose fluctuations are not symmetric and the mean may not be important, better approaches may include measures such as the interquartile range, percent variation above a threshold, *M* value, MAGEs, "liability index," and "Average Daily Risk Range." These methods do not, however, take into account the temporal order or the interdependence of the data. He suggested developing a measure based on a target range, say of 70–180 mg/dl, noting the numerically greater range of high rather than low glucose levels, which can be addressed by weighting hyperglycemia less than hypoglycemia. This approach will equalize the variance carried by hypoglycemia and hyperglycemia, with excursions into extreme hypo- and hyperglycemia giving progressively increasing risks. A potential marker of system stability is the SD of the rate of change. Trend prediction typically involves linear models, but as glucose changes are highly nonlinear—particularly at low glucose levels—alternative analytic approaches need to be developed to reduce false hypoglycemia alarm rates and, potentially, in developing control systems.

Geremia Bolli (Perugia, Italy) discussed strengths and weaknesses of interstitial glucose monitoring. Before 1980, A1C measurement was not available, and urinary glucose was used for monitoring, with plasma glucose results only being available after several days, leading to the assumption that hyperglycemia would need to be tolerated. It has now become possible to physiologically treat diabetes, he said, attaining A1C <7% without frequent severe hypoglycemia, although this requires glucose monitoring before and after each meal and at bedtime. The times of glucose testing should be based on the pharmacokinetics of the insulin preparations used, with 2-h PPG measurements optimal using rapid-acting analogs. Such testing is inconvenient, embarrassing, painful, and time consuming and perhaps does not offer sufficient information to make reliable clinical decisions. CGM should be friendly, allowing prolonged use, and affordable. The discrepancy between blood glucose and interstitial glucose may be distressing for patients using the devices, with Bolli reinforcing Wolpert's recommendation that patients must learn to understand this limitation. The lag phenomenon occurs to variable degrees at different times, based on glucose levels and also on insulin levels, so that after insulin administration cellular glucose uptake increases, lowering insterstitial glucose. The lag time is physiological, physical, and also system/software-related and is responsible for much of the lower accuracy of CGM. Sensor calibration becomes an important issue when not performed in a steady-state situation, with consequent discrepancy between glucose concentrations in the two compartments.

Bolli noted that A1C improvements have not been fully demonstrated with CGM and that prevention of hypoglycemia is flawed by the low specificity and high false-alarm rates of this approach. Given these considerations, trend analysis (23) may offer a better approach than the display of individual glucose data points. It is clear, he said, that CGM is better than capillary glucose testing at detecting peaks of hyperglycemia (24) and in reducing variability, which is associated with hypoglycemia, but he recommended that at this point CGM not be considered a substitute for capillary glucose monitoring but rather an adjunct to reduce the risk of hypoglycemia and an endeavor to improve A1C.

These observations were extended by a number of studies presented at the ADA meeting on aspects of CGM. Potential weaknesses were described by several groups. King et al. (abstract 85) simultaneously placed three sensors in each of 10 individuals. There was acceptable agreement between individual glucose readings, with mean difference ~15%. Using pairs of readings to calculate direction of

glucose change, however, on ~20% of occasions one sensor gave a positive and one a negative change result, suggesting that such information may be somewhat inaccurate. Zisser et al. (abstract 92) compared 1,638 measurements by CGM and simultaneous Yellow Springs Instrument venous blood glucose in 67 diabetic individuals using the DexCon STS-7 System, finding that although the overall correlation was high with $r = 0.91$, 31% of readings differed by >20% and 13% by >30%, with particular inaccuracy during periods with glucose <70 mg/dl. Similarly, Trototaro et al. (abstract 422) compared 60,500 pairs of CGM sensors with capillary glucose readings in an open-label study of 72 type 1 diabetic individuals, finding that 24% of readings differed by >20%.

Dunn and Rebrin (abstract 395) studied 4,734 glucose profiles following meals containing at least 20 g carbohydrate containing at least six measurements over at least 2 h, from 122 insulin-treated type 1 and type 2 diabetic individuals using the FreeStyle Navigator CGM system. A total of 74% of breakfasts, 59% of lunches, and 55% of dinners showed maximum glucose between 30 and 150 min after meal initiation, peaking at 75 min and not reaching baseline at 3 h. Premeal glucose levels were higher before meals, with peak postprandial level occurring at <30 min, and lower before meals with peak after 150 min, suggesting that insulin dosing choices are typically not correctly calibrated to preprandial glucose levels. McGarraugh (abstract 406) studied the behavior of this CGM device in predicting glucose <70 mg/dl as confirmed by capillary glucose testing every 15 min in 58 type 1 diabetic individuals over 212 patient-days of testing. Using 10-, 20-, and 30-min prediction settings, hypoglycemia was correctly predicted on 70, 76, and 80% of occasions, respectively; on an additional 21, 17, and 15% of occasions, respectively, a glucose <75 mg/dl was correctly shown at the time of actual hypoglycemia. False hypoglycemia alarm rates were 7–9%. Mazze et al. (abstract 404) compared glucose patterns obtained by the Guardian RT CGM with capillary glucose levels using either the OneTouch Ultra or Yellow Springs Instruments devices, showing a 22-min lag in PPG peaks with the former, as well as a 19% relative absolute difference between capillary and interstitial glucose measurements.

