JAMA | Original Investigation

Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes
A Randomized Clinical Trial

Lori M. Laffel, MD, MPH; Lauren G. Kanapka, MSc; Roy W. Beck, MD, PhD; Katherine Bergamo, BSN, RN, MS; Mark A. Clements, MD, PhD; Amy Criego, MD; Daniel J. DeSalvo, MD; Robin Goland, MD; Korey Hood, PhD; David Liljenquist, MD; Laurel H. Messer, PhD, RN, MPH; CDE[1O]; Roshanak Monzavi, MD; Thomas J. Mouse, BS; Priya Prahalad, MD; Jennifer Sherr, MD, PhD; Jill H. Simmons, MD; R. Paul Wadwa, MD; Ruth S. Weinstock, MD, PhD; Steven M. Willi, MD; Kellee M. Miller, PhD, MPH; for the CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group

IMPORTANCE Adolescents and young adults with type 1 diabetes exhibit the worst glycemic control among individuals with type 1 diabetes across the lifespan. Although continuous glucose monitoring (CGM) has been shown to improve glycemic control in adults, its benefit in adolescents and young adults has not been demonstrated.

OBJECTIVE To determine the effect of CGM on glycemic control in adolescents and young adults with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between January 2018 and May 2019 at 14 endocrinology practices in the US including 153 individuals aged 14 to 24 years with type 1 diabetes and screening hemoglobin A_{1c} (HbA_{1c}) of 7.5% to 10.9%.

INTERVENTIONS Participants were randomized 1:1 to undergo CGM (CGM group; n = 74) or usual care using a blood glucose meter for glucose monitoring (blood glucose monitoring [BGM] group; n = 79).

MAIN OUTCOMES AND MEASURES The primary outcome was change in HbA_{1c} from baseline to 26 weeks. There were 20 secondary outcomes, including additional HbA_{1c} outcomes, CGM glucose metrics, and patient-reported outcomes with adjustment for multiple comparisons to control for the false discovery rate.

RESULTS Among the 153 participants (mean [SD] age, 17 [3] years; 76 [50%] were female; mean [SD] diabetes duration, 9 [5] years), 142 (93%) completed the study. In the CGM group, 68% of participants used CGM at least 5 days per week in month 6. Mean HbA_{1c} was 8.9% at baseline and 8.5% at 26 weeks in the CGM group and 8.9% at both baseline and 26 weeks in the BGM group (adjusted between-group difference, −0.37% [95% CI, −0.66% to −0.08%]; $P = .01$). Of 20 prespecified secondary outcomes, there were statistically significant differences in 3 of 7 binary HbA_{1c} outcomes, 8 of 9 CGM metrics, and 1 of 4 patient-reported outcomes. The most commonly reported adverse events in the CGM and BGM groups were severe hypoglycemia (3 participants with an event in the CGM group and 2 in the BGM group), hyperglycemia/ketosis (1 participant with an event in CGM group and 4 in the BGM group), and diabetic ketoacidosis (3 participants with an event in the CGM group and 1 in the BGM group).

CONCLUSIONS AND RELEVANCE Among adolescents and young adults with type 1 diabetes, continuous glucose monitoring compared with standard blood glucose monitoring resulted in a small but statistically significant improvement in glycemic control over 26 weeks. Further research is needed to understand the clinical importance of the findings.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03263494

Visual Abstract

Editorial page 2384

Related article page 2397

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 2423

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group members appear at the end of the article.

Corresponding Author: Kellee M. Miller, PhD, Jaeb Center for Health Research, 15310 Amberly Dr, #350, Tampa, FL 33647 (kmiller@jaeb.org).

JAMA. 2020;323(23):2388-2396. doi:10.1001/jama.2020.6940

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

Glycemic control remains suboptimal in the majority of adolescents and young adults with type 1 diabetes, with only 17% attaining the 2019 American Diabetes Association's hemoglobin A_{1c} (HbA_{1c}) target of less than 7.5% and 14% attaining the target of less than 7% in the T1D Exchange clinic registry.[1,2]

Continuous glucose monitoring (CGM) devices provide glucose readings, trends, and alerts to the user in real time to inform diabetes treatment decisions. Although CGM has been shown to improve glycemic control in adults,[3,4] studies have not shown overall benefit in adolescents and young adults (although for the minority of adolescents and young adults who used CGM regularly, a benefit was observed).[3] These studies used older-generation CGM devices.

Substantial improvements in CGM technology have led to greater accuracy and convenience, including approval by the US Food and Drug Administration in 2016 to use CGM for diabetes management without confirmatory blood glucose monitoring (BGM).[5] Considering the improvements in CGM technology, a randomized trial was conducted to evaluate the ability of CGM to improve glycemic outcomes in adolescents and young adults with type 1 diabetes with suboptimal glycemic control.

Key Points

Question Is continuous glucose monitoring effective in improving glycemic control compared with standard blood glucose monitoring in adolescents and young adults with type 1 diabetes?

Findings In this randomized clinical trial that included 153 participants aged 14 to 24 years with type 1 diabetes, treatment with continuous glucose monitoring compared with standard blood glucose monitoring resulted in a significantly lower hemoglobin A_{1c} level after 26 weeks (adjusted difference, 0.37%).

Meaning Among adolescents and young adults with type 1 diabetes, continuous glucose monitoring resulted in a small but statistically significant improvement in glycemic control over 26 weeks.

Methods

Study Conduct and Oversight

This randomized clinical trial was conducted at 14 endocrinology practices in the US. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent/assent forms were approved by institutional review boards. Written informed consent with or without assent was obtained from each participant and parent/legal guardian, as applicable, prior to enrollment. An independent data and safety monitoring board provided trial oversight for review of safety data. The protocol and the statistical analysis plan are available in Supplement 1.

Participants

Major eligibility criteria included clinical diagnosis of type 1 diabetes, age of 14 to 24 years, diabetes duration of at least 1 year, use of either an insulin pump or multiple daily insulin injections, total daily insulin of at least 0.4 units/kg/d, no use of real-time CGM in the 3 months prior to enrollment, and HbA_{1c} of 7.5% to less than 11.0% (see eTable 1 in Supplement 2 for a complete listing of the inclusion and exclusion criteria). The study aimed to enroll at least 33% of participants in the following categories: multiple daily insulin injection users, insulin pump therapy users, individuals with HbA_{1c} of at least 9.0%, and young adults aged 19 to 24 years.

