MD-Logic Overnight Control for 6 Weeks of Home Use in Patients With Type 1 Diabetes: Randomized Crossover Trial

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OBJECTIVE

We evaluated the effect of the MD-Logic system on overnight glycemic control at patients' homes.

RESEARCH DESIGN AND METHODS

Twenty-four patients (aged 12–43 years; average A_{1c} 7.5 ± 0.8%, 58.1 ± 8.4 mmol/mol) were randomly assigned to participate in two overnight crossover periods, each including 6 weeks of consecutive nights: one under closed loop and the second under sensor-augmented pump (SAP) therapy at patients' homes in real-life conditions. The primary end point was time spent with sensor glucose levels below 70 mg/dL (3.9 mmol/L) overnight.

RESULTS

Closed-loop nights significantly reduced time spent in hypoglycemia (P = 0.02) and increased the percentage of time spent in the target range of 70–140 mg/dL (P = 0.003) compared with nights when the SAP therapy was used. The time spent in substantial hyperglycemia above 240 mg/dL was reduced by a median of 52.2% (interquartile range [IQR] 4.8, 72.9%; P = 0.001) under closed-loop control compared with SAP therapy. Overnight total insulin doses were lower in the closed-loop nights compared with the SAP nights (P = 0.04). The average daytime glucose levels after closed-loop operation were reduced by a median of 10.0 mg/dL (IQR −2.7, 19.2; P = 0.017) while lower total insulin doses were used (P = 0.038). No severe adverse events occurred during closed-loop control; there was a single event of severe hypoglycemia during a control night.

CONCLUSIONS

The long-term home use of automated overnight insulin delivery by the MD-Logic system was found to be a feasible, safe, and an effective tool to reduce nocturnal hypoglycemia and improve overnight glycemic control in subjects with type 1 diabetes.

The use of a closed-loop system is gaining recognition as a tool for real-time feedback control of insulin delivery for type 1 diabetes (1). A closed-loop insulin delivery system for type 1 diabetes has been tested in hospital settings for overnight (2–4) and also for day and night glycemic control (5,6). Moreover, it has been used for different populations of patients with diabetes: newly diagnosed patients (7), pregnant women (8), those with type 2 diabetes (9), and critically ill patients (10). The

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challenge now facing us is its use in the patient's home and integration into the everyday routine.

The Diabetes Wireless Artificial Pancreas Consortium (DREAM) was established by three diabetes centers in Slovenia, Germany, and Israel. The DREAM goal is to implement the MD-Logic artificial pancreas (11) to automatically control and manage blood glucose in the daily routine of the patients, seeking to maintain blood glucose within the desired range while lowering the risk of hypoglycemia and reducing the burden of diabetes management.

Over the past 5 years, a number of studies have been carried out to assess the safety and efficacy of the MD-Logic system for overnight glucose control in children, adolescents, and adults in various settings (2,12–14). Results of these studies demonstrate the safety and efficacy of the MD-Logic system, which achieved significantly less hypoglycemia and tighter overnight glucose control than the standard treatment (i.e., continuous subcutaneous insulin infusion or sensor-augmented pump [SAP] therapy) (2,12–14).

The MD-Logic system was designed to have several safety layers and fault detection capabilities to suit the requirements for automated control of overnight insulin delivery. To the best of our knowledge, automated insulin delivery systems have not yet been tested for more than a 3-week period at home. In the current study, we extended the duration of use of the closed-loop system for a relatively long period of time (6 weeks) in the patient's usual home environment, aiming to evaluate the ability of the system to operate safely and efficiently during free-life conditions.

RESEARCH DESIGN AND METHODS

Trial Design

This was a single-center, crossover, randomized trial. The study was conducted in compliance with the protocol, the Declaration of Helsinki, and applicable regulatory and Good Clinical Practice requirements. All patients and parents provided a written informed consent prior to trial initiation. The study is listed on www.clinicaltrials.gov (NCT01238406).

Participants and Eligibility Criteria

In June 2013, 24 eligible patients (12 males, 12 females) from the Schneider Children's Medical Center of Israel were recruited for the study. Main eligibility criteria were subject age above 12 and below 65 years, type 1 diabetes at least 1 year since diagnosis, use of an insulin pump for at least 3 months, a previous experience using continuous glucose monitoring (CGM), HbA_{1c} of $\geq$6.5 and $<$10%, BMI for age below the 95th percentile, and living with at least one other adult person. Main exclusion criteria were concomitant disease, participation in another study, pregnancy, a history of diabetic ketoacidosis or severe hypoglycemia within the last month, or any medications or other conditions that could influence metabolic control, compromise safety, or prevent subjects from completing the study.