Rhee et al. (abstract 417) compared A1C with mean glucose from 74 diabetic individuals with stable diabetes treatment using CGM, finding that an A1C level of 7% corresponded to a mean glucose of 161 mg/dl. Shukla and Krishna (abstract 413) compared CGM with capillary glucose readings from 26 type 1 and type 2 diabetic individuals studied for an average of 65 h, finding postprandial hyperglycemia to average 219 vs. 163 mg/dl, suggesting that the increased testing frequency of CGM allows recognition of considerably greater glycemic levels.

Given these caveats, several encouraging studies were reported of outcomes with CGM. In a randomized controlled study of 138 adult and 40 adolescent type 1 diabetic individuals, Hirsch et al. (abstract 90) compared CGM/sensor-augmented insulin pump versus standard capillary glucose monitoring with pump treatment for 6 months, finding that in both groups A1C fell from 8.5 to 7.8%. Among the intervention group, however, those with <60% use of CGM showed an increase in A1C from 9.5 to 9.6%, while those with 60–80, 80–99, and 100% CGM use showed decreases in A1C from 8.2 to 7.5%, 8.4 to 7.7%, and 8.6 to 7.7%, respectively, suggesting that, in a setting of frequent contact with health care providers, compliance with CGM may lead to improvement in glycemic control. Kovatchev and Clarke (abstract 86) and Bugler and Bell (abstract 419) reported on ~120 individuals performing CMG using the FreeStyle Navigator system. During 20 days masked to real-time data, frequent hypoglycemia occurred in 10%, while it occurred in 3% during 20 days with the patients receiving immediate feedback. The SD of blood glucose decreased, as did the frequency of hyperglycemia, and mean nadir to peak amplitude of glucose excursions (MAGE) was 6–7 mg/dl higher during the masked period, although no change in average glucose was seen, suggesting CGM to reduce glycemic variability.

Given the close relationship of CGM and continuous subcutaneous insulin infusion (CSCII), a presentation by Conwell et al. (abstract 1881) is of note. Dermatologic effects of CSCII of at least 6 months duration in 50 children revealed areas of erythema in 66%, scars <3 mm in 94% and ≥3 mm in 12%, erythematous and nonerythematous subcutaneous nodules in 42 and 20%, respectively, and lipohypertrophy in 48%; no patient had cellulitis or abscess.

Home glucose monitoring

Hanas et al. (abstract 1894) compared glycemic patterns in 68 type 1 diabetic children and adolescents using multiple daily insulin injections and in 44 subjects using CSCII, the latter group typically began this treatment because of poor glycemic control. A1C was 7.7 vs. 8.3%, respectively, and download of glucose meters showed mean 175 vs. 202 mg/dl with an SD of 90 vs. 106 mg/dl, suggesting the SD to be an important parameter of glycemic variability that may be useful in clinical care.

Pan et al. (abstract 981) reported that from 1996 to 2005, the prevalence of home glucose monitoring among adults with diabetes increased from 39 to 63%, with use of hypoglycemic medication, having health insurance coverage, and the number of physician visits correlating with greater use of glucose testing, while male subjects and individuals of Hispanic ethnicity both were 30% less likely to self-monitor. Certainly, glucose testing is important in type 1 diabetic patients. Heinemann et al. (abstract 88) surveyed 36,450 CSCII-treated diabetic individuals, with 14,015 responding. The self-reported capillary glucose testing frequency was strongly associated with reported A1C; those testing 10 or more times daily with A1C 6.5%, 5 times daily with A1C 7%, and 2 or fewer times daily with A1C >7.5%. There is controversy about glucose monitoring in type 2 diabetes. Scherbaum et al. (abstract 91) randomized 202 oral agent–treated type 2 diabetic individuals to capillary glucose testing once versus four times weekly, showing falls in A1C from 7.2 to 7.0% in both groups at both 3 and 6 months, without differences in rates of severe hypo- or hyperglycemia. However, Murata et al. (abstract 87) reported a >2 year observational study of 5,862 such diabetic individuals, finding that although there was no relationship between the frequency of monitoring and A1C in the overall group, more frequent testing was associated with greater likelihood of increasing doses of or addition of a new oral agent, while excluding those whose oral agent treatment increased showed a negative correlation between frequency of testing and A1C, with A1C decreasing by 0.2–0.9% for every 10 tests performed weekly.

New innovations may lead to better diabetes testing. Nguyen et al. (abstract 432) used the HypoMon (AiMedics) noninvasive monitor measuring skin

impedance, heart rate, and rate-corrected QT electrocardiographic interval in 25 type 1 diabetic children during a 4-h study, showing that heart rate and QT increased and skin impedance decreased during hypoglycemia, developing a neural net algorithm with sensitivity 83% and specificity 64% for detection of hypoglycemia. Ghevondian et al. (abstract 439) extended the use of the device in 60 type 1 diabetic children with overnight studies, showing sensitivity 76% and specificity 89%. This approach may be an alternative to CGM in reducing the likelihood of hypoglycemia, although not directly giving glucose information.

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