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Safety and performance of a hybrid closed-loop insulin delivery system with carbohydrate suggestion in adults with type 1 diabetes prone to hypoglycemia

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ABSTRACT

AIMS: To evaluate the safety and performance of a hybrid closed-loop (HCL) system with automatic carbohydrate suggestion in adults with type 1 diabetes (T1D) prone to hypoglycemia.

METHODS: A 32-hour in-hospital pilot study, including a night period, 4 meals and 2 vigorous unannounced 45-minute aerobic sessions, was conducted in 11 adults with T1D prone to hypoglycemia. The primary outcome was the percentage of time in range 70-180 mg/dL (TIR). Main secondary outcomes were time below range <70 mg/dL (TBR<70) and <54 (TBR<54). Data are presented as median (10th-90th percentile ranges).

RESULTS: The participants, 6 (54.5%) men, were 24 (22-48) years old, and had 22 (9-32) years of T1D duration. All of them regularly used an insulin pump and a continuous glucose monitoring system. The median TIR was 78.7% (75.6-91.2): 92.7% (68.2-100.0) during exercise and recovery period, 79.3% (34.9-100.0) during postprandial period, and 95.4% (66.4-100.0) during overnight period. The TBR<70 and TBR<54 were 0.0% (0.0-6.6) and 0.0% (0.0-1.2), respectively. A total of 4 (3-9) 15-g carbohydrate suggestions were administered per person. No severe acute complications occurred during the study.

CONCLUSIONS: The HCL system with automatic carbohydrate suggestion performed well and was safe in this population during challenging conditions in a hospital setting.

KEYWORDS: Hybrid-closed loop system; Hypoglycemia; Exercise; Type 1 Dia**betes.**

INTRODUCTION

Hypoglycemia remains a major limiting factor in attaining and maintaining glycemic targets in type 1 diabetes (T1D). Recurrent episodes of hypoglycemia have not only been associated with reduced quality of life, but also with cardiac arrythmia (1), cardiovascular disease (2,3), and mortality (4). Severe hypoglycemia (SH), defined as an episode requiring assistance of another person for recovery, is experienced by one-third of individuals with T1D at least once a year (5,6) and it is the cause of 4–10% of all deaths in T1D (7).

In 2015, Choudhary et al proposed an evidence-based step-by-step approach to resolving recurrent SH in people with T1D (5): 1) Structured education programs; 2) Continuous subcutaneous insulin infusion (CSII) or continuous glucose monitoring (CGM); 3) Sensor-augmented pump (SAP) with predictive low-glucose suspense (PLGS); 4) Islet or pancreas transplant. However, transplants are limited by associated morbidity, the need for immunosuppression, the lack of accessibility or by several contraindications. Furthermore, setting higher glycemic targets is also recommended in these individuals (8) and resolving recurrent hypoglycemia might come with deterioration of glycemic management. Hence, there is still a need to develop new therapies for this population and more research is essential (9).

Latest clinical practice guidelines consider automated insulin delivery (AID) systems a promising solution for individuals with recurrent hypoglycemia (10–12). Nevertheless, only small trials have evaluated AID systems in this population (13–16) and individuals with recent history of SH and/or impaired awareness of hypoglycemia (IAH) are excluded (17–19) or underrepresented (20–23) in most randomized clinical trials (RCT). More importantly, its performance under physical activity in this population still needs to be specifically assessed and newer strategies probably implemented, as exercise-associated glycemic imbalance remains a challenge with AID systems (24,25).

The SAFE-AP system is a new single-hormone hybrid closed-loop (HCL) controller specifically tuned to prevent hypoglycemia, implemented in the proprietary Android platform jAP for the development of AID systems. It is based on a proportional derivative with an insulin feedback

controller that integrates a safety layer with insulin-on-board constraints and sliding mode reference conditioning. The HCL system includes a second safety feedback loop with a controller that triggers carbohydrate recommendations to the user. Both control loops are coordinated to ensure that the counter-regulatory effect of rescue carbohydrates is not counteracted with insulin. Previous models of this system have proven effective in meals (26) and unannounced exercise (27), the main challenges in AID systems development.

