SYSTEMATIC REVIEW

Diabetes Management

Closed-loop control for pediatric Type 1 diabetes mellitus

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Practice points

- Device use in pediatric Type 1 diabetes is being continually expanded and individualized.
- Clinical trials of closed-loop control are currently enrolling participants.
- Practitioners need to be aware of current open clinical trials so that patients can be expeditiously enrolled resulting in the maturation of closed systems and swift translation to clinical practice over the next decade.

SUMMARY Closed-loop clinical trials have resulted in significant advances with continuous glucose monitoring and control systems modulating insulin delivery. Those trials were performed in closely supervised clinical research settings; while adults with Type 1 diabetes were initially targeted, studies in children with Type 1 diabetes have followed in both clinical research units and pediatric diabetes camps. These studies have been conducted as multicenter and multinational efforts. Pediatric studies have since been piloted in home settings overnight for control during sleep. The stage is now set for accelerating efforts, extending the number of patients enrolled, the amount of time during which the system is active daily and the duration of the clinical trials.

KEYWORDS
• adolescent • artificial pancreas • closed-loop control • Type 1 diabetes

Diabetes management in pediatrics continues to be challenging. Type 1 diabetes is the most common type of diabetes in children. Physical, developmental and sexual maturity, family dynamics, supervision in the home and school environments, are key factors that may impact optimal diabetes care [1]. Diabetes management is particularly difficult in very young children who have unpredictable eating patterns, physical activity levels and increased susceptibility to hypoglycemia and hypoglycemia unawareness [2]. The consistency of diabetes care may also be negatively affected by the different child care providers. School age children become increasingly involved in their diabetes tasks while being assisted by school personnel. They often have organized physical activity in and out of the school setting, requiring careful monitoring of blood glucose (BG). Adolescents typically undergo behavioral changes to establish autonomy, including their diabetes management. They

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can have deterioration in adherence to tasks and glycemic control. Hormonal changes during puberty increase insulin insensitivity, making optimal glycemic control more difficult. Parental involvement can be variable. Thus, management of Type 1 diabetes poses different challenges at different stages of childhood.

There is clear evidence that poor glycemic control increases the risk of long-term macrovascular and microvascular complications in adolescents and adults with Type 1 diabetes. Until 2014, the American Diabetes Association (ADA) recommended target HbA1c for children younger than 6 years of age to be less than 8.5%, less than 8.0% for 6–12 years of age and less than 7.5% for 13–19 years of age [1]. Approximately 30% of children meet the age-specific HbA1c targets [2] and the ADA's new position statement released at the ADA 74th Scientific Sessions calls for a target HbA1c of less than 7.5% for all pediatric age groups [3]. This goal is consistent with the National Institute for Health and Care Excellence recommendations for long-term glycemic control [4]. Type 1 diabetes can be managed by either conventional insulin therapy of two injections per day or intensive insulin therapy of multiple daily injections (MDI) consisting of three or more injections per day or insulin pump therapy. The insulin regimen should be tailored for each individual. Achieving an A1c of ≤7.5% requires tighter glycemic control that will be difficult to achieve without increasing hypoglycemic events with traditional diabetes management [5]. Thus, closed-loop insulin delivery technology will be an important aspect of achieving this goal safely [5,6].

Technologies of continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) have advanced to sophisticated sensor-augmented insulin pump therapy (SAP) with the promise of the 'artificial pancreas' (AP) or closed-loop management on the horizon for Type 1 diabetes. Studies with SAP enrolling 7–18 year old children have shown improvement in HbA1c without increasing hypoglycemic events when compared with insulin injections [7–9]. Closed-loop studies done in clinical research units or at diabetes camp have shown improved glycemic control [10–13] while decreasing the rates of hyperglycemia and hypoglycemia [10,13].

