

ORIGINAL ARTICLE

Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group*

ABSTRACT

BACKGROUND

The value of continuous glucose monitoring in the management of type 1 diabetes mellitus has not been determined.

METHODS

In a multicenter clinical trial, we randomly assigned 322 adults and children who were already receiving intensive therapy for type 1 diabetes to a group with continuous glucose monitoring or to a control group performing home monitoring with a blood glucose meter. All the patients were stratified into three groups according to age and had a glycated hemoglobin level of 7.0 to 10.0%. The primary outcome was the change in the glycated hemoglobin level at 26 weeks.

RESULTS

The changes in glycated hemoglobin levels in the two study groups varied markedly according to age group ($P=0.003$), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change, -0.53% ; 95% confidence interval [CI], -0.71 to -0.35 ; $P<0.001$). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08 ; 95% CI, -0.17 to 0.33 ; $P=0.52$) or among those who were 8 to 14 years of age (mean difference, -0.13 ; 95% CI, -0.38 to 0.11 ; $P=0.29$). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe hypoglycemia was low and did not differ between the two study groups; however, the trial was not powered to detect such a difference.

CONCLUSIONS

Continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes. Further work is needed to identify barriers to effectiveness of continuous monitoring in children and adolescents. (ClinicalTrials.gov number, NCT00406133.)

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DEXCOM EXHIBIT 1061

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DESPITE THE INCREASED USE OF INSULIN pumps and multiple-injection regimens and the introduction of insulin analogues, intensive treatment of type 1 diabetes mellitus often does not achieve the target glycated hemoglobin levels recommended by the Diabetes Control and Complications Trial (DCCT) more than 15 years ago.¹ Although self-monitoring of blood glucose plays an important role in achieving target glycated hemoglobin levels, few patients with type 1 diabetes measure glucose levels after meals or overnight. Consequently, postprandial hyperglycemia and asymptomatic nocturnal hypoglycemia are commonly seen, even in patients with well-controlled type 1 diabetes who measure blood glucose several times daily with a home glucose meter.²⁻⁴ In many patients, fear of hypoglycemia⁵ or development of hypoglycemia-associated autonomic failure⁶ hinders the successful implementation of intensive insulin therapy.

The availability of devices for continuous glucose monitoring permits the measurement of interstitial glucose in an ongoing fashion. However, the first-generation continuous monitors either provided data only for short-term retrospective analysis⁷ or were too difficult and uncomfortable for clinical use.⁸ Although not yet as accurate as blood glucose meters,^{9,10} newer real-time devices for continuous glucose monitoring provide improved accuracy and functionality, such as sounding alarms when the glucose trend projects future hypoglycemia, and are better tolerated by users.¹¹ Although short-term or uncontrolled studies have suggested benefit,¹¹⁻¹⁵ whether these systems help to produce a sustained lowering of glycated hemoglobin levels and reduce hypoglycemia in patients with type 1 diabetes has not been established. Therefore, in this randomized, multicenter clinical trial, we evaluated the efficacy and safety of continuous glucose monitoring in adults and children with type 1 diabetes.

METHODS

PATIENTS

All eligible patients were 8 years of age or older, had received a diagnosis of type 1 diabetes at least 1 year before randomization, either used an insulin pump or received at least three daily insulin injections, had a glycated hemoglobin level of 7.0 to 10.0%, and had not used continuous glucose monitoring at home in the 6 months leading up

to the trial. Patients completed a run-in phase using a continuous glucose monitor that was modified so that the glucose values were recorded in the receiver but were not visible to the patient; we refer to this as a “blinded” continuous glucose monitor. Eligibility required that patients wear a sensor for at least 6 of 7 days before randomization, with a minimum of 96 hours of glucose values including at least 24 hours overnight, and that home blood glucose monitoring be performed at least three times daily.

STUDY TREATMENT

Patients meeting these criteria were randomly assigned to receive continuous glucose monitoring (continuous-monitoring group) or home monitoring with a blood glucose meter (control group) with the use of a permuted-block design stratified according to clinical center, age group (≥ 25 years, 15 to 24 years, and 8 to 14 years), and glycated hemoglobin level ($\leq 8.0\%$ and $> 8.0\%$). A total of 23 patients (1 in the ≥ 25 -year group, 8 in the 15-to-24-year group, and 14 in the 8-to-14-year group) were screened for the study but were not enrolled, either because the run-in phase was not successfully completed or because the patient elected not to enter the study after using the blinded continuous glucose monitor.

Patients in the continuous-monitoring group were provided with one of the following devices: the DexCom Seven (DexCom), the MiniMed Paradigm Real-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic), or the FreeStyle Navigator (Abbott Diabetes Care). Each system consists of a glucose oxidase-based electrochemical sensor, which is placed subcutaneously and replaced every 3 to 7 days (depending on the type of device), along with a receiver to which interstitial glucose measurements are sent wirelessly and stored. Since the purpose of the study was to evaluate a treatment strategy using the technology of continuous glucose monitoring and not a specific device, a device was assigned to each patient by the clinical center on the basis of device features and the patients' preferences. Patients were instructed to use the device on a daily basis and to verify the accuracy of the glucose measurement with a home blood glucose meter (provided by the study) before making management decisions, according to the regulatory labeling of the devices. Patients in the control group were given blood glucose meters and test strips and asked to

perform home blood glucose monitoring at least four times daily.

