ORIGINAL ARTICLE

A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes

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ABSTRACT

BACKGROUND

A closed-loop system of insulin delivery (also called an artificial pancreas) may improve glycemic outcomes in children with type 1 diabetes.

METHODS

In a 16-week, multicenter, randomized, open-label, parallel-group trial, we assigned, in a 3:1 ratio, children 6 to 13 years of age who had type 1 diabetes to receive treatment with the use of either a closed-loop system of insulin delivery (closed-loop group) or a sensor-augmented insulin pump (control group). The primary outcome was the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter, as measured by continuous glucose monitoring.

RESULTS

A total of 101 children underwent randomization (78 to the closed-loop group and 23 to the control group); the glycated hemoglobin levels at baseline ranged from 5.7 to 10.1%. The mean (±SD) percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter increased from 53±17% at baseline to 67±10% (the mean over 16 weeks of treatment) in the closed-loop group and from 51±16% to 55±13% in the control group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; P<0.001). In both groups, the median percentage of time that the glucose level was below 70 mg per deciliter was low (1.6% in the closed-loop group and 1.8% in the control group). In the closed-loop group, the median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95). No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either group.

CONCLUSIONS

In this 16-week trial involving children with type 1 diabetes, the glucose level was in the target range for a greater percentage of time with the use of a closed-loop system than with the use of a sensor-augmented insulin pump. (Funded by Tandem Diabetes Care and the National Institute of Diabetes and Digestive and Kidney Diseases; ClinicalTrials.gov number, NCT03844789.)

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The glycemic target of a glycated hemoglobin level of less than 7% (as recommended by the American Diabetes Association) is attained by less than 20% of children with type 1 diabetes.[1,2] The use of a closed-loop system that automates insulin delivery in a glucose-responsive manner (also referred to as an automated insulin delivery system or artificial pancreas) has the potential to improve glycemic outcomes and quality of life in these children.[3-7] Currently available systems require engagement of the user to inform the system of the insulin bolus dose at mealtimes. A single closed-loop system (MiniMed 670G, Medtronic) was approved in the United States for children 6 to 13 years of age; however, to date, published studies on its efficacy and safety have been limited to single-group studies with no randomization.[8-16] One other system (t:slim X2 insulin pump with Control-IQ Technology, Tandem Diabetes Care) was recently approved by the Food and Drug Administration (FDA) for clinical use in the treatment of type 1 diabetes in patients 14 years of age or older on the basis of the results of a 6-month randomized trial involving 168 adolescents and adults with type 1 diabetes.[17] Whether the significant benefit shown in that trial of glycemic control would be present in younger patients is uncertain. We conducted a randomized trial involving children with type 1 diabetes who were 6 to 13 years of age to assess the efficacy and safety of this closed-loop system in this age range.

Methods

Trial Conduct and Oversight

This multicenter, randomized, open-label, parallel-group trial was conducted at four pediatric diabetes centers in the United States. The protocol, available with the full text of this article at NEJM.org, was approved by a central institutional review board. Written informed consent was obtained from the parent or guardian of each patient, and assent was obtained from each patient when applicable. An investigational device exemption was approved by the FDA. An independent data and safety monitoring board established by the National Institute of Diabetes and Digestive and Kidney Diseases provided trial oversight. The first three authors and the last author wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Funding was provided by Tandem Diabetes Care, which also provided the closed-loop systems and supplies used in the trial and provided technical expertise with respect to device issues. Representatives of Tandem Diabetes Care reviewed the manuscript before submission for publication, but the company was not otherwise involved in the design or conduct of the trial or in the analysis of the data. Additional funding was provided by the National Institute of Diabetes and Digestive and Kidney Diseases.

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Trial Design and Patients

Patients were eligible for inclusion in the trial if they were 6 to 13 years of age, had received a diagnosis of type 1 diabetes at least 1 year before enrollment, had received treatment with insulin for at least 6 months, had a body weight of 25 to 140 kg, and had a total daily insulin dose of at least 10 units (complete eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org). After consent and assent forms were signed and eligibility determined, patients who were not currently using an insulin pump or a Dexcom continuous glucose monitor were required to complete a run-in phase of 2 to 4 weeks that was customized on the basis of whether the patient was already using a pump or continuous glucose monitor. These patients were required to use an insulin pump and continuous glucose monitor daily for at least 11 of 14 days during the run-in phase, which was successfully completed by all patients (Fig. S1). Patients who were already using an insulin pump and a Dexcom continuous glucose monitor for least 11 of 14 days before the trial were not required to complete the run-in phase (68 patients). Patients who were allowed to skip or who successfully completed the run-in phase were randomly assigned in a 3:1 ratio to the closed-loop group or the control group on the trial website with the use of a computer-generated sequence with a permuted block design (block sizes of 4 and 8), stratified according to trial site.