Current therapeutic options

As previously mentioned, T1D can be managed by conventional therapy, intensive therapy with MDI or CSII. In some studies, MDI has improved glycemic control over conventional therapy [14]. A Cochrane review suggests that CSII may have better glycemic control over MDI. It also found reduced severe hypoglycemia and improved quality of life measures [15]. Other studies do not consistently demonstrate that the use of CSII alone improves HbA1c when compared with MDI in children [16]. In one study, utilizing a CGM decreased the amount of time spent in hypoglycemia and hyperglycemia in adults 25 years and older and a decreased amount of time spent in hypoglycemia in 15–24 year olds but it failed to show a substantial change in 8–14 year olds. Additionally, CGM use tended to decrease over time in both the 8–14 year olds and 15–24 year old age groups from 7 days/week to 3.3 and 3.7 days/week respectively after 6 months [17]. Studies comparing the effectiveness of SAP to MDI therapy revealed a significant improvement in HbA1c in the SAP group [8]. Subsequent generation of combination devices have a low glucose suspend function which turns off insulin delivery for up to 2 h if a preset low BG is detected and not responded to. As closed-loop technology moves from clinical research units to home settings, parents and adolescents report positive experiences such as improved sleep, feeling safe and stable BGs with negative experiences of calibration issues, alarms and equipment size with their study experience [18]. In this study, families expressed hope for closed-loop technology and the future of diabetes management [19].

Current clinical closed-loop control efforts

Closed-loop control (CLC) utilizes sophisticated algorithms to act on data from CGM regarding current glucose level and trend, as well as from an individual's insulin sensitivity, to determine an appropriate insulin dose to maintain glucose levels in a desired range. The algorithms in AP systems employ multiple sources of data regarding the patient's current BG status to make a 'state estimate' and then make predictions about expected changes in BG in the near future and how much insulin (or other delivered hormones) is required to achieve a BG that is a certain target level or in the target range. A model of such a system is shown in **Figure 1**, in which the data inputs include BG sensing from a CGM, known estimates of the patient's insulin sensitivity (e.g., from the insulin pump settings just prior to AP use) and the quantity of insulin