Randomization

This was carried out by permuted block-paired randomization stratified according to age and sex and glycemic control. Subjects were randomly assigned to participate either as group A, first 1.5-month period under overnight MD-Logic system (closed-loop arm), or group B, first 1.5-month period under SAP therapy. At the end of the first period, patients were asked to participate in another 1.5-month period, i.e., the other arm (all patients agreed), with a washout period of 5 weeks between arms.

Interventions

Each enrolled subject (and in the case of a minor subject, the caretaker as well) participated in a training session on sensor use, calibration, technical issues, problem solving, safety, and data recording as well as basic diabetes guidelines. Then all subjects underwent a 1-month run-in period of sensor wear. All subjects were using the same insulin pump (Paradigm Veo, Medtronic Diabetes, Northridge, CA), a real-time sensor (Enlite sensor with MiniLink 2, Medtronic Diabetes), and a glucose meter (CONTOUR LINK meter, Bayer HealthCare, Basel, Switzerland). Sensor thresholds for high- and low-glucose alarms were activated and uniformly set at 350 and 75 mg/dL, respectively, and the projected alarms were set to 20 min. The patients were allowed to modify or shut off these alarms according to their usual routine. Patients' profile data were collected and recorded (Supplementary Data), and pump optimization was done after the run-in period. Prior to the initiation of each closed-loop session, patients and their caregivers were given further training on the MD-Logic system and available safety measures. Subjects were instructed and encouraged to continue with their usual daily routine with no specific guidelines relating to physical activities; amount, type, and timing of meals; connection time to the system; and any glucose levels. However, they were advised to bolus for any meal or snack consumed according to the usual carbohydrate-to-insulin ratio and to take finger-stick glucose measurements 30 min before dinner, at bedtime, at wake-up time, and when prompted by the sensor. In fact, they could also take any additional measurements as they wished or upon individual advice by their personal physicians.

Safety Measures

A remote monitoring system was exploited for continuous night supervision of patients using the MD-Logic system at home. The remote system was validated for its safety in both an outpatient setting at diabetes camp and at patient homes (13,14). The remote monitoring system generated alarms for the attention of the supervising team. These alarms were different from those used by the subjects. Participants also learned how to independently respond to alarms or to calibrate the sensor when instructed by the system. In addition, all patients and caregivers were provided with a telephone hotline and a 24-h emergency remote access to an on-call physician and technical support.

Outcomes

The primary end point was defined as the reduction in overall time spent in nocturnal hypoglycemia (glucose levels below 70 mg/dL). A night period was the time between 2300 until 0700 the next morning. Secondary end points included the time spent at target range (70–140 mg/dL) and time spent in relatively high and low glucose levels, above 240 and below 50 mg/dL, respectively.

The daytime glycemic control was evaluated after nights when the closed loop was operated (per protocol) in order to evaluate the effectiveness of the overnight intervention on daytime glycemic control. Other exploratory comparison measurements are provided in a detailed list in the Supplementary

Data. All end points were based on the glucose sensor measurements accumulated during the night sessions.

Setting and Data Collection

Individuals' baseline data during the run-in period (of the sensor, insulin pump, and glucose meter) were downloaded using CareLink software (Medtronic Diabetes) and were used to automatically derive personalized settings for the pump and the MD-Logic system (e.g., a new correction factor, carbohydrate ratio, and basal insulin plan), which were implemented after approval or amendment by the study physician. During the study, subjects and caregivers were instructed to record (in a diary or in the internal pump memory) all physical activity, meals (carbohydrate count), and other events (e.g., technical errors and hypoglycemic episodes). At the end of the study, recorded data were also downloaded using CareLink software.

Statistical Methods

Analyses were based on the intention-to-treat (ITT) population defined as all randomly assigned subjects who ended the study and had at least 12 valid nights. A night session was considered valid if the sensor was active for at least 67% of the time, for both arms, similar to other studies (14,15). All end points were analyzed per arm, while, for each end point, each subject provided just one value as an average of all study nights.

Comparisons between closed-loop and control nights were performed using the paired nonparametric Wilcoxon signed rank test or the paired *t* test with two-tail distribution when the normality assumption holds according to Shapiro-Wilk test. Multiple regression analysis was applied to compare personalized sensor values over time between study arms. Similar predefined per-protocol analysis was conducted using data from only those nights during which the closed loop or sensor was operated for at least 67% of time. For this cohort, additional analysis was done using the Spearman rank correlation and general linear model to evaluate the relations between the overnight glycemic control and the daytime glycemic control.

