Glycemic Treatment in Type 1 and Type 2 Diabetes

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A pilot project is underway to offer the Perspectives on the News commentaries as a monthly Web-based CME activity. Please access www.ada.procampus.net to view our initial efforts. We look forward to your comments.

Postprandial glycemia

At the meeting of the Council on Nutritional Science and Metabolism, Joan V.C. Hill (Natick, MA) introduced a session addressing the implications of postprandial blood glucose monitoring by reminding the audience that the American Diabetes Association (ADA) recommends a target HbA_{1c} (A1C) of ≤7% but that the most recent National Health and Nutrition Examination Survey suggests that >60% of persons with diabetes fail to meet this goal. In a Quest laboratories analysis of 14.3 million A1C tests performed for diabetes diagnosis codes, half were shown to be above goal, although the average decreased from 7.8% in 2001 to 7.2% in 2005. An important question is the contribution of postprandial blood glucose to A1C, with the corollary being the determination of reasonable postprandial blood glucose targets, with Hill asking whether targeting postprandial blood glucose can improve metabolic control or, more importantly, improve outcome, recognizing the difficulty of determining the relationship between postprandial blood glucose and outcome. "The clear message," Hill concluded, is that "achieving A1C close to goal [will require] monitoring postprandial glucose."

Martin Abrahamson (Boston, MA) reminded the audience, "Most of our lives are spent in the postprandial state," with the preprandial state not beginning until 10 h after ingestion of food, perhaps in most persons only from 4:00 to 8:00 A.M. Thus, measurement of fasting glucose may represent a state not particularly representative of that encountered through the day. To achieve the target goal of A1C as close to normal as possible, we are clearly going to need to target postprandial blood glucose. The ADA recommends that glucose levels be <180 mg/dl 2 h after meals, while the American Association of Clinical Endocrinologists recommends levels <140 mg/dl, without specifying the time for optimal measurement. In a clinical study addressing this issue, for those in the highest quintile of A1C (>10.2%), 70% of the elevation in A1C could be explained by fasting hyperglycemia and 30% by postprandial blood glucose. At an A1C of 9.3–10.2%, 40%; at an A1C of 8.5–9.2%, 45%; at an A1C of 7.3–8.4%, 50%; and at an A1C <7.3%, 70% of the A1C could be explained by abnormality in postprandial blood glucose (1). In the DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study, mortality was much more strongly predicted by the 2-h postchallenge glucose than the fasting glucose level. Indeed, a fasting glucose <110 mg/dl with 2-h glucose >200 mg/dl had worse prognostic implication than a fasting glucose >140 mg/dl with normal 2-h glucose (2). Abrahamson noted the association of postprandial blood glucose with oxidative stress, with reduction in postprandial blood glucose lowering plasma levels of nitrotyrosine, a product of peroxynitrite action, while not affecting the triglyceride level (3). What, then, is the effect of intervention targeting postprandial blood glucose? In a study of glyburide-treated patients comparing addition of NPH insulin at bedtime, metformin, and lispro insulin three times daily before meals, lispro was associated with a fasting glucose of 185 mg compared with 150 mg/dl with NPH, but with the lowest postprandial blood glucose level, and A1C was 7.5% with lispro versus 8.5% with NPH (4).

Can we improve outcome? In the Study to Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, 100 mg acarbose three times daily, compared with placebo, in 1,429 persons with IGT followed for 3.3 years decreased the likelihood of developing diabetes by 25% (5). The likelihood of developing hypertension was reduced by 34%, and cardiovascular events by 49%, with a 91% reduction in myocardial infarction (6). "Whether or not this is a direct effect of lowering the [postprandial blood glucose]," Abrahamson noted, is uncertain, but there was a decrease in carotid intima-media thickness in STOP-NIDDM, suggesting true antiatherosclerotic benefit (7). He referred to two presentations addressing aspects of postprandial blood glucose regulation. Scribner et al. (abstract 1693) compared mice fed a diet with carbohydrate solely as the branched chain glucose polymer amylopectin, which is hydrolyzed in the small intestine relatively quickly, or containing 40% amylopectin and 60% amylose, the linear carbohydrate form hydrolyzed more slowly, the latter diet associated with 18% less total body fat, with reduction in hepatic fat levels, despite similar energy intake and body weight. Fowler et al. (abstract 898) reported the fascinating observation that among 3,682 individuals in the San Antonio Heart Study followed for 7–8 years, the mean BMI increased 1.45 vs. 1.00 kg/m^2 in users versus nonusers of artificial sweeteners, adjusted for age, sex, ethnicity, baseline BMI, socioeconomic status, education, and coffee and tea use, with a 71% greater adjusted