Each participant was required to complete a 14- to 21-day prerandomization period using a masked CGM device in which sensor glucose values were not visible to participants. To be eligible for randomization, the participant needed at least 200 hours (equivalent to 8.3 days) of masked CGM glucose data during the prerandomization period. In addition, the individual had to perform a mean of at least 2 daily fingerstick blood glucose meter checks confirmed from download of home meter and calibration of the masked CGM device a mean of 1.8 times daily (per the manufacturer's recommendation of 2 daily calibrations).

Randomization

Eligible participants were randomly assigned on the study website, via a computer-generated sequence, to use CGM (Dexcom G5, Dexcom, Inc.) with fingerstick blood glucose meter checks as needed or to continue BGM with a blood glucose meter without CGM in a 1:1 ratio, using a permuted block design (block sizes of 2 and 4) stratified by site. Study investigators and personnel were masked to randomization sequence created by a coordinating center statistician, but not to treatment assignment. Participants were not masked to treatment assignment. The central laboratory was masked to treatment assignment. CGM outcomes were analyzed by a statistician at the coordinating center who was not masked to treatment assignment.

Intervention and Procedures

The CGM system included a transmitter, receiver, and disposable sensor that was inserted under the skin for 7 days (and then replaced), with glucose concentrations measured from interstitial fluid every 5 minutes. The CGM system required 2 daily calibrations from BGM.

Participants with compatible mobile phones were given the option to use either a study-provided CGM receiver or the CGM smartphone application on their mobile phone. Training on real-time CGM was provided using standardized materials developed for the study (eAppendix in Supplement 2). Additionally, participants in the CGM group received a handout at each study visit highlighting the benefits and features of CGM, such as the reduced need for fingerstick blood glucose meter measurements and the utility of the smartphone application (eAppendix in Supplement 2).

Participants in both groups received general diabetes management education and were provided a study blood glucose

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

meter and test strips (Bayer Contour Next USB, Ascensia Diabetes Care) if they did not have their own downloadable meter (8% of participants received a study meter). Clinicians were encouraged to review downloaded glucose data (CGM and BGM data) at each visit to inform treatment recommendations, which were at the clinician's discretion. The BGM group was asked to perform fingerstick blood glucose meter checks at least 4 times daily.

Both study groups had scheduled in-clinic visits at 4, 6, 13, and 26 weeks and contacts (via phone or video conference) at 1, 2 (in-clinic or remotely for the CGM group), and 19 weeks following randomization. The BGM group wore a masked CGM device for 1 week following the 13-week visit and for 2 weeks prior to the 26-week visit (clinic visit at 24 weeks for CGM device placement).

Central laboratory HbA_{1c} was measured at randomization and 13 and 26 weeks at the University of Minnesota using the Tosoh A_{1c} 2.2 Plus Glycohemoglobin Analyzer method. Participants completed patient-reported outcome assessments prior to randomization and at 13 and 26 weeks.

Data Collection and Outcomes

Participant sociodemographic data, including fixed categories for race/ethnicity, were collected from medical records and confirmed by the participants to describe the study cohort and provide information to inform generalizability.

Primary Outcome

The primary outcome was change in central laboratory-measured HbA_{1c} from baseline to 26 weeks, adjusted for baseline value.

Prespecified Secondary Outcomes

Prespecified secondary HbA_{1c} outcomes included the percentages of participants with HbA_{1c} less than 7.0%, HbA_{1c} less than 7.5%, HbA_{1c} target for their age group met (<7.5% for age <19 years and <7.0% for age ≥19 years), relative reduction in HbA_{1c} of at least 10%, absolute reduction in HbA_{1c} of at least 0.5%, absolute reduction in HbA_{1c} of at least 1%, and absolute reduction in HbA_{1c} at least 0.5% or HbA_{1c} less than 7.0%.

CGM-measured outcomes were calculated at follow-up using data pooled from up to 7 days before or after the 13-week visit and 14 days prior to the 26-week visit. Prespecified secondary CGM outcomes included percentage of time in which glucose level was in the target range (70-180 mg/dL), greater than 180 mg/dL, greater than 250 mg/dL, greater than 300 mg/dL, less than 70 mg/dL, and less than 54 mg/dL; mean glucose; coefficient of variation; and rate of CGM-measured hypoglycemic episodes.

Prespecified secondary patient-reported outcomes described herein were measured using the following instruments: Problem Areas in Diabetes-Pediatric survey,[6] Glucose Monitoring Satisfaction Survey,[7] Hypoglycemia Confidence Scale,[8] and Pittsburgh Sleep Quality Index[9] (see eTable 12a in Supplement 2 for descriptions). Additional questionnaire outcomes on CGM efficacy and technology attitudes will be reported separately given their application mainly to the CGM group.

Exploratory Outcomes

Prespecified exploratory outcomes included the mean number of blood glucose meter checks per day, total daily insulin dose per kilogram, number of short-acting injections for injection users, and number of bolus doses for pump users.

Safety Outcomes

Reportable adverse events included severe hypoglycemia (defined as an event that required assistance from another person due to altered consciousness), hyperglycemia resulting in evaluation or treatment at a health care provider facility or that involved diabetic ketoacidosis (as defined by the Diabetes Control and Complications Trial[10]), device-related events with potential effects on participant safety, and all serious adverse events regardless of causality.

Statistical Methods

A sample size of 140 participants was determined to have 90% power to detect a between-group difference in mean HbA_{1c}, assuming a population difference of 0.5%, SD of 0.9%, and a 2-sided type I error rate of 5%. This number was increased to 150 participants to account for missing follow-up data.

