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ARTIFICIAL PANCREAS DEVELOPMENT IN TYPE 1 DIABETIC PATIENTS

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ABSTRACT

Introduction and background: In type 1 diabetic patients good glycaemic control is associated with complication reduction. Nevertheless a minority of patients, also treated with insulin pumps and continuous glucose monitoring (SAP therapy) achieve a satisfactory metabolic control. Several researchers are developing automatic systems, called artificial pancreas (AP) or Closed Loop Control (CLC). This system are composed by an insulin pump, a continuous glucose monitoring device and a control algorithm which modifies insulin infusion from data derived by continuous glucose monitoring. Several AP models exist, composed by different insulin pumps, different continuous glucose monitoring system and by different control algorithms that determine the precision of glucose control.

Method: we evaluated our AP model efficacy and safety at patients home compared to SAP therapy. In our AP model, the Algorithm is installed in a smartphone (DiAS, Diabetes Assistant) that communicate with pump and CGM thought blue tooth connection. We developed 5 studies that tested the system in free life condition, first during evening and night, than for 24 hours and for longer period (6 months). We finally evaluated this system in pediatric population.

Results: In a randomized cross over study of 2 month AP use during evening and night vs SAP therapy, system usage improved time in target (70-180 mg/dl) from 58.1% to 66.7% ($P < 0.0001$), reduce mean glucose concentration (162 mg/dl vs 167 mg/dl, $P=0.0053$) and time spent in hypoglycemia (<70 mg/dl) from 3.0% to 1.7% ($P < 0.0001$) and lead to reduction in HbA1c values. Extension of this study for a month using AP 24 hours/day demonstrated an improvement of time in target vs SAP ($64.7 \pm 7.6\%$ vs. $59.7 \pm 9.6\%$, $P = 0.01$), reduction of time below the target ($1.9 \pm 1.1\%$ vs. $3.2 \pm 1.8\%$, $P = 0.001$).

A third trial evaluated a different algorithm for 2 weeks during overnight e for 2 weeks for 24 hours, comparing these period with 2 weeks of SAP therapy. In overnight period AP improved glucose metric vs SAP: time spent in hypoglycaemia dropped from 3.0% to 1.1% ($P < 0.001$), time in target increased from 61% to 75% ($P < 0.001$) , time spent above 180 mg/dl dropped from 37% to 24% ($P < 0.001$), the mean glucose concentration dropped from 163 to 150 mg/dL ($P = 0.002$). Similarly, metrics of glucose control in the 24-hour AP usage vs SAP demonstrated reduction of the time below target from 4.1% to 1.7% ($P < 0.001$), increase of time in target from 65% to 73% ($P < 0.001$), decrease of time above target from 32% to 25% ($P = 0.001$). Comparing the overnight and 24 hours CLC, a reduction in time spent in hypoglycaemia was observed when AP was used for 24 hours. A subgroup of patients extended AP use for other 5 months, confirming AP efficacy (time in target:77% vs. 66%, $P<0.001$, time in hypoglycaemia: 4.1% vs 1.3%, $P < 0.001$, time above target 31% vs 22%, $P = 0.01$). Finally we tested the system in paediatric population, enrolling in a summer camp 30 subject 5-9 years old. During the night AP reduced time in hypoglycaemia ($P < 0.002$), with no difference in time in target. During 24 hours we observed reduction of the time in hypoglycaemia, from 6.7% to 2.0% ($P < 0.001$), but an increase of mean glucose (147 mg/dL vs. 169 mg/dL, $P < 0.001$) and a decrease of time spent in target (63.1% vs. 56.8%, $P = 0.022$)

Conclusions: These results demonstrated our model safety and efficacy. Some improvements are necessary to ameliorate glycaemiec control on pediatric population and during day time.

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease characterized by pancreatic beta cell destruction with reduced or absent insulin production, leading to hyperglycaemia and abnormalities in lipid, protein and glycaemic metabolism. In normal subjects, insulin is produced continuously by beta cells to maintain regular basal metabolism and through peaks after meals to avoid postprandial hyperglycaemia.

Insulin absence is quickly fatal and, until the discovery of insulin in 1921, diabetic subjects had no possibility of survival due to diabetic ketoacidosis. In the years several improvements in insulin therapy have been discovered. Human insulin, which has fewer collateral effects than animal insulin, was synthesized through molecular biology techniques in 1984. In the late 1990s, researchers created human insulin analogues[1] with faster absorption from subcutaneous tissues to obtain postprandial glycaemic control, as well as analogues with slower absorption to ensure adequate insulin basal levels.

It has been demonstrated that hyperglycaemia is associated with chronic disease complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease that reduce life expectancy and quality of life in diabetic patients[2]. Furthermore, several clinical trials have demonstrated that good glycaemic control is associated with reduction of complications and an increase in life expectancy[3-5]. These studies, underling the importance of glycaemic control avoiding hyperglycaemia, urge patients to control their glucose levels by administering several insulin injections per day. Metabolic control is evaluated through glycated haemoglobin (HbA1c), derived by non-enzymatic glycation due to plasma glucose haemoglobin exposition, which identifies the three-month average plasma glucose concentration[6]. HbA1c reduction reflects metabolic control improvements and is associated with the reduction of complications. The American Diabetes Association recommends a

HbA1c level below 7% (53 mmol/mol) for adults with T1D, which corresponds to a mean glucose value below 155 mg/dl (8.6 mmol/L)[7-8].

The most limiting factor for achieving good glycaemic levels is represented by hypoglycaemia, defined as glycaemic values lower than 70 mg/dl (<3.9 mmol/L), often due to excessive insulin administration. Hypoglycaemia impacts quality of life and leads to acute complications like seizures and coma, as well as and chronic issues[9-14]. Furthermore, fears of hypoglycaemia lead patients to accept higher glycaemic values, making it more difficult to achieve good metabolic control.

Insulin is administrated through subcutaneous injections. Every day, diabetic patients have to administer several injection, one for each meals to avoid postprandial hyperglycaemia[16], and one or more basal insulin injections to maintain basal insulin concentration. Alternatively, patients administer insulin through insulin pumps, small devices that continuously deliver basal insulin subcutaneously at pre-programmed rates. Insulin inserted into insulin pumps are fast insulin analogues that are administered in small boluses and guarantee a personalized basal concentration. Patients deliver prandial and corrective boluses of insulin, for example during a meal, through pump. Prandial boluses are calculated using insulin carbohydrates ratio[17], defined as grams of carbohydrates metabolized by one unit of insulin. Correction boluses are calculated through a correction factor, defined as the reduction of glycaemia caused by one unit of insulin. Insulin pumps are composed of:

- A subcutaneous needle that patients must change every two or three days,
- A small catheter that connects the insulin cartridge to the needle, and
- An insulin cartridge inserted into a device with a small piston that pushes insulin in the catheter at a pre-programmed infusion rate.

Modern insulin pumps have different advanced functions to ameliorate problems with glucose control and improve patients' quality of life. For example, all insulin pumps have an

integrated bolus advisor[18] that simplifies decisions regarding meal and correction boluses on the basis of carbohydrate consumption and glycaemic values. Another function is temporary basal rate, which allows patients to increase or decrease the insulin basal rate for a determined period, for example during physical activity or illness. Extended boluses[19] can improve postprandial control when patients consume a meal rich in protein or fat or in case of delayed gastric emptiness that leads to a latehyperglycaemia.

It has been demonstrated that insulin pumps lead to better metabolic control with fewer hypoglycaemic events than multi-injection therapy and less complications incidence[20-25]. For Example, Pickup demonstrated in a meta-analysis that insulin pumps lead to a reduction in HbA1c values of 0.5% over multi-injective therapy[21]. Furthermore, insulin pumps provide a reduction in insulin requirements and higher patient satisfaction[26-27] compared to multi-injection therapy, due to fewer injections, less pain, and increased portability.

To avoid hypoglycaemia and achieve good glycaemic control, patients must check their blood glucose levels with a glucometer, a device that can report a glycaemic value from a blood drop obtain through the puncture of a finger in just a few seconds. These devices employ enzymes (like glucose oxidase or glucose reductase) that interact with glucose in the blood, subsequently determining electrochemical reactions that generate an electric current proportional to the amount of glucose in the blood that has reacted with the enzyme. Electric current is then transformed into a glycaemic value. Self-monitoring blood glucose control (SMBG) is important to determining the insulin bolus at meals and to evaluating glycaemic levels. It has been demonstrated that glucometer usage leads to improvements in HbA1c levels and a reduction in hypoglycaemic events[28].

Continuous glucose monitoring (CGM) devices have been introduced in the last few decades. These systems measure continuously glucose level in subcutaneous interstitial fluid, providing patients with glucose values every few minutes. CGMs are composed of:

- A small sensor applied in subcutaneous tissue by patients through an easy applicator. This sensor uses electrochemical technologies to transform glucose concentration into an electric impulse and then into a glycaemic value.
- A transmitter that receives and analyses data from the sensor, improving accuracy with different software measurements, and then sends this data to a receiver.
- A receiver that displays data to patients. Patients can see glucose values, trends arrows, and glycaemic values from the previous 24 hours.

Though CGM systems are valid devices, there are some limitations in their use. First, there is a 15-minute lag between blood and subcutaneously measured glucose. Second, the accuracy of CGM systems can be poor, especially in the hypoglycaemic range. Third, CGM systems need to be calibrated at least twice a day through finger-stick glucose measurements. However, any therapeutic decision (such as hypo/hyperglycaemia corrections or the size of insulin boluses before meals) should be based on the finger-stick glycaemic value instead of CGM values. Currently available evidence shows that CGM helps lower HbA1c levels without increasing the incidence of severe hypoglycaemic episodes in patients with T1D[29-32].Nowadays, the gold standard in T1D therapy is the association between insulin pumps and continuous glucose monitoring: this associated therapy is called sensor augmented pump (SAP) therapy[33]. With SAP therapy, patients can modify insulin doses administered through insulin pumps on the basis of glucose values registered by the glucose sensor and measured through the glucometer. Nevertheless, patients with apparently good metabolic control, as demonstrated by HbA1c values, spend several hours per day out of the optimal glycaemic range, defined as glycaemic values from 70 to 180 mg/dl (3.9-10.0 mmol/l)[34].

Artificial Pancreas

In the last few years, a new technology called the artificial pancreas (AP), or closed loop control (CLC), has been developed to optimize glycaemic control[35]. As shown in Fig. 1, the AP uses a mathematical control algorithm that automatically modifies insulin infusion from values obtained by the CMG. Different approaches are currently under investigation, including systems using only insulin infusion and systems that combine insulin infusion with glucagon infusion.