The aim of this pilot study was to evaluate the safety and performance under challenging conditions of the SAFE-AP system in adults with T1D prone to hypoglycemia.

SUBJECTS, MATERIALS AND METHODS

2.1 Study design and participants

A single-arm interventional proof-of-concept pilot study was conducted at the Hospital Clínic de Barcelona (Spain). The study was approved by the local Ethics Commitee and all participants gave informed consent. It was performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study is also listed on clinicaltrials.gov under the registration number NCT05628662.

Participants were enrolled if they were aged 18 years or older, had a clinical diagnosis of T1D for at least 5 years, were treated with CSII for 6 months or longer, were trained to carbohydrate counting and were prone to hypoglycemia, despite optimal diabetes management and hypoglycemia-specific education programs, as defined by >4 hypoglycemic episodes [<70 mg/dL (<3.9 mmol/L)] per week and at least one of the following: a) occurrence of at least 2 SH during the last 2 years (need for third party); b) IAH (Clarke questionnaire ≥4 (28,29)); or c) occurrence of at least 1 SH during the last year and high glycemic variability (coefficient of variation >36%).

Exclusion criteria were pregnancy or breastfeeding, history of drug or alcohol abuse, advanced micro- or macrovascular complications or a serious disease or treatment that could interfere with the study results. Additionally, a positive SARS-CoV-2 PCR test performed at arrival with nasopharyngeal and oropharyngeal swabs was also an exclusion criterion.

2.2 Procedures

Screening visit

The screening visit included informed consent acquisition, a detailed physical examination and confirmation of the inclusion/exclusion criteria. Basal CGM-derived glucometrics from 90 consecutive days were collected from uploads from each participant. These data were also used to calculate individual daily glycemia risk index (GRI), a single-number summary of the quality of glycemia with 0 being the best profile and 100 being the worst (30). GRI score, which considers both

hypoglycemia and hyperglycemia risk components, can also be distributed into five risk zones: Zone A (0-20), Zone B (21-40), Zone C (41-60), Zone D (61-80), and Zone E (81-100). Participants also answered the short version of the International Physical Activity Questionnaire and Clarke questionnaire. IAH was defined as a Clarke score ≥4, but specific evaluation of the hypoglycemia awareness component of the questionnaire (items 1, 2, 5-6, 7, and 8) was further performed to avoid major influence of the SH experience component (items 3 and 4). A cutoff value of ≥2 in the five-item hypoglycemia awareness component was considered indicative of IAH, as previously proposed by Sepúlveda et al (31).

Subsequently, eligible participants were instructed to use an unblinded CGM device and a CGM sensor (Dexcom G6, Dexcom, San Diego, CA) was inserted on the abdomen or, otherwise, on the back of the upper arm. Additionally, the study insulin pump (Dana Diabecare R, Sooil, Seoul, Korea) was initiated in manual mode with participants' usual parameters (insulin to carbohydrates ratio, sensitivity factor, and basal insulin needs) and individuals were carefully trained to use it, while their usual insulin pump (Medtronic 640G; Medtronic-Minimed, Northridge, CA, USA) was disconnected. The fast-acting insulin analogues lispro or aspart were used in all cases, according to participants' usual treatment. Individuals regularly using SAP with PLGS were informed that such function would not be available during the study and accepted it. All the participants were able to contact a 24-hour/7-day telephone helpline.

