ORIGINAL ARTICLE

Nocturnal Glucose Control with an Artificial Pancreas at a Diabetes Camp

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ABSTRACT

BACKGROUND

Recent studies have shown that an artificial-pancreas system can improve glucose control and reduce nocturnal hypoglycemia. However, it is not known whether such results can be replicated in settings outside the hospital.

METHODS

In this multicenter, multinational, randomized, crossover trial, we assessed the short-term safety and efficacy of an artificial pancreas system for control of nocturnal glucose levels in patients (10 to 18 years of age) with type 1 diabetes at a diabetes camp. In two consecutive overnight sessions, we randomly assigned 56 patients to receive treatment with an artificial pancreas on the first night and a sensor-augmented insulin pump (control) on the second night or to the reverse order of therapies on the first and second nights. Thus, all the patients received each treatment in a randomly assigned order. The primary end points were the number of hypoglycemic events (defined as a sensor glucose value of <63 mg per deciliter [3.5 mmol per liter] for at least 10 consecutive minutes), the time spent with glucose levels below 60 mg per deciliter (3.3 mmol per liter), and the mean overnight glucose level for individual patients.

RESULTS

On nights when the artificial pancreas was used, versus nights when the sensor-augmented insulin pump was used, there were significantly fewer episodes of nighttime glucose levels below 63 mg per deciliter (7 vs. 22) and significantly shorter periods when glucose levels were below 60 mg per deciliter ($P=0.003$ and $P=0.02$, respectively, after adjustment for multiplicity). Median values for the individual mean overnight glucose levels were 126.4 mg per deciliter (interquartile range, 115.7 to 139.1 [7.0 mmol per liter; interquartile range, 6.4 to 7.7]) with the artificial pancreas and 140.4 mg per deciliter (interquartile range, 105.7 to 167.4 [7.8 mmol per liter; interquartile range, 5.9 to 9.3]) with the sensor-augmented pump. No serious adverse events were reported.

CONCLUSIONS

Patients at a diabetes camp who were treated with an artificial-pancreas system had less nocturnal hypoglycemia and tighter glucose control than when they were treated with a sensor-augmented insulin pump. (Funded by Sanofi and others; ClinicalTrials.gov number, NCT01238406.)

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Intensive insulin therapy is considered to be the standard treatment for tight blood glucose control in patients with type 1 diabetes, since it prevents long-term complications. Several studies have promoted the use of insulin pumps, glucose sensors, or a combination of the two devices (sensor-augmented pump)[1-3] to improve glucose control. However, the risk of hypoglycemia is still present with the use of all currently available therapies.[4-6]

Maintenance of nocturnal euglycemia is extremely important and is challenging, since most cases of severe hypoglycemia occur at night.[7,8] Such episodes account for 75% of total hypoglycemic seizures in children[9] and may be associated with 6% of deaths in patients under the age of 40 years who have type 1 diabetes.[10]

Fully automated artificial-pancreas systems have been suggested as a means to control nocturnal glucose levels. Such systems link glucose sensors with insulin pumps through computerized control algorithms, which dictate insulin delivery in response to real-time sensor data. Recent studies that have been carried out in hospitals have shown that such systems can improve glucose control and reduce the risk of nocturnal hypoglycemia in children, adolescents, and adults.[11-14] Although such studies are encouraging, the major challenge ahead is a successful implementation of such systems outside the hospital.

To address this challenge, the Diabetes Wireless Artificial Pancreas Consortium (DREAM) was established to test the MD-Logic Artificial Pancreas system[15,16] for nocturnal blood glucose control in patients with type 1 diabetes, in settings outside the hospital under real-life conditions. After successful feasibility[17] and inpatient multicenter studies, we performed a multinational, prospective, randomized, crossover study at three youth camps, one each in Israel, Slovenia, and Germany. Each of the camp periods lasted for 3 days. The objective of the study was to evaluate the safety and efficacy of the artificial-pancreas system in young persons with type 1 diabetes, with an aim of achieving a substantial reduction in nocturnal hypoglycemia with near-normal overnight glucose control in a youth-camp setting.