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Abbreviations: ADA, American Diabetes Association; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DAISY, Diabetes Autoimmunity Study in the Young; DCCT, Diabetes Control and Complications Trial; DirectNet, Diabetes Research in Children Network; DKA, diabetic ketoacidosis; GADA, GAD antibody; IA-2, insulinoma-associated antibody 2; STOP-NIDDM, Study to Prevent Noninsulin-Dependent Diabetes Mellitus.

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

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likelihood of development of obesity among persons not obese at baseline, leading to the question of whether use of artificial sweeteners "in fact supports or undermines weight control." Abrahamson discussed the potential adverse effects of higher–glycemic index foods on postprandial blood glucose, noted that glucagon-like peptide 1 is secreted when carbohydrate reach the reach the distal small bowel, and speculated that this may be related to the cardiovascular benefit reported in STOP-NIDDM, pointing out that glucagon-like peptide 1 may have direct protective effects in reducing coronary and cerebral vascular disease. The use of new pharmacologic agents to address postprandial blood glucose is fascinating, with Abrahamson describing "the challenge for many of us in clinical practice [of] when do we use these drugs," remarking that dietary approaches to reduce postprandial blood glucose may have different effects from those of pharmacologic interventions. There may be a subgroup of patients with relatively normal A1C but markedly elevated postprandial blood glucose, with new tests such as the Glycomark assay having the potential to assess postprandial glycemia and perhaps identifying persons at particularly increased risk of adverse outcome. Persons who have had gastric bypass exhibit hypoglycemic postprandial dips and may constitute another interesting group to study. Given these considerations, Abrahamson suggested that postprandial blood glucose monitoring, either with fingerstick capillary glucose testing or with the new continuous interstitial fluid continuous glucose monitoring (CGM) devices, may become important.

Joseph Wolfsdorf (Boston, MA) discussed carbohydrate counting as the basis for intensive glycemic treatment of type 1 diabetic children. He stressed the importance of diet behaviors in the Diabetes Control and Complications Trial (DCCT), with an association between specific diet behaviors and lower A1C levels (8). At the time of the DCCT, the dietary recommendation was for 45–55% of calories from carbohydrate, <35% of calories from fat, and 12–20% of calories from protein, while current recommendations are that 60–70% of calories be from carbohydrate plus monounsaturated fats, 15–20% from protein, and <10% from saturated and ~10% from polyunsaturated fat. The majority of persons in the intensive arm of the DCCT used multiple insulin doses, at a time when rapid-acting insulin and the long-acting insulins glargine and detemir were not available. In the DCCT, exchange systems, carbohydrate counting, "total available glucose," weighing and measuring foods, and estimating food portions were taught, often with a variety of different programs for different participants. Of the 711 intensively treated patients in the study, 623 completed a diet behavior questionnaire, addressing their approaches to diet implementation, adherence to meal plans, management of expected changes in food intake, treatment of reactions, consumption of concentrated sweets, timing of insulin in relationship to meals, and snacking habits. There was an association between "following prescribed meal plan," by self report and A1C, with study participants who reported that they followed the plan >90% of the time having mean A1C 6.7%, while those who reported following the plan <45% of the time had mean A1C 7.6%. The mean A1C was 6.9 vs. 7.4% in those who never versus usually corrected hypoglycemia by eating "until they feel better." Adjusting insulin doses for meal size and consistent use of evening snacks were also associated with better control, as were prompt treatment of hyperglycemia by adjusting food and/or insulin and avoiding extra snacks not on the meal plan. In the post-DCCT era, dietary carbohydrate has increasingly been recognized as being important in the prevention and management of diabetes (9). The total carbohydrate content of meals and snacks has been thought to be the most important determinant of postprandial glucose response and has been widely used in determining premeal insulin dosages, suggesting the importance of formulating insulin-carbohydrate ratios, either with efforts to precisely estimate carbohydrate intake using food labels, food lists, and meal planning books or by using a carbohydrate exchange system approach, with each portion having ~15 g carbohydrate. Wolfsdorf pointed out that in fact "it is not linear," so that at very low and very high carbohydrate levels, the insulin-carbohydrate ratio concept "falls apart." Furthermore, one must be sure that patients do not misinterpret the message to believe, "You can eat what you like; just cover the carbs," or that "a carb is a carb is a carb." Patient accuracy of carbohydrate estimation may be limited. Wolfsdorf showed a study of adults with a long history of type 1 diabetes using insulin pumps. Surprisingly, few accurately estimated the carbohydrate content of an apple and that of a bowl of rice. Furthermore, the concept of glycemic index is important, so, for example, white bread has a considerably greater glucose-raising effect than the same amount of carbohydrate presented in the form of soybeans. In a meta-analysis of low versus high glycemic index, there is evidence among persons with type 2 diabetes suggesting a role in improving glycemia (10). Still more important is the glycemic load, the product of glycemic index and carbohydrate load, which Wolfsdorf characterized as being "really where the money is." Furthermore, protein and fat do affect glycemia, with protein in large amounts (>90 g, or 3 oz) increasing glucose levels and high fat loads delaying the absorption of nutrients, "so that there are multiple influences determining the insulin dose requirement, as well as the optimal duration of insulin bolus for a given dietary stimulus." Thus, a meal comprised mainly of carbohydrates might be treated with a rapid on-off bolus, a high-fat meal with a square-wave/extended bolus, and a large, mixed protein and carbohydrate meal with a dual-wave bolus. In the SEARCH for Diabetes in Youth study, 1,697 children were studied, 89% with type 1 diabetes (11). On average, fat comprised 37% of calories, with only 6.5% meeting the ADA recommendation of <10% saturated fat and with 35% overweight, suggesting that "there is a critical need" to improve diet in youth with type 1 diabetes. Optimal dietary management is complex and challenging, with a balanced approach necessary and focus on carbohydrate counting alone insufficient.