All participants were analyzed according to their randomization group and included in the primary analysis. For the primary analysis, the difference in change in HbA_{1c} from baseline to 26 weeks between the 2 treatment groups was assessed in a longitudinal linear regression model including the HbA_{1c} value at baseline, 13 weeks, and 26 weeks and clinical center as a random effect. Missing data were handled by direct likelihood, which maximizes the likelihood function integrated over possible values of the missing data.[11] Analyses of prespecified secondary and exploratory continuous outcomes paralleled those for the primary outcome (CGM data were pooled across follow-up time points). Binary secondary HbA_{1c} outcomes were compared between treatment groups using available cases only in a logistic regression model adjusting for baseline HbA_{1c} and clinical center as a random effect.

Additional analyses for select CGM glucose outcomes were performed separately for daytime (6:00 AM to 11:59 PM) and nighttime (12:00 AM to 5:59 AM) hours. Additional analyses were performed on HbA_{1c} and select CGM outcomes with data obtained through 13 weeks using the same methods as those used during the entire follow-up period of 26 weeks.

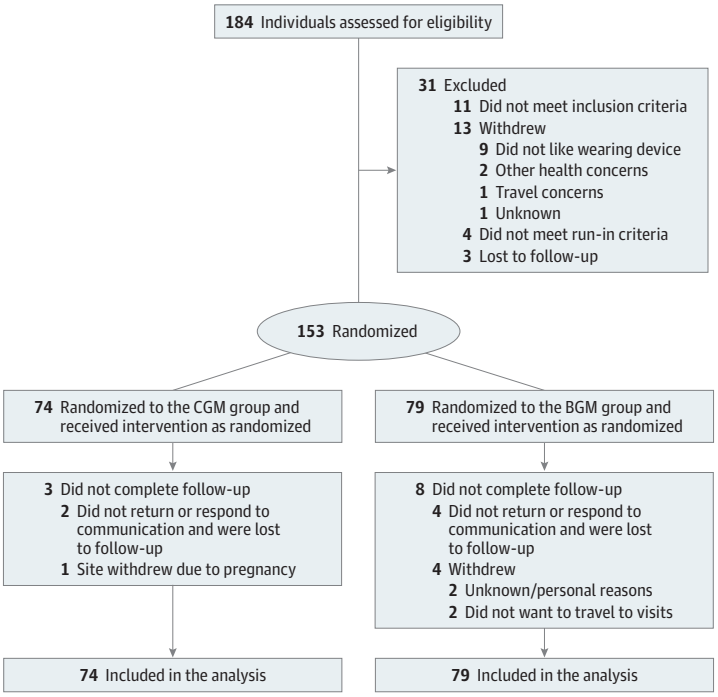
Modification of the treatment effect by baseline variables was assessed by including an interaction term in the primary model. Sensitivity analyses (with adjustment for potential confounding and including only participants who met per-protocol criteria) were performed as described in the statistical analysis plan (Supplement 1).

For all secondary and exploratory analyses (65 comparisons total), 2-sided *P* values and 95% CIs were adjusted for multiple comparisons to control the false discovery rate using the adaptive Benjamini-Hochberg procedure[12] (eTable 2 in Supplement 1). The choice of summary statistics for all outcomes was based on the distribution. Mean and SD were used if the outcome was approximately normal and

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

Figure 1. Flow of Participants in a Study of the Effect of Continuous Glucose Monitoring (CGM) vs Standard Blood Glucose Monitoring (BGM) on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes



Information on patients screened but not enrolled was not collected for this study. One participant in the BGM group and 1 participant in the CGM group were determined to be ineligible following randomization (inadequate hours of data during CGM run-in for the CGM participant and real-time CGM used within 3 months prior for the BGM participant). One participant in the BGM group initiated real-time CGM before completing the 26-week visit and was analyzed as randomized. Missing data for the primary outcome were handled by direct likelihood, which maximizes the likelihood function integrated over possible values of the missing data. All participants had data for at least 1 point and were included in the model.

median and interquartile range (IQR) were used if the outcome was skewed. Analyses were conducted with SAS software, version 9.4 (SAS Institute Inc).

Results

Between February 2018 and November 2018, 153 participants were randomly assigned to the CGM group (n = 74) or BGM group (n = 79). Thirty-one participants were consented for the study but not randomized (**Figure 1**). Participant characteristics are shown in **Table 1**. The 26-week visit was completed by 71 participants (96%) in the CGM group and 71 participants (90%) in the BGM group (Figure 1 and eFigure 1 in Supplement 2). Unscheduled visits and contacts are reported in eTable 3 in Supplement 2.

Device use in the CGM group was initially high, with 82% of participants using CGM for a mean of at least 5 days per week in the 28 days prior to the 6-week visit (eTable 4 in Supplement 2). This dropped by week 26, with 68% of participants using CGM for a mean of at least 5 days per week. At 26 weeks, 10 participants (14%) in the CGM group had no CGM use, including 3 participants who dropped out. Nine CGM device issues were reported over the 26-week study period, none of which were related to an adverse event (eTable 5 in Supplement 2). One participant in the BGM group initiated CGM use prior to the 26-week visit.

In the CGM group, the median (25th, 75th percentile) of each individual's mean number of BGM checks per day was 3.9 (3.0, 5.0) at baseline and 2.3 (1.9, 3.0) at follow-up compared with 3.5 (3.0, 4.5) at baseline and 3.0 (2.5, 4.3) at follow-up in the BGM group (adjusted bewteen-group difference, −0.8 [95% CI, −1.4 to −0.4]; $P < .001$). Among participants in the CGM group who were actively using CGM, the percentage who reported using CGM to dose insulin without blood glucose meter confirmation was 92% at the 2-week visit and increased to 98% at the 26-week visit. Insulin data are reported in eTable 6 in Supplement 2.

Primary Outcome: Hemoglobin A_{1c}

Mean HbA_{1c} was 8.9% at baseline and 8.5% at 26 weeks in the CGM group and was 8.9% at both baseline and 26 weeks in the BGM group (adjusted between-group difference, −0.37% [95% CI, −0.66% to −0.08%]; $P = .01$) (**Table 2**, **Figure 2**, and eFigure 2 in Supplement 2). Significant improvement in glucose control was observed by the 13-week visit, with a mean HbA_{1c} of 8.4% in the CGM group and 8.9% in the BGM group (adjusted between-group difference, −0.50% [95% CI, −0.79% to −0.21%]; $P < .001$) (Figure 2 and eTable 7 in Supplement 2).