METHODS

STUDY PARTICIPANTS

Eligible patients were 10 to 18 years of age and had at least a 1-year history of type 1 diabetes. Additional eligibility criteria were receipt of insulin-pump therapy for at least 3 months, a glycated hemoglobin level of 7 to 10%, a body-mass index (BMI) below the 97th percentile for the patient's age, and an ability to adhere to the trial instructions. The main exclusion criteria were a concomitant disease, participation in another study, pregnancy, a history of diabetic ketoacidosis or severe hypoglycemia within the past month, and the use of medications or the presence of other conditions that might influence metabolic control, compromise safety, or prevent participants from completing the study. Parents and patients provided written informed consent and assent, respectively, according to national regulations. The study protocol and amendments are available with the full text of this article at NEJM.org.

STUDY TREATMENT

In two consecutive overnight sessions, we randomly assigned 56 patients to receive treatment with an artificial pancreas on the first night and a sensor-augmented insulin pump (control) on the second night (group A) or the reverse order of therapies on the first and second nights (group B). Thus, all the patients received each treatment in a randomly assigned order.

All participants attended a precamp evaluation session ranging from 5 to 10 days in which they used an insulin pump (Paradigm Veo, Medtronic) with the same insulin preparation that they used at home, a sensor (Enlite Sensor, Medtronic), and a glucose meter (Contour Link, Bayer). Sensor alarms for high glucose readings (>350 mg per deciliter [>19.4 mmol per liter]) and low glucose readings (<75 mg per deciliter [<4.2 mmol per liter]) were set with a 20-minute prediction time, and the patients were allowed to modify or shut off these alarms according to their usual routine. The patients were asked to record all meals and relevant events (e.g., hypoglycemic episodes and exercise) either in a diary or in the internal pump memory. The documented data were used to derive personalized settings for the artificial-pancreas device. These data were also available to the camp physicians so that they could modify each child's pump settings for camp days and control nights.

Standard treatment procedures and guidelines for diabetes camp were followed.[18-21] The study team was allowed to modify insulin treatment according to these guidelines at any time during the day and on nights when the sensor-augmented

insulin pump was used. All the patients participated in social and physical activities (including 45 to 60 minutes of swimming in the morning). A buffet dinner was served between 6:30 and 7 p.m., and patients calculated the amount of insulin required to cover the meal. A snack was offered at around 9 p.m. At 10:30 to 11 p.m., the patients were encouraged to go to bed. Capillary blood glucose levels were checked at meals, 2 hours after a meal, and at bedtime and then at 3-hour intervals throughout the night. The sensor-calibration protocol was identical in the two study treatments (for details, see the Supplementary Appendix, available at NEJM.org).

The study team manually documented all events (e.g., sensor calibration and hypoglycemia treatments). For the nights when the artificial-pancreas system was used, it was connected at 4 to 5 p.m. and activated at mealtime (6:30 to 7 p.m.) until wakeup time (7 a.m.) for fully automated control of basal and bolus doses of insulin. For the nights when the sensor-augmented insulin pump was used, the patients followed their standard glycemia-management regimen.

Patients who had a capillary glucose measurement in the hypoglycemic range (<60 mg per deciliter [<3.3 mmol per liter]) or symptomatic hypoglycemia were treated with carbohydrates. Predictive alarms for hypoglycemia were provided by the system's safety module during nights when the artificial-pancreas system was used and were provided by the sensor during nights when the sensor-augmented pump was used. Hypoglycemic episodes that triggered alarms were treated with carbohydrates at the discretion of the physician. At the end of the camp, data from all the devices were downloaded with the use of CareLink Pro software, version 2.3b (Medtronic).