In-hospital pilot study

After a 4-to-6-day period at home with the study insulin pump set and CGM system, participants arrived at the investigational clinical site at 8:00 AM after having a standardized breakfast of 50 grams of carbohydrates at home. Although participants received instructions on breakfast protocol, compliance was not checked. A SARS-CoV-2 PCR test with nasopharyngeal and oropharyngeal swabs was performed at arrival, as well as an electrocardiogram and a safety clinical laboratory analysis. In women of childbearing age, a urine test for pregnancy was also performed. Data from CGM were used to optimize the following parameters: insulin to carbohydrates ratio, sensitivity factor, and basal insulin settings. Such parameters are needed for system operability. At

9:00 AM, the AID mode was initialized and 28-hour CGM data collection began at 12:00 PM. The safety and performance of the system was then evaluated in challenging conditions, including 4 standardized mixed meals, 2 unannounced vigorous aerobic exercise sessions and one overnight period (Figure 1, Panel A). The participants remained at the hospital during 32 consecutive hours with the on-site supervision of a specialized nurse and a diabetologist, as well as an engineer in on-site or remote control.

Mixed meals

An announcement with carbohydrate content was made before each standardized meal (50-60 g carbohydrates, 15-20 g fat, 25-30 g protein), triggering the automatic administration of an augmented bolus, defined as a standard bolus (calculated from insulin/carbohydrates ratio) plus the amount of basal insulin that would be delivered in the next hour according to initial basal settings (26).

Exercise sessions

Each exercise session consisted of three 15-minute sets on a cycle ergometer (Wattbike Pro, Wattbike Ltd, UK) at 70% of maximum heart rate with 5 minutes of rest between sets. Participants wore a heart rate monitor (Polar RCX3, Kempele, Finland) to ensure the desired exercise intensity, calculated as: HRexercise = HRrest + 70 (HRmax − HRrest)/100 where heart rate HRexercise is the heart rate (beats per minute (bpm)) during the physical activity period, HRmax is the maximum heart rate (bpm), and HRrest is the rest heart rate (bpm). No exercise announcement was made prior to the start of the activity.

2.3 Devices and assays

The HCL system is based on the SAFE-AP glucose controller (32–37) built in an Android platform designed for investigational purposes (java Artificial Pancreas [jAP]). The system was installed in a Samsung S7 (4 GB RAM, 32 GB memory) smartphone with Android 7.0 (kernel 3.18.14-12365438) including only the preinstalled applications and our jAP platform. The smartphone was wirelessly connected to both the study insulin pump (Dana Diabecare R, Sooil, Seoul, Korea) and

CGM system (Dexcom G6, Dexcom, San Diego, CA) using Bluetooth technology, enabling jAP platform to retrieve glucose/insulin data and set insulin treatment. A backup Asus ZenBook laptop (i7-7500U, 2.70 GHz, 16 GB RAM, Windows 10 Home v18362.418) was prepared for troubleshooting issues and connection errors.

The HCL system in this study consisted in an adaptation of previous investigations (26,27), and was designed, tuned, and validated using Matlab (R2017a, MathWorks, Natick, MA). The controller requires individual's sensitivity factor, insulin to carbohydrates ratio, and basal insulin settings for its operation. It receives glucose measurements from a CGM device every 5 minutes and calculates two control actions: insulin delivery and a fast-acting rescue carbohydrate intake recommendation. Calculated insulin is delivered automatically by changing the basal rate of the insulin pump during the next time interval. When necessary, recommendations of carbohydrate intake by the controller are given as a predefined amount of fast-acting carbohydrates (15 g) to prevent hypoglycemia. Both control loops are coordinated, and when CH administration is suggested, the insulin infusion is also reduced.

2.4 Safety monitoring

Data were uploaded to a server used as a remote monitoring tool and a web application allowed the authorized users to remotely monitor the status of the participant in each trial. Data like CGM, infused insulin, insulin on board, and other useful controller parameters were presented in timed graphics in order to follow the whole trial in real time.

Additionally, venous blood samples were collected every 10 minutes during exercise and every 15 minutes before exercise and during recovery, in order to measure glucose levels with a blood glucose meter (Contour Next Link Meter 2.4, Ascensia Health Care, Basel, Switzerland). Glucose levels were also checked every 15 minutes during each postprandial period. If any blood glucose value reading was below 55 mg/dL (3.0 mmol/L) [or below 70 mg/dL (3.9 mmol/L) with symptoms of hypoglycemia], 15 g of glucose were provided (Gluc Up gel). Furthermore, if that happened during exercise, the session was interrupted until symptoms had resolved and blood glucose levels were

above 70 mg/dL (3.9 mmol/L). Calibrations of CGM were only contemplated if a sustained (>2 hours) and significant (>30%) discrepancy between CGM system and glucose meter was observed outside exercise, postprandial or overnight periods.