An HbA_{1c} reduction from baseline to 26 weeks of at least 0.5% was observed in 44% of the CGM group vs 21% of the BGM group (adjusted between-group difference, 23% [95% CI, 7%-37%]; $P = .005$) and a reduction of at least 1.0% was shown in 25% of participants in the CGM group vs 6% in the BGM group (adjusted between-group difference, 19% [95% CI, 8%-31%]; $P = .003$) (Table 2).

The significant treatment effect for HbA_{1c} at 26 weeks remained when adjusting for duration of diabetes, sex,

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

Table 1. Baseline Characteristics of Participants in a Study of the Effect of Continuous Glucose Monitoring (CGM) on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes

Characteristic	No. (%)	
	Continuous glucose monitoring (n = 74)	Blood glucose monitoring (n = 79)
Age, y		
14-<19	48 (65)	53 (67)
19-<25	26 (35)	26 (33)
Mean (SD) [range]	17 (3) [14-24]	18 (3) [14-24]
Diabetes duration, mean (SD) [range], y	9 (5) [1-21]	10 (5) [1-21]
Sex		
Female	33 (45)	43 (54)
Male	41 (55)	36 (46)
Race/ethnicity	(n = 73)	(n = 79)
White, non-Hispanic	48 (66)	47 (59)
Black, non-Hispanic	3 (4)	9 (11)
Hispanic or Latino	18 (25)	15 (19)
Asian	1 (1)	5 (6)
American Indian/ Alaskan Native	0	1 (1)
More than 1 race	3 (4)	2 (3)
Health insurance	(n = 73)	(n = 79)
Private	43 (59)	47 (59)
Public	30 (41)	32 (41)
CGM use		
Past but not current	24 (32)	30 (38)
Never	50 (68)	49 (62)
Insulin pump use	36 (49)	47 (59)
HbA_{1c} at screening[a]		
<9%	34 (46)	33 (42)
≥9%	40 (54)	46 (58)
Mean (SD) [range], %	9.1 (1.0) [7.5-10.9]	9.1 (1.0) [7.5-10.9]
HbA_{1c} at randomization[b]		
<9%	42 (57)	43 (54)
≥9%	32 (43)	36 (46)
Mean (SD) [range], %	8.9 (1.0) [6.8-10.8]	8.9 (1.0) [6.4-10.9]
C-peptide	(n = 74)	(n = 78)
Detectable C-peptide[c]	41 (55)	30 (38)
C-peptide >0.2 nmol/L[c]	13 (18)	6 (8)
Total daily insulin dose/kg, mean (SD)	0.92 (0.36)	0.91 (0.25)
≥1 Severe hypoglycemia event in the past 12 mo[d]	7 (9)	2 (3)
≥1 Diabetic ketoacidosis event in the past 12 mo[e]	5 (7)	5 (6)

[a] Screening hemoglobin A_{1c} (HbA_{1c}) was measured by point-of-care device or local laboratory and used to determine eligibility.

[b] Randomization HbA_{1c} was measured by central laboratory.

[c] Random C-peptide. The detection limit of the assay was 0.003 nmol/L. Presence of C-peptide suggests some insulin production by the β cells in the pancreas.

[d] Severe hypoglycemia was defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions.

[e] Diabetic ketoacidosis was defined as an episode when the participant had ketosis that necessitated treatment in a health care facility.

insulin delivery method, and C-peptide. There was no significant interaction of the effect of study treatment on 26-week HbA_{1c} according to baseline age, sex, insulin delivery method, and baseline HbA_{1c} (eTable 8 in Supplement 2). In a per-protocol analysis, the 26-week adjusted between-group difference for the CGM vs BGM group was −0.69% ([95% CI, −1.01% to −0.36%]; $P < .001$) (eTable 9 in Supplement 2).

CGM Metrics

The mean percentage of time in target glucose range of 70 to 180 mg/dL was 37% (9.0 h/d) at baseline and 43% (10.3 h/d) during follow-up in the CGM group and 36% (8.7 h/d) at baseline and 35% (8.3 h/d) during follow-up in the BGM group (adjusted between-group difference, 6.9% [1.7 h/d] [95% CI, 3.1%-10.7%]; $P < .001$) (Table 2 and eTable 10 and eFigure 3 in Supplement 2). The percentages of time in target glucose range during daytime and nighttime hours are provide in eTable 11 in Supplement 2. Mean time in hypoglycemia (glucose <70 mg/dL) was significantly lower in the CGM group than the BGM group (adjusted between-group difference, −0.7% [95% CI, −1.5% to −0.1%]; $P = .002$) (Table 2). Results for other CGM outcomes are provided in Table 2 and eTable 10 and eFigure 3 in Supplement 2. Results of CGM outcomes at 13 weeks are reported in eTable 7 in Supplement 2.

Adverse Events

Severe hypoglycemic events occurred in 3 participants (4%) in the CGM group and 2 (3%) in the BGM group. Diabetic ketoacidosis occurred in 3 participants (4%) in the CGM group and 1 (1%) in the BGM group (**Table 3**). Additional adverse events are shown in Table 3.

Patient-Reported Outcomes

The CGM group reported significantly higher glucose monitoring satisfaction, measured via the Glucose Monitoring Satisfaction Survey score, at 26 weeks than the BGM group (adjusted between-group difference, 0.27 [95% CI, 0.06-0.54]; $P = .003$; eTable 12b in Supplement 2). No statistically significant between-group differences were observed for problem areas in diabetes, hypoglycemia confidence, or sleep quality (eTable 12b in Supplement 2).

Discussion

This randomized trial among adolescents and young adults with type 1 diabetes showed a small but statistically significant lowering of HbA_{1c} over 26 weeks of CGM use compared with standard BGM. This finding offers potential for clinical importance with a meaningful shift in the HbA_{1c} distribution toward improved glycemic control; however, further research of longer duration and with clinical outcomes is needed before reaching definitive conclusions about the clinical value of the study's findings.