Type 1 diabetes: additional treatment considerations

Peter Chase (Denver, CO) discussed an important practical aspect of the care of persons with type 1 diabetes: the impact of missed meal boluses. Normal physiologic insulin production can be conceptualized as being comprised of basal and meal bolus components. In studies using the Glucowatch CGM device, eating a meal without a bolus increased glucose levels from ~150 to peak levels of ~300 mg/dl. In a study of 56 type 1 diabetic youth aged 7–23 years beginning continuous subcutaneous insulin infusion (CSII), A1C decreased on average from 8.5 to 8%, with 64% decreasing by 1% or maintaining levels <8%, but 20% having an increase in A1C of >0.5% (12). In a larger current study of 300 youth using

CSII, A1C decreased from 8.7 to 8.2% and the frequency of severe hypoglycemia decreased from 8.9 to 7.8 per 100 patient-years. Of 100 using the pump for >5 years, A1C decreased from 8.7% before CSII to 8.2% at 1 year but increased to 8.4% at 5 years. In this group, A1C decreased by >0.5% in 51%, but for 30% of patients, the levels stayed within 0.5% of baseline, and in 19% the A1C increased by >0.5%. Improvement was particularly likely in preadolescents.

Given the frequency of failure to improve and of worsening, particularly among adolescents, Chase reviewed causes of increased A1C in patients treated with CSII. The availability of "pump downloads" of insulin administration patterns allows such an analysis. Among 48 youth aged 7–20 years, 17 omitted less than one bolus per week, with mean A1C 8%, while 31 missed one or more boluses weekly, with mean A1C 8.8% (13). Comparing patient recall with downloaded information, on average patients missed one more meal bolus per week than they acknowledged. There was no relationship of the A1C level with disconnection of the pump for exercise or with use of boluses before disconnecting. A trend was seen associating use of boluses before versus after meals with A1C levels. Chase concluded that, particularly for older children, it is important to bolus before meals and to bolus before each meal. For every two meal boluses missed per week based on the insulin log download, or for every meal missed based on patient recall, the A1C increased on average by 0.5%. Furthermore, persons administering greater numbers of daily boluses tend to have lower A1C levels. In a study on the use of reminder alarms, A1C decreased initially, from 9.3 to 8.9%, in association with more meal bolus use, while a control group showed an A1C decrease from 8.9 to 8.7% (14). At 6 months, there was no significant difference in A1C between the groups, but a correlation continued to be seen between the number of missed meal boluses and A1C. Chase noted that some girls with type 1 diabetes deliberately skip insulin (or deliberately lower the insulin dose) for weight loss (15), so that technology alone may not always solve behavioral problems. In the future, he suggested, treatment of type 1 diabetes will be greatly changed by CGM, with knowledge of the relationship between high glucose levels and missed boluses potentially allowing improvement in glycemic control.