2.5 Endpoints

To examine the performance of HCL system during the clinical study, the primary outcome was the percentage of time spent in the target blood glucose range [70-180 mg/dL (3.9-10.0 mmol/L); TIR] during the study duration, from 12:00 PM of the first day until 16:00 PM of the following day. As secondary outcomes we also examined TIR during the postprandial period (until 4 hours after the meal announcement), overnight period (12:00 AM – 06:00 AM) and exercise and recovery period (until 3 hours after exercise starting time).

Other secondary outcomes were: a) percentage of time spent <54 mg/dL (<3.0 mmol/L; TBR<54), <70 mg/dL (<3.9 mmol/L; TBR<70), >180 mg/dL (>10.0 mmol/L; TAR>180) and >250 mg/dL (>13.9 mmol/L; TAR>250) of CGM glucose during the study and the postprandial, overnight, and exercise and recovery periods; b) glucose management indicator (GMI) and coefficient of variation (CV); c) number of rescue carbohydrate events during the study; d) proportion of participants achieving CGM-derived glycemic targets (38,39); and e) safety outcomes (SH and ketoacidosis).

2.6 Statistical analyses

Due to the exploratory nature of this study, sample size calculations were not formally performed. Descriptive statistics, including the mean standard deviation, median, 10th to 90th percentile range, and CV were computed to describe the sample characteristics and results.

RESULTS

The baseline characteristics of the cohort are reported in Table 1. All participants (n=12) completed the study, but one participant was excluded from analysis due to multiple infusion set failures during the study period that compromised interpretation. Analyzed participants (n=11) were 54.5% men and 24 (22-48) years old and had 22 (9-32) years of T1D duration and a 5-year HbA1c mean of 7.8% (5.8-8.4). None of the participants were in the low physical activity category according to IPAQ Questionnaire and 72.7% of them accomplished American Diabetes Association's aim for at least 150 minutes of moderate-to-vigorous-intensity aerobic exercise per week. A total of 81.8% of the participants had experienced an SH in the last 2 years and only 36.3% of the patients had preserved hypoglycemia awareness according to Clarke score. Further baseline characteristics of the cohort are reported in Table 1.

Regarding 90-day CGM data before inclusion, median TIR was 63.0% (47.9-69.7), median TBR<70 was 3.3% (2.1-6.0) and median CV was 39.6% (34.3-43.0) (Table 2). Median GRI was 42.9 (30.9-71.0) (0-100 scale, higher values indicating increased risk) and daily GRI with hypoglycemia and hyperglycemia components were displayed graphically on a GRI Grid (Figure 2, panel A).

The glycemic outcomes were calculated using the glucose readings from CGM during the study period, which resulted in 28 hours of data (Figure 1, panel B). The HCL auto-mode system remained active 100% of time in all cases. The median (10th-90th percentile ranges) proportion of TIR during the study period was 78.7% (75.6-91.2), with median TBR<70 0.0% (0.0-6.6), median TBR<54 0.0% (0.0-1.2) and median CV 26.7 (22.6-34.1) (Table 2). Global CGM-derived data and GRI Grid per subject are also reported in Table 3 and Figure 2 (Panel B), respectively.

Regarding the postprandial period, median (10th-90th percentile ranges) proportion of TIR was 79.3% (34.9-100.0), with TBR<70 0.0% (0.0-2.0) and TBR<54 0.0% (0.0-0.0). The last meal was not included in the subanalysis of postprandial CGM-derived data, as postprandial glucose assessment was limited to only 2 hours following the intake.