The patients in the closed-loop group were trained in the use of the closed-loop system, which consisted of a t:slim X2 insulin pump with Control-IQ Technology (a software algorithm developed at the University of Virginia[18-20]) and a continuous glucose monitor (Dexcom G6, Dexcom), which transmitted glucose values to the pump. Additional information about the closed-loop system is provided in the Supplementary

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Appendix. The patients in the control group used Dexcom G6 sensors, which were provided by the trial investigators. Those who had been using an insulin pump before the trial continued to use their personal pumps, and those who had been receiving insulin injections before the trial were provided with a t:slim X2 pump with a predictive low-glucose suspend feature. Adjustments to pump settings could be made in accordance with the judgment of the investigator. The patients in both groups received blood glucose meters and strips (Roche Accu-Chek Guide, Roche Diabetes Care) and ketone meters and strips (Abbott Precision Xtra, Abbott Diabetes Care).

The patients in both groups had trial visits at 2, 8, and 16 weeks and were contacted by telephone at 1, 4, 6, 10, 12, and 14 weeks. Data from the devices were downloaded and reviewed at each visit and during the telephone contacts. Glycated hemoglobin level was measured at the time of randomization and at 16 weeks by a central laboratory at the University of Minnesota Advanced Research and Diagnostic Laboratory. Questionnaires on quality of life and treatment satisfaction were completed at baseline and at 16 weeks (results not reported here).

Reportable adverse events included serious adverse events, adverse events occurring in association with a trial device or procedure, severe hypoglycemia (defined as hypoglycemia leading to the need for assistance because of altered consciousness), diabetic ketoacidosis as defined according to the criteria of the Diabetes Control and Complications Trial,[21] and hyperglycemia with ketonemia for which a health care provider was contacted.

OUTCOMES

The primary outcome was the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), as measured by continuous glucose monitoring. The main secondary outcomes, tested in a hierarchical fashion to maintain the type 1 error at 5%, included the percentage of time that the glucose level was above 180 mg per deciliter (>10.0 mmol per liter); mean glucose level; glycated hemoglobin level at 16 weeks; the percentage of time that the glucose level was below 70 mg per deciliter (3.9 mmol per liter), below 54 mg per deciliter (3.0 mmol per liter), or above 250 mg per deciliter (13.9 mmol per liter); and the coefficient of variation in the sensor glucose measurement. Continuous glucose-monitoring data from the time of randomization through the 16-week visit were pooled in the calculation of each metric. Additional secondary outcomes are listed in the statistical analysis plan, which is included with the protocol. Key safety outcomes included the frequency of severe hypoglycemia and diabetic ketoacidosis.

STATISTICAL ANALYSIS

We calculated that a sample size of 60 patients and a randomization ratio of 3:1 between the closed-loop group and control group would provide the trial with 90% power to reject the null hypothesis that there would be no between-group difference with respect to the primary outcome, with the following assumption: the mean percentage of time with the glucose level in the target range in the closed-loop group would be 10 percentage points higher than that in the control group, with a standard deviation of 10% and a two-sided, type 1 error rate of 0.05. The sample size was increased to 100 to increase the number of patients with exposure to the closed-loop system and thereby enhance the safety and feasibility assessments.

Statistical analyses were performed on an intention-to-treat basis, and all the patients were included in the primary and all secondary analyses unless otherwise noted. For the primary analysis, the percentage of time that the glucose level was in the target range during the 16-week trial period was compared between the two groups with the use of a linear mixed-effects regression model. Analyses of the secondary continuous outcomes were conducted by the same method that was used in the primary analysis. Modifications of the treatment effect on the percentage of time with the glucose level in the target range, the percentage of time with the glucose level below 70 mg per deciliter, and the glycated hemoglobin level were assessed according to baseline variables in exploratory subgroup analyses by including an interaction term in the linear mixed-effects regression models. Binary outcomes were analyzed with the use of a logistic-regression model. All models and reported between-group differences included adjustment for the baseline level of the dependent variable, age, previous use of a continuous glucose monitor and pump, and clinical center (random effect). Additional details about the statistical methods are provided in the Supplementary Appendix.