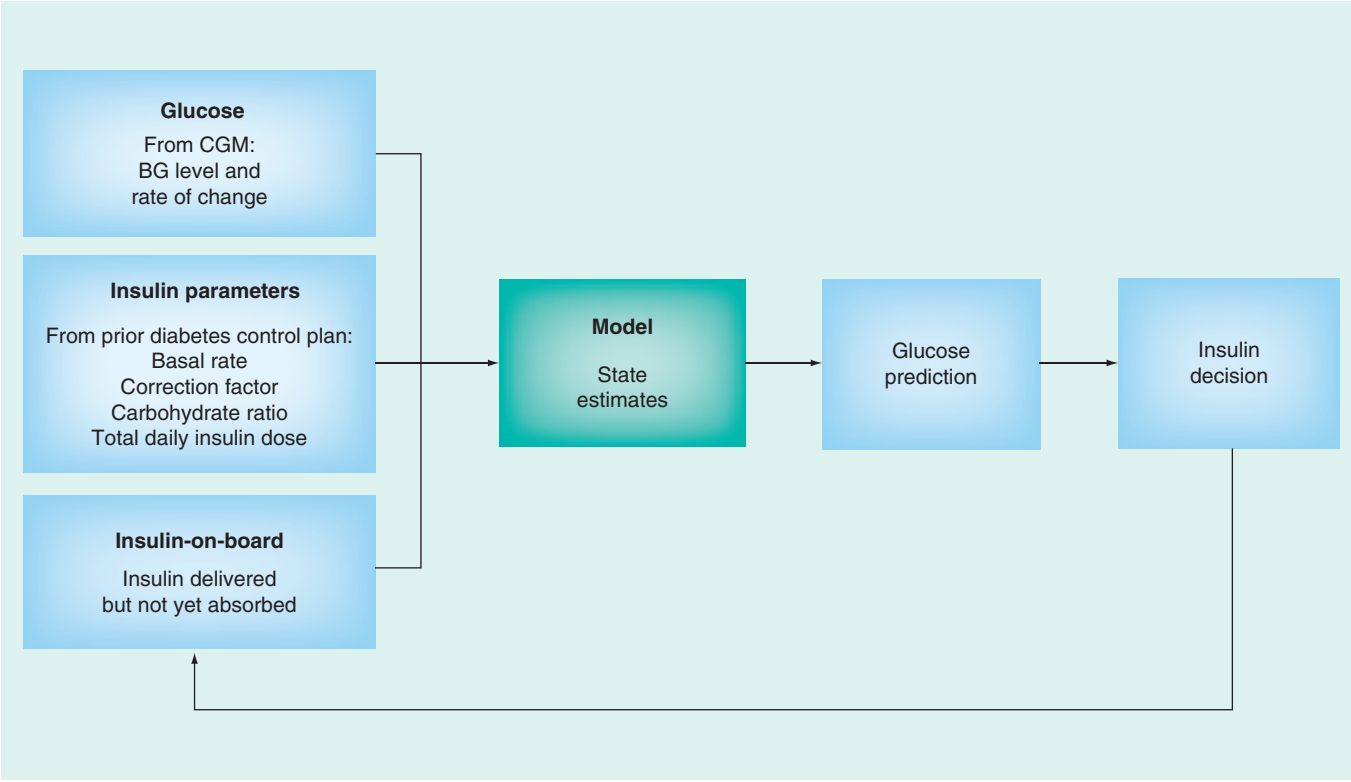

Figure 1. Model of a closed-loop system. Inputs regarding glucose trends, the patient's insulin sensitivity and recent insulin delivery are placed in a model using complex mathematical algorithms to provide a state estimate and current insulin needs. The calculated dose of insulin is then communicated to the insulin pump. This proceeds in a cyclical basis with minimal input from the user.

that has been administered but not yet had time to be absorbed ('insulin on board'). Additional inputs not shown can include announcement of impending exercise or meal ingestion. The AP then uses complex mathematical equations based on glucose physiology from human clinical studies to process these data and generate a state estimate and a projection of the direction and timing of the patient's glucose excursions in the future (e.g., over the next 15–60 min). Based on this prediction the system calculates the dose of insulin (or other hormones) required to favorably alter the BG level. The system then sends commands to the insulin pump to raise or lower insulin delivery. The insulin that is then injected is taken into account as insulin-on-board for further calculations. As shown in **Figure 1**, these systems operate as a 'closed loop,' using a process of continuous adjustment with no or limited user input. To streamline control, these systems frequently operate as modules distributing the control tasks to algorithms running concurrently, each with a focused goal such as hypoglycemia prevention or hyperglycemia mitigation, with a central supervising system integrating these outputs in a way to maximize safety while still keeping BG as close as possible to target levels [20].

There are multiple research teams around the globe involved in research in children and adolescents related to the AP and development of unique systems, with some degree of interaction between these teams. While most of the research and testing has been performed in adult cohorts, there is a growing amount of evidence regarding the safety and efficacy of AP systems in children and adolescents.

Search strategy

We searched PubMed, Ovid MEDLINE, EMBASE, Cochrane CENTRAL and Web of Science databases for the terms 'diabetes' and 'closed loop' or 'AP' or 'bionic pancreas' and 'child' or 'children' or 'adolescent' or 'pediatric.' Identified articles and abstracts were then reviewed for their appropriateness for this topic. We identified 196 of titles, of which 177 were eliminated for not relating to the AP, pertaining only to adult studies, for being related only to technical (nonclinical) aspects of the AP or for

being abstracts from scientific meetings, yielding 19 clinical studies of AP use in children and adolescents **(Table 1)**.

Current consortia

The current research teams involved in AP testing have utilized a variety of AP systems and tested these in multiple settings. **Table 1** includes publications from these teams with subcategories identified on the basis of the timing of periods when the AP was active during the trial, from daytime-only to nighttime-only to 24-h closed loop.