ARTIFICIAL PANCREAS AND REMOTE MONITORING SYSTEM

The MD-Logic is a wireless, fully automated, closed-loop system[15] that uses an algorithm based on fuzzy-logic theory (a form of probabilistic logic), a learning algorithm,[16] and an alerts module and personalized system setting. The alerts module includes real-time alarms such as impending hypoglycemia and long-standing hyperglycemia (see the Methods section in the Supplementary Appendix). The algorithms for alerts integrate information derived from past glucose levels, insulin delivery (time and dose), and models of insulin pharmacodynamics. The hypoglycemia alarms are designed to operate in instances in which impending hypoglycemia cannot be avoided by only withholding the dose of insulin. By introducing the alerts module, we updated the patient's settings with new controller glucose-target settings for post-hypoglycemia.

A remote monitoring system was set up for real-time wireless transmission of all data from all patients to a remote-control center located within the camp. This allowed for continuous, simultaneous follow-up of all patients and immediate interventions by attending physicians when required. Having confirmed the safety of nighttime monitoring with the use of the sensor-augmented insulin pump in the first camp, we connected the remote monitoring system only when the artificial-pancreas system was in use during subsequent evaluations.

END POINTS

The primary end points were the number of hypoglycemic events (defined according to the European guidelines for hypoglycemia as a sensor value of <63 mg per deciliter [3.5 mmol per liter] for at least 10 consecutive minutes), the time during which glucose levels were below 60 mg per deciliter (according to the latest Food and Drug Administration draft guidelines[22] for hypoglycemia evaluation), and mean overnight glucose levels for individual patients. Secondary end points included overnight measures of glycemic control and glucose variability, including the standard deviation of glucose variability and control-variability grid analysis.[23] The latter is used to measure the glucose-control quality of the artificial-pancreas system by assessing the minimum and maximum glucose values during the overnight period (for details, see the Supplementary Appendix). We also used Clarke error grid analysis[24] to measure the clinical accuracy of blood glucose estimates. All end points were evaluated on the basis of the sensor data accumulated during the night (from 11 p.m. to 7 a.m.).

TRIAL OVERSIGHT

The study was approved by the institutional or national ethics committee at each site. The study protocol was conducted in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

The MD-Logic system is owned and was

designed and programmed by four of the authors who are affiliated with the Schneider Children's Medical Center of Israel. The authors designed the study, generated and analyzed the data, collectively wrote the manuscript, made the decision to submit it for publication, and vouch for the completeness and accuracy of the data and the fidelity of the study to the protocol. All study sensors, glucose test strips, and insulin-pump disposables were purchased from local distributers. Neither Sanofi, which solely provided funds to support the study, nor the device manufacturers and other funders were involved in the study design, data collection and analysis, or manuscript preparation.

STATISTICAL ANALYSIS

To estimate the power of the nonparametric tests for all three primary end points, we performed power simulations (MATLAB 2011b, MathWorks) before the trial, using sensor data from standard treatment at home for 146 patients who met the eligibility criteria (see the Supplementary Appendix). On the basis of previous inpatient studies with this artificial pancreas,[17] we estimated a reduction of 50% in the average number of episodes in which the sensor glucose level was less than 63 mg per deciliter, a reduction of 60% in the number of episodes in which the glucose level was less than 60 mg per deciliter, and a reduction of 13 mg per deciliter (0.7 mmol per liter) in the mean overnight glucose level. We calculated that enrollment of 56 participants would provide a power of 90% to detect such differences on the basis of a two-sided significance level of 0.05, assuming the withdrawal of 8 participants.

Analyses were performed on the basis of the intention-to-treat principle. We used the paired nonparametric Wilcoxon signed-rank test to evaluate the differences in end points between the two study treatments. We used a paired McNemar's test for categorical nonparametric comparisons and multiple regression analysis for comparisons of between-treatment differences in personalized sensor values over time.