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All P values are two-tailed. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

Between June 21, 2019, and August 30, 2019, a total of 101 patients (19 to 28 per trial site) were randomly assigned to the closed-loop group (78 patients) or the control group (23 patients). At baseline, the ages of the patients ranged from 6 to 13 years, the duration of diabetes from 1 to 12 years, and the glycated hemoglobin level from 5.7 to 10.1%. Before the trial, 81 patients (80%) had been using insulin pumps, and 20 patients (20%) had been receiving multiple daily injections; 93 patients (92%) had been using a continuous glucose monitor (Table 1). During the trial, 15 of the 23 patients in the control group used the t:slim X2 pump with a predictive low-glucose suspend feature. The 16-week trial was completed by all the patients in the closed-loop group and by all but 1 patient in the control group (Fig. S2).

Among the 100 patients who completed the trial, 99.3% of the trial visits and 99.2% of the telephone contacts were completed. A total of 19 unscheduled visits occurred in the closed-loop group and 1 in the control group (Table S2). In the closed-loop group, all the patients were using the closed-loop system at the end of 16 weeks; the median percentage of continuous glucose monitor use over the 16 weeks was 97% (interquartile range, 95 to 98), and the median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95) (Table S3 and Fig. S3). The reported problems with the use of the closed-loop system are summarized in Table S4. In the control group, the median percentage of continuous glucose monitor use over the 16 weeks was 96% (interquartile range, 91 to 98) (Table S3), and all patients (excluding the 1 patient who did not complete the trial) were using a sensor-augmented pump at the end of 16 weeks.

EFFICACY OUTCOMES

In the primary analysis, the mean (±SD) percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter increased from 53±17% at baseline to 67±10% (the mean over 16 weeks of treatment) in the closed-loop group and from 51±16% to 55±13% in the control group, with a mean adjusted difference (the value in the closed-loop group minus the value in the control group) of 11 percentage points (95% confidence interval [CI], 7 to 14; P<0.001) (Table 2). The results of the sensitivity analyses were similar to those of the primary analysis (Table S5). The treatment effect was evident in the first month and appeared to be consistent over 4 months (Fig. 1A). The mean percentage of time that the glucose level was in the target range during the daytime (6 a.m. to midnight) was 63% in the closed-loop group and 56% in the control group, and the corresponding values during the nighttime (midnight to 6:00 a.m.) were 80% and 54% (Fig. 1B). A similar pattern was seen for mean glucose level, with lower daytime and nighttime values in the closed-loop group than in the control group (Fig. S4). The percentage of time that the glucose level was in the target range consistently favored the closed-loop group over the control group across a broad range of baseline characteristics, including age, sex, body-mass index, household income, parental education, previous insulin pump or injection use, and glycated hemoglobin level (Table S6). The results of subgroup analyses of the changes in the percentage of time with the glucose level below 70 mg per deciliter and the glycated hemoglobin level from baseline to 16 weeks are provided in Tables S7 and S8, respectively.

Treatment effects that favored the closed-loop group over the control group were also observed for the percentage of time with the glucose value above 180 mg per deciliter and for the mean glucose level (Table 2). The mean adjusted between-group difference in the glycated hemoglobin level at 16 weeks was −0.4 percentage points (95% CI, −0.9 to 0.1; P=0.08), which did not meet the threshold for statistical significance. Therefore, the remaining outcomes in the hierarchical analysis were not formally compared between groups (percentages of time with the glucose level <70 mg per deciliter, <54 mg per deciliter, and >250 mg per deciliter and the coefficient of variation in the sensor glucose measurement). In both groups, the median percentage of time with the glucose level below 70 mg per deciliter was low (1.6% and 1.8% in the closed-loop group and the control group, respectively) (Table 2).

The glycemic target of a glycated hemoglobin level of less than 7% (as recommended by the American Diabetes Association) was met in 39 patients (51%) in the closed-loop group and in 4 patients (18%) in the control group at 16 weeks