When it comes to the exercise and recovery period, median (10th-90th percentile ranges) proportion of TIR was 92.7% (68.2-100), with TBR<70 0.0% (0.0-28.3) and TBR<54 0.0% (0.0-2.6) (Table 2). As for the overnight period following exercise, median (10th-90th percentile ranges) TIR was 100.0% (76.0-100.0), with TBR<70 0.0% (0.0-0.0) (Table 2).

Regarding the percentage of participants achieving CGM-derived glucometric goals, 90.9% (n=10) of the participants achieved a TIR>70%, 63.6% (n=7) a TBR<70 <4% and 81.8% (n=9) a TBR<54 <1% (Table 3). A total of 54.5% (n=6) of participants accomplished all three objectives, and 90.9% (n=10) of the participants achieved a CV<36%.

During the study period, a total of 4 (3-9) automatic suggestions of 15 g of carbohydrates were administered per person: 2 (1-5) during exercise and recovery, 1 (0-3) after meals and 0 (0-1) overnight. Only 1 (0-3) automatic bolus was omitted due to either current meal consumption or recently administered manual rescue event. The median manual rescue carbohydrates given was 0 (0-2). No technical issues occurred and there were no severe acute complications during the study.

DISCUSSION

The HCL system with carbohydrate suggestion, achieved optimal glycemic targets without significant hypoglycemia in adults with T1D prone to hypoglycemia in a 32-hour clinical study under challenging conditions, including vigorous unannounced aerobic exercise, meals and a night period following exercise.

Hypoglycemia remains a major limiting factor in achieving optimal glycemic targets in T1D. Relaxation of glycemic targets and a step-by-step approach including educational, technological and transplant interventions is recommended to resolve recurrent hypoglycemia (5,8). Nevertheless, the evaluation and implementation of new technologies is still needed to resolve recurrent hypoglycemia without deteriorating glycemic management in a significant subset of individuals. Despite the potential of HCL systems, their efficacy and safety cannot be extrapolated from clinical trials to this population, as history of SH and/or IAH usually remain exclusion criteria. Conversely, most of the participants in our study had experienced an SH in the last 2 years and hypoglycemia awareness was not preserved in most cases. Even if time in hypoglycemia in previous 90-day CGM data was relatively low, it should be noted that participants were under structured educational programs with frequent contact with our diabetes team and followed routines to avoid hypoglycemia before inclusion. Despite this and the use of diabetes technology systems (CSII with CGM or SAP with PLGS), participants were still experiencing frequent hypoglycemic events, while not achieving glycemic targets (HbA1c <7% and CGM-derived glucometrics goals) (38). Furthermore, they had a remarkably high CV (median CV 39.6% (34.3-43.0)), an indicator of glycemic variability with a close relationship with hypoglycemia. Finally, median GRI in the intermediate risk zone (Zone C; ranked from lowest to highest: A-E)(30) also indicated the need for further glycemic optimization.

During the study duration, our sample of individuals prone to hypoglycemia maintained a tight glycemic control (TIR 78.7%) without significant hypoglycemia, despite the challenging conditions they were exposed to. Interestingly, participants maintained a low glycemic variability and most of them (90%) achieved a TIR>70%. A low risk of hypoglycemia and hyperglycemia was also observed when evaluating individual GRI. Moreover, the HCL system also performed well and was

safe during postprandial period, postexercise and recovery period and night following exercise period. Such performance with a low glycemic variability suggests that automatic carbohydrate recommendation was helpful in hypoglycemia prevention and over-correction avoidance in high-risk individuals. Notably, there were considerable differences in the number of rescue events required to prevent hypoglycemia, indicating that glucose response during and after individual exercise events is highly variable among subjects with T1D(40).

Physical activity is beneficial in terms of cardiovascular risk factors and glycemic management in individuals with T1D (41) and the American Diabetes Association recommends a minimum of 150 minutes of moderate-to-vigorous-intensity aerobic exercise per week (42). However, exercise management when using a HCL system remains a challenge (40,43) and many individuals need to come out of automatic mode or suspend insulin delivery for aerobic exercise (44,45). Furthermore, pre-exercise consumption of carbohydrates without meal announcement might lead to a subsequent rise in automated insulin delivery and a paradoxical risk of hypoglycemia. Some HCL systems have an option to raise the glucose target and even make the algorithm less aggressive, but exercise planning remains important with these settings (25,46).