We evaluated possible associations between baseline characteristics and the three primary end points, using general linear models or ordinal regression. We used an analysis of variance to evaluate possible effects of the sequence of the sessions (independent variable) on the primary end points (dependent variable). All analyses were

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Value
Age (yr)	13.8±1.8
Weight (kg)	56.0±13
Height (cm)	162.9±11.5
Body-mass index†	
Value	20.8±2.9
SD score	0.4±0.8
Glycated hemoglobin	
Measured as a percentage	8.0±0.7
Measured in mmol/mol‡	63.6±7.6
Diabetes duration (yr)	7.0±3.5
Pump-therapy duration (yr)	4.8±2.8
Daily insulin dose	
Total units	46.4±17.7
Units/kg	0.8±0.3

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ This measurement meets the recommendations set out by the International Federation of Clinical Chemistry and Laboratory Medicine.

Table 2. Primary End Points in the 54 Patients.*

Variable	Artificial Pancreas	Control
Total number of episodes of glucose levels <63 mg/dl†	7	22
Time that glucose level was <60 mg/dl (min)‡		
Median	0	0
Interquartile range		0–27.5
Overnight glucose level (mg/dl)		
Median	126.4	140.4
Interquartile range	115.7–139.1	105.7–167.4

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† The numbers of patients who had at least one episode of hypoglycemia (glucose level, <63 mg per deciliter) were 7 with the artificial pancreas and 20 with the sensor-augmented pump. P=0.003 for the between-treatment comparison after adjustment for multiple testing with the use of Hochberg's method.[25]
‡ P=0.02 for the between-treatment comparison after adjustment for multiple testing with the use of Hochberg's method.[25]

conducted with the use of SPSS software, version 19 (IBM), and SAS software, version 9.1 (SAS Institute). We applied Hochberg's method for adjustment for multiple testing separately for the primary end points and secondary end points.[25] A P value of less than 0.05, after adjustment for multiple testing, was considered to indicate statistical significance. All reported P values are two-sided.

RESULTS

STUDY PARTICIPANTS

From September 2011 through January 2012, a total of 56 patients (31 boys and 25 girls) were enrolled and underwent randomization. Only one participant had a standard-deviation score for BMI between the 95th and 97th percentiles. His daily insulin dose was 0.7 units per kilogram of body weight (with a glycated hemoglobin level of 7.3%), which was not significantly different from the mean (±SD) daily insulin dose for all the participants (0.8±0.3 units per kilogram per day) or from the mean glycated hemoglobin level (8.0±0.7%). One patient in group A was excluded from the intention-to-treat analyses because of a sensor crash, which disabled the assigned intervention and the delivery of any personalized sensor data. Another patient, in group B, withdrew from the study after the first night of camp. Thus, there were 54 patients (27 in each group) in the intention-to-treat analyses (Fig. S1 in the

Table 3. Secondary End Points.*

Variable	Artificial Pancreas	Control	Difference
Glucose control			
Median time within range (interquartile range) — hr			
70–140 mg/dl†	4.4 (2.8 to 6.7)	2.8 (1.5 to 4.4)	1.4 (–0.5 to 3.4)
63–140 mg/dl	5.5 (3.6 to 6.8)	3.8 (2.1 to 6.1)	1.2 (–0.5 to 3.0)
80–120 mg/dl†	3.9 (2.3 to 5.7)	2.2 (1.2 to 4.1)	0.9 (–0.5 to 3.1)
Median continuous glucose-monitoring reading (interquartile range) — mg/dl			
Total	123.5 (115.0 to 136.2)	137.3 (100.0 to 164.4)	–7.5 (–37.0 to 28.0)
At bedtime	117.5 (97.5 to 153.7)	108.5 (84.0 to 137.0)	5.0 (–17.0 to 40.0)
At wakeup†	122.0 (103.2 to 145.7)	147.5 (113.2 to 199.5)	–25.5 (–85.0 to 14.0)
Median capillary glucose (interquartile range) — mg/dl			
All patients	133.2 (108.7 to 163.8)	151.0 (111.1 to 191.2)	–13.9 (–49.5 to 9.0)
At bedtime	125.0 (104.0 to 153.2)	114.0 (86.0 to 143.0)	15.5 (–22.0 to 46.0)
At wakeup†	132.0 (112.0 to 159.0)	168.5 (134.5 to 227.0)	–30.5 (–110.0 to 10.0)
SD of glucose variability — mg/dl‡	26.4 (19.2 to 33.6)	30.9 (17.2 to 54.9)	–5.3 (–27.4 to 5.5)
Control-variability grid analysis zone A or lower B — %†§	61	22	NA
Hypoglycemia			
No. of events			
<70 mg/dl†	12	36	NA
<60 mg/dl	6	18	NA
Median time at glucose level (interquartile range) — min			
<70 mg/dl†	0	10.4 (0 to 79.7)	0 (–78.9 to 0)
<63 mg/dl	0	0 (0 to 42.5)	0 (–35.0 to 0)
Median area under the curve for glucose values (interquartile range) — mg/dl¶			
<70 mg/dl†	0	0.1 (0 to 1.3)	–0.03 (–1.2 to 0)
<63 mg/dl	0	0 (0 to 0.4)	0 (–0.3 to 0)
Median Kovatchev's Low Blood Glucose Index (interquartile range)‖	0.3 (0.02 to 0.8)	0.4 (0.1 to 3.3)	–0.2 (–2.4 to 0.3)