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closed Loop (N=78)	Control (N=23)
Age — yr		
Mean	11.3±2.0	10.8±2.4
Range	6.48–13.99	6.63–13.98
Age group — no. (%)		
6 to <10 yr	21 (27)	8 (35)
10 to <14 yr	57 (73)	15 (65)
Duration of diabetes — yr		
Mean	5.0±2.8	6.0±2.8
Range	1.2–12.0	1.1–12.0
Means of insulin administration — no. (%)		
Insulin pump	62 (79)	19 (83)
Multiple daily injections	16 (21)	4 (17)
Current continuous glucose monitor use — no. (%)	72 (92)	21 (91)
Body-mass index z score	0.4±1.0	0.5±1.0
Female sex — no. (%)	38 (49)	12 (52)
Race or ethnic group — no. (%)†		
White, non-Hispanic	64 (82)	18 (78)
Hispanic or Latino	6 (8)	2 (9)
Black	0	0
Asian	1 (1)	1 (4)
Multiracial	7 (9)	2 (9)
Highest parent education level — no. (%)		
Less than high school diploma	2 (3)	0
Associate's degree or some college but no degree	5 (6)	1 (4)
Bachelor's degree	32 (41)	9 (39)
Master's degree	34 (44)	11 (48)
Doctoral or professional degree	5 (6)	2 (9)
Annual household income — no./total no. (%)		
<$25,000	0/74	0/21
$25,000 to <$35,000	2/74 (3)	0/21
$35,000 to <$50,000	1/74 (1)	2/21 (10)
$50,000 to <$75,000	5/74 (7)	0/21
$75,000 to <$100,000	13/74 (18)	4/21 (19)
$100,000 to <$200,000	27/74 (36)	8/21 (38)
≥$200,000	26/74 (35)	7/21 (33)
Private medical insurance — no. (%)	70 (90)	21 (91)
Glycated hemoglobin level at screening		
Mean — %	7.7±1.1	8.0±1.1
Range — %	5.7–11.0	5.9–10.5
Glycated hemoglobin level at randomization		
Mean — %	7.6±1.0	7.9±0.9
Range — %	5.7–10.0	6.0–10.1
Distribution — no. (%)		
<8.0%	50 (64)	11 (48)
8.0% to <9.0%	20 (26)	10 (43)
≥9.0%	8 (10)	2 (9)
Daily insulin dose		
Patients with available data — no.	77	23
Mean no. of units per kg of body weight per day	0.89±0.24	0.94±0.24

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Table 1. (Continued.)

Characteristic	Closed Loop (N=78)	Control (N=23)
≥1 Event of diabetic ketoacidosis in last 12 mo — no. (%)	4 (5)	0
≥1 Event of severe hypoglycemia in last 12 mo — no. (%)	0	0
Detectable level of C-peptide — no. (%)‡	20 (26)	5 (22)

* Plus–minus values are means ±SD. The patients were randomly assigned to receive treatment with either a closed-loop system (closed loop) or a sensor-augmented pump (control).
† Race or ethnic group was reported by the parent of the trial participant.
‡ Random, nonfasting C-peptide testing was performed at the central laboratory. The detection limit of the assay was 0.009 ng per milliliter (0.003 nmol per liter).

(Table S9). The goal of a percentage of time with the blood glucose level in target range (70 to 180 mg per deciliter) of at least 70% plus a percentage of time with the glucose level below 70 mg per deciliter of less than 4%[22] was attained in 33 patients (42%) in the closed-loop group and in 3 patients (14%) in the control group (Table S10). The results of the other secondary and exploratory outcome analyses are provided in Tables S10 and S11.

The median number of fingerstick blood glucose measurements performed per day was 0.37 (interquartile range, 0.18 to 0.64) in the closed-loop group and 0.36 (interquartile range, 0.13 to 0.72) in the control group. The daily insulin amount per kilogram of body weight and the change in body weight appeared to be similar in the treatment groups (Tables S12 and S13).

ADVERSE EVENTS

A total of 16 adverse events were reported in 15 patients (19%) in the closed-loop group, and 3 adverse events were reported in 2 patients (9%) in the control group (number of events per 100 person-years, 65.3 and 41.3, respectively; P=0.50) (Table 3). Severe hypoglycemia or diabetic ketoacidosis did not occur in either treatment group. A total of 14 events of hyperglycemia or hyperketosis that met the reporting criteria in the protocol (but that did not meet the criteria for diabetic ketoacidosis) were reported in the closed-loop group, and 1 such event was reported in the control group. Other safety-related events are listed in Table 3.