In a recently published study, switching to HCL did not alter patterns of glycemia around moderate-intensity exercise, emphasizing the demand for novel strategies for glycemic management with AID systems during exercise(47). In this sense, our approach with carbohydrate suggestion was effective and safe in both announced and unannounced exercise in a previous clinical trial(27). In the present study the HCL system was further evaluated under unannounced exercise in subjects prone to hypoglycemia, describing both good performance and safety. Such results were attained with a median of 22.5 (15-45) grams of carbohydrates per person and exercise session, which is within the recommendations for hypoglycemia prevention during exercise in T1D considering duration and type of activity(48).

Our study has several limitations. First, it was an uncontrolled pilot study including a small sample size and it was conducted in a well-controlled in-hospital environment. Carbohydrate counting was precise and insulin doses were not missed or delayed. Accordingly, neither superiority to other therapies nor long-term safety and efficacy conclusions can be drawn. Most of the controller

parameters were kept the same across all participants to generalize the tuning and make it as simple as possible, only the proportional and derivative controller gains were individualized according to the total daily insulin from the participants open-loop therapy. In free-living conditions, the control parameters should be further individualized to each specific participant and adapted to optimize performance and enhance safety. Due to the small duration and the exploratory nature of this study, it was not possible to address this issue. Finally, information on users' experience, an increasingly important outcome with AID systems(49), was not collected.

It also has several strengths, one of the main strengths being that it is among the first studies to evaluate an HCL system in individuals with T1D and disabling and recurrent hypoglycemia (15,16). Furthermore, despite only assessing 28 hours, it included specially challenging conditions such as two unannounced exercise sessions, a night period following exercise and four meals with 50-60 grams of carbohydrates. To our knowledge, this is the first study to assess the efficacy of such a system around physical exercise in this population. Apart from reducing patient burden by eliminating user-initiated exercise settings, being safe and effective during unannounced exercise might be crucial for a HCL aimed for subjects prone to hypoglycemia. Moreover, the inclusion of carbohydrate recommendation can be helpful in optimizing both timing and quantity of CH needed during exercise.

In conclusion, the HCL system, based on the SAFE-AP control algorithm designed to safeguard against hypoglycemia, performed well and was safe during challenging conditions in subjects with T1D prone to hypoglycemia despite structured education and advanced diabetes technologies. The system was able to achieve glycemic targets without increasing the risk of hypoglycemia in this population. Longer term and randomized outpatient studies are required to further assess the efficacy and safety of this system in free-living conditions and with a larger sample size.

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AUTHORS’ CONTRIBUTIONS

A.M. performed and supervised all the experimental studies, analyzed and interpreted data, and wrote the manuscript. A.B. conceived, designed, implemented, tested, and validated all control strategies; performed the statistical analysis; analyzed and interpreted the data; and wrote the manuscript. J.F.M.S.J developed and validated the jAP platform, the remote monitoring site, the communication between devices, and revised the manuscript. J. Viaplana performed and supervised all the experimental studies and revised the manuscript. J.B. conceived and designed the study, designed and supervised the implementation of the jAP system, contributed to the development of control strategies, interpreted data, obtained funding, and critically revised the manuscript. J. Vehí conceived and designed the control strategies, conceived and designed the study, interpreted data, obtained funding, and critically revised the manuscript. I.C. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding, and critically revised the manuscript. M.G. conceived and designed the study, supervised clinical studies, interpreted data, obtained funding, and critically revised the manuscript. All authors contributed to the review of the report and approved the final version for submission. I.C. and M.G are the guarantors of this work and, as such, had full access

to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DECLARATION OF COMPETING INTEREST

The authors have nothing to disclose.