Michael Tansey (Iowa City, IA) discussed a number of issues related to exercise based on the Diabetes Research in Children Network (DirectNet) study. In a study of the relationship between late afternoon exercise and overnight hypoglycemia, 50 type 1 diabetic children aged 10–18 years, 54% using pumps with A1C<10%, had two 24-h inpatient examinations, one with and one without four 15-min afternoon exercise sessions at 55% $V_{O_{2max}}$ (16). During exercise, glucose decreased ~60 mg/dl, with only one patient's blood glucose increasing after exercise. All of the patients whose baseline glucose was <120 mg/dl developed hypoglycemia (≤70 mg/dl), 44% became hypoglycemic with baseline levels of 120–180 mg/dl, and 28% became hypoglycemic with baseline levels >180 mg/dl. Treatment of hypoglycemia with oral glucose (15 g) increased blood glucose by only ~20 mg/dl, with more than one-third of patients needing a second 15-g oral glucose dose to complete the exercise regimen, suggesting that a 30-g glucose equivalent is required for "rescue" from exercise hypoglycemia. After exercise, glucose levels were significantly lower from the beginning of exercise through 4:00 A.M. that night. Hypoglycemia developed on both nights in 22%, only on the night following exercise in 26%, and did not develop on either night in 46% (17). Glucose levels exceeded 200 mg/dl in 32% of patients on both nights, in 48% on neither night, in 18% on the sedentary night only, and in 2% only on the exercise night. The glucose level before the bedtime snack was a predictor of hypoglycemia, with levels of ≤130 mg/dl associated with 57 and 55% overnight hypoglycemia frequency on exercise and sedentary nights, respectively, while at a bedtime glucose >130 mg/dl, hypoglycemia occurred on 36% of exercise nights and 8% of sedentary nights. Tansey discussed his study (Tansey et al. [abstract 1016]) of 49 type 1 diabetic children (aged 8–17 years) using insulin pumps, finding that glucose levels decreased with continued basal insulin, while suspension of basal insulin was associated with stable glycemia during exercise, with the likelihood of hypoglycemia decreased from 43 to 16%, although increasing the likelihood of glucose >200 mg/dl at the end of exercise from 2 to 12%. Tansey recommended that the insulin infusion be suspended for no more than 2 h to avoid hyperglycemia.

William Tamborlane (New Haven, CT) discussed outcome data for use of pumps in youth, recalling his original study on the topic published in 1979 (18). There was limited use of CSII in children before the DCCT because of size and technical limitations of early pumps, psychosocial issues, and lack of certainty of the benefits of intensive therapy. Tamborlane noted that although a 1994 American Academy of Pediatrics position statement stated that "most children and adolescents should be treated with intensive therapy to prevent or markedly delay diabetic complications," many pediatric endocrinologists were reluctant to recommend pump therapy. Among adolescents in the DCCT, A1C decreased to a mean of 8.1% with severe hypoglycemia in 39% during the first 12 months and in 27% overall, and there was doubling of the risk of weight gain. In the Yale Clinical Outcome Study of 161 youth treated with CSII, A1C decreased from 7.1 to 6.5% among children <7 years of age, from 7.9 to 7.3% for those aged 7–11 years and from 8.1 to 7.4% for those age 12–18 years (19). Hypoglycemia causing seizure or coma occurred in 36% during the year before CSII, decreasing to 24% during the first 12 months of pump treatment. There was a particularly great 50% decrease in hypoglycemia in those <7 years of age. Tamborlane reviewed seven studies of 543 youth receiving CSII. A1C decreased ~0.5%, to a mean of 7.6%, hypoglycemia was consistently reduced, and there was little change in weight. The Yale clinic now has ~650 patients using CSII, with mean A1C 7.4%.