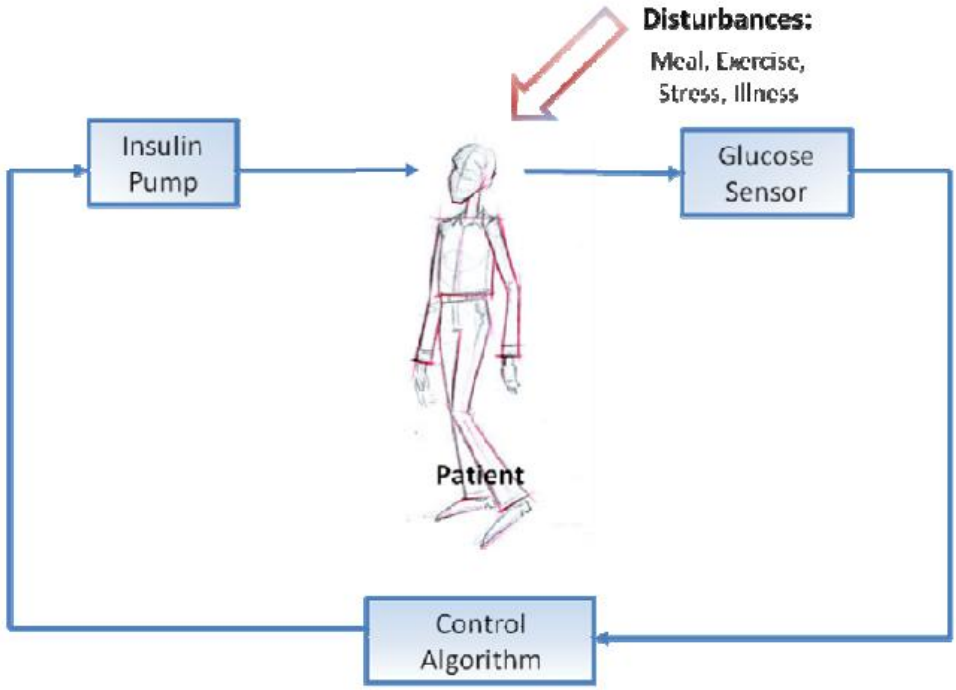

Fig 1: Artificial pancreas model

Technology has played an important role in the lives of T1D patients, as demonstrated by progressive improvements in CGM devices and precision in insulin pumps. From the end of 1970, with the introduction of the insulin pump, researchers have tried automatic insulin

infusion methods using different approaches[36-42]. Partial automation has already developed and been commercialized to help prevent hypoglycaemia. A system called low glucose suspend (LGS) has been available from some years. This system suspends insulin infusion when sensors reveal low glucose values and protects patients from severe hypoglycaemia[43]. Another step in automatic insulin infusion is the predictive low glucose suspend (PLGS) system, which suspends insulin infusion when the sensor predicts a risk of hypoglycaemia before it occurs and reducing the risk of glycaemia below the threshold[44].

AP development should guarantee complete automation also for hyperglycaemic control. Current APs are composed of a CGM device, an insulin pump (a glucagon pump when applicable), and a control algorithm. The control algorithm is the brain of the system and different algorithms are used by different groups to drive insulin infusion. So far, three different control algorithms have been used: model predictive control (MPC), proportional-integral derivative (PID) control, and fuzzy logic.

Control Algorithms

MPC

The MPC algorithm[45-46] uses mathematical models to calculate future blood glucose levels on the basis of present glucose levels, glucose trends, and the insulin already administered. MPC administers insulin on the basis of glucose prediction and can modify its strategy every few minutes when new glucose values and a new future glucose prediction become available.

PID

The PID algorithm[47] continuously adjusts insulin infusion rates by considering deviations of the patient's blood glucose level from ideal levels (the proportional

component), the area under the curve between ambient and target blood glucose (the integral component), and the rate of change of the patient's blood glucose (the derivative component). The notable difference with MPC is that the MPC algorithm can be considered proactive, which this algorithm is just reactive.

Fuzzy Logic

This algorithm tries to imitate medical decisions[48]; it takes into account an individual patient's treatment characteristics and imitates medical decision-making with respect to glucose control, modulating insulin delivery on the basis of approximate rules derived from empirical knowledge acquired by diabetes practionners

Our Artificial Pancreas Model

In the last decade, a University of Padova group composed of a clinical and engineering team, cooperating with several European and American research centres, has developed an AP model based on the MPC control algorithm. The MPC approach is powered by a modular architecture composed of independent but compatible modules, each performing a specific control[49-50]. It includes three interacting control modules: a safety module that prevents hypoglycaemia[51], a range control module responsible for insulin corrections and glycaemia optimization[49], and an insulin-on-board module preventing insulin stacking[52]. This system is called the multi model predictive control (MMPC).

The control algorithm uses patient parameters to choose better strategies to control glycaemic values. In fact, the system starts with the usual insulin basal rate, weight, total daily insulin, correction factor, and insulin carbohydrate ratio to optimize control.

Preliminary Studies

The algorithm was first tested using an *in silico* model, which has accelerated the progress of AP development. In 2008, the US Food and Drug Administration (FDA) accepted a simulator as a substitute to animal trials for the testing of CLC strategies. The simulator was based on a sophisticated model of glucose-insulin dynamics[53-54], and included a virtual population of 300 subjects, created on the basis of real glycaemic values. Three age groups of virtual patients exist, including children, adolescents, and adults[55]. Simulation experiments now allow that CLC system to be tested *in silico*, prior to their use in clinical trials, in a rapid and cost-effective way.

After *in silico* testing, the AP was tested in inpatient clinical trials between 2008 and 2011. The aim of these trials was to evaluate the efficacy and safety of the closed loop system previously tested *in silico*. In these early studies, insulin pump commands were entered manually by clinicians when it was considered safe for patients[56]. Most of these studies demonstrated the superiority of CLC over standard insulin pump therapy (continuous subcutaneous insulin infusion, CSII) or SAP therapy in terms of increased time within target glucose range, better overnight control and a reduced incidence of hypoglycaemia[57-58]. Automated communication between devices (CGM devices, insulin pumps, and control algorithms) was made possible with introduction of platform "Artificial Pancreas Software (APS)", which led to automated data transfer[59]. First trial involving our Center was published in 2012. This study enrolled 38 patients and tested two different control algorithms[60].

The Diabetes Assistant (DiAs) and Outpatient Studies

Results obtained through *in silico* and inpatient studies allowed researchers to test the system outside hospitals. These outpatient studies were conducted in a safe and convenient location, like a hotel, where the clinical team could meet together with patients. The transition to CLC testing in an outpatient setting began in 2011 with the introduction of the Diabetes Assistant (DiAs)[61-62], our first wearable AP platform for outpatient settings, developed at the University of Virginia. In the wearable AP, the model control algorithm was uploaded to a smartphone that can communicate through a wireless Bluetooth connection to the CGM and the insulin pump. When equipped with a Bluetooth system, the DiAs can communicate with different CGMs and pumps. The DiAs can operate in four different modes:

- CLC mode: the DiAs is connected to a pump and a sensor, and the algorithm is activated.

- Open loop (OL) mode: the pump and sensor are connected, but the algorithm is not active, so patients can see sensor data and the system delivers the normal basal rate, as with usual therapy.

- Sensor only: the sensor is connected, but the pump is not. Patients can see sensor values and insulin is delivered directly by the pump with normal settings.

- Safety mode: A variant of the CLC mode, the algorithm is activated to reduce insulin on the basis of glycaemia to mitigate the risk of hypoglycaemia, but can't administer more insulin than usual. This mode is used to avoid hypoglycaemia when patients engage in potentially dangerous activities like driving.

The patient interacts with the system through a touch-screen graphical user interface, as shown in Fig. 2, which allows real-time inputs like meal announcements, pre-meal capillary glucose levels, or self-administered hypoglycaemia treatment. It is a semi-automatic AP because patients have to manually input carbohydrate intake to obtain a meal bolus suggestion on the basis of glycaemic values and insulin infusion until that moment, which patients can then accept or modify.

The platform is easy to use and allows outpatient studies that were not possible with systems composed of a personal computer and wired connections, used in an inpatient setting. Furthermore, a 3G Smartphone connection enables the sending of data to a remote, secure website where the clinical team can control glycaemic trends and system function.

In October 2011, DiAs was used in two pilot trials of portable outpatient AP conducted simultaneously in Padova and Montpellier[66]. These two-day pilot trials found that the DiAs is a feasible prototype for a portable outpatient CLC system and that enabled a subsequent multi-site feasibility study of ambulatory AP.