The power of the nonparametric tests for the primary end point was estimated on the basis of the results of power simulations (MATLAB 2013b, MathWorks), which were performed using sensor data from 165 patients with the eligibility profile under standard treatment at home (see Supplementary Data). On the basis of previous in- (12) and outpatient (13,14) studies, we calculated that enrollment of 24 participants in total would provide a power of 80% for detecting a 30% reduction in the time below 70 mg/dL at a 0.05 two-sided significant level, assuming that only 70% of the nights would be valid for analysis.

RESULTS

Twenty-four subjects (12 male) with type 1 diabetes were enrolled and underwent randomization. Table 1 shows the characteristics of these subjects at baseline. Two patients withdrew from the study after the first study period (one subject from the control arm and one from the closed-loop arm) because of noncompliance with the sensor, and one subject moved to live alone (not compatible with the inclusion criteria) and therefore could not continue in the study. Thus there were 21 subjects who completed the study (Supplementary Fig. 1).

Analyses of the ITT population included 19 subjects who met the criteria for inclusion in these analyses. The ITT analysis covered 1,063 valid nights out of 1,482 expected nights. There were no sensor data available for the whole night in 13% of closed-loop and 26% of open-loop nights. The main reason for lack of sensor data were probably noncompliance with sensor wear. An additional 7% of closed-loop and 10% of open-loop nights were excluded from analysis since they did not met the criteria for evaluable nights (more than 67% of sensor data at each night). Thus 590 closed-loop nights (80%) and 473 open-loop nights (64%) were available for the ITT analysis. Median duration of closed-loop therapy was 5.9 h (interquartile range [IQR] 0, 7.4 h). The wireless PC platform was able to communicate with the pump and sensor 83.8% of the time. Miscommunication most probably occurred because of the distance or interference between the communication dongle and the pump (technical faults during closed-loop control are presented in Supplementary Table 1).

In 49 out of the 590 nights of the closed-loop arm, the patients did not operate the system at all since they were away from home. When excluding those 49 nights, we received the per-protocol analysis, where 18 subjects met the criteria for inclusion in these analyses. During control nights, 15 subjects used the glucose sensor alarms for the whole or part of the time, while 3 also used the low-glucose suspend (LGS) feature in their pump (see Supplementary Data). Remote monitoring communications overnight are presented in Supplementary Table 2. The mean absolute relative difference of the sensor was 15.8% for the closed-loop and 15.9% for the open-loop arm.

Primary and Secondary End Points—ITT and Per-Protocol Analysis

During the 3 months of the study, subjects in the closed-loop arm reduced the time spent at hypoglycemia by a median of 40.2% (IQR 7.9, 70.9%) as compared with subjects in the sensor-augmented insulin pump arm (P = 0.02) (Table 2),

Table 1—Baseline patient characteristics

	Adults (N = 11)	Children and adolescents (N = 13)	All (N = 24)
Age (years)	28.6 ± 8.2	14.9 ± 1.4	21.2 ± 8.9
BMI (kg/m^2)	23.4 ± 4.0	22.2 ± 4.1	22.7 ± 4.0
BMI*	−0.1 ± 1.2	0.4 ± 1.3	0.2 ± 1.3
A_{1c} (%)	7.0 ± 0.5	7.8 ± 0.8	7.5 ± 0.8
A_{1c} (mmol/mol; IFCC)	53.4 ± 5.1	62.0 ± 8.7	58.1 ± 8.4
Diabetes duration (years)	15.8 ± 11.1	7.9 ± 3.9	11.5 ± 8.8
Pump therapy duration (years)	9.1 ± 5.2	6.0 ± 3.9	7.4 ± 4.7
Daily insulin dose (total units)	45.8 ± 19.3	55.2 ± 20.8	51.1 ± 20.3
Daily insulin dose per body mass (units/kg)	0.6 ± 0.3	0.9 ± 0.2	0.8 ± 0.3

*SD score.

while the percentage of time spent within 70–140 mg/dL (3.9–7.8 mmol/L) increased by a median of 21.8% (IQR 14.7, 36.2%; $P = 0.003$) (Table 2).