Tamborlane acknowledged that the question of whether CSII truly offers better glycemic outcome than multiple dose insulin treatment is still unanswered. In a comparison of glargine plus preprandial aspart versus CSII, A1C decreased from 8.2 to 8.1% vs. from 8.1 to 7.1%, with 12 vs. 50% achieving A1C <7% (20). At the conclusion of treatment, the fasting glucose level was 150 mg/dl in both groups, suggesting similar basal dose optimization, but glucose levels increased before lunch and dinner and at bedtime levels in patients randomized to glargine plus aspart, while those treated with CSII remained at 150 mg/dl throughout the day. Four other randomized controlled trials with 78 patients in total, however, did not show CSII to lead to improved glycemic outcome. Other reported benefits of CSII include decreased glucose variability, more flexible lifestyle/easier coping, and greater treatment satisfaction, reflected in

low discontinuation rates. Consequently, Tamborlane endorsed the recommendation of a Consensus Conference on Pumps in Pediatrics held this year in Berlin that all pediatric patients with type 1 diabetes be considered candidates for CSII, particularly children with recurrent severe hypoglycemia, A1C above target, unacceptable fluctuations, microvascular complications, or an insulin regimen compromising lifestyle. (Of course, it is difficult to imagine any type 1 diabetic child not satisfying one or more of these criteria.) CSII may also be beneficial in the very young patient, in adolescents with eating disorders, in those with an exaggerated dawn phenomenon, and in athletes. Furthermore, Tamborlane pointed out that the full potential of CSII will not be realized until real-time CGM, with appropriate tools for analysis and response to glycemic change, is available, allowing improved bolus dosing, retrospective data analysis to optimize carbohydrate-insulin ratios and correction doses, improved overnight control using hypoglycemia alarms, and constantly updated retrospective data analysis to optimize overnight basal rates. In a CGM pilot study of 30 pump patients using the Navigator device, glucose measurements were accurate within 10–15% for up to 5 days, the instrument was used ~130 h/week, parents and patients were very satisfied, and A1C decreased from 7.1 to 6.8%, with decreased glucose variability and an increased percentage of glucose values in the target range, although with a slightly greater frequency of hypoglycemia. Tamborlane concluded that "No treatment will ever be perfect until there is feedback regulation" with a closed-loop system.

At another symposium, Ingrid M. Libman (Pittsburgh, PA) discussed the diagnosis and management of the patient with "double diabetes" (having features of both type 1 and type 2 diabetes). The existence of different forms of diabetes has been recognized for millennia, classically with one form developing rapidly and affecting children and young adults and the other having gradual onset and affecting older, overweight persons. The distinction between insulin sensitivity and insulin resistance in the two forms became recognized after the development of insulin as a therapeutic modality in the 1920s. This paradigm is, however, changing. In the Allegheny County Diabetes Registry of cases of diabetes treated with insulin since onset, incidence among Caucasians versus African Americans had been relatively constant around 20–25 vs. 10–15 per 100,000 until 1990, subsequently increasing in the latter group to >25 per 100,000 (21). Is this type 1 diabetes? Libman pointed out that type 2 diabetes increased dramatically in children between the mid-1980s and the mid-1990s. Using the Pittsburgh Children's Hospital registry to identify 113 African-American and 117 Caucasian children who had developed insulin-requiring diabetes, with mean age of onset 10 years, prevalences of one or more of islet cell antibody, GAD antibody (GADA) or the transmembrane protein tyrosine phosphatase insulinoma-associated antibody 2 (IA-2), at diagnosis were 70 and 90%, respectively, and 43 and 11% were obese. African Americans had higher acanthosis nigricans prevalence. Of 34 antibody-negative African-American children, 83% were obese and 48% had acanthosis, but, Libman noted, 24 and 5% of African-American children with at least one positive antibody also had these characteristics. These children may, she suggested, be considered to have characteristics of both disease processes: "double diabetes" (22). The prevalence of obesity in antibody-positive children with insulin-treated diabetes has increased markedly over the past 2 decades. Diabetic ketoacidosis (DKA) was present at onset of diabetes in 83% of African-American children with antibodies, but 48% of those with negative antibodies had positive urine ketones and 23% had DKA. Libman reviewed a study of children with diabetes who had other characteristics of type 2 diabetes such as obesity, ethnicity, and family history, with a high prevalence of antibody positivity. In a study of 7,000 children, 36% of those clinically diagnosed to have type 2 diabetes were antibody positive. Children with clinical type 2 diabetes with and without β-cell antibodies have similar age and BMI, but the former are more insulin sensitive and more likely to require insulin, with lower C-peptide levels.