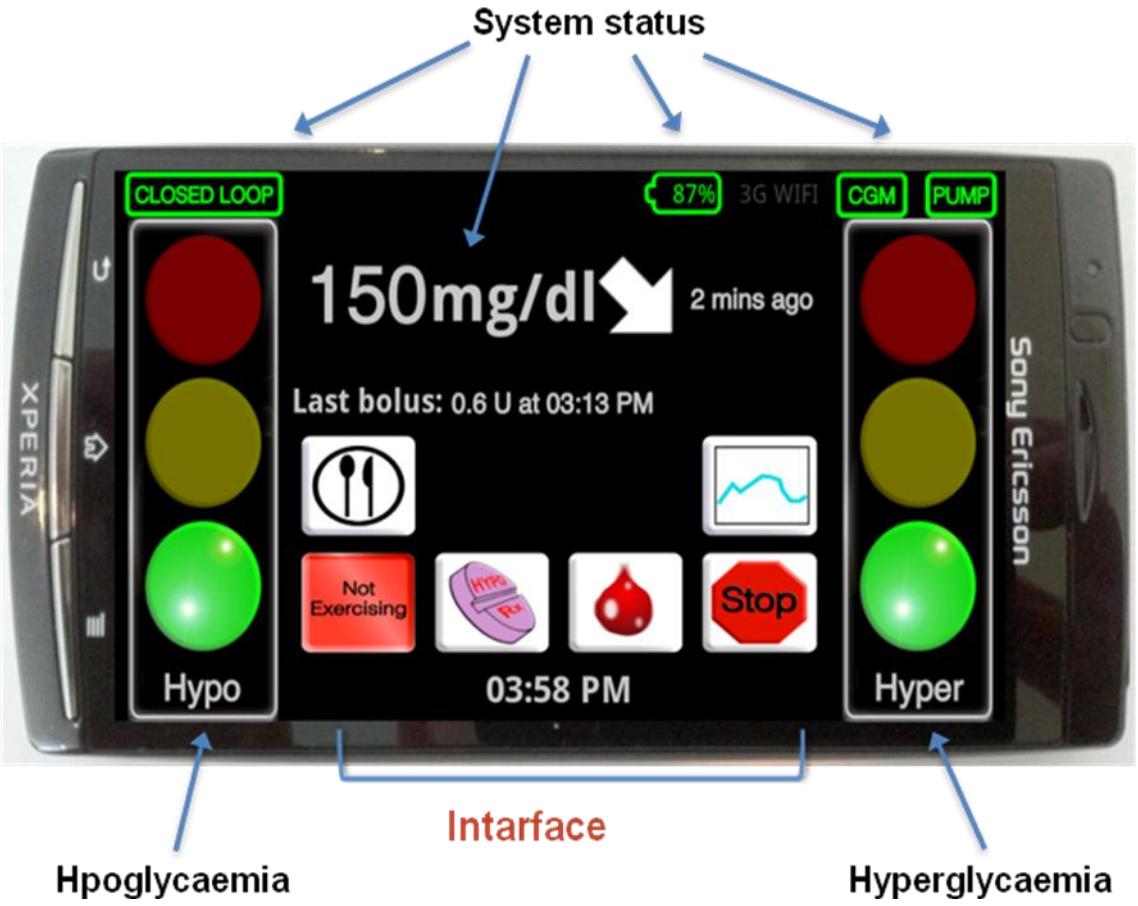

Fig.2 : DiAs interface. It's possible observe connection status between Dias and insulin pump or CGM, glycemic values registered by CGM and hypoglycemia and hyperglycemia risk through traffic light. Patient could insert glycemic values measured through glucometer, carbohydrate intake at meal, eventual hypoglycaemia treatment.

After this feasibility study, several safety and efficacy studies with the DiAs were conducted from 2011 to 2014. In these studies, the DiAs was used in several conditions, during physical activity, and with adolescents, demonstrating its efficacy and safety compared to sensor augmented pump therapy[64-65].

For example, our group was involved in a trial in a hotel setting where AP was used overnight, while patients returned home and managed their therapy with pump and sensor during the daytime. This trial of 44 patients demonstrated that using CLC from 23:00 to 7:00

significantly improved time in target (70-180 mg/dL, 3.9-10 mmol/L) vs. SAP during the night (85.7% vs. 67.6%, P < 0.001) but also over 24 hours (78.3% vs. 71.4%, P = 0.003). Time spent in hypoglycaemia (<70 mg/dl, <3.9 mmol/L) decreased with CLC during the overnight period from 3.2% to 0.9% (P < 0.001) and during 24 hours from 4.3% to 2.5% (P = 0.002). The mean glucose at 07:00 was also improved with CLC (124 vs. 145 mg/dL; 6.8 vs. 8.0 mmol/L, P < 0.001)[66].

Monitoring Service

The possibility of controlling glycaemic trends and CLC function has been fundamental to developing trials of AP use in patients' homes. In fact, clinical teams must be able to check DiAs activity at any time, and call the patient if necessary in case of system malfunction or persistent hypoglycaemia. Remote website control was necessary in the first trials for safety and to obtain approval from ethical committees and regulatory boards. With this system shown in Fig. 3, clinicians can always check glucose values, hypo- and hyperglycaemia risk (traffic lights), insulin administered by the system, insulin administered by patients through boluses, DiAs mode activity, and carbohydrate intake[67].

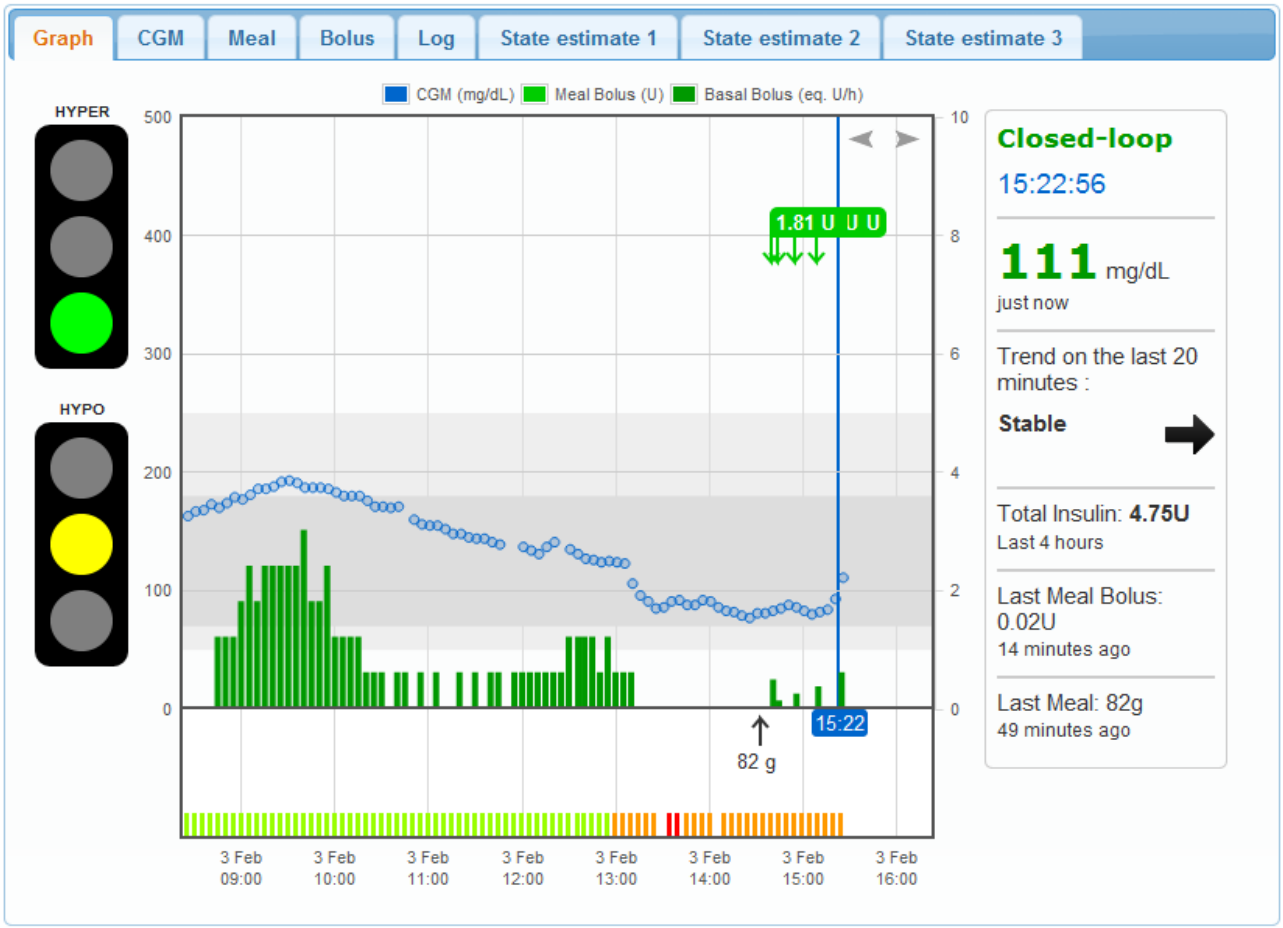

Fig 3: screenshot of web monitoring site. Green bars are insulin basal rate administered by system, blue circles are CGM values.

AIM

The aim of this thesis was to describe ourAP use at patients' homes and the results of studies conducted from 2014-2017. As shown in Fig. 4, the AP system used in these trials was composed of DiAs system using a Dexcom G4 as the CGM with Accu-Chek Spirit Combo insulin pumps.

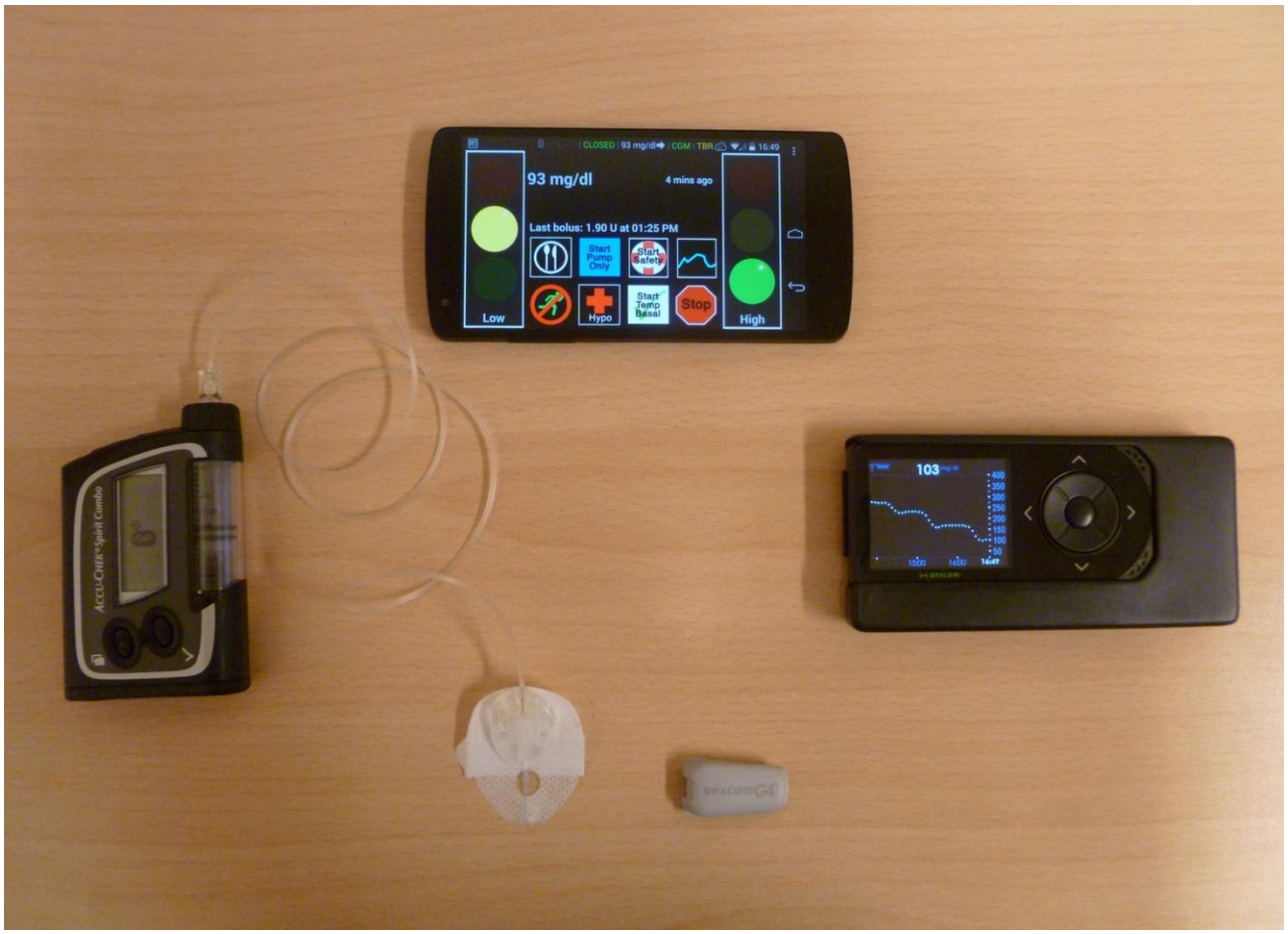

Fig 4: Our artificial pancreas model including DiAs, insulin pump (Accuchek Spirit Combo®, Roche Diabetes Care) and CGM (Dexcom G4®, Dexcom) inserted in relay box to allow Bluetooth communication between receiver and DiAs

Dexcom G4

As the CGM for these studies, the Dexcom G4, developed by DexCom (San Diego, CA), was used. As shown in Fig. 5 the system is composed of four different parts:

- A small electrochemical sensor placed just under the skin,
- A one-use injector,
- A transmitter connected to the sensor, and
- A monitor that receives sensor signals and provides real-time results.