Table 3. (Continued.)

Variable	Artificial Pancreas	Control	Difference
Hyperglycemia			
Median time at glucose level (interquartile range) — min			
>140 mg/dl	146.2 (58.4 to 231.1)	233.8 (13.4 to 327.5)	−39.4 (−180.2 to 110.9)
>180 mg/dl†	0 (0 to 65.4)	28.4 (0 to 177)	0 (−149.1 to 21.3)
>250 mg/dl†	0	0 (0 to 66.2)	0 (−45.9 to 0)
Median area under the curve for glucose values (interquartile range) — mg/dl¶			
>140 mg/dl	4.1 (0.8 to 15.5)	13.9 (0.3 to 38.5)	−1.6 (−32.1 to 4.0)
>180 mg/dl	0 (0 to 2.4)	0.3 (0 to 17.4)	0 (−15.1 to 0)
>250 mg/dl†	0	0 (0 to 0.75)	0 (−0.8 to 0)
Median Kovatchev's High Blood Glucose Index (interquartile range)**	1.3 (0.6 to 2.8)	3.2 (0.4 to 7.2)	−0.6 (−5.5 to 0.9)

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. NA denotes not applicable because the values are categorical variables rather than continuous variables.
† P<0.05 for the comparison of the artificial pancreas and the control after adjustment for multiple testing with the use of Hochberg's method.[25]
‡ The standard deviation (SD) of glucose variability indicates the median of the glucose SD calculated per patient for each night, with values in parentheses indicating the interquartile range.
§ Control-variability grid analysis zone A or lower B indicates the proportion of nights for each treatment in which the minimum glucose level was above 70 mg per deciliter and the maximum glucose level was below 180 mg per deciliter.
¶ Values for the area under the curve were calculated with the use of the trapezoidal rule and then averaged over the nighttime duration of 8 hours.
‖ Kovatchev's Low Blood Glucose Index theoretically ranges from 0 to 100, with values of less than 2.5 indicating a low risk of severe hypoglycemia and values of more than 5 indicating a high risk of severe hypoglycemia.[26,27]
** Kovatchev's High Blood Glucose Index theoretically ranges from 0 to 100, with values of less than 4.5 indicating a low risk of hyperglycemia and values of more than 9 indicating a high risk of hyperglycemia.[26,27]

Supplementary Appendix). No significant associations were found between the baseline characteristics of the participants (Table 1) and the primary and secondary end points of the trial.