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TABLES

Table 1. Baseline characteristics of the study participants.

	Analyzed participants (n=11)
Male (%)	6 (54.5%)
Age (years)	24 (22-48)
Diabetes duration (years)	22 (9-32)
BMI (kg/m^2)	25.8 (20.8-26.9)
HbA1c (%)	
1-year mean	7.3 (6.1-8.0)
5-year mean	7.8 (5.8-8.4)
Therapy (%)	
CSII+CGM	6 (54.5%)
SAP	5 (45.5%)
Insulin pump experience (years)	10 (3-15)
Total daily insulin (U/day)	34.3 (26.7-56.4)
Fast-acting insulin analogue used (%)	
Lispro insulin	7 (63.6%)
Aspartic insulin	4 (36.4%)
Average daily carbohydrate intake (g/day)	166 (124-223)
Regular CGM system (%)	
Medtronic Sensor 3	5 (45.5%)
Dexcom G6	4 (36.4%)
FreeStyle Libre 2	2 (18.2%)
Severe hypoglycemia episodes (last 2 years)	
At least 1 episode	9 (81.8%)
Mean number of episodes	2 (0-4)
Clarke questionnaire (score) †	4 (1-5)
Awareness of hypoglycemia (out of 5 points)	3 (0-4)
Experience of hypoglycemia (out of 2 points)	1 (1-1)
Impaired awareness of hypoglycemia	
Clarke score ≥4	6 (54.5%)
Awareness of hypoglycemia component ≥2†	7 (63.6%)
Moderate to vigorous intensity exercise at least 150 minutes/week	8 (72.7%)
Mean energy expenditure	
Vigorous (MET-min/week)	720 (0-2400)
Total (MET-min/week)	1884 (1173-5358)
Physical activity category*	
Low	0 (0%)
Moderate	6 (54.5%)
High	5 (45.5%)

*According to International Physical Activity Questionnaire (IPAQ).

† Clarke questionnaire components: awareness of hypoglycemia (items 1, 2, 5-6, 7, and 8) and experience of hypoglycemia (items 3 and 4).

Data are shown as median (10th-90th percentile ranges) or n (percentage).

Table 2. CGM-derived glucometric data from study population before and during study inclusion.

	Mean glucose [mg/dl (mmol/L)]	TBR<54 (%)	TBR<70 (%)	TIR (%)	TAR>180 (%)	TAR>250 (%)	CV (%)	Administered automatic rescue events	Omitted automatic rescue events†	Manual rescue events
90-day CGM data before inclusion*	162 (149-184) [9.0 (8.3-10.2)]	1.0 (0.3-2.0)	3.3 (2.1-6.0)	63.0 (47.9-69.7)	34.0 (43.4-46.9)	9.0 (6.0-22.3)	39.6 (34.3-43.0)	N.A.	N.A.	N.A.
Global results	142 (118-152) [7.9 (6.6-8.4)]	0.0 (0.0-1.2)	0.0 (0.0-6.6)	78.7 (75.6-91.2)	17.4 (4.7-24.4)	0.0 (0.0-5.0)	26.7 (22.6-34.1)	4 (3-9)	1 (0-3)	0 (0-2)
Postprandial period	145 (108-194) [8.1 (6.0-10.8)]	0.0 (0.0-0.0)	0.0 (0.0-2.0)	79.3 (34.9-100)	20.2 (0.0-65.1)	0.0 (0.0-0.0)	19.1 (13.1-29.9)	1 (0-3)	0 (0-1)	0 (0-1)
Exercise and recovery period	120 (90-148) [6.7 (5.0-8.2)]	0.0 (0.0-2.6)	0.0 (0.0-28.3)	92.7 (68.2-100)	1.5 (0.0-14.7)	0.0 (0.0-0.0)	20.6 (13.5-31.4)	2 (1-5)	1 (0-1)	0 (0-2)
Overnight period	131 (107-152) [7.3 (5.9-8.4)]	0.0 (0.0-0.0)	0.0 (0.0-0.0)	100.0 (76.0-100)	0.0 (0.0-24.0)	0.0 (0.0-0.0)	17.8 (9.8-26.1)	0 (0-1)	0 (0-0)	0 (0-0)