The time spent in relatively high blood glucose above 240 mg/dL (13.3 mmol/L) was reduced by a median of 52.2% (IQR 4.8, 72.9%; $P = 0.001$). The time spent in hypoglycemia below 50 mg/dL (2.8 mmol/L) was low in both groups ($P = 0.124$) (Table 2).

Similar results were obtained for per-protocol analysis when the closed-loop system was on, but the time that glucose levels spent in hypoglycemia below 50 mg/dL (2.8 mmol/L) was significantly less during the closed-loop nights than the control nights ($P = 0.04$) (Table 2).

Exploratory Comparisons—ITT

Prespecified exploratory comparisons of closed-loop versus control nights are presented in Table 3. Although fewer total overnight insulin doses were delivered per subject on nights when the closed loop was used (median [IQR] 9 [7, 18.7] units) compared with nights when the SAP was used (median [IQR], 10.2 [8, 18.8] units; $P = 0.04$), the mean overnight glucose level was significantly reduced by median of 15 mg/dL (IQR 0.4, 27.5; $P = 0.008$).

The fasting morning blood glucose was reduced by a median of 8.7 mg/dL (IQR 0.8, 19.7; $P = 0.005$).

The two study arms showed no difference in blood glucose fluctuations, as measured by glucose SD and coefficient of variation (Table 3). However, converging glucose levels over time demonstrated a significant narrowing in the SD ratio ($P < 0.01$) only on the closed-loop nights.

The number of hypoglycemic events per night was low for both groups, but the mean area under the curve for nocturnal hypoglycemic events was 62.5% lower in the closed-loop group than in the control group ($P = 0.036$). The low blood glucose index (LBGI) (16) was significantly lower ($P = 0.044$).

All tested parameters of hyperglycemia demonstrated a significant improvement during the closed-loop nights (Table 3).

Daytime Glycemic Control—Per Protocol

Data analysis showed a significant positive relation between the mean overnight glucose and the mean daily glucose for both closed-loop and SAP therapy (Spearman rank correlation coefficient was 0.36 and 0.436, respectively; $P < 0.0001$). Moreover, when taking into account the treatment arm and intersubject variation (general linear model analysis), we found that the closed-loop treatment had a significantly greater impact on the mean daily glucose than the SAP treatment ($\beta_{closed\text{-}loop} = -6.371$; $SE_{closed\text{-}loop} = 2.005$; $P = 0.002$).

The per-protocol analyses showed that the morning fasting glucose levels were significantly lower after nights of closed-loop operation by a median of 15.3 mg/dL (IQR 0.5, 29.0; $P = 0.02$).

A significant improvement was found in the percentage of glucose readings within 70–180 mg/dL during the days (daytime defined from 0700 to 2300) after closed loop compared with the days after sensor-augmented nights (median [IQR] 66.1 [60.7, 80.0] and 62.3 [52.7, 69.0], respectively; $P = 0.006$). The area above glucose levels of 140, 180, and 240 mg/dL were significantly reduced ($P = 0.009$, 0.01, and 0.02, respectively). The average daytime glucose levels were also reduced by a median of 10.0 mg/dL (IQR −2.7, 19.2; $P = 0.017$) while total day insulin doses were lower ($P = 0.038$). No change was found in the number and duration of hypoglycemic events during the daytime. Figure 1 delineates the comparison between closed-loop and SAP therapy for daytime and for 24 h (day- and nighttime).

Other exploratory comparisons for the per protocol are presented in Supplementary Table 3.

Adverse Events

Severe nocturnal hypoglycemia occurred in one participant during the control arm. Although the sensor alerted, he failed to respond. When his wife tried to wake him, he was confused, showing eye rolling. She had to place some honey in his mouth. There were five events of pump occlusion in the closed-loop arm and four events during the control arm. One event of hyperglycemia with ketonuria occurred because of faulty insulin in the control arm. There were no cases of diabetic ketoacidosis in either of the study arms. Five subjects had a local skin allergy related to the CGM-sensor adhesive (Supplementary Table 4).

