Diabetes Care

American Diabetes Association

CGM Metrics Identify Dysglycemic States in Participants From the TrialNet Pathway to Prevention Study

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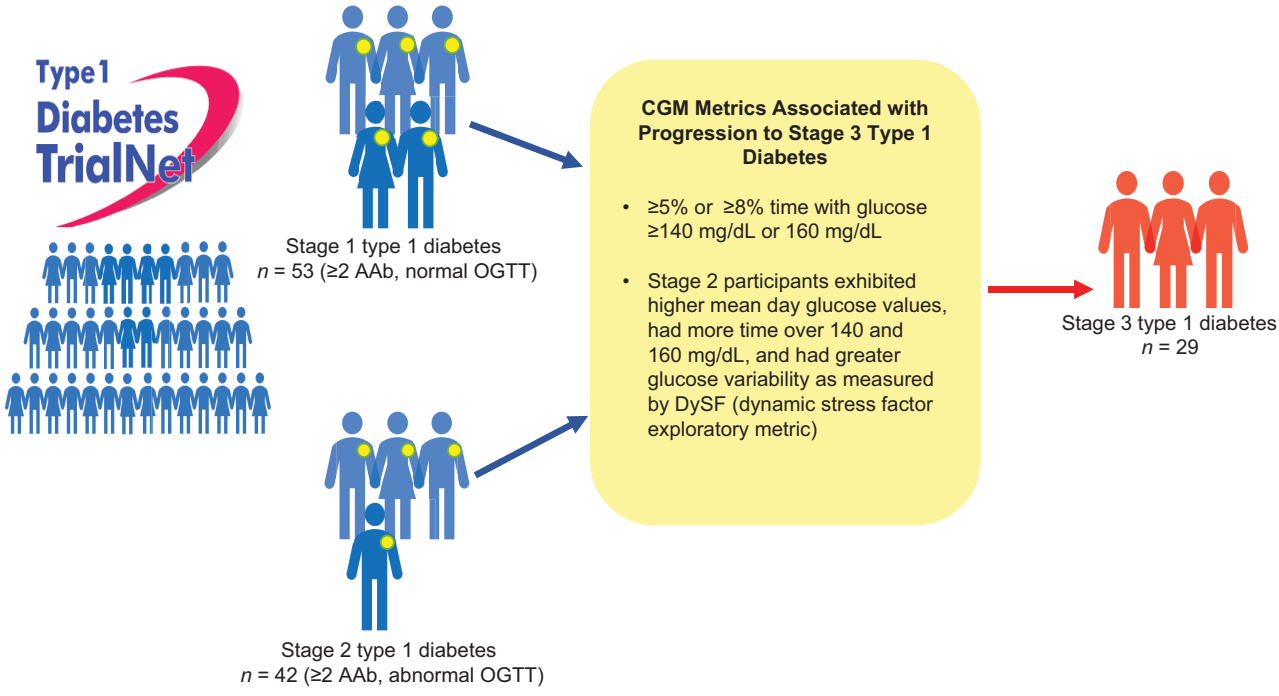
Diabetes Care 2023;46(3):526–534 | https://doi.org/10.2337/dc22-1297



Abbreviations: Autoantibodies (AAb); Oral Glucose Tolerance Test (OGTT)

ARTICLE HIGHLIGHTS

- We aimed to determine whether CGM metrics provide additional insights into progression to clinical stage 3 type 1 diabetes.
- We asked if the percent time above various glucose thresholds identifies first-degree relatives likely to progress to clinical stage 3 type 1 diabetes.
- We found that stage 2 participants, and those who progressed to stage 3, exhibited higher mean daytime glucose values; spent more time with glucose values over 120, 140, and 160 mg/dL; and had greater glucose variability.
- CGM findings may improve current understanding of dysglycemia preceding clinical stage 3 type 1 diabetes onset, possibly influencing decision-making for future prevention trials.

ORIGINAL ARTICLE

CGM Metrics Identify Dysglycemic States in Participants From the TrialNet Pathway to Prevention Study

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OBJECTIVE

Continuous glucose monitoring (CGM) parameters may identify individuals at risk for progression to overt type 1 diabetes. We aimed to determine whether CGM metrics provide additional insights into progression to clinical stage 3 type 1 diabetes.

RESEARCH DESIGN AND METHODS

One hundred five relatives of individuals in type 1 diabetes probands (median age 16.8 years; 89% non-Hispanic White; 43.8% female) from the TrialNet Pathway to Prevention study underwent 7-day CGM assessments and oral glucose tolerance tests (OGTTs) at 6-month intervals. The baseline data are reported here. Three groups were evaluated: individuals with *1*) stage 2 type 1 diabetes (*n* = 42) with two or more diabetes-related autoantibodies and abnormal OGTT; *2*) stage 1 type 1 diabetes (*n* = 53) with two or more diabetes-related autoantibodies and normal OGTT; and *3*) negative test for all diabetes-related autoantibodies and normal OGTT (*n* = 10).

RESULTS

Multiple CGM metrics were associated with progression to stage 3 type 1 diabetes. Specifically, spending ≥5% time with glucose levels ≥140 mg/dL (*P* = 0.01), ≥8% time with glucose levels ≥140 mg/dL (*P* = 0.02), ≥5% time with glucose levels ≥160 mg/dL (*P* = 0.0001), and ≥8% time with glucose levels ≥160 mg/dL (*P* = 0.02) were all associated with progression to stage 3 disease. Stage 2 participants and those who progressed to stage 3 also exhibited higher mean daytime glucose values; spent more time with glucose values over 120, 140, and 160 mg/dL; and had greater variability.

CONCLUSIONS

CGM could aid in the identification of individuals, including those with a normal OGTT, who are likely to rapidly progress to stage 3 type 1 diabetes.