"The classic paradigm," then, "seems not to be valid anymore," at least in the large subset of children with characteristics of both forms of diabetes. Libman suggested that it is important to establish the magnitude of this problem, to evaluate risk factors and temporal changes, and to assess whether obesity and insulin resistance may be accelerators of type 1 diabetes, with implications for treatment. Many of these children appear to benefit from the addition of metformin, particularly the African Americans. Among unanswered questions, she asked, should other sensitizers be used? Should all children with the type 2 diabetes phenotype have antibody determination, with insulin treatment if positive? Certainly exercise and diet should be encouraged. Those with double diabetes should be screened for hypothyroidism, with Libman's studies suggesting that 20% have antithyroid antibodies and 5% are hypothyroid. Furthermore, in the Pittsburgh Epidemiology of Diabetes Complications study of insulin-requiring diabetic persons followed every 10 years from 1986, by 8-year follow-up, 119 of 656 had evidence of coronary artery disease, which was found to be associated with evidence of insulin resistance and with having a family history of type 2 diabetes. Other studies have shown high incidence of nephropathy. These children, then, may be at particularly high risk of complications.

Etiology of type 1 diabetes

A number of studies presented at the ADA meeting addressed aspects of type 1 diabetes, including the overlap between type 1 and type 2 diabetes. Dietary considerations are clearly important for type 1 diabetic patients, with Conway et al. (abstract 1652) reporting weight gain among 545 type 1 diabetic persons followed in the Pittsburgh Epidemiology of Diabetes Complications study, finding that after 10 years, the prevalences of overweight and obesity increased by 42%, with overweight modestly protective but obesity associated with excess mortality.

Arslanian et al. (abstract 57-LB) compared insulin secretion and sensitivity of 23 adolescents with clinical type 2 diabetes with and without positive islet cell autoantibodies. All were aged 15–16 years with body fat 41–43%, A1C 6.4–6.7%, and diabetes duration 5–7 months. The eight who were antibody negative had insulin sensitivity 41% that of the seven with both GADA and IA-2 and had 2.2-fold greater first-phase C-peptide release, although β-cell function measured estimated from the disposition index was similar; the eight having just one positive autoantibody showed intermediate findings. Cai et al. (abstract 1184) studied 351 newly diagnosed adults with type 2 diabetes, without ketonuria or DKA, finding 12% islet cell antibody and 22% GADA positive, in association with lower first-phase insulin secretion on intravenous glucose tolerance testing. Vadacca et al. (abstract 1204) studied 501 adults with

type 2 diabetes, 62 of whom were GADA positive. Metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III criteria) was present in 54% of GADA-negative and 45% of GADA-positive men but in 80% of GADA-negative and 30% of GADA-positive women, with positive family history of diabetes in 65% of GADA-negative vs. 46% of GADA-positive women. Blood pressure and lipid treatment were required in 53 and 50% of GADA-negative females, respectively, but in 20 and 15% of GADA-positive females, further suggesting differences between persons with clinical type 2 diabetes with and without islet autoimmunity. Agardh et al. (abstract 1173) reported 2-year follow-up of 47 GADA-positive type 2 diabetic adults who had received recombinant GAD65 (Diamyd) at doses of 0, 4, 20, 100, or 500 μg. GADA increased transiently after the 500-μg dose, and those who received the 20-μg dose showed decreased A1C in association with increased fasting and stimulated C-peptide levels, suggesting a possible approach to modulation of the autoimmune response.

In analysis of types of childhood diabetes, Lipman et al. (abstract 934) reported a population-based survey of Philadelphia schools representing 252,896 children, which identified 492 school children with diabetes, of whom 355 had type 1 diabetes, 88 type 2 diabetes (25% treated with insulin), and 49 type unknown, for overall prevalences of type 1 and type 2 diabetes of 1.58 and 0.35 per 1,000, respectively. Vehik et al. (abstract 239), using data from the Colorado type 1 diabetes registry (1978–1988) and the SEARCH for Diabetes in Youth study (2002–2004), showed that the incidence of type 1 diabetes increased from 14.8 to 23.9 per 100,000/year from 1978–1988 to 2002–2004, with similar 2.5%/year increase among non-Hispanic white and 1.7%/year increase among Hispanic children. Oriordan et al. (abstract 955) studied 167 10- to 20-year-old children with cystic fibrosis, finding that 67% had normal glucose tolerance, 23% impaired glucose tolerance, and 10% diabetes, half of the latter triggered by glucocorticoid therapy.