Table 2—Primary end points analysis—ITT and per protocol

	Closed loop₸	Control₸	Paired difference¥	*P*
Variable ITT (*N* = 19)				
Primary				
Time glucose level spent below 70 mg/dL (%)	2.53 (1.33, 3.78)	5.16 (2.03, 7.32)	−1.86 (−4.85, −0.33)	0.020
Secondary				
Time within 70–140 mg/dL (%)	47.41 (35.13, 55.86)	36.36 (30.76, 40.90)	13.48 (1.33, 20.55)	0.003
Time glucose level spent below 50 mg/dL (%)	0.25 (0.01, 1.07)	0.64 (0.12, 1.35)	−0.26 (−0.87, 0.06)	0.124
Time glucose level spent above 240 mg/dL (%)	5.01 (2.63, 7.77)	8.82 (5.94, 19.23)	−3.69 (−10.67, −0.89)	0.001
Variable per protocol (*N* = 18)				
Primary				
Time glucose level spent below 70 mg/dL (%)	2.09 (0.90, 2.67)	4.72 (1.97, 7.43)	−1.77 (−5.05, 0)	0.014
Secondary				
Time within 70–140 mg/dL (%)	49.14 (36.48, 57.42)	36.21 (29.99, 41.30)	15.19 (3.04, 21.36)	0.002
Time glucose level spent below 50 mg/dL (%)	0.07 (0.00, 0.34)	0.51 (0.11, 1.12)	−0.24 (−0.86, 0.13)	0.044
Time glucose level spent above 240 mg/dL (%)	3.83 (2.52, 5.07)	8.71 (5.52, 18.07)	−5.32 (−8.45, −2.98)	0.001

₸Median values with the IQR in parentheses. ¥Closed loop minus control. A positive value indicates the value was higher on the closed loop compared with control.

Table 3—Exploratory comparisons—ITT

Variable ($N = 19$)	Closed loop₮	Control₮	Paired difference¥	*P* valueΦ
Glucose control				
Time within 70–180 mg/dL (%)	72.87 (67.83, 79.94)	58.72 (51.28, 67.60)	12.24 (7.92, 22.9)	0.001
Mean CGM readings (mg/dL)*	147.72 ± 15.84	161.28 ± 25.10	−13.6 ± 19.9	0.008
Fasting glucose level (mg/dL)*	138.44 ± 18.15	156.49 ± 32.02	−18.04 ± 19.9	0.006
Glucose variability				
SD (mg/dL)*	33.87 ± 5.76	35.74 ± 7.32	−1.86 ± 6.62	0.235
% Coefficient variable*	0.23 ± 0.03	0.24 ± 0.05	0	0.455
Hypoglycemia				
Total events <70 mg/dL	0.16 (0.10, 0.26)	0.21 (0.14, 0.32)	0 (−0.13, 0.06)	0.376
Total events <60 mg/dL	0.06 (0.03, 0.14)	0.14 (0.04, 0.19)	−0.05 (−0.09, 0)	0.016
Area below 70 mg/dL (mg/dL×min)	110.16 (58.82, 231.96)	216.21 (84.46, 502.01)	−106.2 (−372.08, 60.5)	0.036
Area below 65 mg/dL (mg/dL×min)	56.62 (28.40, 160.72)	125.50 (44.73, 311.51)	−76.00 (−237.24, 28.55)	0.044
LBGI‡	0.66 (0.45, 0.95)	0.88 (0.64, 1.64)	−0.2 (−1.1, 0.09)	0.044
Hyperglycemia				
Time >140 mg/dL (%)	50.65 (42.55, 60.82)	56.89 (50.60, 65.48)	−9.79 (−17.8, 1.57)	0.013
Time >180 mg/dL (%)	22.29 (15.86, 30.81)	36.63 (27.64, 42.67)	−7.80 (−23.39, −4.98)	0.002
Area above 140 mg/dL (mg/dL×min)	11,468.82 (7,097.15, 14,744.16)	15,568.33 (13,052.78, 23,406.39)	−5,423.63(−10,655.14, −2,218.73)	0.003
Area above 180 mg/dL (mg/dL×min)	4,226.85 (2,407.29, 6,299.40)	6,883.98 (5,603.48, 13,010.86)	−3,628.56 (−7,296.24, −510.16)	0.003
High blood glucose index¶	5.21 (3.42, 6.49)	6.82 (5.76, 10.45)	−2.5 (−5, −0.7)	0.002
Overnight insulin delivery (units)				
Total night dose	9.02 (6.96, 18.74)	10.19 (8.00, 18.82)	−0.5 (−1.4, 0.03)	0.044
Delivered basal amount during the night	4.91 (3.96, 8.75)	5.57 (4.49, 9.74)	−0.68 (−1.06, −0.52)	<0.001
Delivered bolus amount during the night	4.41 (2.99, 8.95)	5.11 (3.02, 6.74)	0.24 (−0.89, 0.95)	0.968

₮Median values with the IQR in parentheses. ¥Closed loop minus control. A positive value indicates the value was higher on the closed loop compared with control. ΦComparisons between closed-loop and control nights were performed using the paired nonparametric Wilcoxon signed rank test, unless stated otherwise. *Average values with the SD. ‡Kovatchev LBGI to measure glucose variability (16). ¶Kovatchev high blood glucose index to measure glucose variability (16).