PRIMARY AND SECONDARY END POINTS

On nights when the artificial pancreas was used, as compared with nights when the sensor-augmented insulin pump was used, there were significant decreases in the number of episodes in which the glucose level was below 63 mg per deciliter (7 vs. 22) and in the time during which the level was below 60 mg per deciliter (P=0.003 and P=0.02, respectively). There were no significant between-treatment differences in the median overnight glucose levels (calculated from the means of approximately 96 glucose values per night per patient), which were 126.4 mg per deciliter (interquartile range, 115.7 to 139.1 [7.0 mmol per liter; interquartile range, 6.4 to 7.7]) with the artificial pancreas and 140.4 mg per deciliter (interquartile range, 105.7 to 167.4 [7.8 mmol per liter; interquartile range, 5.9 to 9.3]) with the sensor-augmented pump (Table 2).

Analyses of prespecified secondary end points showed significant improvements in several measures of glycemic control and glucose variability with the artificial pancreas as compared with the sensor-augmented pump (Table 3).[26,27] In addition, total overnight insulin doses were significantly higher during nights when the artificial pancreas was used than during nights when the sensor-augmented pump was used (Table S1 in the Supplementary Appendix), although basal insulin doses were not significantly different.

Glucose levels were significantly more stable over time with the artificial pancreas than with the sensor-augmented pump (Fig. 1). More bolus injections of insulin were delivered during the nights when the artificial pancreas was used than during the nights when the sensor-augmented pump was used. In the latter case, bolus injections were provided by the study medical staff in response to episodes of high blood glucose levels (Fig. 1).

No significant between-treatment differences were found in the number of hypoglycemia