The largest and most referenced randomized trial that examined CGM use in this age group was the JDRF (Juvenile

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

Table 2. Glycemic Outcomes in a Study of the Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes

Outcome	Randomization		26 weeks[a]		Adjusted between-group difference (95% CI)[a]	*P* value[b]
	Continuous glucose monitoring (n = 74)	Blood glucose monitoring (n = 79)	Continuous glucose monitoring (n = 71)	Blood glucose monitoring (n = 71)		
Primary outcome						
HbA_{1c}, mean (SD), %	8.9 (1.0)	8.9 (1.0)	8.5 (1.2)	8.9 (1.2)	−0.37 (−0.66 to −0.08)	.01
Change in HbA_{1c} from baseline, mean (SD), %			−0.4 (1.0)	0.1 (0.8)		
Secondary outcomes						
HbA_{1c} <7.0%, No. (%)	1 (1)	2 (3)	6 (8)	4 (6)	4 (−4 to 11)	.30
HbA_{1c} <7.5%, No. (%)	3 (4)	7 (9)	13 (18)	8 (11)	9 (−1 to 18)	.11
Met HbA_{1c} target (<7.5% for age <19 y and <7.0% for age ≥19 y), No. (%)	2 (3)	6 (8)	9 (13)	7 (10)	4 (−6 to 12)	.42
Relative reduction in HbA_{1c} ≥10%, No. (%)			20 (28)	6 (8)	19 (8 to 32)	.005
Absolute reduction in HbA_{1c}, No. (%)						
≥0.5%			31 (44)	15 (21)	23 (7 to 37)	.005
≥1.0%			18 (25)	4 (6)	19 (8 to 31)	.003
≥0.5% or HbA_{1c} ≤7.0%			19 (27)	8 (11)	15 (3 to 28)	.02
	Baseline		**Follow-up (13 and 26 weeks pooled)[c]**			
Secondary continuous glucose monitoring metrics	**Continuous glucose monitoring (n = 73)[c]**	**Blood glucose monitoring (n = 79)**	**Continuous glucose monitoring (n = 68)**	**Blood glucose monitoring (n = 72)**		
Hours of continuous glucose monitoring data, median (IQR)	302 (269 to 324)	311 (268 to 378)	376 (262 to 475)	426 (371 to 477)		
Time in target glucose range (70-180 mg/dL), mean (SD), %	37 (13)	36 (12)	43 (15)	35 (12)	6.9 (3.1 to 10.7)	<.001
Glucose, mean (SD), mg/dL	209 (36)	212 (36)	199 (36)	217 (35)	−14.3 (−23.6 to −5.1)	.003
Coefficient of variation, mean (SD), %[d]	42 (7)	42 (7)	39 (6)	42 (7)	−2.2 (−3.9 to −0.5)	.01
Hyperglycemia						
Time with glucose >180 mg/dL (hyperglycemia), mean (SD), %	58 (15)	59 (15)	54 (18)	61 (14)	−5.8 (−10.0 to −1.7)	.007
Time with glucose >250 mg/dL, mean (SD), %	32 (15)	34 (15)	26 (15)	35 (14)	−7.9 (−12.3 to −3.4)	<.001
Time with glucose >300 mg/dL, median (IQR), %	15 (9 to 26)	17 (11 to 28)	11 (5 to 19)	20 (12 to 26)	−5.1 (−8.2 to −2.3)	<.001
Hypoglycemia						
Time with glucose <70 mg/dL, median (IQR), %	3.2 (1.3 to 7.7)	3.7 (1.7 to 6.7)	2.2 (1.0 to 5.0)	3.2 (1.9 to 6.2)	−0.7 (−1.5 to −0.1)	.02
Time with glucose <54 mg/dL, median (IQR), %	1.0 (0.4 to 3.2)	1.3 (0.3 to 3.0)	0.7 (0.2 to 1.4)	1.3 (0.5 to 2.5)	−0.4 (−0.7 to −0.1)	.002
Rate of hypoglycemic events per week[e]	1.5 (0.6 to 3.3)	1.7 (0.6 to 3.2)	1.4 (0.4 to 2.6)	1.7 (1.0 to 3.1)	−0.3 (−0.7 to 0.1)	.11

Abbreviation: IQR, interquartile range.

[a] Three participants in the CGM group and 8 participants in the BGM group were missing central laboratory hemoglobin A_{1c} (HbA_{1c}) values at 26 weeks. Missing data for continuous outcomes were handled using direct likelihood. Binary outcomes were analyzed using available cases only.

[b] Continuous outcomes were analyzed in a longitudinal regression model including baseline and follow-up with adjustment for clinical center as a random effect. The reported number of participants is for those with available baseline and follow-up data, but all participants were included in the statistical model. The hypoglycemia metrics and percentage of time with glucose greater than 300 mg/dL had skewed distributions and were modeled using a rank-based transformation. For these skewed outcomes, point estimates and CIs for the treatment group difference were calculated using the technique described by Hodges and Lehmann.[13] Binary HbA_{1c} outcomes were analyzed in a logistic regression model adjusted for baseline HbA_{1c} and clinical center as a random effect. For these outcomes, risk-adjusted differences were calculated according to the method of Kleinman and Norton.[14] *P* values and 95% CIs for all secondary outcomes were adjusted for multiple comparisons to control the false discovery rate.

[c] Baseline CGM data for 1 participant in the CGM group were lost after the site confirmed they met the eligibility criteria. Six participants in the CGM group and 7 in the BGM group were missing follow-up CGM data. All participants had data for at least 1 time point. Missing data were handled using direct likelihood.

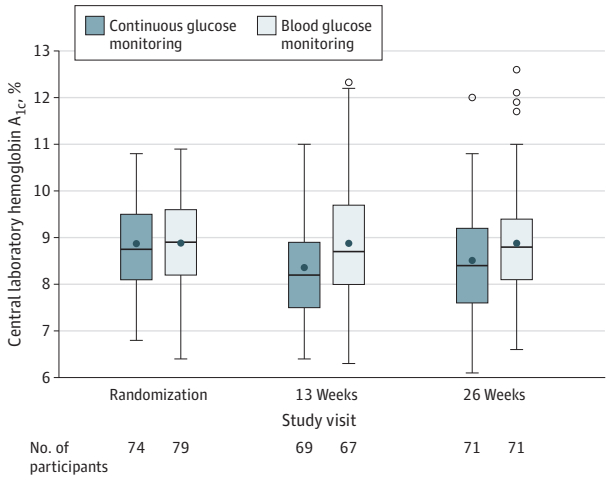
[d] Coefficient of variation is defined as SD divided by the mean.

