Early Hyperglycemia Detected by Continuous Glucose Monitoring in Children at Risk for Type 1 Diabetes

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OBJECTIVE
We explore continuous glucose monitoring (CGM) as a new approach to defining early hyperglycemia and diagnosing type 1 diabetes in children with positive islet autoantibodies (Ab+).

RESEARCH DESIGN AND METHODS
Fourteen Ab+ children, free of signs or symptoms of diabetes, and nine antibody-negative (Ab−) subjects, followed by the Diabetes Autoimmunity Study in the Young, were asked to wear a Dexcom SEVEN CGM.

RESULTS
The Ab+ subjects showed more hyperglycemia, with 18% time spent above 140 mg/dL, compared with 9% in Ab− subjects (P = 0.04). Their average maximum daytime glucose value was higher, and they had increased glycemic variability. The mean HbA1c in the Ab+ subjects was 5.5% (37 mmol/mol). Among Ab+ subjects, ≥18–20% CGM time spent above 140 mg/dL seems to predict progression to diabetes.

CONCLUSIONS
CGM can detect early hyperglycemia in Ab+ children who are at high risk for progression to diabetes. Proposed CGM predictors of progression to diabetes require further validation.

Prospective studies of subjects at high risk for type 1 diabetes have demonstrated a period of “dysglycemia” that precedes diagnosis of diabetes by months or years (1,2). The ability to reliably identify the dysglycemic period and implement early treatment may have important implications for preservation of endogenous insulin secretion and prevention of diabetes complications (3). The oral glucose tolerance test (OGTT) has a value in predicting progression to diabetes (4); unfortunately, OGTT results are highly variable during dysglycemia, and repeated OGTTs are poorly accepted by children. HbA1c is easier to measure but, as a single measurement, less sensitive than OGTTs (5).

In this exploratory study, we analyzed the feasibility and potential utility of continuous glucose monitoring (CGM) in high-risk individuals.

RESEARCH DESIGN AND METHODS
Study Population
Since 1993, the Diabetes Autoimmunity Study in the Young (DAISY) has followed two cohorts of young children at increased risk of type 1 diabetes. The details of screening and follow-up have been previously published (6). Since October 2011,
DAISY subjects with ≥2 positive antibodies (Ab+) were asked to wear a CGM device at their regular study visits every 3–6 months. Fourteen Ab+ children and nine antibody-negative (Ab−) subjects were included in this study, after excluding three Ab− subjects, as they did not have the minimum of 96 h of monitoring. Ab− subjects, either siblings or general population children of DAISY, were matched for age and sex and have never tested positive for islet autoantibodies. Informed consent and assent when applicable were obtained for each study subject. The Colorado Multiple Institutional Review Board approved all study protocols.

CGM
Subjects were asked to wear a Dexcom SEVEN Plus System (7) for 5–7 days. Participants were not able to see real-time CGM readings but were given a One-Touch Ultra (LifeScan Inc., Johnson and Johnson, Milpitas, CA) meter for blood glucose calibrations twice per day. For patient safety, the results were reviewed by a study physician at the end of monitoring. This pilot study presents the baseline CGM data, i.e., initial CGM data in Ab+ subjects. While longitudinal data collection is currently ongoing.

Statistical Analysis
Statistical analyses were performed using SAS software version 9.2. The first 12 h of CGM data were removed from the analyses since the accuracy of CGM data is often poor initially. If more than 20% of the data were missing on any given day, the data for that day were also excluded. Measures of glycemic control included HbA1c (DCA2000, Siemens, Bayer Corporation, Elkhart, IN), the overall mean of glucose values, percentage of values above 140 or 200 mg/dL, as well as area under the curve (AUC) of glucose calculated by the trapezoidal rule. Primary variables to characterize glycemic variability included glucose range, the overall SD, and the coefficient of variation (CV). A two-tailed P value with an α-level for significance was set at 0.05. We used Wilcoxon–Mann–Whitney tests to compare CGM statistics between groups. We calculated the individual means first and then compared the mean of the individual means between the groups. Additionally, we calculated the AUC of the receiver operating characteristic curve for association with the development of diabetes among Ab+ subjects.