CONCLUSIONS

In this crossover, randomized, controlled study of long-term home use of a closed-loop control, the MD-Logic automated insulin delivery system proved to be a safe and effective tool for overnight treatment of type 1 diabetes. Glycemic control with MD-Logic showed significantly reduced nocturnal hypoglycemia, with increased time within range and lower mean glucose levels, when used during real-life conditions in patients' homes.

Hypoglycemia remains the major concern and obstacle with respect to methods for controlling nocturnal blood glucose (17,18). The use of LGS was recently found, in a large cohort, to lower the rate and duration of nocturnal hypoglycemia with mild concomitant hyperglycemia in patients prone to hypoglycemia (19). Our study clearly demonstrated that with the MD-Logic system, there was a significantly lesser risk of hypoglycemia even in a nonselected group. The time and area under the curve for nocturnal hypoglycemic events were significantly reduced. The considerable 45% reduction in the area under the curve for 65 mg/dL (this was the primary outcome measurement in the LGS study) during the closed-loop control was accompanied by better control and, contrary to the LGS, reduced risk for overnight hyperglycemia. It is likely that the closed-loop system holds even greater potential for patients who are prone to nocturnal hypoglycemia and also for those who are poorly controlled and less motivated. Overnight closed loop has the potential to mitigate the risk of nocturnal hypoglycemia and has an added value over the LGS in maintaining tighter overnight glycemic control, reducing hyperglycemia, improving glucose variability, and reducing patient fasting blood glucose and thus may consequently improve the daytime control (20).

In this study, we did not select subjects who were necessarily prone to hypoglycemia, and the prestudy number of nocturnal hypoglycemic events was low. Therefore, the time below 50 mg/dL was initially low and did not change significantly with the use of a closed-loop system in the ITT analysis. However, if we analyze only nights during which the closed-loop system was in use, this reduction in time below 50 mg/dL becomes significant. The number of hypoglycemic events below 70 mg/dL showed a tendency to decrease. Yet, with the more clinically important cutoff below 60 mg/dL, the incidence of hypoglycemia was significantly reduced with closed-loop control.

A major advantage of the system is that the reduction in the risk of hypoglycemia was accompanied by better glycemic control. Time within range was increased, and the time and area above 140, 180, and 240 mg/dL were significantly reduced as were the mean overnight glucose levels. Glucose levels were significantly more stable over time, with narrowing of the IQR and convergence into a narrow desired range. The significantly lower fasting morning glucose levels achieved by the MD-Logic system were found to have a positive effect on daytime glycemic control.

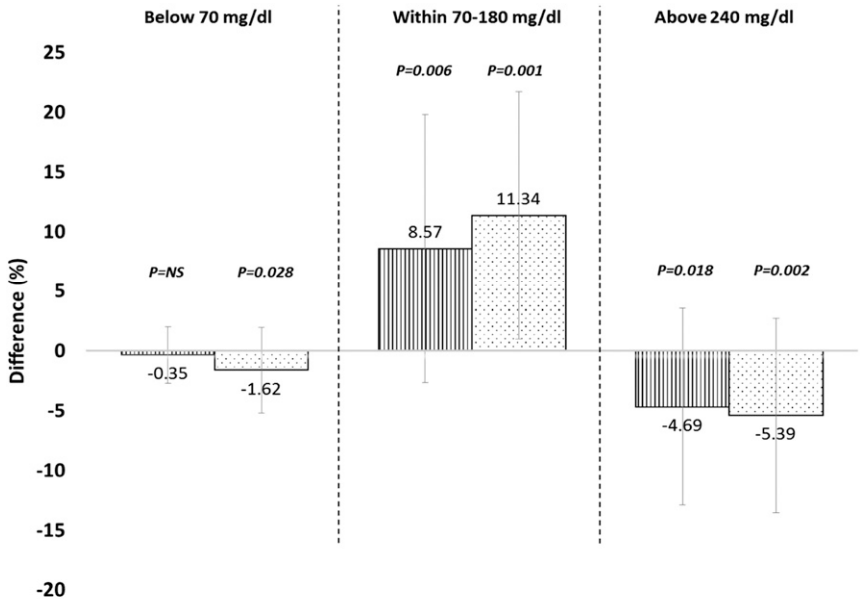

Figure 1—Daytime comparison between the closed-loop and SAP group. Mean daytime difference between the closed-loop and SAP groups in different glucose ranges. The striped boxes represent the daytime only (between 0700 and 2300), and the dotted boxes represent the entire day comparison (0000 to 2400). Comparisons were performed using the paired nonparametric Wilcoxon signed rank test.