• MD-Logic Artificial Pancreas System

The research group led by Moshe Phillip has developed an AP system running a set of insulin-delivery algorithms known as MD Logic. Built into the system is an iterative process that adjusts its estimate of insulin sensitivity based on past function of the system. The control algorithm utilizes treatment logic from quantitative and qualitative data gathered from a detection algorithm with subsequent automatic adjustments. The technology was largely developed at Tel Aviv University in Israel and has been tested by the DREAM consortium including investigators in Slovenia and Germany. DREAM 1 was a validation study in a research setting that demonstrated the benefit of overnight closed-loop insulin delivery using the MD-Logic Artificial Pancreas System (MDLAP).

DREAM 2 utilized the MDLAP to improve overnight glucose control without increasing hypoglycemia in a research in patient setting [22]. DREAM 3 was the first study to move out of the clinical setting into a pediatric diabetes camp. This study in Europe and Israel in 2011 and 2012 showed success in achieving overnight tighter glucose control with less hypoglycemia than those utilizing SAP [13]. Fifty-four children age 10–18 years were randomized to a night of closed-loop AP control using an Enlite Sensor CGM, a Paradigm Veo insulin pump and the MDLAP system on a laptop computer. Time with BG between 70–140 mg/dl was 4.4 h during AP nights and 2.8 h on usual-care nights, with an average BG of 126 versus 140 mg/dl and reduced episodes of hypoglycemia less than 63 mg/dl of 7 versus 22% (all $p < 0.05$). DREAM 4 moved the research setting into the participant's home to evaluate MDLAP overnight. This study is ongoing (NCT01726829).

• Cambridge group

The group led by Roman Hovorka at the University of Cambridge, Cambridge, UK has utilized their AP system in multiple studies involving children and adolescents. The Florence closed-loop system consists of a laptop which runs the CLC system. CGM data are collected with a specific CGM (Navigator CGM) and insulin is continuously delivered with a specific insulin pump (Dana R Diabecare, Seoul, South Korea). CGM data are used every 12 min to change insulin delivery using a model predictive control system. The system is initialized using the patient's basal insulin pump profile, weight and total daily insulin.

Initial reports on their system in children and adolescents focused largely on feasibility and safety. This includes overnight trials system among adolescents in a cross-over study design in a clinical research facility, reporting control that was similar between the usual care and CLC nights as a demonstration of system safety [24]. Elleri *et al.* reported a randomized cross-over clinical trial of 12 adolescents on either conventional pump therapy or CLC, studied at a research facility over two 36-h periods [11]. Compared with conventional therapy, their AP system resulted in more time with BG in the target range 71–180 mg/dl (84 vs 49%, $p < 0.05$) and lower average BG levels (128 vs 165 mg/dl, $p < 0.05$). This study also attempted additional tests of CLC, including moderate-intensity exercise (both walks and time on an exercise bicycle) and unannounced carbohydrate ingestion. Over the course of the 36-h trial there were similar numbers of hypoglycemic events (nine in conventional care and ten in CLC, five of which followed exercise) – underscoring persistent risks of hypoglycemia, even on a closed-loop system.

The Cambridge group followed this study with a home-based study of overnight AP control in which 16 adolescents received 3 week periods of either their CLC system or SAP for overnight glucose control. They found that during their time on the AP system, adolescents have lower mean glucose levels (reduced by 14 mg/dl on average) with a reduction in episodes with BG less than 63 mg/dl [26].

• University of Virginia consortia

The University of Virginia (UVa) and the University of Padova, Italy have collaborated with Sansum Diabetes Research Institute, University of California Santa Barbara and

Table 1. Studies of closed-loop control of diabetes in children and adolescents, organized by consortia group, with additional study details.