Continuous glucose monitoring (CGM) is an important tool for type 1 diabetes management (1–3). While efforts to decipher the contributions of immunologic and metabolic abnormalities in type 1 diabetes progression have consistently remained strong, more attention has recently been given to understanding the role of dysglycemia and CGM metrics during the natural history of type 1 diabetes. The potential to integrate CGM data into models that better stage and predict disease

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Received 30 June 2022 and accepted 28 November 2022

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This article contains supplementary material online at https://doi.org/10.2337/figshare.21667085.

**A complete list of the members of the Type 1 Diabetes TrialNet Study Group can be found in the supplementary material online.*

progression in at-risk individuals (4,5) has been driven, in part, by studies directed toward understanding the dynamic development of dysglycemia captured from CGM-based metrics measured during stages of preclinical type 1 diabetes (6–8). The presence of two or more type 1 diabetes-associated islet autoantibodies is highly predictive of the eventual development of clinical disease and now serves as the basis for defining stage 1 type 1 diabetes (9–12). The addition of dysglycemia, diagnosed by oral glucose tolerance tests (OGTT), defines stage 2 type 1 diabetes and provides functional evidence for deteriorating insulin secretion and glucose regulation as the disease progresses to clinical type 1 diabetes (stage 3) (13).

The concept of type 1 diabetes stages has facilitated the design of prevention trials whereby OGTT is used as an entry or outcome criterion. Staging has also proven crucial for explaining the concepts of risk and disease progression to regulators, health care professionals, and people at risk for type 1 diabetes. However, it has long been recognized that OGTT-defined categories have limitations (14), particularly for identifying the transition from stage 2 to stage 3 disease, where the OGTT results frequently vary between impaired glucose levels and those results that meet diagnostic thresholds for stage 3 disease on repeated testing.

To date, limited data from pilot studies suggest that CGM metrics can improve the prediction of type 1 diabetes progression in autoantibody-positive participants with normal OGTT (8,15). In the Autoimmunity Screening for Kids (ASK) study, various CGM metrics, both individual and combined CGM variables, predict progression to stage 3 disease within 12 months in children with islet autoantibodies (15). To the best of our knowledge, an integrated approach providing a comprehensive and accurate assessment of glycemic excursions during the preclinical state of type 1 diabetes has not yet been applied to the TrialNet population. Therefore, the main objective of this study was to determine whether various CGM metrics, particularly the percent time above various thresholds, obtained from the baseline CGM data can maximize the identification of first-degree relatives who are likely to progress to the clinical onset of type 1 diabetes. In addition to comparing those participants who progressed to stage 3 type 1 diabetes, we compared participants in stage 1 with those in stage 2 type 1 diabetes. Early identification of high-risk individuals may prevent acute complications at clinical diagnosis (like diabetic ketoacidosis) and aid in the selection of participants for clinical trials of potential therapies to preserve endogenous insulin secretion and delay the onset of stage 3 type 1 diabetes.

RESEARCH DESIGN AND METHODS

Participant Population

We enrolled a total of 105 participants (median age 16.8 years; 89% non-Hispanic White; 43.8% female) from the NIH TrialNet Pathway to Prevention (PTP) study TN01 (16) in the TrialNet-approved TN01-CGM Metrics and Dysglycemia ancillary study. All participants had a first- or second-degree relative with type 1 diabetes. Three groups of relatives were evaluated based on the following eligibility criteria performed within 1 year of enrollment: individuals with *1*) two or more islet autoantibodies and normal glucose tolerance (stage 1, $n = 53$); *2*) two or more islet autoantibodies and abnormal glucose tolerance (stage 2, $n = 42$); and *3*) confirmed negative islet autoantibody tests and normal OGTT (low risk, $n = 10$) (9). Abnormal glucose tolerance was defined as fasting plasma glucose levels $\geq$110 mg/dL and $<$126 mg/dL, 2-h plasma glucose levels $\geq$140 mg/dL and $<$200 mg/dL, or 30-, 60-, and 90-min plasma glucose levels during OGTT of $\geq$140 mg/dL and $<$200 mg/dL (11). Participants did not undergo a confirmatory OGTT prior to staging or CGM placement. Asymptomatic individuals with two consecutive, diabetic OGTTs within 1 year of follow-up testing were excluded from the CGM study. Individuals who were pregnant, lactating, or currently enrolled in a type 1 diabetes prevention trial were also excluded from enrolling in the study.

OGTT and autoantibody data were obtained from each participant's most recent TrialNet PTP visit (within 1 year of enrollment in this CGM study). In accordance with the institutional review board-approved protocol across all participating sites, participants were consented/assented to undergo up to three CGM assessment periods, $\sim$6 months apart, coincident with their TrialNet PTP-TN01 study visits. Data from baseline (visit 1) are analyzed in this report. Each participant and/or their legal guardian provided informed consent and assent at each respective TrialNet enrollment site where the study was performed. American Diabetes Association criteria (13) were used to diagnose stage 3 type 1 diabetes, and the diagnosis was confirmed during the participant's regular PTP-TN01 follow-up. This investigation was an ancillary study of the TrialNet Patway to Prevention of T1D monitoring phase, clinical trial reg. no. NCT00097292.

CGM

Study participants had no acute illnesses at the time of CGM placement. During the study period of 2015–2018, these individuals agreed to wear the Dexcom G4 Platinum CGM system (Dexcom, San Diego, CA) for up to 7 days while continuing their daily routines. Participants were blinded to their glucose readings while wearing the sensor. They were provided with a home glucometer (Contour Next EZ; Ascensia Diabetes Care, Parsippany-Troy Hills, NJ) for required calibrations. While wearing the Dexcom G4 sensor, participants were instructed to forgo acetaminophen ingestion due to known interference with sensor glucose readings, resulting in erroneously elevated interstitial glucose values (17). The first 12 h of CGM readings were excluded from the analysis, given that issues with less accurate measures are known to occur on the day of the CGM placement with the devices used. Additionally, the data were truncated at 6:00 A.M. on the morning of the OGTT, as previously reported (18). If missing $>$20% of data on any given day, the remaining data for that day were excluded. At least 4 full days (96 h) of evaluable CGM data were required for analysis. We analyzed the data at time of eligibility and baseline (visit 1) CGM data for this report.