Patients in the two groups were provided with written instructions on how to use the data provided by continuous glucose monitoring and blood glucose meters to make real-time adjustments of insulin doses and on the use of computer software (for those with a home computer) to retrospectively review the glucose data to alter future insulin doses.^{16,17} The two study groups had the same target premeal glucose values (70 to 130 mg per deciliter [3.9 to 7.2 mmol per liter]), peak postprandial values (<180 mg per deciliter [10.0 mmol per liter]), and bedtime or overnight values (100 to 150 mg per deciliter [5.6 to 8.3 mmol per liter]). Instructions for the insulin regimen included the determination of a premeal bolus dose on the basis of the glucose level and the patient's insulin-to-carbohydrate ratio and guidelines for correcting high glucose levels outside the target range at other times. Patients using a continuous glucose monitor received additional instructions for modifying their insulin doses and treatment of hypoglycemia on the basis of the glucose trend.

FOLLOW-UP

The number of scheduled contacts with study staff was identical for both study groups. Visits were conducted at 1, 4, 8, 13, 19, and 26 weeks (± 1 week), with one telephone contact between each visit, to review glucose data and adjust diabetes management. After the visits at 13 weeks and 26 weeks, the control group used a blinded continuous glucose monitor for 1 week, which was repeated if fewer than 96 hours of glucose values were obtained. Glycated hemoglobin was measured at baseline and at 13 and 26 weeks at a central laboratory at the University of Minnesota with the use of the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer method.¹⁸ Reportable adverse events included severe hypoglycemia (which was defined as an event that required assistance from another person to administer oral carbohydrate, glucagon, or other resuscitative actions¹⁹), hyperglycemia resulting in ketoacidosis, unexpected study-related or device-related events, and serious adverse events regardless of cause.

STUDY DESIGN

The protocol was approved by the institutional review board at each of the 10 participating centers, which included academic, community, and man-

aged care-based practices. Written informed consent was obtained both from adult patients and patients who were minors; the parents or guardians of minors also provided written consent. Details of the study protocol have been reported previously.¹⁶

The authors designed the study, collectively wrote the manuscript, and vouch for the completeness and accuracy of the data. Continuous glucose monitors and sensors were purchased at a bulk discount price from DexCom, Medtronic, and Abbott Diabetes Care. Home glucose meters and test strips were provided to the study by LifeScan and Abbott Diabetes Care. The manufacturers had no involvement in the study design, data accrual or analysis, or preparation of the manuscript.

STATISTICAL ANALYSIS

The primary outcome was the change in the mean glycated hemoglobin level from baseline to 26 weeks, as determined by a central laboratory. A sample size of 110 patients in each of three age groups (≥ 25 years, 15 to 24 years, and 8 to 14 years) was planned to have a power of 90% within each age group to detect a difference in the mean glycated hemoglobin level between study groups, assuming a population difference of 0.5%, a standard deviation of 0.9 at 26 weeks, a correlation between baseline and 26-week values of 0.58, an alpha level of 0.05, and a loss to follow-up of no more than 15%. An interim estimation of sample size that was based on only the observed variance in the change in glycated hemoglobin levels indicated that 86 patients would be needed in each age group to provide sufficient statistical power.

All analyses were performed according to the intention-to-treat principle. The primary analysis was a comparison between the two study groups of the change in the glycated hemoglobin levels from baseline to 26 weeks in analysis of covariance (ANCOVA) models, conducted separately in each of the three age groups and adjusted for the baseline glycated hemoglobin level and clinical center. There was a highly significant interaction between study group and age group ($P=0.003$) in an ANCOVA model containing an age group–treatment group interaction term, a finding that confirmed the need to analyze outcomes separately for each age group. As a result, a P value of 0.0167 was considered the significance level for the primary analysis in each age group to maintain an overall type I error rate of 0.05.

Table 1. Baseline Characteristics of the Patients, According to Age.*

Variable	Age Group					
	≥25 Yr		15–24 Yr		8–14 Yr	
	Continuous-Monitoring Group (N=52)	Control Group (N=46)	Continuous-Monitoring Group (N=57)	Control Group (N=53)	Continuous-Monitoring Group (N=56)	Control Group (N=58)
Female sex — no. (%)	31 (60)	26 (57)	29 (51)	38 (72)	27 (48)	29 (50)
Age — yr	41.2±11.2	44.6±12.3	18.8±3.0	18.2±2.7	11.4±2.0	11.6±2.1
Non-Hispanic white race — no. (%)†	52 (100)	41 (89)	47 (82)	51 (96)	51 (91)	54 (93)
Body-mass index z score — no. (%)‡						
Less than −0.5	8 (15)	9 (20)	6 (11)	5 (9)	2 (4)	1 (2)
−0.5 to 0.5	34 (65)	28 (61)	18 (32)	18 (34)	16 (29)	11 (19)
>0.5	10 (19)	9 (20)	33 (58)	30 (57)	38 (68)	46 (79)
Duration of diabetes — yr	23.6±10.6	21.8±10.4	9.5±4.8	8.8±4.0	6.2±3.1	5.3±2.8
Insulin administration — no. (%)						
Pump	43 (83)	39 (85)	38 (67)	40 (75)	47 (84)	49 (84)
Multiple daily injections	9 (17)	7 (15)	19 (33)	13 (25)	9 (16)	9 (16)
Glycated hemoglobin — %	7.6±0.5	7.6±0.5	8.0±0.7	7.9±0.8	8.0±0.7	7.9±0.6
7.0–8.0% — no. (%)	43 (83)	40 (87)	34 (60)	36 (68)	32 (57)	34 (59)
8.1–8.9% — no. (%)	8 (15)	5 (11)	18 (32)	11 (21)	18 (32)	23 (40)
≥9.0% — no. (%)	1 (2)	1 (2)	5 (9)	6 (11)	6 (11)	1 (2)
One or more episodes of severe hypoglycemia during previous 6 mo — no. (%)§	7 (13)	3 (7)	5 (9)	4 (8)	2 (4)	3 (5)
Daily home glucose-meter reading — no./day	6.5±2.3	6.6±2.2	5.6±2.0	6.1±2.6	6.7±2.1	7.0±2.5
College graduate (patient or primary caregiver) — no. (%)	42 (81)	36 (78)	35 (61)	37 (70)	48 (86)	52 (90)

* Plus-minus values are means ±SD.