Year published	Patients (n)	Age (years)	Setting	CL length	Control type	Controller	Therapeutic systems	CL meal	Meal bolus	Exercise	Results	Comments	Ref.
MD Logic													
2012	7	Pediatric + adult	Inpatient	N 8 h	FL	Laptop	Paradigm Veo + Medtronic	Yes	Yes	Yes	↑time spent in normal glucose range; ↓NH events	Compared with CSII	[21]
2013	12	19 ± 10.4	Home	N 8 h	FL	Laptop	MD Logic with SAP	Yes	Yes	No	↑time spent in normal glucose range; ↓NH events	Compared with CSII	[22]
2013	56	10–18	Outpatient bedside	N 12 h	FL	Laptop	Enlite + Paradigm	Yes	Yes	Yes	Improved overnight glucose range; shorter periods of hypoglycemia	Compared with SAP	[13]
Cambridge													
2010	19	5–18	Inpatient	12 h	MPC	Laptop	FreeStyle Navigator + Deltec Cozmo	Yes	Yes	Yes	↓NH events; ↑time spent in target glucose range	Compared with CSII	[23]
2011	8	9.4 ± 2.7	Inpatient	D/N 14 or 11 h	MPC	Laptop	FreeStyle Navigator + Deltec Cozmo	Yes	Yes	No	Time spent in target glucose range was 50.7 and 58% in closed vs. open loop.	Automated CL delivery system compared on two separate nights	[24]
2012	8	14.3 ± 1.7	Inpatient	D/N 14 or 11 h	MPC	Laptop	FreeStyle Navigator + Aviator 2	Yes	Yes	Yes	Time spend in target glucose range was 82% when started at 18:00 and 64% when started at 21:00	Automated CL delivery system compared on two separate nights with different starting times	[25]
2014	16	12–18	Outpatient bedside	N 8 h	MPC	Laptop	FreeStyle Navigator + Dana R Diabecare	No	No	No	↑time spent in target glucose range; ↓frequency of NH	Unsupervised home use of CL	[26]
University of Virginia													
2012	11	12–18	Inpatient	22 h	MPC	Laptop	DexCom 7 or Navigator + Omnipod	Yes	Yes	Yes	↓hypoglycemia; ↑time spent in target glucose range; tighter glycemic control	Utilized standard and enhanced control-to-range as sequential steps to decrease glucose variability and tighten glycemic control	[27]

↑: Increased; ↓: Decreased; CGM: continuous glucose monitoring; CL: Closed loop; CLC: Closed-loop control; CSII: Continuous subcutaneous insulin infusion; D: Day; D/N: Day/night; FL: Fuzzy logic; IFB: Insulin feedback; MDI: Multiple daily injections; MPC: Model predictive control; N: Night; NH: nocturnal hypoglycemia; OL: open loop; PID: Proportional integral derivative; SAP: Sensor-augmented insulin pump therapy; USS: Unified Safety System.

Table 1. Studies of closed-loop control of diabetes in children and adolescents, organized by consortia group, with additional study details (cont.).

Year published	Patients (n)	Age (years)	Setting	CL length	Control type	Controller	Therapeutic systems	CL meal	Meal bolus	Exercise	Results	Comments	Ref.
University of Virginia (cont.)													
2014	26	15 ± 1	Inpatient	22 h	MPC	Laptop	DexCom 7 + Omnipod	Yes	Yes	Yes	In range 53% daytime, 82% overnight	Difficulty preventing postmeal excursions above target range	[28]
2014	20	15.1 ± 3.2	Outpatient bedside	N 6–8 h	USS	Smartphone	DexCom G4 Platinum + SAP	No	No	Yes	↑time spent in target glucose range; ↓frequency of NH	Compared with SAP	[29]
Stanford													
2013	68	13.3 ± 5.7	Inpatient	D/N 72 h	Insulin/ glucagon	Laptop	Guardian + MiniMed	Yes	Yes	No	CLC followed by SAP vs usual care of MDI did not preserve B-cell function	Decrease in CGM use over time	[30]
Boston University													
2014	12		Inpatient	D/N 48 h	Insulin/ glucagon	Smartphone	FreeStyle Navigator + Omnipod	Yes	Yes	Yes	Adaptive meal priming improved mean glucose without increasing hypoglycemia		[31]
2014	32	12–21	Outpatient free living	D/N 6 days	Insulin/ glucagon	Smartphone	Dexcom G4 + Tandem t:slim	Yes	Yes	Yes	Improved mean glycemic levels with ↓frequency of interventions for hypoglycemia	Automated bihormonal pump vs CSII	[32]
Yale, Medtronic													
2008	17	15.9 ± 1.6	Inpatient	D/N 34 h	PID	Laptop	MiniMed	Yes	Yes	No	The addition of manual priming bolus premeal improved postprandial glycemia		[33]
2012	4	15–28	Inpatient	D/N 24 h	PID and PID-IFB	Smartphone	Paradigm 715 + Guardian	Yes	No	No	↓frequency of hypoglycemia with PID-IFB vs PID	Higher average blood glucose levels with PID-IFB	[34]
2012	8	15–28	Inpatient	D/N 48 h	Pramlintide + PID-IFB	Smartphone	Sof-Sensor + Paradigm 715	Yes	No	No	↓magnitude of glycemic excursion with pramlintide vs no pramlintide	Pramlintide delayed the time to peak postrprandial glucose	[35]