The 13mm long sensor probe is positioned at a 45° angle under the skin. It is placed with the help of an inserter and can be used for up to seven days. Using amperometry, the sensor uses a working electrode coated with a sensing element (Wired Enzyme) that converts glucose concentration to electrical current. The transmitter snaps into the sensor and sends glucose information through a secured wireless connection to the receiver every five minutes. The receiver has a large screen that displays glucose values and glucose trends, as well as customizable alarms that can inform patients about potential hypo- or hyperglycaemia. The receiver can store up to 30 days of data.

Fig 5: Dexcom G4Continuos Glucose Monitoring system: on the right there is sensor with its applicator, on the left the transmitter and the receiver where patient could visualize glycemic values.

Once installed, the system needs a two-hour warm-up period of initialization before it can provide continuous glucose data. According to the manufacturer's recommendations, the sensor must be calibrated two hours after insertion, and at least twice a day thereafter. Calibration values must be manually entered by the patient when performing a capillary glucose control with the glucometer. The Dexcom G4 is not equipped with a Bluetooth connection, so the Dexcom receiver was linked to a dedicated Bluetooth-USB hub, called a relay box, to allow glycaemic data transmission from the CGM to the DiAs.

Accu-Chek® Spirit Combo

The Accu-Chek® Spirit Combo Insulin Pump is a fully integrated insulin delivery system developed by Roche (Switzerland). As shown in Fig. 6, the system includes two components:

- An external insulin pump, which can be connected to a subcutaneous catheter. Pump contains an insulin reservoir with a capacity of 315U . The basal rate can be reduced to a minimum of 0.05 U/hour, delivering a bolus in 20 intervals over the course of the hour.
- A glucometer, which patients can use to control their capillary blood glucose. This also includes an integrated a remote control that can communicate with the insulin pump and used to perform an insulin bolus.

Fig 6: Accuchek Spirit Combo insulin pump. On the left the glucometer and on the right insulin pump. They are equipped with blue tooth connection possibility.

Bluetooth technology is embedded in the insulin pump, allowing data transfer either to the remote control or to an AP system. During AP use, a communication link is established between the insulin pump and the AP platform.

The Accu-Chek glucometer was used as the reference study glucometer.

This AP prototype was used in several studies, first during the night-time period, next for a 24-hour period, and then for progressively longer periods. Finally, it was tested on a paediatric population.

The principal studies described in this thesis are:

- **2 month evening and night closed loop glucose control in patients with type 1 diabetes under free-living conditions: a randomized cross-over trial**
- **Day and night closed loop glucose control in patients with type 1 diabetes under free-living conditions**
- **Multinational Home Use of Closed-Loop Control Is Safe and Effective**
- **Feasibility of long term closed-loop control: a multicenter 6 month trial of 24/7 automated insulin delivery**
- **Randomized Summer Camp Crossover Trial in 5- to 9-Year-Old Children: Outpatient Wearable Artificial Pancreas Is Feasible and Safe.**

2 MONTH EVENING AND NIGHT CLOSED LOOP GLUCOSE CONTROL IN PATIENTS WITH TYPE 1 DIABETES UNDER FREE-LIVING CONDITIONS: A RANDOMISED CROSS-OVER TRIAL

This trial[68] was the first two-month randomized controlled crossover study that investigated evening and night period control with a closed loop system during truly free-living conditions. It was a multi-centre trial involving the University of Padua, the University of Montpellier, and the University of Amsterdam. We used an MMPC control algorithm created by the University of Padua and Pavia[69]. This study evaluated the efficacy of CLC during the evening and night period, from before dinner to waking up, because night-time seems like the easiest period to improve glucose control because changes in meals and exercise predominantly occur during the daytime[70-71]. The use of the overnight CLC was extended at home with the addition of the evening period to increase CLC use and test the system during a meal, maximizing the time of glucose control that is possible at home because most high-risk activities—including strenuous sports and driving—are not done at home. During daytime, patients managed diabetes using SAP therapy.

Methods

The study was a randomized crossover study with patients either starting two months of AP using during evening and night period and SAP during daytime or two months using 24 hours SAP therapy (open loop period, OL). During two study periods, patients were encouraged to maintain the same schedules, especially regarding physical activity.

The main inclusion criteria were patients aged 18–69 years, with a diagnosis of T1D for at least six months according to the American Diabetes Association criteria, a BMI of less

than 35 kg/m², and a concentration of HbA1c between 7.5% and 10% (58–86 mmol/mol). All patients were experienced insulin pump users and trained in carbohydrate counting. To mitigate risk, patients with severe hypoglycaemia in the past year or ketoacidosis in the past six months were excluded. Patients were also excluded if they were pregnant or breastfeeding, used medication that substantially altered their glucose metabolism, had uncontrolled hypertension (resting >140/90 mm Hg), worked during the night or expected to be away from home for longer than 25% of the study duration, had no family or friends nearby, had a malignant disease, had an acute cardiovascular event during the previous year, had renal insufficiency (creatinine >150 μmol/L), had impairment of liver function (levels of liver enzymes more than twice the upper limit of normal), or had impaired cognitive or psychological abilities. During the trial, a monitoring website was active so that the clinical team could evaluate system functioning for patient safety when necessary.

After a screening and two-week run-in period, patients were randomized into two groups and instructed either to use AP during the evening and night-time or to use SAP therapy 24 hours for eight weeks. The two periods were separated by a four-week washout in which patients used the study pump with or without CGM according to their pre-study treatment. HbA1c was measured at the beginning and end of each period (Fig. 7). The aim of the study was to evaluate time in target changes during AP use, and the secondary outcome was the evaluation of HbA1c changes between two periods.

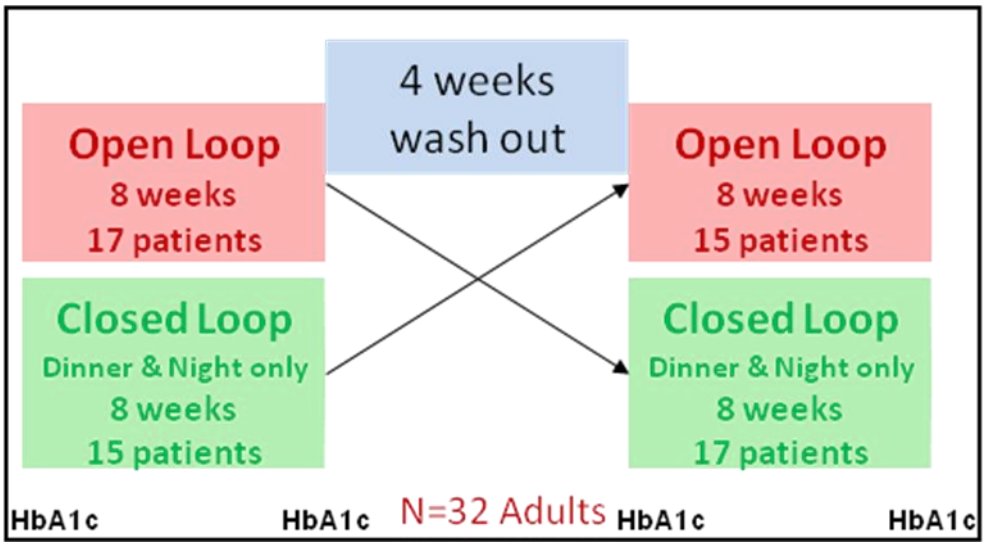

Figure 7: study design. 17 patients started open loop period and 15 closed loop one. After 4 wash out weeks patients changed their treatment.

Results

Table 1 shows the characteristics of the 32 patients who completed this study. Data from the first two weeks of both arms were considered the training period and excluded from analysis.

Characteristic	Study Population (n=32)
Age (years)	47 ± 11.2
Sex (male)	18 (56%)
BMI (Kg/m^2)	25.1 ± 3.5
HbA1c (%)	8.2 ± 0.6
Diabetes duration (years)	28.6 ± 10.8

Table1: baseline characteristic of 32 patients. Data are described as mean ± standard deviation or number (%)

CGM values were analysed over two study periods. During AP use, from 20.00 in the evening to 8:00 in the morning (Table 2), time in target (70-180 mg/dl, 3.9-10.0 mmol/L) was higher than in the two months when patients used OL (66.7% vs. 58.1%; P < 0.0001). Mean glucose concentration was also lower during the AP period than during the control period (162 vs 167 mg/dl, 9.0 mmol/L vs. 9.3 mmol/L, P = 0.0053). AP reduced time spent in hypoglycaemia (<70 mg/dl, <3.9 mmol/L) from 3.0% in the control period to 1.7% in the AP period (P < 0.0001).