† Race was self-reported.

‡ The body-mass index z scores were adjusted for age and sex on the basis of scores for a healthy population.

§ A severe episode of hypoglycemia was defined as an event that required assistance from another person to administer carbohydrate, glucagon, or other resuscitative actions.

Within each age group, in addition to the primary ANCOVA analysis, five prespecified binary outcomes for glycated hemoglobin at 26 weeks (a relative decrease of ≥10%, a 26-week level of <7.0%, an absolute decrease of ≥0.5%, a relative increase of ≥10%, and an absolute increase of ≥0.5%) were evaluated in logistic-regression models, adjusted for the baseline glycated hemoglobin level and clinical center. In a post hoc analysis, a binary outcome of a glycated hemoglobin level of less than 7.0% with no severe hypoglycemic events at 26 weeks was similarly analyzed. Prespecified exploratory analyses were conducted to assess the consistency of the treatment effect on the change

in the glycated hemoglobin level from baseline to 26 weeks in subgroups that were based on the type of insulin delivery (pump or multiple daily injections) and the baseline glycated hemoglobin level (≤8.0% or >8.0%).

Data regarding continuous glucose monitoring in both groups after the 26-week visit (blinded monitors in the control group and unblinded monitors in the continuous-monitoring group) were used to estimate the amount of time per day the glucose level was hypoglycemic (≤70 mg per deciliter or ≤50 mg per deciliter [≤3.9 or ≤2.8 mmol per liter]), hyperglycemic (>180 mg per deciliter or >250 mg per deciliter [10.0 or 13.9 mmol per

Table 2. Glycemic Outcomes at 26 Weeks, According to Age.*

Variable	Age Group					
	≥25 Yr		15–24 Yr		8–14 Yr	
	Continuous-Monitoring Group (N=52)	Control Group (N=46)	P Value	Continuous-Monitoring Group (N=57)	Control Group (N=53)	P Value
Glycated hemoglobin level†						
At baseline — %	7.6±0.5	7.6±0.5		8.0±0.7	7.9±0.8	
Change from baseline to 26 weeks — %‡	−0.50±0.56	0.02±0.45	<0.001	−0.18±0.65	−0.21±0.61	0.52
Relative decrease by ≥10% — no. (%)	13 (26)	2 (4)	0.003	8 (14)	5 (10)	0.46
Absolute decrease by ≥0.5% — no. (%)	24 (48)	5 (11)	<0.001	20 (36)	19 (37)	0.57
Relative increase ≥10% — no. (%)	0	1 (2)	0.48	2 (4)	2 (4)	0.98
Absolute increase ≥0.5% — no. (%)	0	5 (11)	0.02	7 (13)	7 (14)	0.84
26-week level <7.0% — no. (%)	17 (34)	4 (9)	0.005	8 (14)	9 (18)	0.80
26-week level <7.0%, with no severe hypoglycemic events — no. (%)	15 (30)	3 (7)	0.006	7 (13)	7 (14)	0.67
Glucose level§						
Mean min per day in 3 ranges — baseline/26 wk						
71–180 mg/dl	854/986	811/840	<0.001	691/761	697/761	0.79
>180 mg/dl	497/394	549/519	0.002	650/591	641/591	0.85
>250 mg/dl	149/101	181/161	<0.001	271/215	265/242	0.44
Mean mg/dl/min — baseline/26 wk¶	0.73/0.68	0.72/0.74	0.07	0.85/0.84	0.86/0.87	0.48

* Plus-minus values are means ±SD.

† At 26 weeks, data regarding glycated hemoglobin levels were not available for five patients who dropped out of the study (in the continuous-monitoring group, two patients who were 25 years of age or older and one who was 15 to 24 years of age; in the control group, two who were 15 to 24 years of age).

‡ The between-group difference was significant among patients 25 years of age or older (mean difference, −0.53%; 95% confidence interval [CI], −0.71 to −0.35) but not among those 15 to 24 years of age (mean difference, 0.08; 95% CI, −0.17 to 0.33) nor those 8 to 14 years of age (mean difference, −0.13; 95% CI, −0.38 to 0.11).

§ Data regarding continuous glucose monitoring were obtained after completion of the 26-week visit with the use of an unblinded device in the continuous-monitoring group and a blinded device in the control group. Data were missing in the continuous-monitoring group for two patients who were 25 years of age or older, seven patients who were 15 to 24 years of age, and two patients who were 8 to 14 years of age; data were missing in the control group for two patients who were 8 to 14 years of age.

¶ This value was the absolute rate of change.

Figure 1. Glycated Hemoglobin Levels during 26-Week Study Period, According to Age.

Shown are glycated hemoglobin levels for patients 25 years of age or older (Panel A), 15 to 24 years (Panel B), and 8 to 14 years (Panel C) who were receiving either continuous glucose monitoring or usual monitoring (control group). Points below the diagonal line represent an improvement in the glycated hemoglobin level from baseline. The horizontal dotted line represents the American Diabetes Association target of 7.0%.

liter]), and in the target range (71 to 180 mg per deciliter [3.9 to 10.0 mmol per liter]). Variability in glucose levels was assessed by computing the absolute rate of change.¹⁹ Comparisons between study groups were performed with the use of ANCOVA models based on van der Waerden normal scores and adjusted for the corresponding baseline value, baseline glycated hemoglobin level, clinical center, and type of continuous glucose monitor. In the continuous-monitoring group, the association between age group and the amount of sensor use during the 26-week period was evaluated with the use of the Kruskal–Wallis test. The association between sensor use and the baseline glycated hemoglobin level was evaluated with Spearman's correlation coefficients.