DISCUSSION

During our multicenter, randomized trial involving children with type 1 diabetes who were 6 to 13 years of age, the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter (as measured by continuous glucose monitoring) was 11 percentage points higher among those who used the closed-loop system than among those who used a sensor-augmented pump, a difference that reflects 2.6 hours less time per day in a hyperglycemic state with closed-loop control. The magnitude of the treatment effect was virtually identical to that observed in a randomized trial involving adults and adolescents who used the same closed-loop system.[17] The beneficial effect was evident within the first month of closed-loop use and was more prominent overnight than during the day. The frequency of hypoglycemia was low in both groups, a finding that is perhaps related to the fact that about two thirds of the patients in the control group used an insulin pump with a predictive low-glucose suspend feature, which has been shown to reduce hypoglycemia.[23] Although the change from baseline in the glycated hemoglobin level did not differ significantly between the treatment groups, the results suggested that a glycated hemoglobin level below 7% was attained by a higher percentage of patients in the closed-loop group than in the control group, and the recently established goal of a percentage of time with the blood glucose level in the target range (70 to 180 mg per deciliter) of at least 70% plus a percentage of time with the blood glucose level below 70 mg per deciliter of less than 4% was attained by a substantially higher percentage of patients in the closed-loop group than in the control group.[22]

The closed-loop system was used without apparent difficulty, with no reported events of severe hypoglycemia or diabetic ketoacidosis. More adverse events, primarily associated with hyperglycemia and ketonemia caused by pump infusion set failure, were reported in the closed-loop group

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Table 2. Primary and Secondary Hierarchical Efficacy Outcomes.*

Outcome	Baseline†		16-Wk Trial Period‡			
	Closed Loop (N=77)	Control (N=23)	Closed Loop (N=78)	Control (N=22)	Risk-Adjusted Difference (95% CI)§	P Value
Hours of sensor data	306±33	311±23	2637±134	2609±128		
Primary outcome: glucose level in range of 70 to 180 mg/dl — % of time	53±17	51±16	67±10	55±13	11 (7 to 14)	<0.001
Secondary hierarchical outcomes in prespecified order¶						
Glucose level >180 mg/dl — % of time	45±18	47±17	31±10	43±14	−10 (−14 to −6)	<0.001
Glucose level — mg/dl	183±34	189±34	162±18	179±26	−13 (−20 to −7)	<0.001
Glycated hemoglobin level — %‖	7.6±1.0	7.9±0.9	7.0±0.8	7.6±0.9	−0.4 (−0.9 to 0.1)	0.08
Glucose level <70 mg/dl — median % of time (IQR)**	1.2 (0.5 to 2.4)	1.0 (0.2 to 2.1)	1.6 (0.8 to 2.4)	1.8 (1.1 to 3.0)	−0.40 (−0.83 to −0.02)	NA
Glucose level <54 mg/dl — median % of time (IQR)**	0.1 (0.0 to 0.4)	0.1 (0.0 to 0.3)	0.2 (0.1 to 0.4)	0.3 (0.1 to 0.6)	−0.07 (−0.19 to 0.02)	NA
Glucose level >250 mg/dl — median % of time (IQR)**	17.2 (8.6 to 27.6)	20.7 (12.4 to 32.6)	7.8 (5.1 to 14.3)	18.4 (9.4 to 24.6)	−5.8 (−8.7 to −3.0)	NA
Coefficient of variation in the sensor glucose measurement — %	38±5	38±4	38±4	39±4	−1.6 (−2.8 to −0.4)	NA

* Plus–minus values are means ±SD. One patient in the closed-loop group was missing baseline continuous glucose-monitoring data, and 1 patient in the control group was missing follow-up data. All the patients were included in the model on an intention-to-treat basis. Missing data were handled by means of direct likelihood analyses. In the control group, 15 of 23 patients used the t:slim X2 pump with a predictive low-glucose suspend feature (Tandem Diabetes Care), 3 used an OmniPod pump (Insulet), and 5 used a Medtronic pump. To convert the values for glucose to millimoles per liter, multiply by 0.05551. IQR denotes interquartile range, and NA not applicable.

† Baseline outcomes measured by the continuous glucose monitor were calculated with the data obtained in the 14 days before randomization. These data were obtained with the use of a personal Dexcom continuous glucose monitor for the 50 patients in the closed-loop group and the 17 patients in the control group who were allowed to skip the run-in phase. The baseline glycated hemoglobin level was measured at the randomization visit.

‡ Data are means or medians over the 16-week trial period with the exception of glycated hemoglobin level, for which data are the mean at the 16-week trial visit.

§ Differences were calculated as percentage points (the value in the closed-loop group minus the value in the control group) and were model-adjusted for the baseline value of the metric, age, previous continuous glucose monitor and pump use, and clinical center (random effect).

¶ To control the type 1 error, a hierarchical approach was used in which hypothesis testing was performed sequentially in the order listed in the table. When a P value of 0.05 or higher was observed, the outcomes below that finding on the list were not formally tested.

‖ Data on glycated hemoglobin level at baseline were available for 78 patients in the closed-loop group and 23 patients in the control group, and data on glycated hemoglobin level at the 16-week trial visit were available for 77 patients and 22 patients, respectively.