[e] A CGM-measured hypoglycemic event was defined as 15 consecutive minutes with a sensor glucose value less than 54 mg/dL. The end of the hypoglycemic event was defined as a minimum of 15 consecutive minutes with a sensor glucose concentration greater than 70 mg/dL.[15]

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

Figure 2. Hemoglobin A_{1c} Levels During a Study of the Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes



The top and bottom of the boxes denote the 25th and 75th percentile, the line represents the median, and the dot represents the mean. The whiskers represent the minimum and maximum values after removing outliers.

Table 3. Safety Outcomes in a Study of the Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes

Outcome	Participants with ≥1 event, No.	
	Continuous glucose monitoring group (n = 74)	Blood glucose monitoring group (n = 79)
Severe hypoglycemia[a]	3	2
Incidence rate (events per 100 person-years)	8.3	7.8
Diabetic ketoacidosis[b]	3	1
Incidence rate (events per 100 person years)	8.3	2.6
Other serious adverse events		
Overall	2	2
Appendicitis	1	0
Fainting	1	0
Hyperglycemia	0	1
Suicidal ideation	0	1
Syncope	1	0
Nonserious adverse events		
Overall	3	4
Ketosis	0	3
Hyperglycemia	1	0
Lightheadedness	1	0
Panic attack	0	1
Vomiting	1	0

[a] Severe hypoglycemia was defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions.

[b] Diabetic ketoacidosis was defined as an episode when the participant had ketosis that necessitated treatment in a health care facility.

Diabetes Research Foundation) CGM randomized clinical trial conducted more than 10 years ago.[3] In that trial, a benefit of CGM was not seen in adolescents and young adults. However, only 30% used CGM regularly (6-7 d/wk), which is substantially less than observed in the current trial. Enhancements in CGM technology over the past 10 years have reduced the burden of using CGM, which likely accounts for the greater usage found in the current trial. This is evidenced by the improvement observed in patient-reported outcomes related to technology satisfaction and no reported increase in burden, which is noted by no difference in reported diabetes problem areas. Although CGM use in the current trial was higher than that in the JDRF CGM trial,[3] it was substantially lower than the usage rate found in adults with type 1 diabetes using a similar CGM system.[4] This emphasizes the greater challenges faced in managing diabetes in adolescents and young adults compared with older adults.

The strengths of the study include enrollment of a geographically and ethnically diverse sample of adolescents and young adults with type 1 diabetes from 14 diabetes centers and high participant retention, particularly given the recognized life changes that affect older teens and young adults.[16] More than one-third of the cohort were racial and ethnic minority participants and more than 40% had public insurance, providing a pathway to CGM use for this underserved population. These data support the need for expanded reimbursement for CGM, especially for teens and young adults whose private or publicly funded insurance varies widely.

Limitations

There are several limitations of the study. First, CGM used in the trial required twice-daily calibrations with blood glucose measurements, whereas this is no longer required with the current generation of the factory-calibrated CGM devices. Second, in view of the eligibility criteria, the results may not apply to individuals with type 1 diabetes and HbA_{1c} outside the eligibility range of HbA_{1c} of 7.5% to 10.9%. Third, the informed consent process and the run-in phase had the potential to exclude individuals who might be less adherent to CGM use than the cohort that was studied. Fourth, the study included a relatively short intervention period of 6 months. This study also included an extension phase in which the CGM group continued using CGM through 12 months and the BGM group initiated CGM. Results of the extension phase may provide insight into longer-term use of CGM.

Conclusions

Among adolescents and young adults with type 1 diabetes, CGM compared with standard BGM resulted in a small but statistically significant improvement in glycemia over 26 weeks. Further research is needed to understand the clinical importance of this finding.

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

ARTICLE INFORMATION

Accepted for Publication: April 11, 2020.

Author Affiliations: Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts (Laffel); Jaeb Center for Health Research, Tampa, Florida (Kanapka, Beck, Mouse, Miller); University of North Carolina Diabetes Care Center, Chapel Hill (Bergamo); Children's Mercy Hospital, Kansas City, Missouri (Clements); Health Partners Institute, International Diabetes Center, St Louis Park, Minnesota (Criego); Baylor College of Medicine, Houston, Texas (DeSalvo); Naomi Berrie Diabetes Center, Columbia University, New York, New York (Goland); Stanford University, Palo Alto, California (Hood, Prahalad); Rocky Mountain Diabetes & Osteoporosis Center, Idaho Falls, Idaho (Liljenquist); Barbara Davis Center for Childhood Diabetes, Aurora, Colorado (Wadwa); Children's Hospital Los Angeles, Los Angeles, California (Monzavi); Yale Children's Diabetes Program, New Haven, Connecticut (Sherr); Vanderbilt University Medical Center, Nashville, Tennessee (Simmons); SUNY Upstate Medical University, Syracuse, New York (Weinstock); Childrens Hospital of Philadelphia, Philadelphia, Pennsylvania (Willi).

Author Contributions: Dr Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Laffel, Kanapka, Beck, Bergamo, Clements, DeSalvo, Goland, Hood, Messer, Monzavi, Mouse, Sherr, Simmons, Willi, Miller.
Acquisition, analysis, or interpretation of data: Laffel, Kanapka, Bergamo, Clements, Criego, DeSalvo, Goland, Hood, Liljenquist, Messer, Monzavi, Mouse, Prahalad, Sherr, Simmons, Wadwa, Weinstock, Willi, Miller.
Drafting of the manuscript: Laffel, Kanapka, DeSalvo, Miller.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Laffel, Kanapka, DeSalvo, Hood.
Obtained funding: Laffel, DeSalvo, Miller.
Administrative, technical, or material support: Laffel, Beck, Goland, Hood, Messer, Mouse, Simmons, Willi, Miller.
Supervision: Laffel, Beck, Bergamo, DeSalvo, Goland, Hood, Liljenquist, Monzavi, Mouse, Prahalad, Weinstock, Willi.
Other - primary investigator at clinical site: Criego.
Other - participated in planning and progress meetings in person and via web conference: Clements.
Other - trial coordination and data monitoring: Mouse.
Other - patient recruitment, enrollment, follow-up, procedures, and protocol implementations: Monzavi.