Evening and night period			
Metrics	**CLC period**	**OL period**	**P value**
Glucose concentration, mg/dl	162±14.4	167±14.4	0.0053
Glucose standard deviation, mg/dl	55.8±10.8	61.2±10.8	<0.0001
Time in target (70-180 mg/dl), %	66.7±10.1	58.1±9.4	<0.0001
Time in tight target (80-140 mg/dl), %	37.7±9.1	31.2±6.0	<0.0001
Time below target (< 70 mg/dl), %	1.7 (0.8-2.5)	3.0± (1.6-4.9)	<0.0001
Time above target (>180 mg/dl) %	31.6±9.9	38.5±9.7	<0.0001
Hypoglycemic events/week, n	4.3±1.9	5.8±2.9	0.0068
Insulin used, IU	16.2±7.0	18.4±8.7	0.0029

Table 2: results during evening and night period, expressed as mean ± standard deviation, except for time below target expressed as median and 95% CI.

Glycaemic values in the early morning were lower during the closed-loop period than during the control period (144 mg/dl vs. 160 mg/dl, 8.0 mmol/L vs. 8.9 mmol/L; P < 0.0001;), with an increase in time in target from 65.9% to 85.9% (P < 0.0001). As shown in

Table 3, an improvement of glycaemic metrics was observed over a 24 hour period, even if CLC was only used overnight. Use of the AP during the evening and at night also led to a reduction in glucose variability during period use (standard deviation, SD 55.8 vs. 61.2 mg/dl, 3.1 vs. 3.4 mmol/L, P < 0.0001), early morning (0600–0700 h, SD 41.4 vs. 55.8 mg/dl, 2.3 vs. 3.1 mmol/L, P < 0.0001), and over 24 hours (SD 59.4 vs. 61.2 mg/dl, 3.3 L vs. 3.4 mmol/L, P = 0.0009). It's important to highlight that the decrease in mean HbA1c during the AP period was significantly greater than during the control period (–0.3% vs. –0.2%; P = 0.047).

24 hours, day and night			
Metrics	**CLC period**	**OL period**	**P value**
Glucose concentration, mg/dl	160.2 (154.8-165.6)	163.8(158.4-169.2	0.056
Glucose standard deviation, mg/dl	59.4±9	61.2±9	0.0009
Time in target (70-180 mg/dl), %	63.7 (60.4-70.1)	59.4 (56.7-64.3)	<0.0001
Time in tight target (80-140 mg/dl) %	36.3±7.7	32.6±6.3	0.0002
Time below target (< 70 mg/dl), %	2.6±1.4	3.6±2.0	0.0002
Time above target (>180 mg/dl) %	33.5 (27.8-36.7)	36.4 (32.1-39.8)	0.0008
Hypoglycemic events/week, n	5.7±2.5	6.3±2.4	0.15
Insulin used, IU	36.7±11.7	43.2±16.3	<0.0001

Table 3: results during 24 hours, expressed as mean ± standard deviation, or median (95% CI).

During the AP period, mean insulin needs were lower than in the control period, during the evening-night period (16.2 IU vs. 18.4 IU, P = 0.0029), and over 24 hours (36.7 IU vs. 43.2 IU, P < 0.0001).

The telemonitoring website worked correctly, but clinician intervention was not necessary.

At the beginning and end of both periods, patients completed two questionnaire: the Diabetes Treatments Satisfaction Questionnaire (DTSQ)[72] that analyses satisfaction for quality of therapy in diabetic patients and the Hypoglycaemia Fear Survey 2 (HFS2)[73] that investigates patients behaviour in avoiding hypoglycaemic events. There were no differences in questionnaires before and after AP use and between the two periods. Patients also completed a specific AP acceptance questionnaire[74] and 74% fully agreed with the statement "I would want to use an Artificial Pancreas for a prolonged period", demonstrating the feasibility of the system in daily life.

Conclusions

This was the first trial conducted with this AP model in patients' homes and the results were very encouraging; AP improves all glycaemic targets during the evening and night period and increased the time spent in target during the 24 hour period. It's important to underline that this was the first trial conducted in free life conditions. Even though the AP was only used during the evening and night, for a median use of eight hours/day, and just for eight weeks, reduction of the time spent in hyperglycaemia and an increase of time spent in target led to a reduction in HbA1c, a metabolic parameter that usually reflects metabolic control over the previous three months. Use of the AP during dinner, and not just during the night, allowed the study to test the system during a period in which glycaemic control is more difficult to achieve.

DAY-AND-NIGHT CLOSED-LOOP GLUCOSE CONTROL IN PATIENTS WITH TYPE 1 DIABETES UNDER FREE-LIVING CONDITIONS: RESULTS OF A SINGLE-ARM 1-MONTH EXPERIENCE COMPARED WITH A PREVIOUSLY REPORTED FEASIBILITY STUDY OF EVENING AND NIGHT AT HOME

Results obtained in the previous study lead to an extension period[75] in which the AP was used all day, always in free life conditions.

Methods

As shown in Table 4, 20 of 32 patients enrolled in the previous study agreed to continue the study by using the AP 24 hours a day in this single arm study. The study used the same inclusion criteria, monitoring website, and technology as the previous study. For safety reasons, patients were asked to avoid dangerous activity like driving with the AP, so they switched off the DiAs during these activities.

Characteristic	Study Population (n=20)
Age (years)	46.3 ± 11.0
Sex (male)	9 (45%)
BMI (Kg/m^2)	24.9 ± 3.5
HbA1c (%)	8.2 ± 0.7
Diabetes duration (years)	28.9 ± 12.8

Table 4: baseline characteristic of 20 patients. Data are described as mean ± standard deviation or number (%)

Results

All patients completed the four-week extension study. Data derived from the CGM were analysed and compared with data during the OL period and the evening and night AP control period of previous study. As shown in Tables 5 and 6, using AP for the 24 hour period improved the percentage of time in target range over SAP use alone (64.7 ± 7.6% vs. 59.7 ± 9.6%, P = 0.01), and close to significance with the use of AP during evening and night (P = 0.06). Significant improvements came from reducing the percentage of time below the target range using 24 hour CLC versus SAP (1.9 ± 1.1% vs. 3.2 ± 1.8%, P = 0.001), but no difference was found between the use of AP for 24 hours or for evening and night (P = 0.79).

24 hours, day and night			
Metrics (20 patients)	**24h CLC period**	**OL period**	**P value**
Glucose concentration, mg/dl	160.2 (153.0-169.2)	162.0(156.6-171.0)	0.51
Glucose standard deviation, mg/dl	55.8±9	59.4±10.8	0.049
Time in target (70-180 mg/dl), %	64.7±7.6	59.7±9.6	0.01
Time in tight target (80-140 mg/dl), %	35.4±5.8	32.4±7.5	0.16
Time below target (< 70 mg/dl), %	1.9±1.1	3.2±1.8	<0.001
Time above target (>180 mg/dl) %	33.3±7.3	37.0±10.2	0.10
Hypoglycemic events/week, n	5.0±2.4	6.4±3.1	0.03
Insulin used, IU	40.3±15.2	42.3±15.5	0.34

Table 5: results during 24 hours, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

24 hours, day and night			
Metrics (20 patients)	**24h CLC period**	**Evening and night CLC period**	**P value**
Glucose concentration, mg/dl	160.2 (153.0-169.2)	160.2(154.8-171.0)	0.71
Glucose standard deviation, mg/dl	55.8±9	59.4±10.8	0.23
Time in target (70-180 mg/dl), %	64.7±7.6	63.6±9.9	0.79
Time in tight target (80-140 mg/dl), %	35.4±5.8	35.5±9.0	1.00
Time below target (< 70 mg/dl), %	1.9±1.1	2.1±1.3	0.74
Time above target (>180 mg/dl) %	33.3±7.3	34.2±10.0	0.87
Hypoglycemic events/week, n	5.0±2.4	4.9±2.6	0.98
Insulin used, IU	40.3±15.2	36.6±11.6	0.02

Table 6: 24h CLC control vs Evening and night CLC results during 24 hours, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

During evening and night (2000–0800), the percentage of time in the target range and below the target range were significantly improved during both AP periods versus SAP. During daytime (0800–2000), as shown in tables 7 and 8, the percentage of time in the target range and the mean blood glucose levels showed no difference among the three treatments, but a trend toward improvement of the percentage of time in the target range was recorded with 24 hours AP usage versus SAP (64.9 ± 8.1 vs. 60.7 ± 10.3, P = 0.09). The percentage of time spent in hypoglycaemia when AP was used for 24 hours was significantly lower than

with SAP (2.3 ± 1.3% vs. 3.4 ± 2.2%, P = 0.01), but was not significantly different compared with AP used during the evening and night (2.3 ± 1.3% vs. 2.9 ± 1.9%, P = 0.25).

Daytime (8:00-20:00)			
Metrics (20 patients)	**24h CLC period**	**SAP therapy**	**P value**
Glucose concentration, mg/dl	162±9	163.8±18	0.38
Glucose standard deviation, mg/dl	57.6±10.8	59.4±10.8	0.15
Time in target (70-180 mg/dl), %	64.9±8.1	60.7±10.3	0.09
Time in tight target (80-140 mg/dl), %	35.6±6.5	33.4±8.8	0.46
Time below target (< 70 mg/dl), %	2.3±1.3	3.4±2.2	0.01
Time above target (>180 mg/dl) %	32.8±7.8	35.8±11.4	0.34
Hypoglycemic events/week, n	3.3±1.8	3.9±2.3	0.34
Insulin used, IU	19.3 (16.1-31-8)	22.9 (18.2-27.5)	0.71

Table 7: results during daytime of 24 hours CLC vs SAP, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

Daytime (8:00-20:00)			
Metrics (20 patients)	**24h CLC period**	**Evening and night CLC period**	**P value**
Glucose concentration, mg/dl	162±9	165.6±21.6	0.38
Glucose standard deviation, mg/dl	57.6±10.8	61.2±12.6	0.003
Time in target (70-180 mg/dl), %	64.9±8.1	61.2±11.7	0.15
Time in tight target (80-140 mg/dl), %	35.6±6.5	34.1±9.3	0.72

Time below target (< 70 mg/dl), %	2.3±1.3	2.9±1.9	0.25
Time above target (>180 mg/dl) %	25.6±10.7	29.1±10.2	0.32
Hypoglycemic events/week, n	3.3±1.8	3.4±1.9	0.94
Insulin used, IU	19.3 (16.1-31-8)	18.5 (15.5-24.9)	0.74

Table 8: results during daytime of 24 hours CLC vs Evening and night CLC, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

Although the percentage of time above the target range was similar between usage during AP periods and SAP, the percentage of time with glucose above 300 mg/dl (16.5 mmol/L) was significantly lower when AP was used for 24 hours than AP usage in the evening and night period (P = 0.004).

The SD of blood glucose during evening and night usage was significantly reduced with use of AP during the evening night or for 24 hours vs. SAP, but glucose SD during daytime was significantly reduced only when AP was used for 24 hours.