Daytime glycemic control is a challenging task. In day and night closed-loop studies, most of the impact of the closed loop was attributed to the nighttime control and not to daytime benefits. In a 36-h study of 12 adolescents, the percentage of time within the target range (70–180 mg/dL) was significantly improved compared with conventional pump therapy during 24 h without a difference for the daytime (21). In another study of 24-h closed-loop control comparing two different control algorithms to conventional insulin pump treatment, the use of both algorithms reduced hypoglycemia, but in the expense of hyperglycemia and elevated mean blood glucose compared with patients' own treatment (5). On the other hand, better overnight control and morning glucose levels have shown to improve daytime control (22). Observation patterns recorded from CGM found that improved overnight control has the greatest impact on overall glycemic control (20). The current study demonstrated that the improved MD-Logic overnight control had a significant impact on the daytime control, with increased time spent within target range and reduced hyperglycemia with no increase in hypoglycemia. The lower insulin doses needed during the day may reflect an improvement in insulin sensitivity that was translated into beneficial effects through the day. These findings suggest that a closed-loop system could be of benefit to patients with type 1 diabetes even when its use is limited to the overnight period.

Although during closed-loop nighttime use the total insulin dose was slightly less than during SAP therapy and the amount of insulin bolus needed was similar, the overnight mean blood glucose was significantly reduced during closed loop. These findings may be related to better insulin treatment with closed loop for meals and for an oncoming hypoglycemia and hyperglycemia. The better control achieved may lead to better insulin sensitivity over time, a possibility not tested in the current study.

Our study showed a significant improvement (by a median of 16.9%) in time spent within range (70–180 mg/dL) during the nights of closed loop, as compared with control nights, with a significant reduction in time spent at hypoglycemia and no increase in insulin doses. These findings are similar to those of our previous study, also conducted at home during 4 nights (14). To the best of our knowledge, so far there has been only one other study, recently published by Hovorka et al. (3), which implemented a closed-loop system overnight at home during a 3-week period with a similar methodology. Hovorka et al. (3) also showed an improvement in time spent within range overnight (by a median of 12%), but this was achieved by a significantly greater amount of insulin given overnight and an increase (though not significant) in time spent at hypoglycemia at any level. In both studies, the mean glucose level overnight was similarly reduced by a median of 14 mg/dL, but with a higher SD in the Hovorka study. The major strength of the current study is the relatively long-term overnight use of the MD-Logic closed-loop system under unrestricted real-life conditions, including physical activities, different meals, summer school vacations, various system connection times, and various readings of glucose level at system connection. Longer periods of use may better reflect the actual degree of acceptance of the system by patients. Indeed, the rate of closed-loop use was high despite the fact that the algorithm was placed in a laptop computer and that participants had to wear the sensor continuously. The use of a wireless laptop-based system may limit the ability of patients to move freely at home. Its size and weight and the need to connect it to electricity (the battery can last 4 h) all might limit its use. Nevertheless, when used during the nighttime, as in our study, this factor would be of lesser importance. Interestingly, more subjects used the sensor during the closed-loop period than during the open-loop period, despite the same number of visits and follow-up contacts.

This may indicate greater satisfaction and therefore better compliance with sensor use during the closed-loop period. The advanced technology of SAP therapy demands almost unremitting attention by patients and caregivers (23) and is still being used only by a small number of patients (24,25). Many of those who did begin to use it subsequently discontinued its use (26,27), mainly because of the intense effort and decision making involved, fraught with tension and anxiety. This is particularly true for the pediatric age-group and adolescents, who often lack compliance in treating their diabetes (26). An automated insulin delivery system could reduce considerably the burden of daily management of this chronic, attention-demanding disease, making it a more attractive treatment option.