↑: Increased; ↓: Decreased; CGM: continuous glucose monitoring; CL: Closed loop; CLC: Closed-loop control; CSII: Continuous subcutaneous insulin infusion; D: Day; D/N: Day/night; FL: Fuzzy logic; IFB: Insulin feedback; MDI: Multiple daily injections; MPC: Model predictive control; N: Night; NH: nocturnal hypoglycemia; OL: open loop; PID: Proportional integral derivative; SAP: Sensor-augmented insulin pump therapy; USS: Unified Safety System.

Table 1. Studies of closed-loop control of diabetes in children and adolescents, organized by consortia group, with additional study details (cont.).

Year published	Patients (n)	Age (years)	Setting	CL length	Control type	Controller	Therapeutic systems	CL meal	Meal bolus	Exercise	Results	Comments	Ref.
Yale, Medtronic (cont.)													
2013	12	12–26	Inpatient	D/N 48 h	PID-IFB	Smartphone	Sof-Sensor + Paradigm 715	Yes	Yes	Yes	↑time spent in normal glucose range; ↓NH events, regardless of afternoon activity level		[36]
2012	8	16 ± 3.9	Inpatient	N 10 h	PID+IFB	Smartphone	Medtronic Enlite + Paradigm Veo	No	No	No	↑time spent in normal glucose range; ↓time spent in hypoglycemia	Portable glucose control system as an automated CL device is safe	[37]
Other													
2012	10	18–75	Inpatient	D	PID: insulin and glucagon	Laptop	Bihormonal D-Tron + pumps (2) + Medtronic CGM	Yes	Yes	Yes	Postbreakfast glucose was lower in OL vs CL with the opposite at lunch Postexercise glucose was similar in CL and OL. Two events of hypoglycemia in OL vs four events in CL	CL glucose control was comparable to OL control in a day with two meals and exercise. Glucagon seemed mostly effective at preventing hypoglycemia	[38]

↑: Increased; ↓: Decreased; CGM: continuous glucose monitoring; CL: Closed loop; CLC: Closed-loop control; CSII: Continuous subcutaneous insulin infusion; D: Day; D/N: Day/night; FL: Fuzzy logic; IFB: Insulin feedback; MDI: Multiple daily injections; MPC: Model predictive control; N: Night; NH: nocturnal hypoglycemia; OL: open loop; PID: Proportional integral derivative; SAP: Sensor-augmented insulin pump therapy; USS: Unified Safety System.

University of Montpelier, France in testing a control-to-range algorithm in adolescents [27]. This system maintained usual basal rates when the BG was in the target range but delivered additional insulin or a reduction in insulin if low/or high blood sugars were present or were predicted. This system utilized either Dexcom 7 (Dexcom, Inc., CA, USA) or Navigator (Abbott Diabetes Care, CA, USA) CGM devices and Omnipod (Insulet Corp, MA, USA) insulin pumps, with the algorithm run on a laptop computer. In adolescents, the percent time spent with BG 70–180 mg/dl increased from 50.2% on usual care to 65.1%. In this trial, the increase in time in tight control 80–140 mg/dl was higher in adults than in adolescents. This was likely due to increased glucose variability in adolescents compared with adult participants, underscoring some of the additional challenges that are likely to be encountered in pediatric and adolescent application of the AP.