Patients spent 80.4% in the closed loop during the 24-hour period, demonstrating a good but improvable connection system between devices, particularly during daytime when patients had work activities, with a CLC usage of 73.9% (70.7% in the morning, from 08:00 to 12:00, and 75.5% in the afternoon, from 12:00 to 20:00).

No serious adverse events occurred during the AP use for the 24-hour test, with no severe hypoglycaemic episodes and no hospitalization for ketoacidosis.

Conclusions

This trial was the first to compare the efficacy and safety of two AP approaches (24 hour usage and evening and night usage) vs. SAP during several weeks in free-living conditions. It was also our first trial to measure AP use for 24 hours a day. Other groups

evaluated day and night efficacy of closed loop control versus SAP in a well-designed trial with good results in glycaemic control during the day. This study was not designed to evaluate day and night efficacy because it was an extension of a previous study, but the results were encouraging. In particular, AP usage during daytime reduced glucose variability, which is associated with chronic diabetes complications. It was not surprising that AP use during the night improved glycaemic control also in daytime, which was demonstrated in previous studies in outpatients setting[65].

Insulin dose with 24-hour AP usage was greater than evening and night AP usage, but not different from SAP therapy. It can be argued that AP used less insulin during the evening-night control, but the 24-hour revealed that there was an increase in the insulin basal rate in the post-meal period to reduce hyperglycaemia and variability.

Although glycaemic control with AP usage for 24 hours was better than with SAP therapy, the control algorithm had to be retuned to ameliorate daytime control compared to AP use in the night-time period. Nevertheless, it's important to stress that in this first 24-hour usage of the AP model, there were no adverse events and patient acceptation of the device was great. There were some connection problems between the pump-CGM and DiAs that could further challenge the limited expected benefits of AP on glucose control during the daytime, so a more integrated system with fewer disconnection problems could increase the efficacy of the system.

MULTINATIONAL HOME USE OF CLOSED-LOOP CONTROL IS SAFE AND EFFECTIVE

Conducted between 2015 and 2016, this trial[76] was an international trial involving patients form our centre and from three different centre in the US (the University of Virginia, Stanford University, and the William Sansum Diabetes Center), Europe (the University of Montpellier,) and Israel (the Institute of Endocrinology and Diabetes, Tel Aviv). The aim of this study was to evaluate the efficacy of the wearable, wireless AP system, DiAs, on glucose control at home, in an overnight period and during a 24-hour usage period. In contrast from previous studies, in this trial, the algorithm used in the DiAs was not the Padova-Pavia algorithm, but the Unified Safety System (USS), an algorithm developed at the University of Virginia. It is a multi-modular MPC algorithm, but with some differences. In fact, while the University of Padua-Pavia algorithm can modulate only the basal infusion rate, the USS can also administer correction boluses if glycaemia is rising too fast.

Methods

Thirty patients were enrolled in this study, broken into groups of five for each centre. Major eligibility criteria included patients aged between 18 and 69 years old, suffering from T1D for at least one year and using an insulin pump for at least six months, with HbA1c values <10%, continuous access to the Internet to download data from the monitoring website, cell phone service in case of necessity, and the presence of a companion who lives with the patient. Exclusion criteria were diabetic ketoacidosis or severe hypoglycaemia with seizure or loss of consciousness in the prior 12 months, hypoglycaemia unawareness, as well as medical conditions or laboratory abnormalities that could affect study participation. After the enrolment period, depending on the participant's current experience with CGM use, patients spent a two-week period at home using both the study pump and the CGM. These

two weeks of SAP therapy at home were considered the baseline control period. After these two weeks, there was a training session to educate patients on DiAs usage, then two weeks of AP usage during the overnight period. In contrast to the previous study, dinner was not included in the testing and the patients were asked to start AP usage just before sleep. After these two weeks, the patients continued with two weeks of 24-hour system usage. The primary outcome was CGM sensor glucose values below target (<70 mg/dL, <3.9 mmol/L). During the periods of at-home CLC usage, remote safety monitoring was available to clinical staff.

Results

All participants completed the full four study weeks. Table 9 shows the characteristics of the patients in the study.

Characteristic	Study Population (n=30)
Age (years)	44 (18-66)
Sex (male)	17 (57%)
BMI (Kg/m^2)	25 (23-27)
HbA1c (%)	7.3 (7.1-7.7)
Diabetes duration (years)	19(13-28)

Table 9: baseline characteristic of 30 patients. Data are described as median (25^{th}-75^{th} quartile) or number (%)

As shown in Table 10, all metrics regarding glucose control were improved in the night-time period. Time spent in hypoglycaemia (<70 mg/dl, <3.9 mmol//L) dropped from 3.0% during baseline to 1.1% during overnight-only CLC ($P < 0.001$), while time in target (70-180 mg/dl, 3.9-10.0 mmol/L) increased from 61% to 75% ($P < 0.001$) and time spent

above 180 mg/dl (10 mmol/L) dropped from 37% to 24% (P < 0.001). Furthermore, the mean glucose concentration dropped from 163 to 150 mg/dL (P = 0.002) and glucose variability was improved by using AP, with a reduction of the median coefficient of variation (36% vs. 30%, P < 0.001).

Overnight period			
Metrics	**SAP therapy**	**CLC overnight**	**P value**
Glucose concentration, mg/dl	163±23	150±12	0.002
Glucose standard deviation, mg/dl	61 (50-69)	47 (42-51)	<0.001
Time in target (70-180 mg/dl), %	61(53-73)	75 (69-80)	<0.001
Time below target (< 70 mg/dl), %	3.0 (1.1-6-3)	1.1 (0.2-1.6)	<0.001
Time above target (>180 mg/dl) %	37 (24-45)	24 (19-28)	<0.001

Table 10: results during overnight, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

As shown in Table 11, metrics of glucose control in the 24-hour usage test improved during the day and night closed loop action compared with metrics recorded during SAP therapy. In particular, the time below 70 mg/dl (3.9 mmol/L) dropped from 4.1% to 1.7% (P < 0.001), time in target increased from 65% to 73% (P < 0.001), time above target decreased from 32% to 25% (P = 0.001), and the median coefficient of variation dropped from 38% to 34% (P < 0.001). There was an insignificant difference in mean glucose concentration (157 vs. 153 mg/dL, P = 0.14). Comparing the overnight and 24-hour AP usage on glycaemic control during day and night, a reduction in time spent in hypoglycaemia was observed when AP was used for 24 hours, with no differences in glucose concentration, time in target, and time above target (Table 12).

Day and night			
Metrics	**SAP therapy**	**24 hours CLC**	**P value**
Glucose concentration, mg/dl	157 ± 18	153 ± 12	0.14
Glucose standard deviation, mg/dl	61 (53-69)	51 (47-55)	<0.001
Time in target (70-180 mg/dl), %	65 (59-69)	73 (68-76)	<0.001
Time below target (< 70 mg/dl), %	4.1 (2.0-7.8)	1.7 (1.1-2.7)	<0.001
Time above target (>180 mg/dl) %	32 (25-36)	25(22-28)	0.001

Table 11: results during day and night, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

Day and night			
Metrics	**Overnight CLC**	**24 hours CLC**	**P value**
Glucose concentration, mg/dl	149 ± 12	153 ± 12	0.06
Glucose standard deviation, mg/dl	52 (48-58)	51 (47-55)	0.41
Time in target (70-180 mg/dl), %	73 (65-78)	73 (68-76)	0.91
Time below target (< 70 mg/dl), %	2.6 (1.6-3.6)	1.7 (1.1-2.7)	<0.001
Time above target (>180 mg/dl) %	24 (20-31))	25(22-28)	0.26

Table 12: results during day and night of 2 AP approaches, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

Comparing the overnight CLC system and 24 hour CLC usage in daytime control, results showed that median time <70 mg/dL, which was 3.2% during overnight-only CLC, was further reduced to 2.3% during 24/7 CLC (P < 0.001), but daytime mean glucose, median

time in target, 70–180 mg/dL (3.9-10 mmol/L), and median time above 180 mg/dL (10 mmol/L) were not significantly different.

There were no adverse events and no cases of severe hypoglycaemia or diabetic ketoacidosis during the trial.

Conclusions

This study also demonstrated that glucose control, using a different control algorithm, was significantly improved during both overnight-only and 24/7 CLC, compared with baseline SAP.

As previously noted, overnight-only CLC provided a benefit in overall glycaemia, also in daytime. This effect is particularly evident during the morning, underling the fact that good glucose before breakfast improves glucose control during the whole morning period. During overnight CLC patients used DiAs during the day in OL mode. Some of the improvement could have been derived from more engaged patients, but this possibility is excluded by the results of the previous study in which the DiAs was switch off during the daytime.

In any case, AP usage during the day is better than overnight CLC for the prevention of daytime hypoglycaemia. Using of an AP during the day doesn’t reduce hyperglycaemia because of the difficulty of the system in controlling meals and physical activity, which represent typical challenges of real life.

FEASIBILITY OF LONG TERM CLOSED-LOOP CONTROL: A MULTICENTER 6 MONTH TRIAL OF 24/7 AUTOMATED INSULIN DELIVERY

Methods

As shown in Table 13, a subgroup of 14 patients from the previous study continued AP use 24 hours a day for another five months in free life conditions[77]. Patients were selected to continue the study based on clinician judgment. Patients were contacted weekly by phone and had monthly visits to download data.

Characteristic	Study Population (n=14)
Age (years)	45 (34-51)
Sex (male)	10 (71%)
BMI (Kg/m^2)	27 (25-29)
HbA1c (%)	7.2 ± 0.6
Diabetes duration (years)	27(17-34)

Table 13: baseline characteristic of 14 patients. Data are described as median (25^{th}-75^{th} quartile) or number (%)

Baseline CGM data and HbA1c values were considered from two weeks of previous SAP study. It should be noted that since the HbA1c outcome measured at the end of the extension phase only reflects glucose control over the previous three months, CGM data were obtained from the last three months to be consistent with HbA1c outcomes.

Results

Results confirmed data from the previous study; patients reached 77% of time in target using AP vs. 66% using SAP therapy at baseline, with a significant reduction in time spent in hypoglycaemia and hyperglycaemia. As shown in Table 14, time in hypoglycaemia was reduced from 4.1% to 1.3% ($P < 0.001$), while time above target dropped from 31% to 22% ($P = 0.01$). Time spent in severe hypoglycaemic and hyperglycaemic values was also reduced, with a ten fold reduction of glucose values below 50 mg/dl (2.8 mmol/L), from 1% to 0.1%, and an important decrease of time above 250 mg/dl (13.9 mmol/L) from 6% to 3%. There was not a reduction of HbA1c during the six months of AP use (7.2% vs. 7.0%, $P = 0.23$).