TBR<54: percentage of time spent below range 54 mg/dL (3.0 mmol/L); TBR<70: percentage of time spent below range 70 mg/dL (3.9 mmol/L); TIR: time in range 70-180 mg/dL (3.9-10.0 mmol/L); TAR>180: percentage of time spent above 180 mg/dL (10.0 mmol/L); TAR>180: percentage of time spent above 250 mg/dL (13.9 mmol/L); CV: coefficient of variation.

*CGM data of one participant could only be obtained from last 30 days.

†Automatic bolus omitted due to either current meal consumption or recently administered manual rescue event

Table 3. Individual CGM-derived data during the study period.

Subject number	Median glucose (mg/dl)	TBR <54 (%)	TBR <70 (%)	TIR (%)	TAR >180 (%)	TAR >250 (%)	CV (%)	Administered automatic rescue events	Omitted automatic rescue events	Manual rescue events
#1	103 (74 – 139) [5.7	1.3	8.2	89.3	2.4	0.0	26.6	4	0	2

	(4.1-7.7)]									
#2	141 (83 – 196) [7.8 (4.6-10.9)]	0.0	1.3	78.7	20.0	0.0	30.7	7	2	0
#3	118 (81 – 149) [6.6 (4.5-8.3)]	1.2	4.1	91.2	4.7	3.1	33.0	19	6	1
#4	152 (101 – 199) [8.4 (5.6-11.1)]	0.0	0.0	82.6	17.4	0.0	23.5	3	0	0
#5	137 (97 – 184) [7.6 (5.4-10.2)]	0.0	0.0	88.3	11.7	0.0	22.3	3	1	0
#6	159 (100 – 208) [8.8 (5.6-11.6)]	0.0	0.0	64.2	35.8	0.0	25.1	3	0	0
#7	146 (94 – 211) [8.1 (5.2-11.7)]	0.0	0.0	77.1	22.9	0.0	30.0	9	1	0
#8	142 (80 – 205) [7.9 (4.4-11.4)]	0.3	6.6	77.2	16.2	5.0	34.1	5	1	2
#9	144 (79 – 223) [8.0 (4.4-12.4)]	0.5	4.8	75.8	19.3	6.2	39.4	4	1	2
#10	152 (104 – 193) [8.4 (5.8-10.7)]	0.0	0.0	75.6	24.4	0.0	22.6	5	1	0
#11	122 (88 – 161) [6.8 (4.9-8.9)]	0.0	0.0	92.8	7.2	0.0	26.7	4	3	1

TBR<54: percentage of time spent below range 54 mg/dL (3.0 mmol/L); TBR<70: percentage of time spent below range 70 mg/dL (3.9 mmol/L); TIR: time in range 70-180 mg/dL (3.9-10.0 mmol/L); TAR>180: percentage of time spent above 180 mg/dL (10.0 mmol/L); TAR>180: percentage of time spent above 250 mg/dL (13.9 mmol/L); CV: coefficient of variation.

FIGURE LEGENDS

Figure 1. A: Clinical study protocol. Automatic mode initiated at 09:AM and data analysis began at 12:00 PM. The day of arrival included lunch at 01:00 PM, first exercise session at 05:00 PM, and dinner at 08:00 PM. The second day included breakfast at 07:00 AM, an exercise session at 11:00 PM, and lunch at 14:00 PM. **B:** CGM sensor values in median (IQR) since automatic mode initiation.

CGM, continuous glucose monitoring; IQR, interquartile range.

Figure 2. A: Glycemia Risk Index (GRI) grid showing the hyperglycemia component versus the hypoglycemia component for all the participants over the previous 90 days before inclusion. Each circle denotes a single day of every study participant. **B:** GRI grid showing the hyperglycemia component versus the hypoglycemia component over the 28 hours of study. Each circle represents a study participant.