To quantify glucose variability, SD, coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE) (19), mean of daily differences (MODD) (20), dynamic stress factor (DySF) (used as an exploratory metric) (21), and continuous overall net glycemic action (CONGA) were used (22). MAGE is commonly used to gauge the degree of glucose level fluctuations (23). DySF quantifies glucose volatility by considering the speed and magnitude of glycemic excursions between clinically defined states. DySF can pick up variations in the data due to its ability to track significant changes

in glucose levels over the course of hours and is not limited to averages over longer time periods that are seen in the other metrics. DySF employs the transition density profile from CGM-GUIDE (24), which analyzes glucose excursions and transitions across different glycemic ranges to predict the likelihood of onset of severe hypoglycemic episodes in patients with type 1 diabetes. Based on continuous glucose dynamics, DySF represents a measure of a patient's daily glucose volatility. CONGA assesses glucose variability within a predetermined time window; calculation of this parameter is based on assessment of the differences between glucose values measured at regular time intervals and then on the SD of these differences (22). Daytime was defined as 6:00 A.M. to midnight for the analysis.

Islet Autoantibodies

Islet autoantibodies were measured by the TrialNet PTP core laboratories at the University of Colorado Barbara Davis Center for Diabetes in Aurora, CO, and the University of Florida Diabetes Institute in Gainesville, FL. Autoantibodies specific for insulin, glutamic acid decarboxylase (GAD65), insulinoma-associated protein 2 (IA-2), and zinc transporter 8 (ZnT8) were assessed by standardized radioimmunoassay (25). Islet cell autoantibodies were measured by indirect immunofluorescence using human blood group O pancreas (26).

OGTT and HbA_{1c}

The OGTT and hemoglobin A_{1c} (HbA_{1c}) analyses were performed as part of PTP scheduled monitoring, with one exception: autoantibody-negative participants had a 6-month visit added to their annual monitoring schedule. The window around this target was -2 to $+2$ days (i.e., days 5–9). If the OGTT was unable to occur while the participant was wearing the CGM, these procedures were performed separately as long as both occurred within the target window of every 6 months ±6 weeks.

Statistical Analysis

Data were analyzed using GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA) and SPSS 23.0 (SPSS, Chicago, IL). Life table analysis was applied to estimate the cumulative risk of developing type 1 diabetes with data censored according to the length of follow-up. Kaplan-Meier curves were compared using the log-rank test. Results confirmed the highly satisfactory performance of the exact procedure conditioning on realized follow-up, particularly in the case of unequal follow-up. Categorical data were compared using χ^2 or Fisher's exact tests. Student's *t* tests were used to compare CGM metrics between two groups and one-way ANOVA for comparisons across all three groups. Since age was not normally distributed, results are expressed as median and interquartile range (IQR). The ages in the three risk groups were compared using Kruskal-Wallis test for nonnormal distributed data. The ages of the progressors versus nonprogressors were compared using the Mann-Whitney *U* test for nonnormally distributed data. Bonferroni correction was not used, as the conclusions of this study were not based on either a false-positive contingency or the data from the low-risk group. Individual means for a given CGM metric were calculated using all evaluable data for the participant over the entire collection period and were then compared between the groups. *P* values <0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves (27,28), using continuous data, were generated to compare the area under the curve of percent time over the threshold values of 140 and 160 mg/dL interstitial glucose for type 1 diabetes prediction. The ROC curves were created by plotting the true-positive rate (sensitivity) against the false-positive rate (1 − specificity) for both threshold settings. Sensitivity, specificity, positive predictive value, and negative predictive value for diabetes prediction were calculated for the optimal CGM metric cutoffs. We used the R package stats to compare the predictive effect of the variables of percent time CGM $\geq$140 mg/dL and percent time CGM $\geq$160 mg/dL and to distinguish diabetes progressors from nonprogressors using logistic regression models accounting for sex, number of islet autoantibodies, first-degree-relative status (FDR), and age at sampling. The data set analyzed during the current study is available from the corresponding author upon reasonable request. Longitudinal analysis of 6- and 12-month data will be presented in a subsequent publication.

RESULTS

Table 1 shows demographic characteristics and baseline CGM data from 105 participants who were followed as part of the TrialNet PTP study for a median (IQR) time of 31.7 (24.1–36.4) (autoantibody-negative participants), 35.7 (23.9–53) (stage 1 participants), and 28.3 (15.9–39.3) (stage 2 participants) months. There were no significant differences in age, reported race, sex, or BMI across the three study groups.

Compared with the low-risk participants, individuals with stage 1 and stage 2 type 1 diabetes exhibited higher mean glucose levels (particularly during daytime hours) and had greater percent time over the threshold values of 120, 140, and 160 mg/dL (Table 1, Fig. 1*A*–*E*). HbA_{1c} values were slightly elevated and statistically significant compared with those of the low-risk group; however, the statistical significance was not as great between groups with increased disease risk (Table 1, Fig. 1*F*). Glucose variability, as measured by DySF, was significantly higher in the stage 2 group compared with stage 1 participants (2.5 vs. 3.8; $P = 0.01$) (Table 1, Fig. 1*G*).

During follow-up, 29 (30.5%) of the multiple islet autoantibody-positive participants progressed to clinical type 1 diabetes (stage 3) in a median time of 18.1 (8.6–31.2) months and at a median age of 12 (8.6–16) years. Race and BMI were similar between islet autoantibody-positive participants who progressed to diabetes and those who did not progress to the disease. Those who progressed to type 1 diabetes were younger ($P = 0.002$) and more likely to be male ($P = 0.04$) (Table 1). Baseline HbA_{1c} was significantly higher in progressors than in nonprogressors (5.3% vs. 5.1%, respectively; $P = 0.008$) (Table 1, Fig. 2*B*). Progressors also exhibited higher mean daytime glucose levels and had greater percent time over the threshold values of 120, 140, and 160 mg/dL as well as a significantly higher glycemic variability (mean SD 22 vs. 19.2 mg/dL; CONGA 21.2 vs. 18.5; DySF 4 vs. 2.6; MAGE 44.3 vs. 38.4; and MODD 21.7 vs. 18.5) (Table 1, Fig. 2*C*–*I*). The number and distribution of specific islet autoantibodies among the autoantibody-positive participants who did and did not progress are shown in Supplementary Table 1.