Day and night			
Metrics	**Baseline**	**CLC**	**P value**
Glucose concentration, mg/dl	154.8 ± 19.8	149.4 ± 10.8	0.25
Time in target (70-180 mg/dl), %	66 (59-69)	77 (73-81)	<0.001
Time below target (< 70 mg/dl), %	4.1 (2.9-7.5)	1.3 (0.6-1.7)	<0.001
Time above target (>180 mg/dl) %	31 (23-38)	22 (19-27)	0.01
Insulin used, IU/kg	0.59 ± 0.18	0.57 ± 0.22	NS

Table 14: results during evening and night period, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

This study provided important data for evaluating the acceptance and efficacy of DiAs in a long-term study. DiAs use declined over the months, from 149 to 118 h/week of closed-loop use, but HbA1c reduction was significantly correlated with system use.

Conclusions

This represents the longest trial of AP use conducted in a real-life setting. The importance of this study is focused on the long-term acceptance and efficacy of AP use in the adult population. The impact of AP on daily life was satisfactory, as patients viewed the overnight system as beneficial, though some of them reported additional nuisance of the system on their relationship with their partners due to the alarm system and connectivity issues. Few users in fact affirmed that AP caused interruptions in their daily activities, and these were essentially at work, primarily related with the alarm system. Nevertheless, the alarms represent a safety requirement imposed by the regulatory board. During the last three months of the trial, CLC mode was used 70% of time, while an additional 8% of usage represents time when the DiAs was used in different modes of operation, for example in sensor only mode when the pump was not available or in OL mode when the sensor is not available, demonstrating the feasibility of this wearable AP model. Regarding connectivity issues, they could be solved by new technologies in sensors system (direct connection between CGM receiver and DiAs, without relay box) and by new AP model.

Finally we have to remind that study was not designed to achieve statistically significant result, due to the small number of participants because it was just a pilot study. Nevertheless, long-term efficacy was confirmed, in term of hypoglycaemia reduction and partial HbA1c improvement, related to effective AP usage.

RANDOMIZED SUMMER CAMP CROSSOVER TRIAL IN 5- TO 9-YEAR-OLD CHILDREN: OUTPATIENT WEARABLE ARTIFICIAL PANCREAS IS FEASIBLE AND SAFE

Good results obtained in adult populations allow the testing of the system in paediatricians[78]. Our American colleagues had tested DiAs in adolescents during summer camp with good result in efficacy, feasibility and acceptance[79]. Starting from such premises we decided to evaluate DiAS in paediatric population 5-9 year old, never studied before. This population has some peculiar characteristic such as an higher frequency of hypoglycaemic episodes[80] than adult population, low insulin requirement, a difficult self management of therapy, intense but poorly predictable physical activity and poor dietetic adherence.

Methods

Algorithm used was the Padova-Pavia one, previously tested *in silico* in virtual paediatric population. Three months before this trial, we had a small pilot study to evaluate algorithm safety and AP feasibility in this particular population. This study was a multi-centre Italian study, involving five paediatric centres in Italy (University of Verona, Milan, Turin, Naples, and Rome), coordinated by Padua University. Inclusion criteria were patients aged 5 to 9 years; with a diagnosis of T1D for at least 12 months; use of insulin pump and sensor; HbA1c < 10%, and attendance by at least one relative/caretaker. Exclusion criteria were diabetic ketoacidosis or severe hypoglycaemia within the last month, concomitant disease, as well as any medication or conditions that could influence metabolic control, compromise safety, or prevent study completion.

The study was a randomized crossover study in a summer school setting. Patients were randomized into two groups that used AP or SAP for three days, with a 24-hour washout period between the two treatments (Fig. 8). The activities performed by the patients

were similar in the two periods and standardized every day, with static activities in the morning mimicking activities on school days and moderate physical activity in the afternoon. Carbohydrate levels were maintained at a stable level across different days.

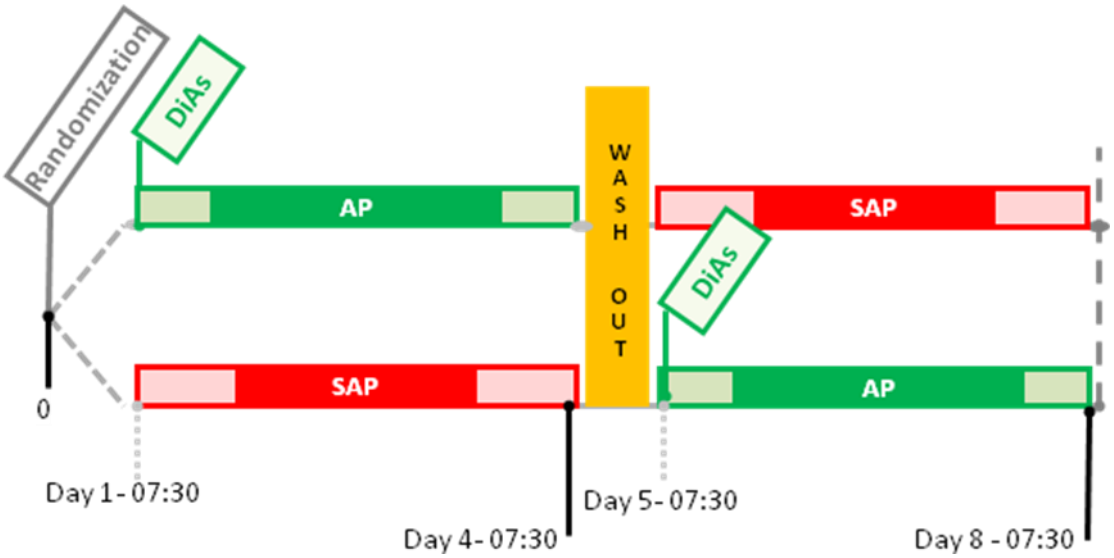

Figure 8: study design

Differently from previous study, we used a new generation Dexcom receiver with blue tooth connection integrated in the receiver, which lead to "relay box" elimination.

Results

Table 15 shows the characteristics of the 30 patients who completed the study.

Characteristic	Study Population (n=30)
Age (years)	7.6±1.2
Sex (male)	19 (63%)
BMI (Kg/m^2)	16.9±2.1
HbA1c (%)	7.3 ± 0.9
Diabetes duration (years)	4.7±1.6

Table 15: baseline characteristic of 30 patients. Data are described as mean ± standard deviation or number (%)

Data gathered during the night-time (Table 16) showed an important reduction of time spent in hypoglycaemia, from 2.2% (0.0–12.3) with SAP to 0.0% (0.0–2.2) with AP usage (P < 0.002), with no difference in time in target between the two arms. Results also showed an increase in mean glucose from 150 mg/dL with SAP usage to 173 mg/dL with AP usage (P = 0.002).

Overnight (00:00-07:30)			
Metrics	**SAP therapy**	**CLC**	**P value**
Glucose concentration, mg/dl	150 ± 39	173 ± 36	0.02
Glucose standard deviation, mg/dl	44±14	47 ± 14	0.24
Time in target (70-180 mg/dl), %	59.7±21.2	56.0 ±22.5	0.43
Time below target (< 70 mg/dl), %	2.2 (0.0-12.3)	0.0 (0.0-2.2)	0.002
Insulin used, IU/h	0.35±0.12	0.37±0.12	0.08

Table 16: results during overnight, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

During the 24-hour usage period (0000–2400), as shown in Table 17, the AP reduced more than three times the time-in hypoglycaemia, from 6.7% (2.3–11.5) with SAP to 2.0% (1.2–4.5), with the AP (P < 0.001). Unfortunately, hypoglycaemia reduction led to a decrease of time spent in target (63.1% with SAP vs. 56.8% with the AP, P = 0.022) and an increase of mean glucose from 147 mg/dL with SAP vs. 169 mg/dL with the AP (P < 0.001).

Day and night			
Metrics	**SAP therapy**	**CLC**	**P value**
Glucose concentration, mg/dl	147 ± 23	169 ± 23	<0.001
Glucose standard deviation, mg/dl	58±10	61 ± 11	0.17
Time in target (70-180 mg/dl), %	63.1±11.0	56.8±13.5	0.02
Time below target (< 70 mg/dl), %	6.7 (2.3-11.5)	2.0 (1.2-4.5)	<0.001
Insulin used, IU/h	0.35±0.12	0.26±0.09	<0.001

Table 17: results during 24 hours, expressed as mean ± standard deviation, or median (25^{th} -75^{th} percentile).

No serious adverse events occurred, and the closed-loop mode remained fully operational for 97.0% (93.5–98.4) of the time.

Conclusions

This study demonstrated the feasibility of the AP model in the paediatric population. The improvement in hypoglycaemic values was encouraging, especially in this population characterized by a higher frequency of hypoglycaemic episodes than adults. The deterioration of time in target and worsening of median glycaemia is related to two elements. First, the characteristic of the population, under very good metabolic control, where mean HbA1c at the start was 7.3%, and characterized by a further reduction in glycaemia during the study period. Furthermore, during SAP therapy, parents were engaged in patients management therapy, in contrast to what happens normally at home, when parents work and children are at school.

Second, the AP algorithm was tuned prudent-by-design both for safety reasons and because this trial was the first with an adolescent-specific version of the MMPC algorithm, previously tested only in adults.

At the end of the AP period, the patients' parents completed an AP acceptance questionnaire in which 94.1% noted the intention for their child to use the AP in the long term and 91.3% thought that AP could improve glucose control. Encouragingly, 70.5% considered AP easy to use[81].

DISCUSSION

This thesis has demonstrated the efficacy of the wearable AP model in different populations and for different time periods. The safety and efficacy of this AP model to ensure glycaemic control, measured as time in range, and metabolic control, measured as HbA1c, was evaluated first during a night-time period, then over a 24-hour period, and finally for progressively longer periods.

The DiAs was tested over 184,000 hours in over 300 patients with T1D, including data from other clinical centres, demonstrating its efficacy and feasibility in real life situations. Results demonstrated the superiority of AP over the actual gold standard Sensor Augmented Pump Therapy.