** Distributions were skewed for the percentages of time with the glucose level below 70 mg per deciliter, below 54 mg per deciliter, and above 250 mg per deciliter and were thus modeled with the use of rank-based transformation.

than in the control group. Because the control group mostly used the same pump and infusion set as the closed-loop group, this difference probably reflects variation in reporting, possibly related to instructions to patients using the closed-loop system to contact staff at their trial site about device problems.

A few randomized trials of closed-loop systems in an outpatient setting have been conducted in this age range with a similar number of participants and trial duration (>1 month). In a 12-week crossover trial, Thabit et al. reported that the percentage of time overnight with the glucose level in the range of 70 to 180 mg per deciliter was 25 percentage points higher with a closed-loop system than with a sensor-augmented pump in 25 children (6 to 18 years of age) with type 1 diabetes,[7] a percentage-point difference that is very similar to the overnight result in the current trial. In an uncontrolled 3-month study involving 105 children 7 to 13 years of age using the 670G closed-loop system, Forlenza et al. reported an increase from baseline in the percentage of time with the glucose level in the range of 70 to 180 mg per deciliter, a decrease in the percentage of time with the glucose level below 70 mg per deciliter, and a decrease in the glycated hemoglobin level, but there was no comparison group.[11] Our results compare favorably with both of these studies.

Strengths of the current trial include the enrollment of patients with no restriction based on glycated hemoglobin level or prior severe hypoglycemia or diabetic ketoacidosis, near 100% patient retention, and a high level of adherence to the use of the assigned devices in both treatment groups. Our trial also had certain limitations. Although eligibility criteria were broad, the trial population was not fully representative of the general population with respect to socioeconomic status, glycated hemoglobin levels, and the use of devices (pumps and continuous glu-

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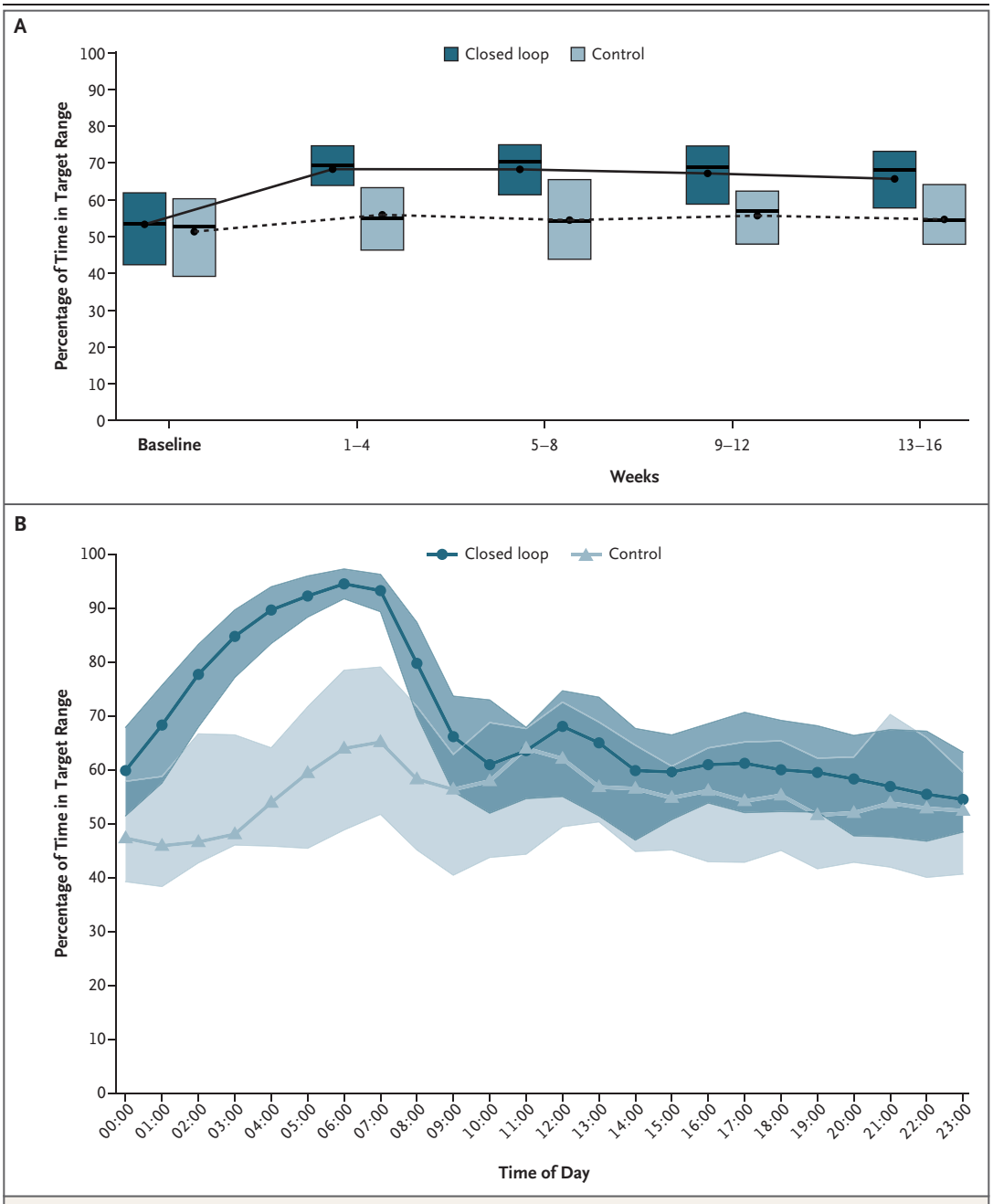