This system was tested for safety in an expanded cohort involving the same consortium with the addition of Stanford University and the Barbara Davis Center for Childhood Diabetes [28]. This multi-national trial involved 27 adults and 26 adolescents to evaluate enhanced control-to-range class algorithm by assessing time spent in hypo and hyperglycemia. The adolescents had a mean glucose level of 166 mg/dl during the study. The time spent in range (71–180 mg/dl) was overall 62% (daytime 53% and night 82%). The algorithm failed to keep six adolescents (24%) in range 30% of the time. Of these six, the algorithm failed to be in range for two for both day and night and another for night only. Although there were no BGs greater than 400 mg/dl, 32% had at least one value greater than 300 mg/dl and 20% had at least one value ≤60 mg/dl. The algorithm included two interacting modules: the Range Correction Module (University of Pavia) and the Safety Supervision Module (UVa). There was an added safety constraint for insulin on board (University of California, Santa Barbara and Sansum Diabetes Research Institute). It was found that postmeal BG levels were above target which they felt may be improved with further individualization of algorithm [28].

UVa collaborated with Stanford University in testing the performance of a unified safety system algorithm, run using the Diabetes Assistant platform on a smart phone and using a Dexcom G4 CGM and Tandem t:slim (Tandem Diabetes Care, CA, USA) insulin pump [39]. This system was tested in diabetes camps for overnight control, demonstrating reduced time in hypoglycemia compared with sensor-augmented pump therapy. The median time spent in range between 70 and 150 mg/dl overnight was 73% for the AP system versus 55% for sensor-augmented pump. The median time spent in range from 70 to 180 mg/dl was 96% for the overnight CL period versus 89% during the sensor-augmented pump period.

• Stanford

In addition to collaborations listed previously, the research team at Stanford University have also been in the lead of a consortium utilizing a hybrid closed-loop control system in an inpatient clinical research unit setting following initial diagnosis of T1D in 68 participants (mean age 13.3 ± 5.7 years) for approximately 6 days. Patients were randomized at the end of the hybrid closed-loop control to SAP (n = 48) versus usual care (multiple daily insulin injections or CSII, n = 20). At 12 months, only 33% continued to use the CGM ≥6 days/week. The primary end point of the study, C-peptide concentrations after a mixed meal, did not differ between groups [30].

• Boston University

The group at Boston University, led by Ed Damiano, has developed a system that administers both insulin and glucagon via separate insulin pumps. The system employs a set of algorithms that requires input of the user's weight and during an approximately 24-h period undergoes an iterative process to arrive at the appropriate insulin and glucagon doses to target BG control. This group utilized this system in a group of 12 adolescents aged 12–20 years in a clinical research center for a randomized trial of using this system with or without doses of insulin prior to meal ingestion [37]. This used the Navigator CGM system and Omnipod insulin pump with the algorithm run using an iPhone. They found that the system yielded better BG values when a meal priming bolus was given (162 vs 175 mg/dl over 48 h, $p < 0.05$), with only one episode of hypoglycemia. This study demonstrated that this AP system managed mealtime BG excursions better when the participant informed the system of meals than without.

In 2013 the same group administered the same dual-hormone system to adolescents at

a diabetes camp [21]. This was performed in a randomized, cross-over design such that the adolescents were placed on the dual-hormone AP system for 5 days or on their usual care. This system was run on an iPhone platform using DexCom G4 platinum as the CGM input and two Tandem t: slim insulin pumps. Adolescents participated in matched camp activities during both trial periods. Overall, participants had a BG with the range 70–180 mg/dl 75.9% of the time on the dual-hormone AP system compared with 64.5% during usual care ($p < 0.001$), with a mean BG of 138 versus 157 ($p < 0.01$). The time spent in hypoglycemia less than 70 mg/dl was similar for the AP and control groups, 3.1 versus 4.9%. Participants required a total of 0.72 mg daily of glucagon in this system. Overall this trial demonstrated potential safety and efficacy on a dual-hormone AP system.