Table 1—Demographic data and CGM measures of interstitial glucose control and variability

Variables	Low risk (n = 10)	Stage 1 (n = 53)	Stage 2 (n = 42)	P value	≥2 AAb$^+$ nonprogressors (n = 66)	≥2 AAb$^+$ progressors (n = 29)	P value
Demographics							
Age, years (median [IQR])	16.3 (15.1–18)	17.2 (11.7–36.4)	15.5 (11.6–37.5)	0.93	21.1 (14.4–42)	12 (8.6–16)	**0.0003**
Sex (male, n [%])	3 (30)	25 (47.2)	18 (42.9)	0.59	25 (37.9)	18 (62.1)	**0.04**
Race (White, n [%])	9/10 (90)	50/50 (100)	39/40 (97.5)	0.38	62/62 (100)	27/28 (96.4)	0.31
Mean BMI z score	−0.01 ± 1.0	0.00 ± 0.99	−0.16 ± 0.36	0.65	−0.11 ± 0.42	0.00 ± 1.0	0.45
Progressors (n [%])	0 (0)	11 (20.8)	18 (44.4)	**0.03**		29	NA
Time to Dx/last contact, months (median [IQR])	31.7 (24.1–36.4)	35.7 (23.9–54)	28.3 (15.9–39.3)	**0.03**	38.9 (27.1–54.3)	18.1 (8.6–31.2)	**0.0001**
HbA_{1c}, %	5.0 ± 0.3	5.1 ± 0.3	5.3 ± 0.3	**0.006**	5.1 ± 0.3	5.3 ± 0.4	**0.008**
No. of days of CGM data (mean [range])	5.0 (4–6)	5.5 (4–6)	5.2 (4–6)	0.20	5.4 (4–6)	5.4 (4–6)	0.93
CGM metrics							
Mean glucose, mg/dL	93.9 ± 6.5	99.3 ± 7.8	102.8 ± 11.8	**0.02**	99.8 ± 9.2	103.1 ± 11.1	0.13
SD, mg/dL	18.4 ± 6.4	19.3 ± 6.9	21.0 ± 5.8	0.33	19.2 ± 6.7	22.0 ± 5.4	**0.05**
CV, mg/dL	19.6 ± 6.7	19.4 ± 6.4	20.3 ± 4.3	0.77	19.2 ± 6.0	21.2 ± 4.2	0.11
Maximum CGM glucose, mg/dL	165.8 ± 36.0	179.6 ± 47.9	183.7 ± 32.8	0.47	179.1 ± 44.5	186.8 ± 34.8	0.41
Minimum CGM glucose, mg/dL	45.4 ± 14.6	54.5 ± 12.2	57.0 ± 12.3	**0.03**	56.6 ± 11.2	53.4 ± 14.3	0.24
Mean glucose range, mg/dL	120.4 ± 43.1	125.2 ± 52.9	126.7 ± 33.0	0.92	122.5 ± 48.8	133.4 ± 34.3	0.28
% Time CGM ≥120 mg/dL	9.4 ± 7.4	14.4 ± 9.4	20.8 ± 15.6	**0.008**	15.3 ± 11.7	21.7 ± 14.3	**0.02**
% Time CGM ≥140 mg/dL	2.4 ± 3.3	3.8 ± 3.7	8.1 ± 8.8	**0.002**	4.7 ± 6.0	8.0 ± 8.0	**0.03**
% Time CGM ≥160 mg/dL	0.6 ± 1.2	1.0 ± 1.8	3.0 ± 4.4	**0.004**	1.4 ± 3.1	3.1 ± 3.6	**0.02**
CONGA	18.2 ± 6.6	18.5 ± 5.5	20.5 ± 4.9	0.17	18.5 ± 5.4	21.2 ± 4.7	**0.02**
DySF	2.8 ± 2.4	2.5 ± 2.0	3.8 ± 2.8	**0.04**	2.6 ± 2.1	4.0 ± 3.0	**0.01**
MAGE	35.5 ± 10.7	38.9 ± 15.1	41.6 ± 10.3	0.35	38.4 ± 14.0	44.3 ± 9.9	**0.04**
MODD	18.2 ± 6.2	18.5 ± 6.1	20.6 ± 5.8	0.19	18.5 ± 6.0	21.7 ± 5.3	**0.02**
Daytime CGM metrics†							
Mean daytime glucose, mg/dL	94.6 ± 4.8	99.3 ± 7.3	103.5 ± 11.5	**0.01**	99.8 ± 8.8	104.0 ± 10.8	**0.04**
Maximum daytime glucose value, mg/dL	165.1 ± 36.5	171.9 ± 37.3	181.7 ± 32.4	0.26	171.8 ± 34.9	186.2 ± 35.0	0.06
Overnight CGM metrics							
Mean night glucose, mg/dL	91.9 ± 12.4	99.3 ± 13.0	100.9 ± 14.4	0.18	99.7 ± 13.1	100.7 ± 14.9	0.74
Maximum night glucose value, mg/dL	136.6 ± 20.3	155.5 ± 47.8	152.2 ± 32.6	0.40	155.1 ± 46.2	151.8 ± 29.0	0.72

Unless otherwise noted, values are the mean ± SD (continuous variables). P values in boldface are statistically significant. AAb$^+$, autoantibody positive; CV, coefficient of variation; Dx, diagnosis; NA, not applicable. †Values between 6:00 A.M. and midnight.