RESULTS
The characteristics of study participants (age, sex, ethnicity, BMI z-score) were similar for Ab+ and Ab− subjects, except for slightly increased percentage of missing CGM data in Ab− subjects (13 vs. 9%). The mean age of the subjects was 13.7 years, and the mean HbA1c in the Ab+ subjects was 5.5% (range 3.2–6.3%);

Table 1—CGM measures of glycemic control and variability among Ab+ versus Ab− subjects and among Ab+ progressors versus Ab+ nonprogressors

| Variables                      | Ab+ subjects | Ab− subjects | P value | Ab+ progressors | Ab− nonprogressors | P value |
|-------------------------------|--------------|--------------|---------|----------------|--------------------|---------|
| Age, years                    | 13.8 ± 3.5   | 13.6 ± 2.0   | 0.88    | 11.7 ± 2.3     | 14.9 ± 3.6         | 0.08    |
| Mean glucose, mg/dL           | 117 ± 13     | 109 ± 11     | 0.07    | 125 ± 16       | 112 ± 8            | 0.19    |
| Mean day† glucose, mg/dL      | 119 ± 13     | 109 ± 11     | 0.06    | 129 ± 15       | 114 ± 8            | 0.06    |
| Mean night glucose, mg/dL     | 111 ± 16     | 111 ± 15     | 0.98    | 115 ± 22       | 109 ± 12           | 0.52    |
| Maximum day† glucose value, mg/dL | 221 ± 53     | 168 ± 31     | 0.011   | 241 ± 38       | 210 ± 58           | 0.44    |
| Maximum night glucose value, mg/dL | 173 ± 35     | 170 ± 44     | 0.57    | 185 ± 34       | 166 ± 36           | 0.36    |
| SD, mg/dL                     | 26 ± 8       | 19 ± 7       | 0.039   | 32 ± 7         | 23 ± 7             | 0.06    |
| CV, mg/dL                     | 22 ± 6       | 17 ± 5       | 0.046   | 26 ± 5         | 20 ± 6             | 0.15    |
| Range, mg/dL                  | 166 ± 53     | 111 ± 43     | 0.016   | 182 ± 37       | 157 ± 60           | 0.3     |
| % Time ≥140 mg/dL             | 0.18 ± 0.15  | 0.09 ± 0.09  | 0.04    | 0.31 ± 0.18    | 0.12 ± 0.07        | 0.04    |
| % Time ≥200 mg/dL             | 0.02 ± 0.03  | 0 ± 0.01     | 0.075   | 0.03 ± 0.04    | 0.01 ± 0.01        | 0.06    |
| AUC, mg/min/dL                | 676,196 ± 72,197 | 627,443 ± 64,823 | 0.16 | 725,629 ± 91,052 | 648,733 ± 44,149 | 0.15 |
| AUC† day, ‡ mg/min/dL          | 514,433 ± 54,758 | 466,436 ± 48,577 | 0.06   | 561,040 ± 61,792 | 488,540 ± 29,180 | 0.02    |
| AUC† night, ‡ mg/min/dL        | 160,977 ± 22,912 | 158,913 ± 22,308 | 0.60 | 164,180 ± 32,128 | 159,198 ± 18,082 | 0.52    |
| HbA1c, % (mmol/mol)           | 5.5 ± 0.8   | 37 ± 8.7    | NA      | 5.9 ± 0.3 (41 ± 3.3) | 5.3 ± 0.9 (34 ± 9.8) | 0.16    |

Values are mean ± SD. NA, HbA1c not done in Ab− subjects. †Day values are between 6:00 A.M. and midnight. ‡AUC calculated by the trapezoidal rule.

Baseline CGM variables are summarized in Table 1 for both Ab+ versus Ab− subjects and Ab+ progressors versus Ab+ nonprogressors. The Ab+ subjects showed more impaired glycemia, with percent time spent above 140 mg/dL of 18% compared with 9% in Ab− subjects (P = 0.04). The range of sensor values was wider, and the maximum daytime glucose value was higher (221 vs. 168 mg/dL; P = 0.011) in Ab+ versus Ab− subjects. Ab+ subjects had increased glycemic variability with both larger SD and larger CV. AUC during daytime was greater in Ab+ subjects. Similarly, the Ab+ progressors showed more impaired glycemia, with percentage of time spent above 140 mg/dL of 31% compared with 12% in Ab+ nonprogressors (P = 0.04). Progressors also had larger SD and greater AUC during daytime. Although mean HbA1c was higher among progressors than nonprogressors (5.9 vs. 5.3% [41 vs. 34 mmol/mol], respectively), this was not statistically significant (P = 0.16). When analyzing only 24 h of CGM data, we found similar results (data not shown). While the results were similar, this study was not powered to formally compare the validity of 24 vs. 96 h.
Among Ab+ subjects, the AUC of the receiver operating characteristic curve for association with the development of diabetes was 0.84 (95% CI 0.60–1.00). For 18% of the time spent above 140 mg/dL, the sensitivity was 80%, with a specificity of 78%, while for 20% of the time spent above 140 mg/dL, the sensitivity was 60%, with a specificity of 89%.