Other aspects of the development of type 1 diabetes received attention at the ADA meeting. Achenbach et al. (abstract 275) characterized GADA affinity in 61 samples from children with median age 4.3 years, finding that the high-affinity antibodies found in 47 were associated with 34% progression to multiple positive antibodies, while none of the 14 with low-affinity GADA developed multiple positive antibodies. Fifteen of 16 who developed type 1 diabetes had high-affinity GADA. Gilliam et al. (abstract 1181) suggested that the autoimmune reactivity in type 1 diabetes is not β-cell specific, with pancreatic islet but not exocrine pancreas autopsy specimens from four type 1 diabetic versus six control persons showing markedly reduced tyrosine hydroxylase, a sympathetic nerve marker, suggesting that reduction in islet innervation may play a role in human type 1 diabetes, as these authors have shown in the islets of BB rats soon after diabetes onset (23).

Stene et al. (abstract 82) presented findings from the Diabetes Autoimmunity Study in the Young (DAISY) in analysis of 48 children who developed islet autoantibodies at a median age of 3.1 years, with follow-up at 3- to 6-month intervals for a mean of 4.9 years; 22 progressed to type 1 diabetes. Nine of the 199 serum specimens from progressors were PCR positive for enteroviral RNA, compared with 1 of 236 specimens from nonprogressors, suggesting that enteroviral infection may increase the rate of progression of genetically susceptible children to type 1 diabetes. Fingerlin et al. (abstract 83) presented further analysis from DAISY, showing three polymorphisms in the interleukin-4 receptor gene that were associated with increased risk of persistent islet autoimmunity in children introduced to cereal either before 4 months or after 6 months, or breast-fed for <3 months, suggesting another gene-environment interaction related to the development of type 1 diabetes. Lamb et al. (abstract 926) reported that of 1,543 DAISY children at risk for type 1 diabetes based on HLA genotype and family history, being large for gestational age was associated with a 71% reduction in risk for islet autoimmunity, while having increased height for age was associated with a 50% greater likelihood, suggesting a relationship of factors lined to body size with predisposition to type 1 diabetes.

Monroy et al. (abstract 948) evaluated the prevalence of serum GADA and tyrosine phosphatase IA-2 in 159 persons with type 1 diabetes screened for islet transplant, finding that of 12, 43, 53, and 51 with duration <10, 10–20, 20–30, and >30 years, respectively, GADAs were present in 33.35, 39.5, 32.1, and 17.6% and IA-2s in 41.7, 37.2, 37.7, and 29.4%. In a study of 99 persons with a 50-year history of type 1 diabetes, Keenan et al. (abstract 278) found that 23.2% were positive for either IA-2 or GADA, 13.1% for IA-2 and 14.1% for GADA, without relationship to clinical characteristics or to residual C-peptide production. Thus, large numbers of persons with type 1 diabetes remain antibody positive over time, although there may be some decline after 30 years.

CGM

A number of studies presented at the ADA meeting reviewed aspects of using commercial devices for CGM, which are now becoming more available. Zissler et al. (abstract 69) reported a study of type 1 diabetic persons comparing fingerstick capillary glucose testing versus CGM using the DexCom device, finding that 53% of insulin dose adjustments with the former but 71% with the latter approach led to glucose levels 3 h later being within the 80- to 200-mg/dl target range, leading the investigators to conclude that "real-time availability" of CGM improved glycemia without worsening hypoglycemia. Garg and Jovanovic (abstract 71) and Garg et al. (abstract 393) used this device for three 7-day periods in 86 insulin-treated patients. There was a 16% mean difference in comparison with 6,357 paired capillary glucose tests. The optimal measurement times distinguishing persons with higher versus lower A1C appeared to be from 4:00 to 7:00 A.M., which they termed the dawn phenomenon/fasting period, and 4:00 P.M. to midnight, a time reflecting evening hyperglycemia. Benefit was seen for both those with poor control and those with good control. Those with A1C >9% had a 95% increase in the time spent at 81–140 mg/dl, while those with A1C ≤7% had a 46% reduction in time spent at glucose <55 mg/dl.