The baseline characteristics and CGM measurements of glycemic control and variability of the 29 participants who progressed to type 1 diabetes from stages 1 and 2 are summarized in Supplementary Table 2. Age, sex, race, and BMI were similar between progressors from the stage 1 group and progressors from the stage 2 group. Baseline HbA_{1c} was higher in the progressors from stage 2 (5.4% vs. 5.1%), but this difference was not statistically significant (P = 0.06). Compared with stage 1 progressors, participants who developed type 1 diabetes among the stage 2 participants had significantly increased glycemic variability measured by MODD (19.3 vs. 23.2; P = 0.05). Progressors from stage 2 spent 10.4% of the time ≥140 mg/dL and 4.2% of the time ≥160 mg/dL compared with 4% and 0.8%, respectively, for progressors from the stage 1 group (P = 0.03 and P = 0.01) (Supplementary Table 2).

Using Kaplan-Meier analysis, we observed that spending ≥5% and ≥8% of the time with interstitial glucose ≥140 mg/dL and ≥160 mg/dL was a good predictor of progression to stage 3 type 1 diabetes (Fig. 3). The risk of progression to type 1 diabetes in 2 years since the baseline CGM was 40% in those relatives who spent ≥5% of the time at ≥140 mg/dL. In contrast, only 6.5% of the participants who spent less than 5% of the time at ≥140 mg/dL developed the disease (P = 0.01) (Fig. 3*A*). Similarly, the risk of progression to stage 3 by 2 years was 62% vs. 40% in participants who spent ≥5% of the time at ≥160 mg/dL vs. those who spent <5% at ≥160 mg/dL ($P \leq 0.001$) (Fig. 3*C*).

In addition, ROC curves evaluating baseline data for the percentage of time spent at ≥140 mg/dL and ≥160 mg/dL supported the use of 5% and 8% as cutoffs without a significant loss of specificity (80–100%). The cutoffs of 5% and 8% of time spent at ≥140 mg/dL had 80% specificity and 48% sensitivity and 90% specificity and 38% sensitivity, respectively, for diabetes prediction. The cutoffs of 5% and 8% of the time spent at ≥160 mg/dL had 100% specificity and 28% sensitivity and 100% specificity and 14% sensitivity, respectively, for diabetes prediction (Supplementary Fig. 1 and Supplementary Tables 3 and 4).

Logistic regression models including age, sex, FDR, and number of islet autoantibodies indicated that the percentage of time spent at CGM ≥140 mg/dL is a significant predictor of progression to stage 3 type 1 diabetes. Over the entire population, the Akaike information criterion (AIC) scoring values of the logistic regression model that used the percentage of time at CGM ≥140 mg/dL (i.e., AIC = 106.34) and one that used percentage of time at CGM ≥160 mg/dL (i.e., AIC = 109.04) showed that the former cutoff is better (see details in Supplementary Table 5) (29). Thus, according to this model, the percentage of time spent at CGM ≥140 mg/dL appears to be a good predictor when