Conflict of Interest Disclosures: Dr Laffel reported receiving personal fees from NovoNordisk, Eli Lilly, Sanofi, Insulet, Convatec, Dexcom, Medtronic, Roche, Boehringer Ingelheim, and Insulogic outside the submitted work. Dr Beck reported receiving grants and nonfinancial support from Dexcom; consulting fees paid to his institution from Bigfoot BioMedical, Insulet, and Eli Lilly; grants and consulting fees paid to his institution from Tandem Diabetes Care; and nonfinancial support from Roche and Ascencia outside the submitted work. Dr Clements reported receiving personal fees from Glooko, Medtronic, and Eli Lilly outside the submitted work. Dr Criego reported receiving grants from DexCom, Medtronic, Insulet, Juvenile Diabetes Research Foundation, the National Institutes of Health, and Abbott and study supplies from Eli Lilly outside the submitted work. Dr DeSalvo reported receiving personal fees and nonfinancial support from Dexcom. Dr Hood reported receiving grants from Dexcom and personal fees from Lifescan Diabetes Institute outside the submitted work. Dr Liljenquist reported receiving grants and nonfinancial support from Abbott and Medtronic outside the submitted work. Dr Messer reported receiving personal fees from Tandem Diabetes Care, Dexcom, Capillary Biomedical, and Clinical Sensors outside the submitted work. Dr Sherr reported receiving grants and personal fees from Medtronic Diabetes and Insulet and personal fees from Sanofi, Eli Lilly, and Bigfoot Biomedical outside the submitted work. Dr Wadwa reported receiving grants, personal fees, and nonfinancial support from Eli Lilly and Dexcom; grants from Bigfoot Biomedical; personal fees from Medtronic; and grants and nonfinancial support from MannKind Corporation, Nordisk, and Tandem Diabetes Care outside the submitted work. Dr Weinstock reported receiving grants from Insulet Corporation, Tolerion Inc, Eli Lilly, Medtronic, Diasome Pharmaceuticals, Boehringer Ingelheim, Oramed Ltd, and Mylan GmbH and personal fees from Insulogic outside the submitted work. Dr Willi reported serving on a data safety monitoring board for the National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health and serving on an advisory panel for Roche Diagnostics outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by a grant provided by the Leona M. and Harry B. Helmsley Charitable Trust given to the Jaeb Center for Health Research. Dexcom Inc provided nonfinancial support by providing continuous glucose monitoring devices and sensors for the study.

Role of the Funder/Sponsor: There was no involvement from the Leona M. and Harry B. Helmsley Charitable Trust or Dexcom in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The Leona M. and Harry B. Helmsley Charitable Trust and Dexcom were sent the manuscript for review but any revisions made based on their comments were at the discretion of the authors and permission for submitting content to journal was not required. There was no approval by the Leona M. and Harry B. Helmsley Charitable Trust or Dexcom required or obtained for manuscript submission.

Meeting Presentation: The trial results were presented at the American Diabetes Association meeting, San Francisco, CA, on June 10, 2019, and the International Society for Pediatric and Adolescent Diabetes meeting, Boston, MA, on October 31, 2019.

Data Sharing Statement: See Supplement 3.