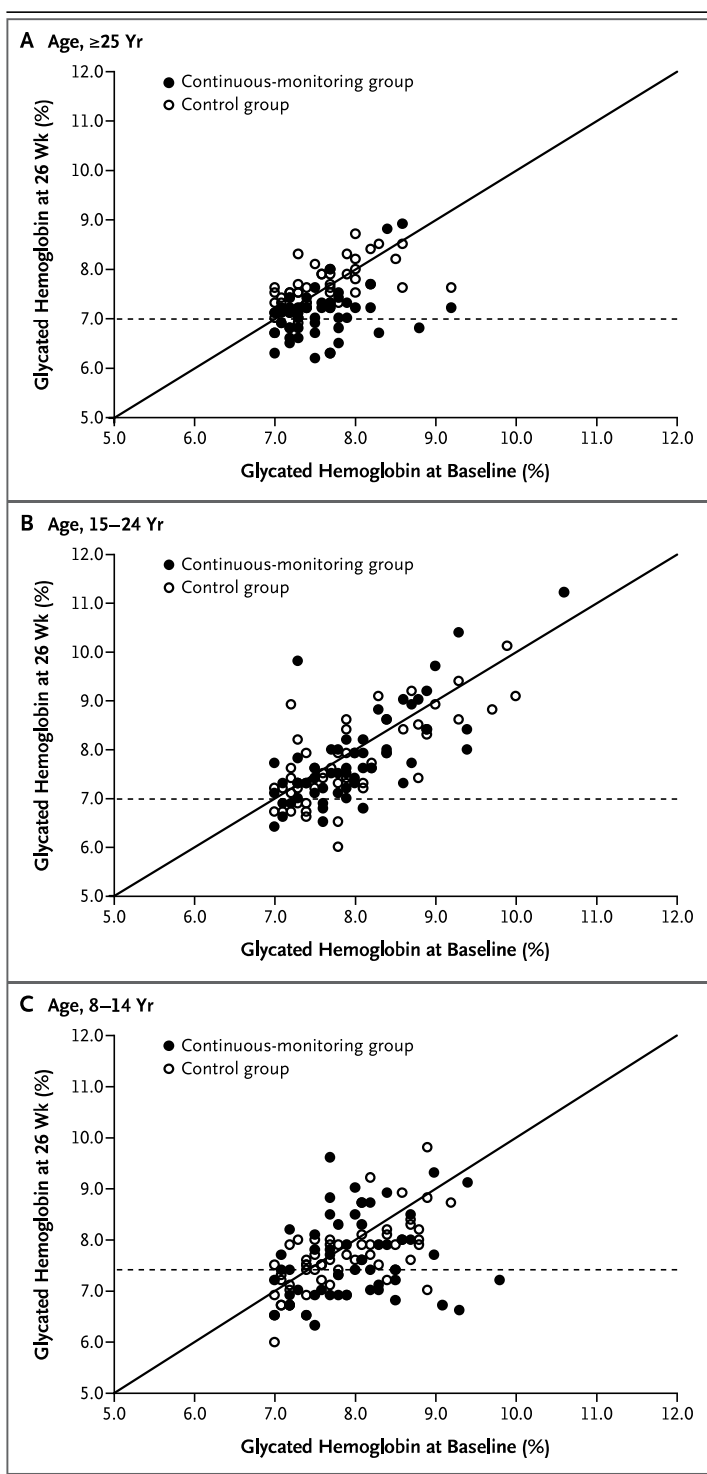
The proportions of patients who had one or more severe hypoglycemic events in each study group were compared with the use of Fisher's exact test. Incidences of hypoglycemic events were compared and confidence intervals for the treatment group difference calculated with the use of permutation tests. Similar analyses were performed for the subgroup of hypoglycemic events associated with seizure or coma.

Analyses were conducted with the use of SAS software, version 9.1 (SAS Institute). All P values are two-sided. Adjustment for imbalances between baseline factors and imputation for missing data with the use of Rubin's method²⁰ did not alter the results (data not shown). Parallel analyses were performed on data regarding glycated hemoglobin levels and continuous glucose monitoring obtained at 13 weeks.

RESULTS

PATIENTS

In 2007, between February and December, 322 patients underwent randomization, with 165 patients assigned to the continuous-monitoring group and



157 to the control group. Of those patients, 98 patients were 25 years of age or older, 110 patients were 15 to 24 years old, and 114 patients were 8 to 14 years old. The majority of patients were non-Hispanic white, were using insulin pumps, were

measuring glucose levels more than five times per day with a home glucose meter, and had a mean glycated hemoglobin level of 8.0% or less (Table 1).

Across the three age groups, the rate of completion of visits in the two study groups was 95 to 100% (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). For protocol-specified telephone contacts, the rate was 93 to 98%. The 26-week visit was completed by all but two patients in the continuous-monitoring group who were 25 years of age or older, by all but one patient in the continuous-monitoring group and two patients in the control group who were 15 to 24 years of age, and by all patients who were 8 to 14 years of age. Two patients in the control group (both 8 to 14 years of age) initiated the use of continuous glucose monitoring before completing the 26-week visit.

GLYCEMIC CONTROL

In the primary analysis, a significant between-group difference in the change in glycated hemoglobin levels from baseline to 26 weeks was seen in patients who were 25 years of age or older favoring the continuous-monitoring group (mean difference in change, -0.53% ; 95% confidence interval [CI], -0.71 to -0.35 ; $P<0.001$) but not in those 15 to 24 years of age (0.08 ; 95% CI, -0.17 to 0.33 ; $P=0.52$) nor in those 8 to 14 years of age (-0.13 ; 95% CI, -0.38 to 0.11 ; $P=0.29$).