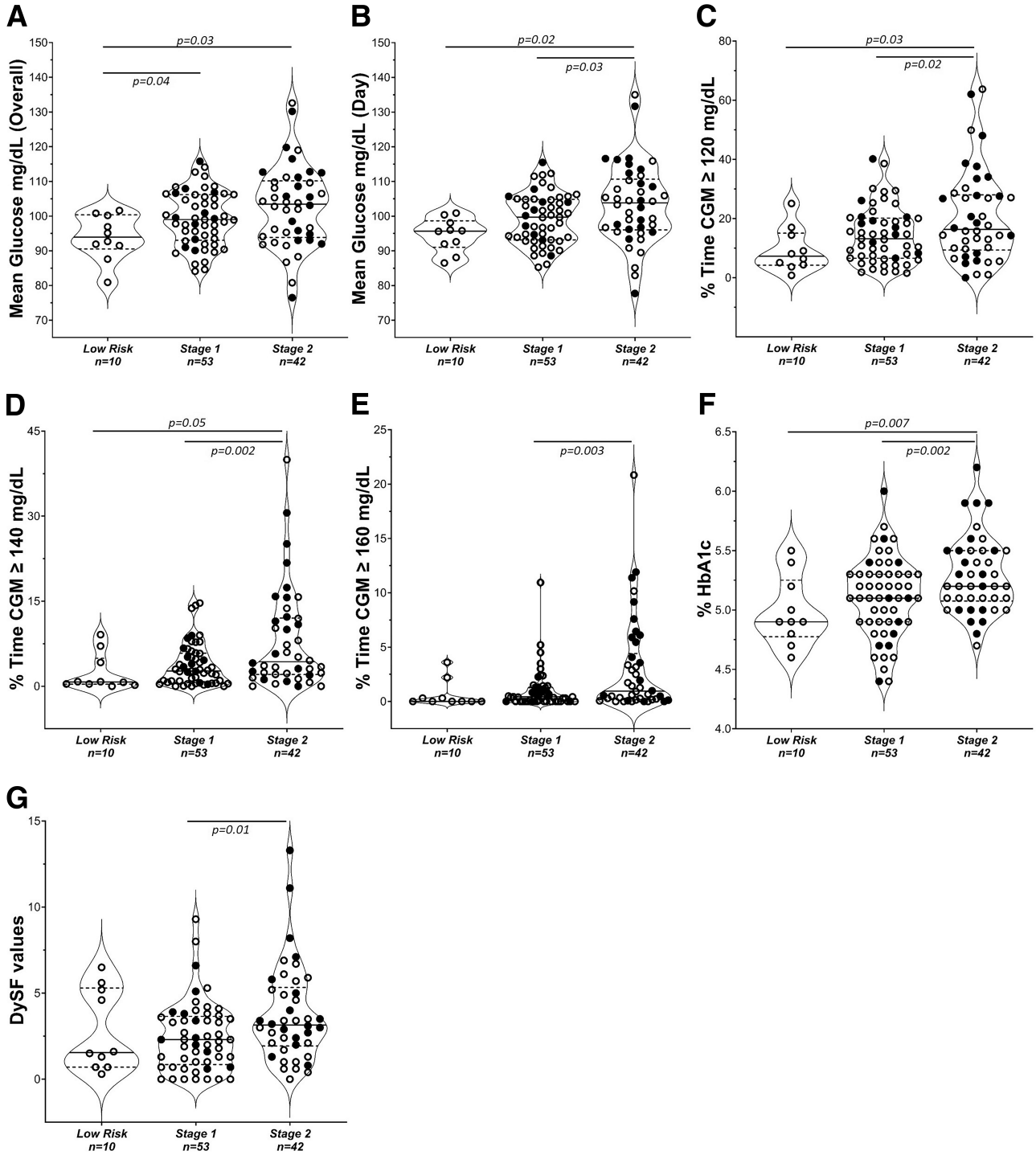

Figure 1—Dot plot violin charts for HbA_{1c} and various CGM metrics between low-risk, stage 1, and stage 2 participants. *A*: Mean overall glucose level; *B*: mean daytime (values between 6:00 A.M. and midnight) glucose level; *C*: time spent ≥120 mg/dL (%); *D*: time spent ≥140 mg/dL (%); *E*: time spent ≥160 mg/dL (%); *F*: HbA_{1c} (%); *G*: DySF (○, nonprogressors; ●, progressors).

other factors, such as age, sex, FDR, and the number of islet autoantibodies, are considered jointly in a prediction model.

CONCLUSIONS

In the current study, we show that the presence of dysglycemia, as identified by CGM metrics, may identify those with a heightened risk of progression to stage 3 type 1 diabetes (Fig. 3). In particular, we found that the percent time ≥140 mg/dL is associated with higher risk of progression in islet autoantibody-positive relatives of type 1 diabetes patients, confirming earlier studies in smaller groups. We have also shown what we believe is a novel finding in that antibody-positive individuals with stage 2 type 1 diabetes have higher values on many CGM metrics than those in stage 3.

The staging of type 1 diabetes has facilitated the design of prevention trials whereby OGTT criteria are used as entry

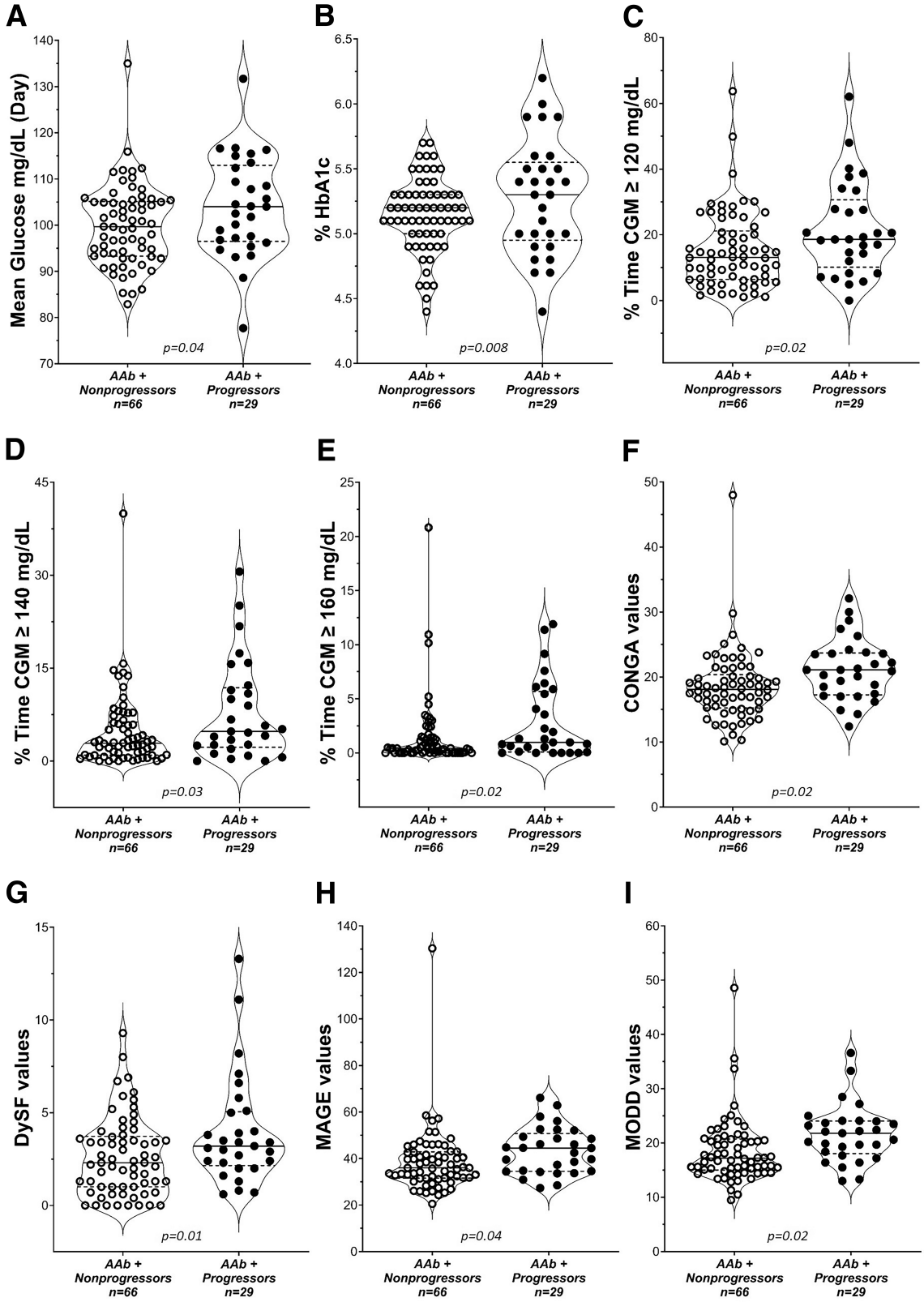

Figure 2—Dot plot violin charts for HbA_{1c} and various CGM metrics between autoantibody-positive (AAb +) progressors and islet antibody-positive nonprogressors. *A*: Mean daytime (values between 6:00 A.M. and midnight) glucose level; *B*: HbA_{1c} (%); *C*: time spent ≥120 mg/dL (%); *D*: time spent ≥140 mg/dL (%); *E*: time spent ≥160 mg/dL (%); *F*: CONGA; *G*: DySF; *H*: MAGE; and *I*: MODD (○, nonprogressors; ●, progressors). Note that the results seen with DySF may appear opposite those of the other metrics, but this is due to its ability to measure volatility. While some outliers may be seen, the averages for all the patients are in line with the other metrics.