While the current study covered a total period of 3 months, with 1.5 months spent in each arm, and provided important information on the prolonged use of the MD-Logic system, it cannot be considered sufficient to determine the long-term impact on glycated hemoglobin and quality of life. The study cohort was heterogeneous, comprising different age-groups and diverse levels of prestudy glycemic control. Since previous studies showed that closed-loop glycemic control in adults and adolescents tends to be similar during the nighttime (28), it seemed reasonable to include them as a single group in the analysis. It must be noted that the current analysis could not include subgroup age analyses (e.g., per age and prestudy glycemic control) because of the small size of the study cohort.

In conclusion, this study demonstrated that the MD-Logic system can be safely incorporated into the daily use of children, adolescents, and adults with type 1 diabetes. This system provides an effective mean to mitigate the risk of nocturnal hypoglycemia and has an added value over other strategies in maintaining tighter overnight glycemic control, reducing hyperglycemia, improving glucose variability, and reducing patient fasting blood glucose, which may improve the daytime control.

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References

1. Kumareswaran K, Evans ML, Hovorka R. Artificial pancreas: an emerging approach to treat Type 1 diabetes. Expert Rev Med Devices 2009; 6:401–410
2. Nimri R, Atlas E, Ajzensztejn M, Miller S, Oron T, Phillip M. Feasibility study of automated overnight closed-loop glucose control under MD-Logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. Diabetes Technol Ther 2012;14:728–735
3. Hovorka R, Elleri D, Thabit H, et al. Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care. 2014;37:1204–1211
4. Dauber A, Corcia L, Safer J, Agus MS, Einis S, Steil GM. Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. Diabetes Care 2013;36:222–227
5. Luijf YM, DeVries JH, Zwinderman K, et al.; AP@home Consortium. Day and night closed-loop control in adults with type 1 diabetes: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. Diabetes Care 2013;36:3882–3887
6. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER. Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Diabetes Care 2012;35:2148–2155
7. Buckingham BA, Beck RW, Ruedy KJ, et al.; Diabetes Research in Children Network (DirecNet) Study Group; Type 1 Diabetes TrialNet Study Group. The effects of inpatient hybrid closed-loop therapy initiated within 1 week of type 1 diabetes diagnosis. Diabetes Technol Ther 2013; 15:401–408
8. Murphy HR, Elleri D, Allen JM, et al. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. Diabetes Care 2011; 34:406–411
9. Kumareswaran K, Thabit H, Leelarathna L, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. Diabetes Care 2014;37:1198–1203
10. Leelarathna L, English SW, Thabit H, et al. Accuracy of subcutaneous continuous glucose monitoring in critically ill adults: improved sensor performance with enhanced calibrations. Diabetes Technol Ther 2014;16:97–101

11. Atlas E, Nimri R, Miller S, Grunberg EA, Phillip M. MD-Logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072–1076
12. Nimri R, Danne T, Kordonouri O, et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. Pediatr Diabetes 2013;14:159–167
13. Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824–833
14. Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes 2014;15:91–99
15. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes Care 2010;33:1004–1008
16. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006;29:2433–2438
17. Bergenstal RM, Tamborlane WV, Ahmann A, et al.; STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010;363:311–320
18. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800
19. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
20. Maahs DM, Chase HP, Westfall E, et al. The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes. Diabetes Technol Ther 2014;16:284–291
21. Elleri D, Allen JM, Kumareswaran K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. Diabetes Care 2013;36:838–844
22. Schmidt MI, Hadji-Georgopoulos A, Rendell M, Margolis S, Kowarski A. The dawn phenomenon, an early morning glucose rise: implications for diabetic intraday blood glucose variation. Diabetes Care 1981;4:579–585
23. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
24. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network. The T1D Exchange clinic registry. J Clin Endocrinol Metab 2012;97:4383–4389
25. Ludwig-Seibold CU, Holder M, Rami B, Raile K, Heidtmann B, Holl RW; DPV Science Initiative; German Working Group for Insulin Pump Treatment in Pediatric Patients; German BMBF Competence Network Diabetes. Continuous glucose monitoring in children, adolescents, and adults with type 1 diabetes mellitus: analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria. Pediatr Diabetes 2012;13:12–14
26. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
27. Nørgaard K, Scaramuzza A, Bratina N, et al.; INTERPRET Study Group. Routine sensor-augmented pump therapy in type 1 diabetes: the INTERPRET study. Diabetes Technol Ther 2013;15:273–280
28. Kumareswaran K, Elleri D, Allen JM, et al. Meta-analysis of overnight closed-loop randomized studies in children and adults with type 1 diabetes: the Cambridge cohort. J Diabetes Sci Tech 2011;5:1352–1362