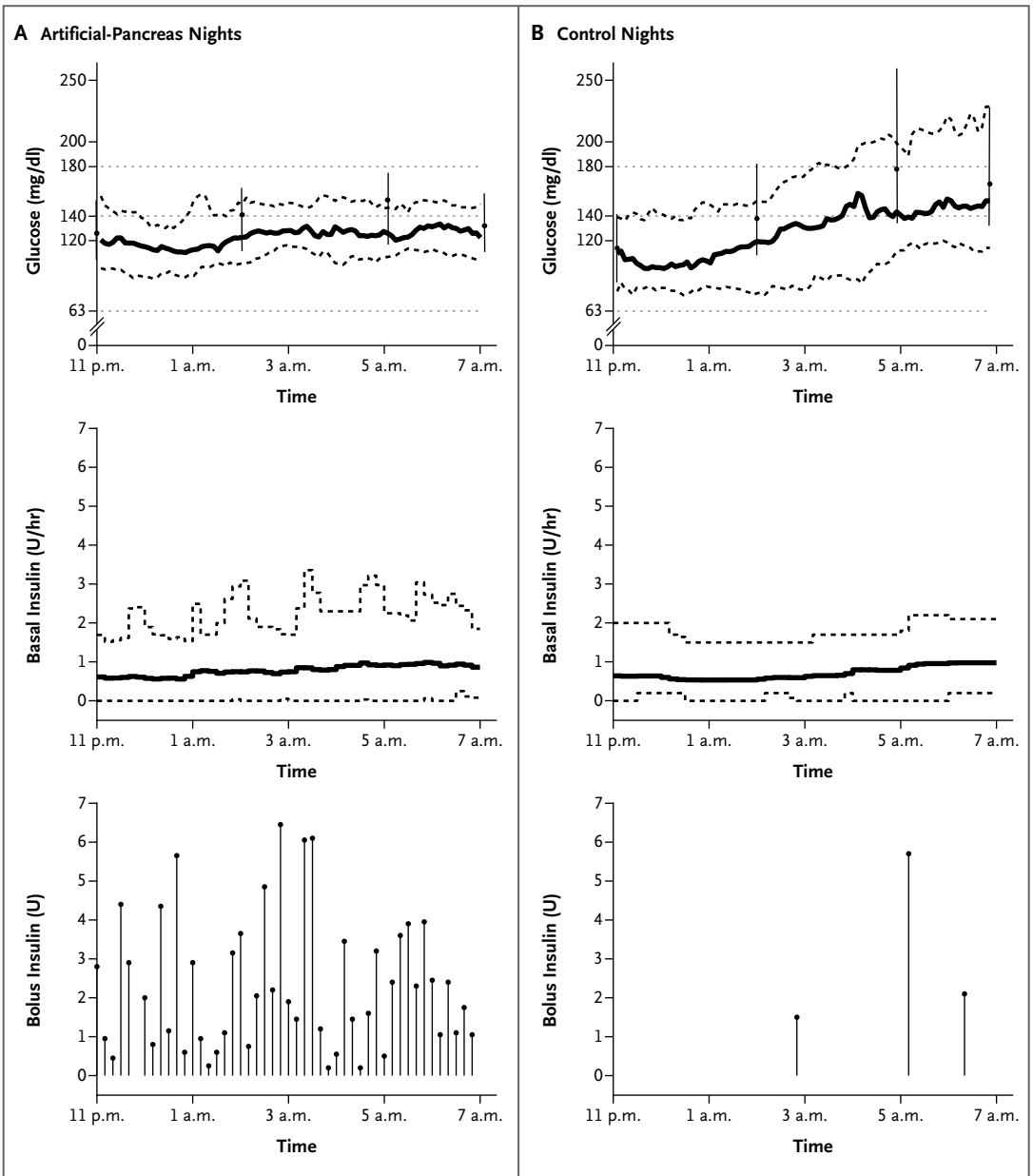

Figure 1. Glycemic Control in the Two Study Treatments.

The upper graphs show the sensor glucose profiles during the nights when the artificial pancreas was used (Panel A) and during the nights when the sensor-augmented insulin pump (control) was used (Panel B), and the middle and lower graphs show the respective profiles for basal and bolus insulin infusions. In the upper graphs, the solid black lines indicate the median glucose levels, and the two dashed lines indicate the interquartile range. The circles indicate the median capillary glucose measurements taken every 3 hours during the overnight sessions (11 p.m. to 7 a.m.), and the vertical lines indicate the interquartile ranges. The horizontal dashed lines indicate glucose measurements of 63 mg per deciliter, 140 mg per deciliter, and 180 mg per deciliter. In the middle graphs, the mean basal rates of insulin infusion are indicated by solid black lines, with dashed lines indicating the ranges. In the bottom panels, the total amounts of insulin delivered over time as bolus doses are indicated by the vertical black lines with circles. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

alarms or subsequent carbohydrate interventions (number of interventions and average amount of carbohydrates per treatment) (Table S2 in the Supplementary Appendix), findings that otherwise could confound results for end points relating to hypoglycemia. The mean blood glucose level at the time of the intervention was higher during nights when the artificial pancreas was used than during nights when the sensor-augmented pump was used (Table S3 in the Supplementary Appendix). During nights when the sensor-augmented pump was used, 36 of the 54 patients used the glucose sensor alarms. There were 13 false hypoglycemia alarms out of 39 alarms during the nights when the artificial pancreas was used, as compared with 27 false alarms out of 41 alarms during the nights when the sensor-augmented pump was used.

No significant differences were found between group A and group B on the basis of the order of the administration of treatments (data not shown). At no time did the research team need to override the decisions of the artificial-pancreas system.

ADVERSE EVENTS

Adverse events included day and nighttime hypoglycemia, as well as headaches, dizziness, and reports of "feeling ill" (Table 4). More such events occurred during nights when the sensor-augmented pump was used than during nights when the artificial pancreas was used. No serious adverse events were reported during the study.

Table 4. Adverse Events and Serious Adverse Events.

Event	Artificial Pancreas	Control
Adverse events		
Hypoglycemia (<63 mg/dl)		
Daytime*	19	28
Nighttime	6	19
Ketosis	0	0
Other†	2	8
Serious adverse events		
Severe hypoglycemia‡	0	0
Diabetic ketoacidosis	0	0

* Daytime events were reported during the hours from 7 a.m. to 11 p.m. preceding the indicated overnight period.
† Other adverse events included headache, dizziness, and generally "feeling ill."
‡ Severe hypoglycemia was defined as an event that required assistance from another person to administer oral carbohydrates or glucagon or to perform another resuscitative intervention.