At 26 weeks, among patients in the continuous-monitoring group who were 25 years of age or older, there were improvements in virtually all measures of glycemic control, as compared with the control group (Table 2 and Fig. 1 and 2). In the secondary analyses, more patients in the continuous-monitoring group had a relative reduction of 10% or more in the mean glycated hemoglobin level, as compared with baseline ($P=0.003$), and more achieved the target glycated hemoglobin level of less than 7.0% ($P=0.005$), as recommended for adults by the American Diabetes Association.²¹ The frequency of the combined outcome of a 26-week glycated hemoglobin level of less than 7.0% and no severe hypoglycemic events was 30% in the continuous-monitoring group and 7% in the control group ($P=0.006$). The amount of time per day within the target glucose range of 71 to 180 mg per deciliter was significantly greater in the continuous-monitoring group than in the control group ($P<0.001$).

Among patients who were 15 to 24 years of age, the mean decrease in glycated hemoglobin levels from baseline to 26 weeks was approximately 0.2% in both study groups. There were no significant differences between groups on any of the secondary glycemic measures.

Among patients who were 8 to 14 years of age, the mean decrease in glycated hemoglobin levels was 0.37% in the continuous-monitoring group, which did not differ significantly from the decrease of 0.22% in the control group. However, secondary indexes of glycemic control were improved in the continuous-monitoring group — namely, more patients had a relative reduction of 10% or more in the glycated hemoglobin level from baseline ($P=0.04$) and more patients had glycated hemoglobin levels of less than 7.0% ($P=0.01$) (Table 2 and Fig. 1 and 2). At 26 weeks, there were no significant differences between the two study group in outcomes as measured by continuous glucose monitoring.

Within the three age groups, the 13-week results were similar to the 26-week results (Table 1 in the Supplementary Appendix). At 26 weeks, results were consistent in subgroups based on the type of insulin delivery (pump vs. multiple daily injections) and baseline glycated hemoglobin levels ($\leq 8.0\%$ vs. $>8.0\%$) (Table 2 in the Supplementary Appendix).

HYPOGLYCEMIA AND OTHER ADVERSE EVENTS

Severe hypoglycemic events were infrequent in the two study groups. In the six age-stratified groups, 5 to 10% of patients had at least one severe hypoglycemic event, with no significant differences between the two study groups on the basis of age (Table 3). Likewise, there were no significant differences in the incidence of severe hypoglycemic events between study groups according to age. One patient in the continuous-monitoring group who was 30 years of age had six events involving either seizure or coma during a period in which he reported not using any long-acting insulin; for four of the six events, he reported that he had not used short-acting insulin on the day of the event.

Biochemical hypoglycemia (blood glucose, ≤ 70 mg per deciliter), which was evaluated by collecting data from continuous glucose monitoring in both study groups after the 26-week visit, was present for only a small portion of the day and did not differ significantly between the two groups