Choudhary et al. (abstracts 387 and 388) and Dunseath et al. (abstract 390) compared venous and capillary glucose with CGM using the Medtronic MiniMed device, finding that during hypoglycemia, interstitial levels were higher than blood glucose levels, while postprandial interstitial levels were lower than simultaneous blood glucose levels, with levels similar in the fasting state. King et al. (abstract 397) discussed a model explaining this phenomenon based on the time lag in interstitial compartment glucose appearance after changes in circulating levels. Daenen (abstract 70) used this device in 99 insulin-treated persons, analyzing the

rates of increase and decrease in glucose following meals and showing that 80% of patients reached peak glucose value in <90 min after meals, with the mean time to peak 72 min. The current recommendation that postprandial glucose be measured 2 h after the start of the meal, then, likely leads to substantial underestimation of the peak glucose value in most patients treated with short-acting insulin analog boluses before meals. Broz and Andel (abstract 384) studied 40 type 1 diabetic persons using the device for 3 days, showing a reduction in symptomatic hypoglycemia episodes from 11 to 7 weekly during the subsequent 16 weeks, suggesting that this approach "enable[d] individuals to personalize their insulin regimen." Cassarella and Cagliero (abstract 386) explored the clinical use of this CGM device in 47 type 1 diabetic patients, 12 for frequent hypoglycemia, and 35 for improvement in glycemic control, with reduction in A1C from 8.7 to 8.4% in the latter group, and with a decrease in severe hypoglycemia from 16 episodes during the year before initiation of this approach to 7 episodes during the year with use of CGM. Newmark and White (abstract 403) studied seven type 1 diabetic children during a crossover trial of two 3-month periods with and without CGM using this device for 12 days per month, with A1C decreasing from 8.8% to 7.7% with CGM, while increasing from increasing from 8.1 to 8.4% during the control period.

In a DirectNet study, Kollman et al. (abstract 399) presented information from assessment of the Abbott Navigator CGM system in 22 type 1 diabetic children using the device during a 24-h in-hospital study. The median differences from laboratory glucose measurements during and not during an exercise session were 17 and 12%, respectively, primarily reflecting a slower rate of fall in interstitial than in blood glucose, similar to that described with the Medtronic MiniMed device, with a 5- to 30-min lag between the nadir CGM and reference glucose levels. Fox et al. (abstract 391), also from the DirectNet group, studied 30 children both during a 24-h study and on an outpatient basis, finding the median differences between interstitial and blood glucose were 13–14% during euglycemia and 10–12% during hyperglycemia, with stable precision during 5 days of use.

Two additional approaches are potentially applicable to improvement of glycemia. Ghevondian et al. (abstract 394) and Nguyen et al. (abstract 404) measured QTc and R-R intervals from the electrocardiogram and skin impedance using the AiMedics Ltd HypoMon device in 25 type 1 diabetic adolescents undergoing a 4-h hyperinsulinemic clamp with eu- and hypoglycemia. The pulse increased 14%, QTc increased 8%, and skin impedance decreased 24%, with a neural net program allowing hypoglycemia detection with sensitivity and specificity of 0.77 and 0.94, respectively, suggesting potential for noninvasive detection of hypoglycemia. Amir et al. (abstract 383) reported use of a noninvasive transcutaneous CGM device utilizing red near-infrared occlusion spectroscopy allowing glucose measurements every 10–15 min, showing a median relative absolute error of 10.4% with 95.8% of glucose measurements in the A and B zones of the Clarke error grid when compared with HemoCue reference readings.

Of course, before we recommend that all type 1 diabetic persons use the devices, cost-benefit analysis is required. The Dexcom STS System Starter Kit retails for $800, and a STS Sensor (5 pack) for $175 (24), while the MiniMed Paradigm REAL-Time System CGM Starter Kit costs $999 through the end of 2006 and will cost $1,399 subsequently (in addition to the cost of the insulin infusion pump), and a 10-pack of glucose sensors costs $350 (25), so that continuous testing with either device, both of which last up to 72 h, will cost $350 monthly, not an inconsiderable amount, and presently not reimbursed by health care insurance.

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