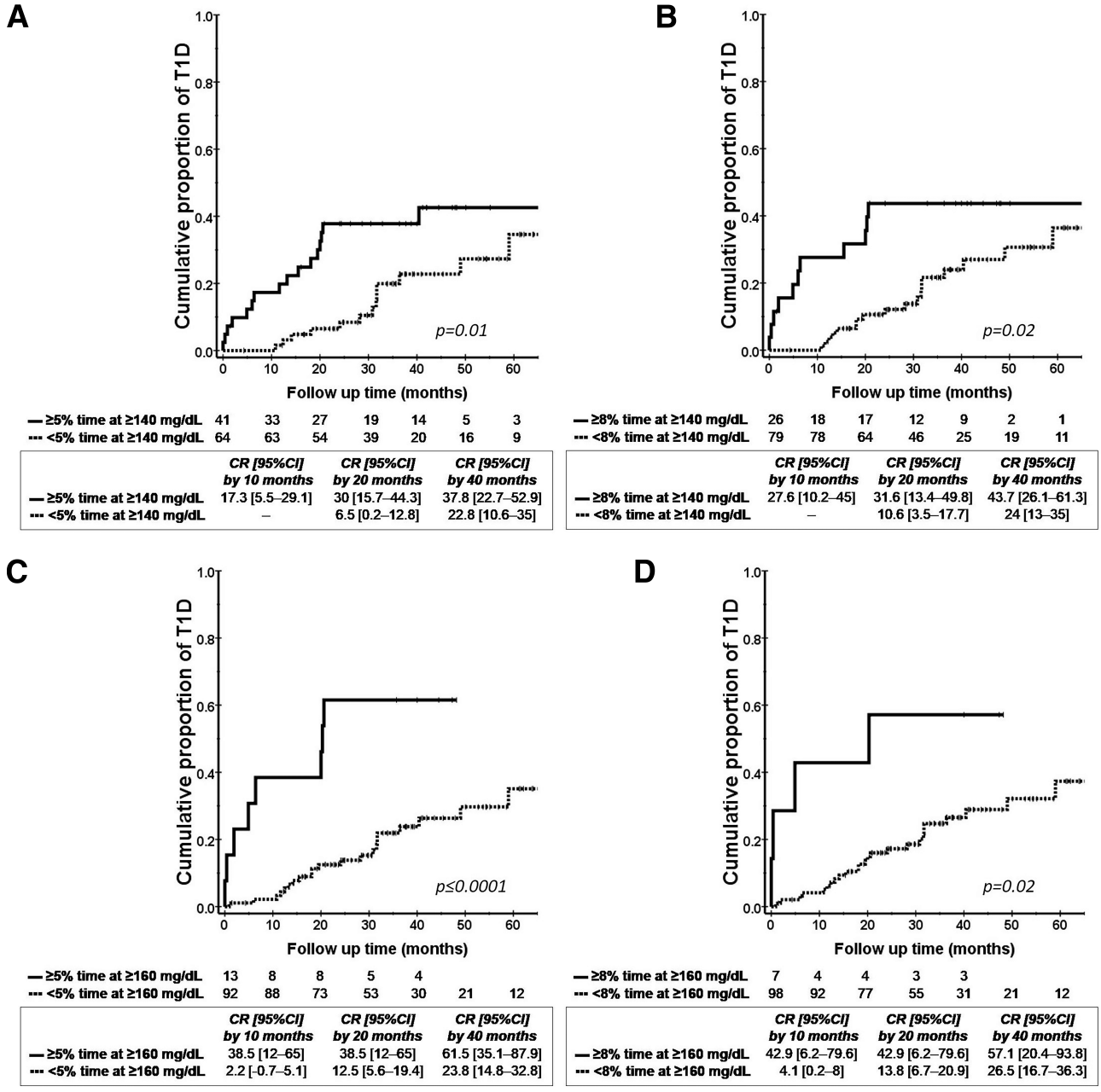

Figure 3—Progression to type 1 diabetes (T1D) by time spent ≥140 mg/dL and ≥160 mg/dL. *A*: Time spent ≥140 mg/dL with cutoff ≥5% vs. <5%; *B*: time spent ≥140 mg/dL with cutoff ≥8% vs. <8%; *C*: time spent ≥160 mg/dL with cutoff ≥5% vs. <5%; and *D*: time spent ≥160 mg/dL with cutoff ≥8% vs. <8%. Follow-up time was defined as the time between baseline CGM and diabetes onset for the progressors or last visit/contact for those who did not develop type 1 diabetes. CR, cumulative risk.

or outcome criteria and has proven important in explaining the concepts of risk and disease progression in people at risk for type 1 diabetes. However, it has long been recognized that OGTT-defined categories, which represent a categorical depiction of continuous data, have limitations (14). Even with standardized testing procedures, there is heterogeneity in OGTT outcomes within disease staging categories with potential implications for disease progression. This was clearly demonstrated by the TrialNet Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus (TN07) trial, in which a subgroup of individuals with stage 1 type 1 diabetes and low first-phase insulin secretion had a markedly different rate of disease progression than stage 1 participants with normal insulin release kinetics (30). As a result, TrialNet has moved beyond traditional risk categories of low, medium, and high to type 1 diabetes staging in recent disease prevention trials (9). For instance, stratification within stages is sometimes performed using demographics and insulin secretion data obtained from baseline OGTT. One of the main objectives of the current study was to determine whether CGM metrics could identify participants who may progress to stage 3 type 1 diabetes.