Figure 1. Percentage of Time with the Glucose Level in the Target Range.

Panel A shows a box plot of the percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), as measured by continuous glucose monitoring, during 4-week periods over 4 months among patients who were assigned to receive treatment with either a closed-loop system (closed loop) or a sensor-augmented pump (control). The black dots denote the mean values, the horizontal bars the median values, and the lower and upper boundaries of each box the 25th and 75th percentiles, respectively. Panel B shows an envelope plot of the same outcome according to the time of day. The data points denote the hourly median values, and the lower and upper boundary of each shaded region the 25th and 75th percentiles, respectively.

cose monitors) in diabetes management. However, the trial results suggested a similar treatment effect on the percentage of time in the target glycemic range across a broad spectrum of baseline characteristics, including among patients who had not previously used insulin pumps. Further

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Table 3. Safety Outcomes during the 16-Week Trial Period.

Event	Closed Loop (N=78)	Control (N=23)	P Value*
Any adverse event			
No. of events	16	3	
No. of patients with an event (%)	15 (19)	2 (9)	
No. of events per 100 person-years	65.3	41.3	0.50
Specific events — no. of patients (%) [no. of events]			
Serious adverse events	1 (1) [1]†	0	
Severe hypoglycemia‡	0	0	
Diabetic ketoacidosis§	0	0	
Hyperglycemia or hyperketosis, without diabetic ketoacidosis, related to an insulin pump problem¶	12 (15) [12]	1 (4) [1]	
Other adverse events	3 (4) [3]‖	1 (4) [2]**	
Other safety outcomes			
Glycated hemoglobin level worsening by ≥0.5% — no. of patients (%)	2 (3)	2 (9)	
Median no. of hypoglycemic events per week (IQR)††	0.5 (0.1 to 0.8)	0.6 (0.1 to 1.0)	0.16
Median no. of hyperglycemic events per week (IQR)‡‡	3.0 (1.7 to 5.2)	5.6 (3.4 to 8.1)	0.001
Days with ≥1 blood glucose measurement <54 mg/dl — no. of days (% per total person-days of follow-up)§§	87 (0.97)	23 (0.87)	
Days with ≥1 blood glucose measurement >350 mg/dl — no. of days (% per total person-days of follow-up)§§	259 (2.89)	114 (4.30)	
Days with ≥1 blood ketone measurement >1.0 mmol/liter — no. of days (% per total person-days of follow-up)§§	24 (0.27)	3 (0.11)	0.19

* P values were calculated only for the outcomes that had been prespecified in the statistical analysis plan.
† The serious adverse event was hospitalization for gastroenteritis leading to ketosis, which was determined not to be related to trial device, as assessed by a trial investigator and adjudicated by the medical monitor.
‡ Severe hypoglycemia was defined as hypoglycemia leading to the need for assistance because of altered consciousness.
§ Diabetic ketoacidosis was defined according to the criteria of the Diabetes Control and Complications Trial.[21]
¶ All events were related to problems with the pump infusion set, except for one in the closed-loop group that was related to an issue involving the insulin pump battery.
‖ Other adverse events in the closed-loop group included one event of hyperglycemia with ketosis due to viral illness (not determined to be related to the trial device), one hypoglycemic event due to too much insulin given in a meal bolus relative to the size of the meal (not determined to be related to the trial device), and one accidental overdelivery of insulin that occurred at the time of priming during an infusion set change (the glucose level dropped, but the patient did not become hypoglycemic).
** Other adverse events in the control group included two occurrences of infection at the site of sensor insertion in one patient.
†† A hypoglycemic event was defined as a period of at least 15 consecutive minutes during which the glucose level was less than 54 mg per deciliter(3.0 mmol per liter), as measured by continuous glucose monitoring.
‡‡ A hyperglycemic event was defined as a period of at least 15 consecutive minutes during which the glucose level was above 300 mg per deciliter (16.6 mmol per liter), as measured by continuous glucose monitoring.
§§ The total number of person-days of follow-up was 8949 in the closed-loop group and 2652 in the control group.