CITY Study Group: A listing of the CGM Intervention in Teens and Young Adults with Type 1 Diabetes (T1D) (CITY) sites with participating principal investigators (PI), co-investigators (I), primary coordinator (PC), and coordinators (C) is included below: *Joslin diabetes Center, Harvard University, Boston, MA*: Lori Laffel, MD, MPH (PI); Dayna McGill, MD (I); Emily Freiner, MSN, RN, NP-C (PC); Alan Schultz, MSN, RN, CPNP (C); Hannah Desrochers, MSN, RN, CPNP (C); Nisha Naik, BA (C); *University of Colorado/Denver, Barbara Davis Center for Diabetes Aurora, CO*: Paul Wadwa, MD (PI); Laurel Messer, RN, MPH, CDE, PhD (I); Todd Alonso, MD (I); Shideh Majidi, MD (I); Emily Simmons, BA (PC); Isabel Weber, MS, RD (C); Michelle Clay, BSN (C); Alex Coakly, BS (C); Tyler Reznick-Lipina, BS (C); *Stanford University, Stanford, CA*: Priya Prahalad, MD, PhD (PI); Darrel Wilson, MD (I); Bruce Buckingham, MD (I); Ryan Kingman, BS (PC); Marissa Ann Town, RN, BSN, CDE (C); *International Diabetes Center/Park Nicollet/HealthPartners Institute Minneapolis, MN*: Amy Criego, MD, MS (PI); Shannon Beasley, NP (I); Sean Dunnigan, RN, BSN (PC); Kathleen McCann, RN, BA (C); *Yale University School of Medicine, New Haven, CT*: Jennifer Sherr, MD, PhD (PI); Kate Weyman, MSN, APRN, FNP-C, CDE (I); Eileen Tichy, MMSc, PA-C, RD, CDE (I); Katie Gibbons, MD (I); Amy Steffen, RN, BSN (PC); Jennifer Finnegan (C); *Naomi Berrie Diabetes Center, Columbia University New York City: NY* Robin Goland, MD (PI); Kristen Williams, MD (I); Sarah Pollak, RN (PC); Eberechi Cecilia Uche, BA (C); Courtney Sahn, RD (C); Analia Alvarez, RN (C); Courtney Melrose, RDN (C); Elizabeth Robinson, BA (C); *University of North Carolina Diabetes Care Center Chapel Hill, NC* Katherine Bergamo, BSN, MSN, FNP-C (PI); John Buse, MD, PhD (I); Jean Dostou, MD, FACE (I); Marian Sue Kirkman, MD (I); Laura Young, MD, PhD (I); Alexander Kass, BSN, RN, CDE (PC); Julie Uehling, BA, MS, CCRP (C); *SUNY Upstate Medical University Syracuse, NY* Ruth Weinstock, MD, PhD (PI); Angela Mojica, MD (I); Suzan Bzdick, RN, CDE (PC); Patricia Conboy (C); *Rocky Mountain Diabetes & Osteoporosis Center, Idaho Fall, ID* David Liljenquist, MD (PI); Carl Vance, MD (I); Mark Sulik, PharmD, CCRP (I); William Hardee, BS, CRC (PC); Christine Duval, BS, CCRC (C); *Children's Hospital Los Angeles, Los Angeles, CA*: Roshanak Monzavi, MD (PI); Jennifer Raymond, MD, MCR (I); Daniel Brimberry, PhD (PC); Debra Miller, RN, BSN, CDE (C); Daniel Bisno, BA (C); *Vanderbilt University Medical Center, Nashville, TN*: Jill Simmons, MD (PI); Jennifer Kelley, MD (I); George Williams, RN, CDE (PC); *Children's Hospital of Philadelphia, Philadelphia, PA*: Steven Willi, MD (PI); Pantea Minnock, RN, MSN, CPNP (I); Diana Olivos, MS (PC); Fiona Stuart, BSN, RN (C); Brian Grant, BSN, RN, CDE (C); Jennifer Smith, MPH (C); *Baylor College of Medicine, Houston, TX*: Daniel J. DeSalvo, MD (PI); Sarah K. Lyons, MD (I); Mary-Kylie DeLaO, MSN, RN, CDE (PC); *Children's Mercy Hospital, Kansas City, MO*: Mark Clements, MD, PhD (PI); Wayne Moore, MD, PhD (I); Ryan McDonough, DO (I); Sarah Tsai, MD, FRCPC (I); Terri Lutjen, MS, RN, CPNP, CCRC (I); Jennifer James, BS, CCRC (PC); Heather Harding, RN (C); Stephen Orlich, RN, ACRP-CP (C); *Jaeb Center for Health Research Tampa, FL*: Kellee M. Miller, PhD; Thomas Mouse, BS, Nicole Reese, BS, David McNabb, AS, Heidi Strayer, PhD, Kamille Janess, BS, Israel Mahr, MS, Lauren Kanapka, MSc, Craig Kollman PhD, Roy Beck, MD, PhD; *CITY Operations Committee Members*: Mark Clements, MD, PhD, Daniel DeSalvo, MD, Korey Hood, PhD, Lauren Kanapka,

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020

MSc, Lori Laffel, MD, MPH, Laurel Messer, PhD, RN, MPH, CDE, Kellee Miller, PhD, Thomas Mouse, BS, Jennifer Sherr, MD, PhD; Ruth Weinstock, MD, PhD; *Data and Safety Monitoring Board (DSMB)*: Diane Wherrett, MD, FRCPC; Randi Streisand, PhD; Leslie Plotnick, MD.

REFERENCES

1. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes-2019. Diabetes Care*. 2019;42(suppl 1):S61-S70. doi:10.2337/dc19-S006

2. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016-2018. *Diabetes Technol Ther*. 2019;21(2):66-72. doi:10.1089/dia.2018.0384

3. Tamborlane WV, Beck RW, Bode BW, et al; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359(14):1464-1476. doi:10.1056/NEJMoa0805017

4. Ruedy KJ, Parkin CG, Riddlesworth TD, Graham C; DIAMOND Study Group. Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND Trial. *J Diabetes Sci Technol*. 2017;11(6):1138-1146. doi:10.1177/1932296817704445

5. US Food and Drug Administration. Premarket approval: Dexcom G5 Mobile Continuous Glucose Monitoring System. Updated May 11, 2020. Accessed May 15, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120005S041

6. Markowitz JT, Volkening LK, Butler DA, Laffel LM. Youth-perceived burden of type 1 diabetes: Problem Areas in Diabetes Survey-Pediatric version (PAID-Peds). *J Diabetes Sci Technol*. 2015;9(5):1080-1085. doi:10.1177/1932296815583506

7. Polonsky WH, Fisher L, Hessler D, Edelman SV. Development of a new measure for assessing glucose monitoring device-related treatment satisfaction and quality of life. *Diabetes Technol Ther*. 2015;17(9):657-663. doi:10.1089/dia.2014.0417

8. Polonsky WH, Fisher L, Hessler D, Edelman SV. Investigating hypoglycemic confidence in type 1 and type 2 diabetes. *Diabetes Technol Ther*. 2017;19(2):131-136. doi:10.1089/dia.2016.0366

9. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4

10. Nathan DM, Genuth S, Lachin J, et al; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329(14):977-986. doi:10.1056/NEJM199309303291401

11. Beunckens C, Molenberghs G, Kenward MG. Direct likelihood analysis versus simple forms of imputation for missing data in randomized clinical trials. *Clin Trials*. 2005;2(5):379-386. doi:10.1191/1740774505cn119oa

12. Benjamini Y, Hochberg Y. On the adaptive control of the false discovery rate in multiple testing with independent statistics. *J Educ Behav Stat*. 2000;25(1):60-83. doi:10.3102/10769986025001060

13. Hodges JL, Lehmann EL. Estimates of location based on rank tests. *Ann Math Stat*. 1963;34(2):598-611. doi:10.1214/aoms/1177704172

14. Kleinman LC, Norton EC. What's the risk? a simple approach for estimating adjusted risk measures from nonlinear models including logistic regression. *Health Serv Res*. 2009;44(1):288-302. doi:10.1111/j.1475-6773.2008.00900.x

15. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603. doi:10.2337/dci19-0028

16. Peters A, Laffel L; American Diabetes Association Transitions Working Group. Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, Children with Diabetes, the Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society). *Diabetes Care*. 2011;34(11):2477-2485. doi:10.2337/dc11-1723

© 2020 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by Kevin Rosteing on 07/16/2020