Supplementary Fig. 1 describes the evolution of the CGM pattern with available HbA1c and OGTT results for one of the Ab+ subjects who progressed to diabetes.

CONCLUSIONS
To our knowledge, this is the first study to perform CGM in a group of subjects at high risk of developing type 1 diabetes. Children with ≥2 Ab+ have a 70% risk for developing diabetes in 10 years following appearance of autoantibodies (8); however, the individual course is highly unpredictable.

Despite nondiabetic HbA1c, the Ab+ subjects had significantly increased glycemic variability and spent more time with glucose above 140 mg/dL than Ab− subjects. The percentage of time above 140 mg/dL in Ab− subjects (9%) was higher than previously reported in 74 healthy, nondiabetic individuals (0.4%) (9), likely due to the fact that these DAISY subjects are at increased genetic risk for diabetes.

We have previously reported that DAISY participants with persistent islet autoimmunity experience steadily increasing HbA1c, within the normal range, during several years preceding diabetes (2). On the other hand, a combined analysis of 1,982 high-risk subjects younger than 21 years of age found that a single value of HbA1c >6.5% was highly specific for diabetes, but the sensitivity to detect impaired glucose tolerance was rather low across the studies (8–42%) (5). In this context, the CGM approach shows potential promise as a minimally invasive and nearly instantaneous way to identify subjects with mild hyperglycemia and diagnose diabetes.

Although our numbers are small, the percentage of time spent >140 mg/dL seems to be predictive of diabetes. The proposed threshold could possibly be modified by age and other factors. The higher prediction of the AUC glucose during the day than the AUC glucose during the night suggests that postprandial glucose levels are predictive. However, this pilot study is too small to determine which CGM variable would be best in predicting development of type 1 diabetes. Further prospective data may help with earlier diagnosis of diabetes and/or more accurate staging of diabetes since intermediate end points will be useful in the future design of type 1 diabetes prevention clinical trials (10).

Mild hyperglycemia can be detected by CGM and may help with earlier diagnosis of diabetes. Confirmation in larger prospective studies is needed to define CGM criteria useful for type 1 diabetes prediction and diagnosis.

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References
1. Mahon JL, Sosenko JM, Rafkin-Merivis L, et al.; TrialNet Natural History Committee; Type 1 Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. Pediatr Diabetes 2009;10:97–104
2. Stene LC, Barriga K, Hoffman M, et al. Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). Pediatr Diabetes 2006;7:247–253
3. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–836
4. Sosenko JM, Palmer JP, Greenbaum CJ, et al.; Diabetes Prevention Trial-Type1 Study Group. Increasing the accuracy of oral glucose tolerance testing and extending its application to individuals with normal glucose tolerance for the prediction of type 1 diabetes: the Diabetes Prevention Trial-Type1. Diabetes Care 2007;30:38–42
5. Vehik K, Cuthbertson D, Boulware D, et al.; TEDDY, TRIGR, Diabetes Prevention Trial-Type1, and Type 1 Diabetes TrialNet Natural History Study Groups. Performance of HbA1c as an early diagnostic indicator of type 1 diabetes in children and youth. Diabetes Care 2012;35:1821–1825
6. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers associated with IDDM: Diabetes Autoimmunity Study in the Young (DAISY). Diabetologia 1996;39:807–812
7. Garg SK, Smith J, Beatson C, Lopez-Baca B, Voelml M, Gottlieb PA. Comparison of accuracy and safety of the SEVEN and the Navigator continuous glucose monitoring systems. Diabet Technol Ther 2009;11:65–72
8. Ziegler AG, Rewers M, Simell O, et al. Serocconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
9. Fox LA, Beck RW, Xing D; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. Diabetes Care 2010;33:1297–1299
10. Krischer JP; Type 1 Diabetes TrialNet Study Group. The use of intermediate endpoints in the design of type 1 diabetes prevention trials. Diabetologia 2013;56:1919–1924