studies will be needed to explore whether the effectiveness of the closed-loop system shown in the current trial would be similar in groups with lower socioeconomic status and less familiarity with technology. The amount of hypoglycemia at baseline was unrepresentatively low in both treatment groups, which, in addition to the fact that most of the patients in the control group used a pump with a predictive low-glucose suspend feature, limited the ability of the trial to assess the effect of the closed-loop system on hypoglycemia. The trial period was 4 months, and it is unknown whether the treatment effect would be sustained over a longer period.

In this 16-week trial involving children 6 to 13 years of age who had type 1 diabetes, the glucose level was in the target range for a greater percentage of time with the use of a closed-loop system than with the use of a sensor-augmented insulin pump.

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architecture for open-loop control of diabetes (licensed to Dexcom), pending patent 62/173.080 PCT/US2016/036729 on continuous glucose monitoring (CGM)–based fault detection and mitigation of insulin delivery and monitoring systems via metabolic state (licensed to Dexcom), and patent 9750438 on CGM-based prevention of hypoglycemia through hypoglycemia rise assessment and smooth reduction of insulin (licensed to Dexcom); Dr. Kanapka, receiving grant support, paid to the Jaeb Center for Health Research, from Tandem Diabetes Care; Dr. Beck, receiving grant support and donated supplies, paid to the Jaeb Center for Health Research, from Abbott Diabetes Care, Ascensia Diabetes Care US, Beta Bionics, and Roche Diabetes Care, grant support, donated supplies, and consulting fees, paid to the Jaeb Center for Health Research, from Dexcom, Novo Nordisk, and Tandem Diabetes Care, grant support and consulting fees, paid to the Jaeb Center for Health Research, from Bigfoot Biomedical, and consulting fees, paid to the Jaeb Center for Health Research, from Eli Lilly and Insulet; Dr. Forlenza, receiving grant support, paid to the Barbara Davis Center, and consulting fees from Abbott Diabetes Care, Dexcom, Insulet, Medtronic MiniMed, and Tandem Diabetes Care, and consulting fees from Eli Lilly; Dr. Schoelwer, receiving grant support, paid to the University of Virginia, from Medtronic and Tandem Diabetes Care; Dr. Ruedy, receiving grant support and donated supplies, paid to the Jaeb Center for Health Research, from Abbott Diabetes Care, Beta Bionics, and Dexcom, and grant support, paid to the Jaeb Center for Health Research, from Tandem Diabetes Care; Dr. Hsu, owning stock in Dexcom and Tandem Diabetes Care; Dr. Kollman, receiving grant support, paid to the Jaeb Center for Health Research, from Tandem Diabetes Care; Dr. Dokken, being employed by and owning stock in Tandem Diabetes Care; Dr. Weinzimer, receiving consulting fees from Eli Lilly, Insulet, Sanofi US Services, and Zealand, grant support, paid to Yale University, from Medtronic, and consulting fees and lecture fees from Tandem Diabetes Care; Dr. DeBoer, receiving grant support, paid to his institution, from Medtronic USA and Tandem Diabetes Care; Dr. Buckingham, receiving grant support, paid to Stanford University, donated supplies, and advisory board fees from Covatec, grant support from Dexcom, grant support and honoraria from Insulet, grant support, paid to Stanford University, and advisory board fees from Medtronic MiniMed, and grant support, paid to Stanford University, from Tandem Diabetes care; Dr. Cherñavvsky, being employed by Dexcom; and Dr. Wadwa, receiving grant support, paid to the University of Colorado, from Bigfoot Biomedical, MannKind, and Novo Nordisk, grant support, paid to the University of Colorado, and lecture fees from Dexcom, grant support, paid to the University of Colorado, and advisory board fees from Eli Lilly and Medtronic, and grant support, paid to the University of Colorado, travel support, and lecture fees from Tandem Diabetes Care. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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