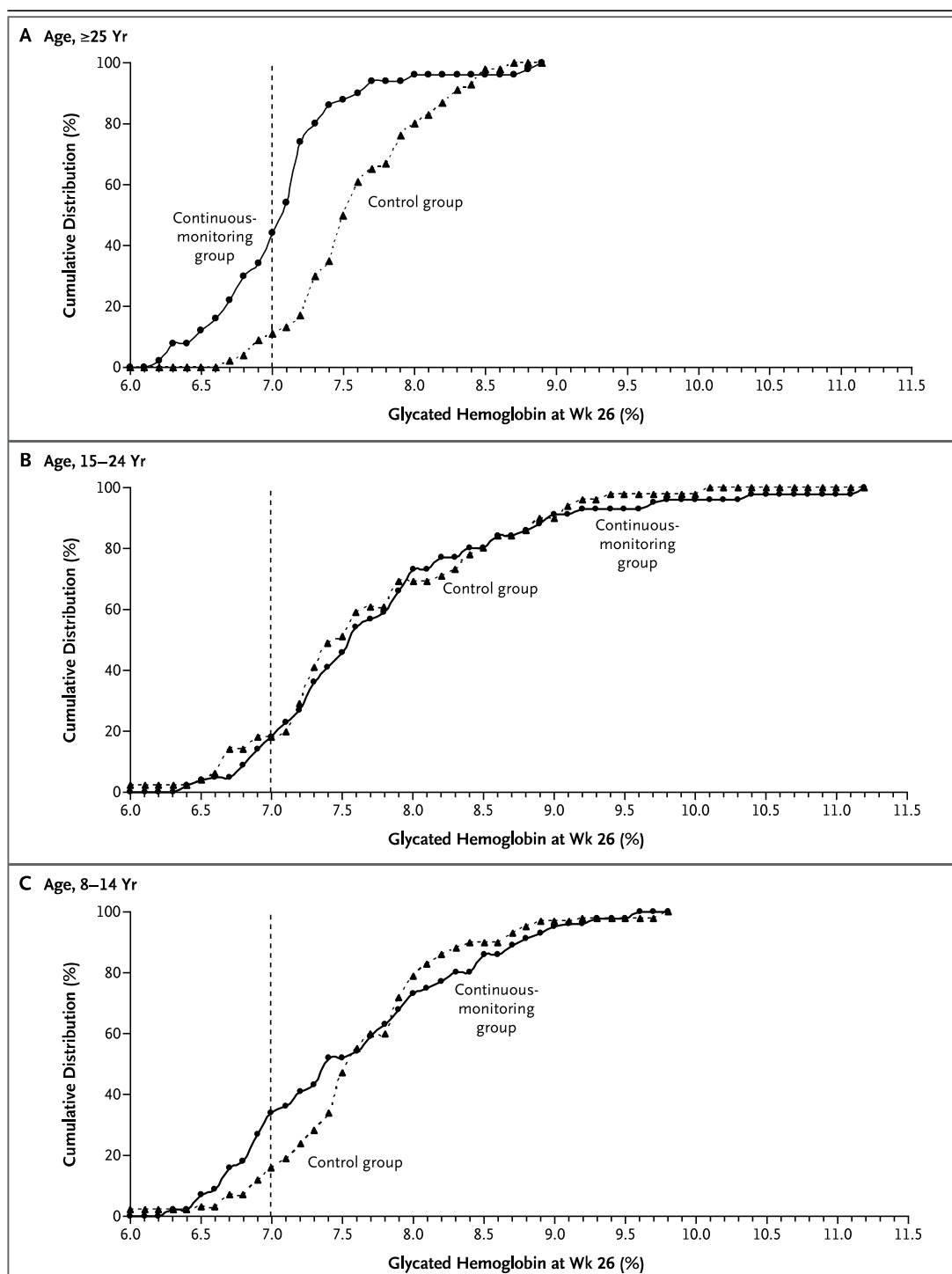


Figure 2. Cumulative Distribution of Glycated Hemoglobin Levels, According to Age.

Shown are glycated hemoglobin levels for patients 25 years of age or older (Panel A), 15 to 24 years (Panel B), and 8 to 14 years (Panel C). The vertical dotted line represents the American Diabetes Association target of 7.0%.

Table 3. Hypoglycemia and Other Adverse Events, According to Age.*

Variable	Age Group					
	≥25 Yr		15–24 Yr		8–14 Yr	
	Continuous-Monitoring Group (N=52)	Control Group (N=46)	Continuous-Monitoring Group (N=57)	Control Group (N=53)	Continuous-Monitoring Group (N=56)	Control Group (N=58)
					P Value†	P Value†
Severe hypoglycemic event‡:						
No. per patient — no. of patients (%)						
0 events	47 (90)	42 (91)	54 (95)	48 (91)	52 (93)	52 (90)
1 event	3 (6)	3 (7)	1 (2)	4 (8)	3 (5)	5 (9)
2 events	1 (2)	0	2 (4)	1 (2)	1 (2)	1 (2)
3 events	0	1 (2)	0	0	0	0
6 events	1 (2)	0	0	0	0	0
Patients with ≥1 event — no. of patients (%)	5 (10)	4 (9)	3 (5)	5 (9)	4 (7)	6 (10)
Events per 100 person-yr — no.	43.4§	26.3	17.9	23.9	17.9	24.4
Severe hypoglycemic episode with seizure or coma¶						
No. per patient — no. of patients (%)						
0 events	51 (98)	45 (98)	56 (98)	50 (94)	56 (100)	58 (100)
1 event	0	1 (2)	1 (2)	3 (6)	0	0
6 events	1 (2)	0	0	0	0	0
Patients with ≥1 event — no. of patients (%)	1 (2)	1 (2)	1 (2)	3 (6)	0	0
Events per 100 person-yr — no.	23.7§	4.4	3.6	11.9	0	0
Glucose level						
Mean min per day in 2 ranges — baseline/26 wk						
≤70 mg/dl	89/60	80/81	99/88	102/88	49/47	59/59
≤50 mg/dl	32/11	22/23	37/29	42/31	17/10	18/13

Other adverse events — no. of patients									
Diabetic ketoacidosis	0	0	0	0	1	0	0	0	0
Cellulitis related to sensor use	0	0	0	0	0	2	0	0	0
Dizziness during blood draw	0	0	0	0	0	0	0	0	1
Anxiety and depression	0	0	0	1	0	0	0	0	0
Kidney laceration	0	0	0	0	1	0	0	0	0
Seizure not caused by hypoglycemia	0	0	0	1	0	0	0	0	0

* NA denotes not applicable.

† Fisher's exact test was used to compare the percentages of patients in each study group who had at least one hypoglycemic event; permutation tests were used to compare the incidence rates and compute the confidence intervals.

‡ The between-group difference was 17.1 (95% confidence interval [CI], –37.4 to 73.5) for patients who were 25 years of age or older, –6.0 (95% CI, –35.8 to 23.7) for those who were 15 to 24 years of age, and –6.5 (95% CI, –33.4 to 20.6) for those who were 8 to 14 years of age.

§ One patient in the continuous-monitoring group who was 25 years of age or older had six episodes of seizure or coma. During this period, he reported that he had not used any long-acting insulin; for four of the six episodes, he reported that he had not used a short-acting insulin on the day of the event. With the exclusion of data from this patient, the incidence rate for severe hypoglycemia was 20.0 per 100 person-years, and the incidence rate for seizure or coma was 0.

¶ The between-group difference was 19.3 (95% CI, –12.8 to 56.3) for patients who were 25 years of age or older and –8.3 (95% CI, –23.4 to 7.0) for those who were 15 to 24 years of age. For patients who were 8 to 14 years of age, there were no events.

|| Data were obtained from continuous glucose monitoring after completion of the 26-week visit with the use of an unblinded device in the continuous-monitoring group and a blinded device in the control group. Data were missing in the continuous-monitoring group for two patients who were 25 years of age or older, seven patients who were 15 to 24 years of age, and two patients who were 8 to 14 years of age; data were missing in the control group for two patients who were 8 to 14 years of age.

in each age group. There were few other adverse events (Table 3).