The Experience of Other Groups with AP

Other groups have demonstrated the efficacy of the AP model in different settings and populations. For example, Professor Hovorka's group at Cambridge University developed another MMPC control algorithm that uses a different predictive control model as well as different insulin pumps and CGM systems[82]. They performed their outpatient and home studies by installing the control algorithm on a tablet or a mobile phone. In a randomized multi-centre (UK, Austria, and Germany) crossover trial, adult patients were randomized to start AP use for 24 hours/day, then use SAP therapy for 12 weeks or vice versa[83]. Results during the night and day usage demonstrated increased time in target (67.7% vs. 56.8%, $P < 0.001$), reduced time above target of 180 mg/dl (10 mmol/L) from 38.9% to 29.2% ($P < 0.001$), and reduced time below target of 70 mg/dl (3.9 mmol/L) from 3.0% to 2.9% ($P = 0.02$). Mean glucose decreased from 168 to 157 mg/dl ($P < 0.001$) and a reduction of glucose variability was also observed.

The same algorithm was then tested in 25 children and adolescents[83] (mean age 12 years old) during night-time usage and results were very encouraging. In fact, during day and night usage in young patients, results demonstrated improved time in target (61.2 vs. 51.6%, $P < 0.001$), reduced time above target (36.0 vs. 44.5%, $P < 0.001$), and reduced mean glucose levels (172 mg/dl vs. 182 mg/dl, $P = 0.01$). The study in adults demonstrated a reduction of 0.3% of HbA1c, from 7.6% to 7.3% ($P = 0.002$).

Also fuzzy logic algorithm, improved by a group from the University of Tel Aviv, Ljubljana, and Hannover, was tested in home-based patients in overnight periods for six weeks in 24 patients from 12 to 43 years old. Nocturnal hypoglycaemia, defined as glycaemia below 70 mg/dl (3.9 mmol/L), was reduced from 5.16% to 2.53% ($P = 0.02$), while time in tight target (70-140 mg/dl) increased from 36.3% to 47.4% ($P = 0.003$)[84].

A different approach was characterized by a bi-hormonal AP. In contrast to studies cited here that used only insulin to optimize glycaemic control, this prototype of the AP used two pumps: one for insulin and one for glucagon, the principal physiological hormone responsible for increase of glycaemia. The possibility of administering glucagon, which can mitigate or prevent hypoglycaemia, allows a more aggressive insulin infusion to reach a tighter control[85].

This AP model was also evaluated in a randomized crossover trial, in which a dual hormone AP was compared with usual patient therapy (SAP or continuous subcutaneous insulin infusion) for 11 days. Results demonstrated the safety of the system over 24 hours with improved glucose variability, as well as a reduction of mean glucose (7.8 vs. 9 mmol/l, $P < 0.0001$) time in hypoglycaemia (1.9% vs. 0.6%, $P < 0.0001$), and time in hyperglycaemia (19.8% vs. 33.6%, $P < 0.0001$)[86]. This model was also tested in paediatric patients, from 6 to 11 years old, in a summer camp. Nineteen patients with a mean age of 9.8 years old were randomized to use AP or an insulin pump for five days, then, after a three-day wash-out, they

used the other treatment[87]. The bi-hormonal AP led to a reduction of mean glucose (137 vs. 167 mg/dl, 7.6 vs. 9.3 mmol/L, P = 0.00037), time below 3.3 mmol/L (1.2% vs. 2.8%, p < 0.0001), and time above 180 mg/dl (10 mmol/L) (16.5% vs. 36.3%, P < 0.0001). Time in target increased from 57.6% to 80.6% (P < 0.0001). Bi-hormonal CLC has some critical points, too. First, it requires the use of two pumps, one for insulin and one for glucagon, in addition to CGM, which is not always well tolerated by patients. Furthermore, it is necessary to find a glucagon formulation that is stable for a sufficient time and to assess the effectiveness of repeated glucagon administration.

The AP was also tested in different situations. For example, Hovorka and his colleagues evaluated CLC efficacy in T1D pregnant women, demonstrating the safety of the system in this critical period[88]. Sixteen pregnant women (from 18 to 45 years old, between 8 and 24 weeks of gestation) were enrolled in a randomized crossover trial that compared four weeks of overnight AP use and SAP therapy. Results demonstrated the superiority of CLC in glycaemic values, reducing time in hypo- and hyperglycaemia. At the end of the randomized period, patients could continue to use CLC for 24-hour periods and during labour and delivery with good results and an absence of adverse events.

AP was also tested in critically ill inpatients, randomized to receive glucose control through the AP or through local protocol of endovenus insulin infusion. Even in these critical patients, CLC was superior to classical therapy[89].

Another example of CLC superiority was demonstrated in adolescents who forget or underdose bolus administration at meals. This happens frequently in young diabetic patients and leads to a worsening of metabolic control. Even though the AP model needs meal announcements (CHO intake or meal size) to administer a meal bolus and avoid postprandial hyperglycaemia, having a meal without announcing it and obviously without bolus is better

controlled using AP than with usual therapy, due to an automatic increase of basal rate or automatic bolus when glycaemia arises[90].

Other studies have compared different algorithms. For example, a comparison between PID and MPC controllers during 27-hour supervised sessions was published in 2016. Results showed that MPC demonstrated better glycaemic control, with a lower mean glycaemia and more time spent in target[91].

A bi-hormonal pancreas was also compared to insulin CLC using an MPC controller in 20 adults and 10 adolescents in a randomized crossover trial that included 24-hour access to a clinical research centre, meals, and physical activity. This bi-hormonal system demonstrated a further reduction of time spent in hypoglycaemia compared with the insulin-alone AP with no differences in mean sensor glucose levels[92].

Critical points

Some critical points remain, for example, the necessity to announce meals to inject a bolus to avoid postprandial hyperglycaemia or to manage physical activity. Controlling postprandial glucose excursions is important for achieving a healthy HbA1c target[93-94]. The main important determinant in controlling postprandial glycaemic peaks is carbohydrate content, which patients usually have to calculate to determine the amount of insulin bolus, based on a carbohydrates-to-insulin ratio. It's not always easy for patients to calculate the amount of carbohydrates before a meal and related errors can deteriorate postprandial glycaemic control[95]. In addition to evaluating the amount of carbohydrates, patients must evaluate their food's glycaemic index[96-97], defined as the speed with which food is absorbed, which determines the time of glycaemic peaks. Obviously, other factors like physical activity and the ingestion of protein, fat, and fibres can influence the pace of carbohydrate absorption[98-99]. Rapid-acting insulin analogues used need 15 minutes to be absorbed from

subcutaneous tissue to blood and perform their actions, with a peak action between one and two hours, while glucose absorption after meals is more rapid[100-101].

Meal announcement is a critical point related to slow insulin action and to the mismatch between insulin and food absorption. Recently, a faster insulin that could minimise the delay in insulin absorption and improve AP efficacy has been introduced in therapy[102-104]. Another technique to accelerate insulin absorption is to combine insulin with hyaluronidase, an enzyme that increases the passage of insulin from subcutaneous tissue to blood[105]. Pramlintide administration before a meal can also delay gastric emptying, leading to better postprandial control[106]. Some studies have evaluated CLC with pramlintide administration demonstrating a postprandial peak reduction[107-108]. In the same way, GLP-1 analogues could also be a promising alternative. These new drugs, often used in type 2 diabetes therapy, lead to delayed gastric emptying and a suppression in glucagon release. The addition of liraglutide (a GLP-1 analogue) to CLC improved overall glucose control and, in particular, postprandial control[109].

Until now, most AP models are hybrid closed loop systems because of the need for meal announcements, inserting CHO intake or meal size[110] to help the algorithm to control postprandial glucose peaks. A fully-automated CLC, with no need to insert meal or physical activity, has also been tested, but in a small number of subjects in an inpatient setting. Optimization of a fully-automated CLC may be possible with new faster insulin or new approaches. This solution could be more appreciated by patients, reducing the risk of errors in CHO calculation[111-113].

Another critical point to note about CLC is that the quick variation in glucose levels during physical activity means that such activity is not always well evaluated by sensors, and such activity must be accurately anticipated or prevented to obtain a complete automation of the system. Different approaches have been evaluated. For example, a heart rate frequency

sensor[114] or accelerometer, to estimate physical activity, inserted in algorithm control could provide other data to prevent hypoglycaemia related to sport, as demonstrated in recent trial in adolescents where heart rate was inserted in algorithm. During physical activity, the heart rate increases, providing important information to the system to optimize control. In fact, a reduction of time spent in hypoglycaemia compared to the classical closed loop system was observed.

Another critical point that impacts the efficacy of AP is the accuracy of the sensors. In recent years, CGM accuracy has rapidly improved, and some sensors have been approved by FDA as a non-adjunctive system[115], replacing the glucometer in diabetes-related patient choices. Furthermore, CGMS performance can be influenced by calibration or signalling errors[116-117]. Patient education is critical to avoiding calibration errors and identifying sensor inaccuracy[118], even if the AP systems have algorithms to determine sensor inaccuracy and often use also glycaemic capillary values to improve control.

The control algorithm could also be improved to obtain better control during the day, maybe developing adaptive algorithm with daily automatic adaption of patients' parameters to optimize glycaemic control, as tested in a pilot study by our group[119].

Also the "platform" could be improved, in particular regarding connections between different devices. For example, Dexcom G4 evolution has Bluetooth connection integrated in the receiver (as used in paediatricians trial). Dexcom G5 (new Dexcom generation) could send data directly from transmitter to AP, with no receiver or relay box requirement, solving some connection problems.

CONCLUSIONS

Important progress has been made in the last five years leading to more positive prospects in the future therapy of T1D patients that have been engaged all their life in controlling glucose levels and avoiding acute and chronic disease complications.

Our data and results from other groups involved in AP development demonstrated the feasibility and efficacy of this technology.

It has been demonstrated that glucose variability is related with complications development in type 1 and type 2 diabetic patients[120]. Several studies demonstrated a reduction in glucose variability using AP, probably leading to a less incidence of complications. Obviously long term studies are necessary to confirm this assumption.

Furthermore also acceptance of the system by patients is encouraging, even if remains problems with connection between devices and alarms are not always well tolerated.

Some months ago, the FDA approved the first Hybrid CLC, the Medtronic one, which uses a PID algorithm, demonstrating the validity of this new therapeutic approach.

Obviously, more data are necessary to translate this technology from research field to clinical application. For example studies of several months in a large cohort of patients to evaluate long-term efficacy, or in not selected patients, for example in worse controlled or less compliant subjects. More studies are necessary in particular populations, as type 1 diabetic pregnant women or very young diabetic patients.

Furthermore the cost-effectiveness of closed-loop systems is to be determined to support access and reimbursement of this technology.

Prolonged multinational closed-loop clinical trials, enrolling hundreds of patients are currently underway or in preparation, to definitively confirm efficacy of Artificial Pancreas for type 1 diabetic patients.

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