• Yale & Medtronic

The research team at Yale University has studied a fully closed-loop system and a hybrid closed-loop system utilizing Medtronic Paradigm 715 insulin pump, Medtronic continuous glucose sensor, laptop computer with the Medtronic ePID (proportional integral derivative) algorithm. This was studied in 17 participants aged 13–20 years. They found that a fully closed-loop AP using a CGM and insulin pump is feasible in adolescents [33]. Further studies have incorporated ePID plus insulin feedback (IFB) algorithm. The IFB algorithm reduced the occurrence of postprandial hypoglycemia without altering meal-related glucose excursions in comparison with the ePID algorithm alone. This was studied in four participants in a 24 h crossover study [34]. Subsequently, this algorithm with IFB was further studied in 12 participants aged 12–26 years in 2013 by evaluating nocturnal hypoglycemia after exercise performed in the afternoon. Researchers noted that after prolonged and vigorous exercise in the afternoon, closed-loop insulin delivery at night could not fully eliminate hypoglycemia but did perform better than open-loop delivery [36]. Currently, Yale researchers are recruiting 12–40 year olds for a study that uses ePID closed-loop system and the InsuPatch. This is a device that applies heat (at 40°C) to the area of the subcutaneous insulin infusion insertion site (NCT01787318). The InsuPatch endeavors to accelerate insulin absorption by controlled heating of the area surrounding the point of infusion [40].

In Perth, Australia, O'Grady and associates evaluated the Medtronic Portable Glucose Control System (PGCS) on eight participants 12.6–24 years of age with a median age of 14.8 years. This automated closed-loop system consisted of a Medtronic Paradigm Veo insulin pump, MiniLink REAL-Time Transmitters with Enlite glucose sensors (Medtronic Minimed), a BlackBerry Storm smart phone and a Medtronic custom-built radiofrequency translator. Remote monitoring was via real-time compressed data sent to a remote monitoring station over wireless cellular network. The control algorithm was PID+IFB. The participants were involved in 145 h of closed loop over 16 nights. Overnight, the mean plasma glucose was 115 ± 31 mg/dl with the time in target (70–144 mg/dl) was 66% before midnight and 85% after midnight. Plasma glucose readings less than 70 mg/dl occurred 13.9% in the first 3 h of the closed loop and 4% after. In 3 of the 16 nights, BG less than 60 mg/dl occurred within the first 3.5 h of the closed loop. The sensor reading indicated that hypoglycemia was less common during closed loop compared with open-loop and was felt to be related to insulin delivered during the earlier open-loop session. The results of this study demonstrated the feasibility and safety of the automated PGCS [37].

Current open trials for closed-loop studies for pediatrics

There are currently 21 closed-loop clinical trials for children or children and adults that are recruiting participants. Four are safety studies that evaluate algorithm and time in target range around meals, 15 are safety/efficacy studies that assess remote monitoring, time in target range in home settings, as well as algorithm evaluation at camps and two are efficacy studies for dual hormone delivery. Overall, the trials exhibit an increase in duration over prior trials with one closed loop taking place over 12 weeks (NCT01778348). The trials are taking place in clinical research units, camp and home settings. Some are dual-hormone while others are pursuing glycemic excursion around meals or exercise. Hyaluronidase is being studied in conjunction with AP systems to accelerate insulin absorption (NCT01945099).

Conclusion & future perspective

AP systems, by providing dynamic responses of insulin and glucagon delivery in response to

glucose excursions, offer the potential for safe improvement of BG control in adolescents. The majority of trials in children and adolescents have demonstrated lower mean BG with a reduction in time with hypoglycemia. Overall, these gains have been greater overnight than during the day. Future directions include the use of AP systems for longer periods of time, in home settings and in children of younger age ranges. In a field that relies on technology, the authors of this review anticipate continued gains in the coming years.

Financial & competing interests disclosure

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