FREQUENCY OF SENSOR USE

In the continuous-monitoring group, the use of sensors was greater among patients who were 25 years of age or older than in the other two age groups ($P<0.001$). The use of sensors was consistently high during the 26-week period among patients in the oldest age group but declined over time in the other two age groups (Fig. 3). Excluding the three patients who dropped out, only one patient who was 25 years of age or older, seven who were 15 to 24 years of age, and two who were 8 to 14 years of age discontinued continuous glucose monitoring before completing the 26-week visit. At least 6.0 days of sensor use per week was the average for 83% of patients who were 25 years of age or older, 30% who were 15 to 24 years of age, and 50% who were 8 to 14 years of age. Sensor use was not associated with the baseline glycated hemoglobin level (Spearman's correlation coefficients, 0.08, –0.02, and 0.03 in the three groups, respectively).

DISCUSSION

In this randomized, controlled trial, we observed that the benefit associated with continuous glucose monitoring was strongly related to age. A significant difference in the primary analysis of the change in glycated hemoglobin levels from baseline to 26 weeks was seen in the predefined group of patients who were 25 years of age or older but not in the two groups of patients who were younger. In patients 25 years of age or older, substantially tighter glycemic control was evident in the continuous-monitoring group in both glycated hemoglobin levels and sensor glucose results, without a significant increase in biochemical hypoglycemia (time per day with values of ≤ 70 mg per deciliter on continuous glucose monitoring). More patients in the continuous-monitoring group than in the control group had a glycated hemoglobin level of less than 7.0% without having a severe hypoglycemic event.

In contrast, comparisons between study groups showed less benefit of continuous glucose monitoring among patients who were 8 to 14 years of age and no benefit among those who were 15 to 24 years of age. Among those 8 to 14 years of age, the between-group difference in mean gly-

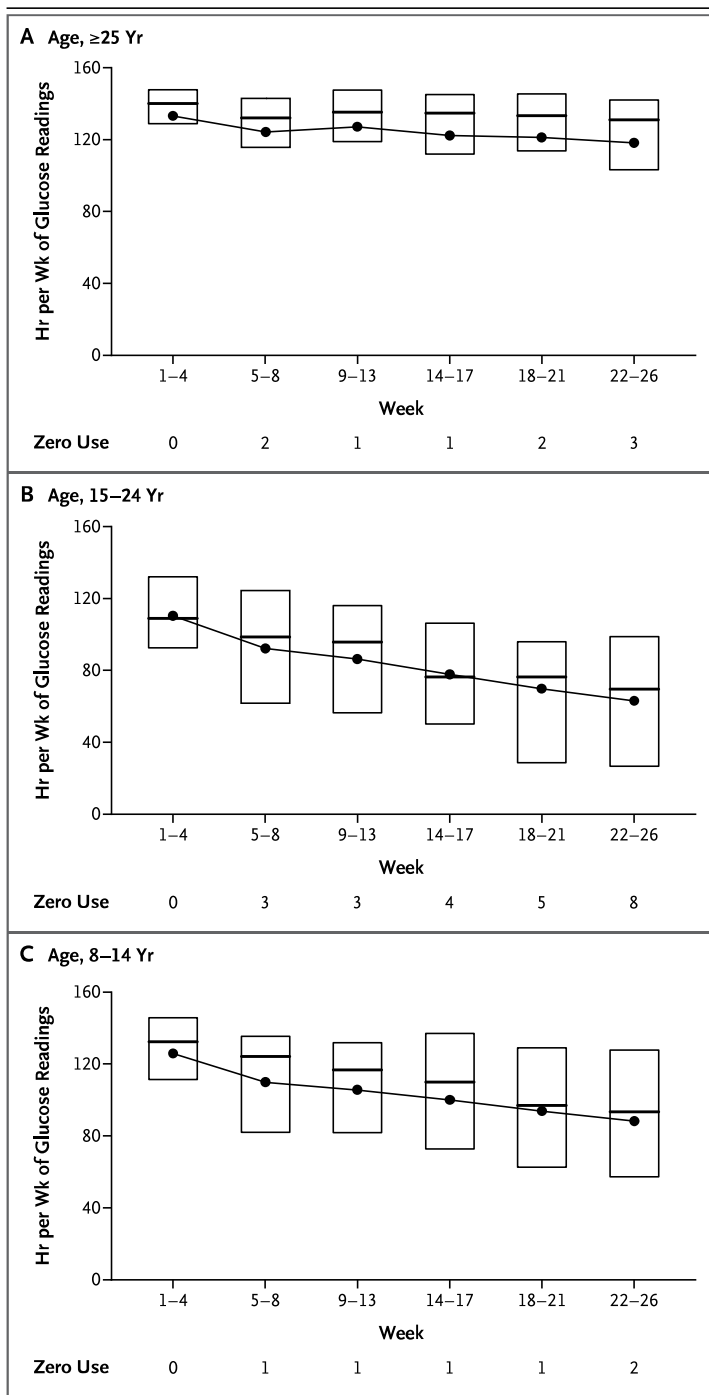


Figure 3. Use of Continuous Glucose Monitors in the Continuous-Monitoring Group, According to Age.

Shown are the hours per week of glucose readings that were recorded during the 26-week study period for 52 patients who were 25 years of age or older (Panel A), 57 patients who were 15 to 24 years of age (Panel B), and 56 patients who were 8 to 14 years of age (Panel C). Each box represents the interquartile range, with the horizontal line in the box representing the median and the dot representing the mean. Patients who withdrew from the trial were considered to have had no use of the monitors after the date of discontinuation. (See Fig. 1 in the Supplementary Appendix for the timing of withdrawals.)