DISCUSSION

Our results show the efficacy of the MD-Logic Artificial Pancreas system, which was associated with a reduced risk of hypoglycemia, as compared with sensor-augmented pump treatment, in young persons at an overnight camp.

Hypoglycemia is currently the major concern with respect to methods for controlling nocturnal blood glucose,[28] even when glucose sensors are used.[28-30] Up to 90% of parents report that they would feel more confident applying a closed-loop system during the night.[31] In our study, the significant improvement in patients' overnight glucose control and the reduction in the number of events and duration of hypoglycemia appeared to be related to the combined effect of better control of the amount of insulin provided and better control of the timing of insulin delivery, together with the presence of an alarm module, in the artificial pancreas. However, no data were collected to differentiate among these possibilities. With the use of the artificial-pancreas system, we did not observe a reduction in the number of carbohydrate interventions that were needed. We did not assess either anxiety about hypoglycemic episodes on the part of the study participants and their parents or quality-of-life measures because of the short duration of the intervention.

The early-alert system for the artificial pancreas is the result of algorithms that use insulin-delivery data and expected glucose dynamics to provide preliminary alerts for impending hypoglycemia that cannot be averted only by withholding the insulin dose (Table S3 in the Supplementary Appendix). Hughes et al.[32] found that the use of data regarding glucose levels and insulin delivery in their hypoglycemia alarm system had a benefit over and above that provided by alarms that use glucose data only.

The setting of a diabetes camp was chosen for the study because it represents a transitional phase between a hospital clinical research center and the

child's home. The camp provides the elements of a real-life setting, in a place where health care needs can still be met by the research team.

Our study has several limitations. Each treatment was evaluated in a one-night session, and the challenges of a closed-loop system for glucose and insulin control may be different in a multinight design. In daily life, patients with diabetes are confronted with recurring glycemic fluctuations, and it is important to distinguish between control of variations during a given night and control of variations on succeeding nights. Another issue is that crossover studies have an intrinsic limitation, since the order in which treatments are administered may affect the outcome. In our study, such an effect was not detected. A further limitation to the generalizability of the results was our need to perform sensor recalibration during the two study nights (see the Supplementary Appendix).

Glucose-level data were based on sensor readings, and therefore the performance of the artificial-pancreas system and the study end points were all based on subcutaneous interstitial sensor measurements, as in other clinical studies, which assessed the effect of pumps and sensors on glucose control.[6,33] To increase our confidence in the results, however, we used additional, parallel approaches. Every 3 hours, the assigned medical personnel evaluated capillary blood glucose levels. These capillary data supported the efficacy of the artificial-pancreas system and confirmed the reported results for the primary outcome (glucose level, <63 mg per deciliter) (see the Methods section and Table S4 in the Supplementary Appendix).

Furthermore, we evaluated the sensor glucose data retrospectively, using stochastic sensor transformation, as proposed by Hovorka et al.,[34] and reassessed the time during which the glucose level was below 60 mg per deciliter in the two study treatments. This analysis also confirmed the reported results with respect to this measurement (see the Methods section and Table S5 in the Supplementary Appendix). In addition, 98% of sensor–glucose meter pairs (two glucose values taken at the same time from the two devices) from the nights when the artificial pancreas was used and 97% of those from the nights when the sensor-augmented pump was used were within the A and B zones of the Clarke Error Grid analysis (values that are within 20% of the reference sensor or that are outside that range but would not lead to inappropriate treatment),[24] findings that are similar to previously reported data.[35] Moreover, during the trial, sensor readings were collected from the two treatments, and identical sensor-calibration protocols were used for both treatments to reduce the risk of bias (see the Supplementary Appendix). Thus, any sensor-related inaccuracy would equally affect the two study treatments.

In conclusion, in this short-term crossover study at a diabetes youth camp, the use of an artificial-pancreas system resulted in less hypoglycemia and tighter control of nocturnal glucose levels than did a sensor-augmented pump system.

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

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