Although CGM is a powerful tool and its use is increasing in clinical practice (31–33), there is a relative paucity of CGM data from underpowered studies in the preclinical stages of type 1 diabetes (7,8). Steck et al. (18) studied 14 autoantibody-

positive and 9 autoantibody-negative adolescents using the Dexcom SEVEN CGM platform. In that study, 35% of 14 autoantibody-positive participants progressed to stage 3 type 1 diabetes. Compared with those who did not develop clinical type 1 diabetes, progressors had a higher percent time with glucose values ≥140 mg/dL (31% vs. 12%) on CGM and a higher daytime glucose area under the curve.

Use of a time-above-range threshold of 140 mg/dL has been supported by other studies assessing those at risk for type 1 diabetes. Helminen et al. (7) compared 10 autoantibody-positive participants with high-risk HLA to 10 autoantibody-negative age- and sex-matched controls from the Type 1 Diabetes Prediction and Prevention (DIPP) study using data collected with the Dexcom G4. In this study, both the percent time with glucose readings ≥140 mg/dL (5.8% vs. 0.4%) on CGM and mean 7-day sensor glucose (97.2 mg/dL vs. 84.6 mg/dL) were higher in the autoantibody-positive group. There were no significant differences at any of the five OGTT time points evaluated, suggesting the potential for more frequent measurements of physiologic glucose disruptions feasible with CGM could be superior to the classical OGTT approach to detect dysglycemia. However, the number of participants was quite small.

Steck et al. (8) compared glucose values from multiple CGM platforms (Dexcom SEVEN Plus before July 2014 and G4 after that date) in 23 autoantibody-positive participants, eight of whom progressed to stage 3 type 1 diabetes within the 26-month mean study follow-up period. From baseline CGM data, they reported the best predictor of progression was ≥18% of the time at CGM ≥140 mg/dL (8). In a larger study from the same group, 91 autoantibody-positive children with a baseline CGM (Dexcom G4 before April 2019 and Dexcom G6 after that date) were followed for the development of diabetes for a median of 6 months. Of these, 16 children progressed to stage 3 disease. They showed that spending more than 10% of the time at CGM readings >140 mg/dL is associated with a high risk of progression to diabetes within 1 year (15).

Given that our findings reinforce the concept that CGM metrics could be useful as markers of progression to stage 3 type 1 diabetes, one would need to balance the burden of 7 days of CGM use with the added value for prediction. While there are clear differences between progressor and nonprogressor groups for most of the CGM parameters, there is substantial overlap among each participant's individual values. This limits the predictive value for an individual participant.

Limitations of the current study include that the participants were all relatives of individuals in type 1 diabetes probands. Additionally, the majority were of non-Hispanic Caucasian descent, which reflects, at least in part, the high prevalence of type 1 diabetes in this ethnic group in the U.S. This may limit our understanding of CGM variations in preclinical type 1 diabetes stages in individuals with different ancestry. Moreover, some of our analyses categorize continuous data using specific thresholds, e.g., ≥5% time over 140 mg/dL, potentially losing important information. At the time of this study's initiation, the available Dexcom G4 sensor required calibration by the participants. Newer sensors such as the Dexcom G6, Freestyle Libre 2, and Medtronic Guardian 4 offer the advantage of factory calibration with improvements in sensor accuracy. As this report summarizes the baseline data, further work is needed to evaluate the time-dependent predictive value of CGM metrics for disease progression using the participant's longitudinally collected glucose sensor data. As this is a cross-sectional study, we do not precisely know where a particular participant is along their path to stage 3 type 1 diabetes. Those who are closer to stage 3 will likely arrive sooner. Future analysis combining various CGM variables with the longitudinal data may add value to determining risk and rate of progression to stage 3. Because changes in glucose measures are secondary consequences of the pathophysiology of disease progression, such as loss of β-cell mass, more precise measures of endogenous insulin secretion may be a more direct way of looking at disease progression.

In summary, the current study adds to the knowledge about the metabolic abnormalities in the months to years preceding clinical stage 3 type 1 diabetes onset and contributes to the mission of the TrialNet PTP study. These CGM findings may lead to a deeper understanding of dysglycemia during the natural history of type 1 diabetes, which could influence decision-making for future type 1 diabetes prevention trials.

Acknowledgments. The Dexcom G4 Platinum CGM systems were purchased at a reduced cost from Dexcom.

M.P. is deceased.

Funding. This work was supported by the National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (DP3DK101083), JDRF (SRA-2019-763-A-N), and the McNair Medical Institute at The Robert and Janice McNair Foundation. The Type 1 Diabetes TrialNet Study Group is a clinical trials network funded through a cooperative agreement by the National Institutes of Health through the NIDDK, the National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (through UC4 DK106993), and the JDRF. Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award numbers UL1TR003142 (Stanford) and URL1TR001427 (University of Florida).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Duality of Interest. D.M.W. served on a data and safety monitoring board for Intrexon T1D Partners and is on the advisory board for Enable Biosciences. J.L.S. reports research support from the NIDDK and research support from Insulet and Medtronic outside the submitted work. She has served on advisory boards for Bigfoot Biomedical, Cecelia Health, Insulet, Medtronic Diabetes, and Vertex. She did consulting work for Cecelia Health, Eli Lilly, Lexicon, Insulet, and Medtronic. J.L.D. is a current employee of Janssen Research and Development, LLC. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.M.W., S.L.P., and M.P. designed the study. D.M.W., S.L.P., M.A.-C., M.A.A., and M.P. wrote manuscript. S.L.P. coordinated the data. M.A.-C., S.H., D.S., C.J.G., M.A.A., and M.P. conducted the statistical analysis. D.A. and P.W.N. conducted the statistical analysis. P.W.N. developed the CGM GUIDE and DySF used in the data analysis. All authors reviewed and edited the manuscript. D.M.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Publication. This study was presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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