DCCT showed that a relative reduction of 10% in glycated hemoglobin levels is associated with a reduction of more than 40% in the rate of development and progression of early diabetic retinopathy.^{22,23}

The observed age effect may be related to substantially greater use of sensors in the adults than in patients in the two younger groups. Imperfect adherence with many aspects of diabetes management has long been recognized as an obstacle to successful intensive treatment in adolescents and young adults with type 1 diabetes.²⁴⁻²⁷ Greater parental involvement could be the reason that patients in the continuous-monitoring group between the ages of 8 and 14 years had greater sensor use than the patients between the ages of 15 and 24 years. In adolescents, the transition from parental assistance with management of diabetes to patient-only management is often accompanied by deterioration of glycemic control.^{25,28}

Severe hypoglycemic events were infrequent and did not differ significantly according to study group. This finding must be interpreted with caution, since the trial was not powered to detect a between-group difference in such events. In the two groups, the rate of severe hypoglycemia was much lower than that reported in the DCCT.^{1,29} The use of a blinded continuous glucose monitor in the control group also provided the opportunity to compare the exposure of the two groups to biochemical hypoglycemia, which is often asymptomatic. In this regard, among patients 25 years of age or older, it was noteworthy that the decrease in glycated hemoglobin levels was not associated with an increase in hypoglycemia. This finding is in direct contrast to that of the DCCT, which showed that the rate of hypoglycemic events increased in patients who lowered their glycated hemoglobin levels.^{1,29}

cated hemoglobin levels did not achieve statistical significance. However, in this age group, in secondary analyses, more patients in the continuous-monitoring group than in the control group had glycated hemoglobin levels of less than 7.0% and more had a relative reduction of 10% or more in glycated hemoglobin levels from baseline values. The latter observation is important, since the

With respect to the generalizability of the results, it is important to recognize that before the study, patients were receiving intensive insulin therapy with either an insulin pump or multiple daily injections and frequent home blood glucose monitoring, and most had better-than-average glycated hemoglobin levels.^{30,31} In addition, to be eligible for the study, patients needed to show the ability to wear a sensor and insert a new sensor at home. Therefore, the results do not shed light on the use of such devices in a less well controlled, less motivated population of patients with type 1 diabetes. Although the results in patients using multiple daily injections were similar to the results in those using an insulin pump, the number of patients using multiple daily injections was too small for a definitive assessment.

The results of our study indicate that continuous glucose monitoring improves glycated hemoglobin levels and may enhance the management of type 1 diabetes in adults who have the motivation to use this technology and the capability to incorporate it into their own daily diabetes management. Further work is needed to identify and

address the lack of effectiveness of continuous glucose monitoring in children and adolescents.

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APPENDIX

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REFERENCES

1. The 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;329:977-86.
2. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 2001;24:1858-62.
3. Kaufman FR, Austin J, Neinstein A, et al. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. *J Pediatr* 2002;141:625-30.
4. Bode BW, Schwartz S, Stubbs HA, Block JE. Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes: normative values. *Diabetes Care* 2005;28:2361-6.
5. Thompson CJ, Cummings JF, Chalmers J, Gould C, Newton RW. How have patients reacted to the implications of the DCCT? *Diabetes Care* 1996;19:876-9.
6. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272-9.
7. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care* 2005;28:1231-9.
8. Diabetes Research in Children Network (DirecNet) Study Group. A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. *Diabetes Care* 2005;28:1101-6.
9. Wilson DM, Beck RW, Tamborlane

- WV, et al. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. *Diabetes Care* 2007;30:59-64.
10. Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008;31:1160-4.
 11. Diabetes Research in Children Network (DirecNet) Study Group. Continuous glucose monitoring in children with type 1 diabetes. *J Pediatr* 2007;151:388-93.
 12. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 2006;29:44-50.
 13. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. *J Pediatr* 2007;150:103-5.
 14. Diabetes Research in Children Network (DirecNet) Study Group. FreeStyle Navigator continuous glucose monitoring system use in children with type 1 diabetes using glargine-based multiple daily dose regimens: results of a pilot trial. *Diabetes Care* 2008;31:525-7.
 15. Deiss D, Bolinder J, Riveline J-P, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29:2730-2.
 16. JDRF CGM Study Group. JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. *Diabetes Technol Ther* 2008;10:310-21.
 17. Diabetes Research in Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). *Pediatr Diabetes* 2008;9:142-7.
 18. Gibb I, Parnham A, Fonfrède M, Lecock F. Multicenter evaluation of Tosoh glycohemoglobin analyzer. *Clin Chem* 1999;45:1833-41.
 19. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther* 2005;7:849-62.
 20. Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley, 1987.
 21. American Diabetes Association. Standards of medical care in diabetes — 2008. *Diabetes Care* 2008;31:Suppl 1:S12-S54.
 22. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 1995;44:968-83.
 23. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the Diabetes Control and Complications Trial — revisited. *Diabetes* 2008;57:995-1001.
 24. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LMB. Family conflict, adherence, and glycaemic control in youth with short duration Type 1 diabetes. *Diabet Med* 2002;19:635-42.
 25. Insabella G, Grey M, Knafl G, Tamborlane W. The transition to young adulthood in youth with type 1 diabetes on intensive treatment. *Pediatr Diabetes* 2007;8:228-34.
 26. Laffel LM, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. *J Pediatr* 2003;142:409-16.
 27. Wysocki T, Iannotti R, Weissberg-Benchell J, et al. Diabetes problem solving by youths with type 1 diabetes and their caregivers: measurement, validation, and longitudinal associations with glycemic control. *J Pediatr Psychol* 2008;33:875-84.
 28. Moreland EC, Tovar A, Zuehlke JB, Butler DA, Milaszewski K, Laffel LM. The impact of physiological, therapeutic and psychosocial variables on glycemic control in youth with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2004;17:1533-44.
 29. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 1991;90:450-9.
 30. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-53.
 31. Petitti DB, Imperatore G, Palla SL, et al. Serum lipids and glucose control: the SEARCH for Diabetes in Youth study. *Arch Pediatr Adolesc Med* 2007;161:159-65.

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