Acta Diabetologica (2023) 60:151–161
https://doi.org/10.1007/s00592-022-01929-5

REVIEW ARTICLE

Automated insulin delivery systems: from early research to routine care of type 1 diabetes

Eric Renard[1,2,3]

Received: 11 February 2022 / Accepted: 22 June 2022 / Published online: 22 August 2022

Abstract

Automated insulin delivery (AID) systems, so-called closed-loop systems or artificial pancreas, are based upon the concept of insulin supply driven by blood glucose levels and their variations according to body glucose needs, glucose intakes and insulin action. They include a continuous glucose monitoring device which provides a signal to a control algorithm tuning insulin delivery from an infusion pump. The control algorithm is the key of the system since it commands insulin administration in order to maintain blood glucose in a predefined target range and close to a near-normal glucose level. The last two decades have shown dramatic advances toward the use in free life of AID systems for routine care of type 1 diabetes through step-by-step demonstrations of feasibility, safety and efficacy in successive hospital, transitional and outpatient trials. Because of the constraints of pharmacokinetics and dynamics of subcutaneous insulin delivery, the currently available AID systems are all 'hybrid' or 'semi-automated' insulin delivery systems with a need of meal and exercise announcements in order to anticipate rapid glucose variations through pre-meal bolus or pre-exercise reduction of infusion rate. Nevertheless, these AID systems significantly improve time spent in a near-normal range with a reduction of the risk of hypoglycemia and the mental load of managing diabetes in everyday life, representing a milestone in insulin therapy. Expected progression toward fully automated, further miniaturized and integrated, possibly implantable on long-term and more physiological closed-loop systems paves the way for a *functional cure* of type 1 diabetes.

Keywords Automated insulin delivery · Closed-loop · Algorithm · Insulin pump · Continuous glucose monitoring

Introduction

Loss of insulin secretion in type 1 diabetes (T1D) implies the vital need of insulin administration which became available shortly after the discovery of insulin in 1921. The results of the Diabetes Control and Complications Trial (DCCT) documented the need for targeting near-normal glucose restoration in patients with T1D in order to prevent diabetes complications [1]. Reaching optimal glucose control in order to prevent these complications with the use of multiple daily insulin injections or insulin pumps without the availability of insulin analogues and continuous glucose monitoring (CGM) was, however, hardly achievable without a highly burdensome commitment of the patients and an intensive support from the diabetes health care providers, as shown by the post-study Epidemiology of Diabetes Interventions and Complications (EDIC) during which HbA1c levels increased by an average 1% (5 mmol/mol) in the DCCT "intensive control" arm [2]. Moreover targeting normoglycemia was associated with an increased risk of severe hypoglycemia during the DCCT [3]. These hurdles in reaching and maintaining near-normal glucose control in free life are related to the variability of body insulin needs due to the many factors which influence blood glucose levels, resulting in a difficult matching of timely delivery of insulin according to T1D patient's need [4]. Recently reported observatories of glucose control in T1D patients in North America and the other continents highlight the current failure in reaching optimal

Managed by Tadej Battelino.

✉ Eric Renard
e-renard@chu-montpellier.fr

[1] Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital, Montpellier, France

[2] INSERM Clinical Investigation Centre CIC 1411, Montpellier, France

[3] Department of Physiology, Institute of Functional Genomics, CNRS, INSERM, University of Montpellier, Montpellier, France

goals in the majority of patients in spite of the incremental use of insulin analogues, insulin pumps and CGM systems [5, 6]. In order to allow fast tuning of insulin delivery, continuous insulin infusion automatically modulated according to blood glucose levels and trends is needed. This is the concept of automated insulin delivery (AID) systems, aka "artificial pancreas" (AP) or "closed-loop systems" [7], depicted as early as in the 1970s. The 3 key components of these closed-loop systems include continuous insulin delivery, CGM and a control algorithm. This narrative review paper describes the 'closed-loop' saga from early research investigations to routine care of T1D (Fig. 1).

Early approaches of AID systems

Bedside artificial (endocrine) pancreas models have been developed in the 1970s, almost simultaneously in Europe, Japan and Northern America [8–10]. These systems, such as the Biostator®[11], included intravenous (IV) insulin infusion from a motor-driven syringe, CGM by an extracorporeal enzymatic sensor from an access to IV blood and a computing system that drove insulin delivery to keep glucose levels in a close to normal range based upon proportional-derivative (PD) algorithms. These feedback algorithms modulate insulin delivery according to the difference between current glucose level and the target level (proportional component) and the glucose rate-of-change (derivative component). An IV glucose infusion line was also available in case of glucose lowering toward hypoglycemia. These systems were shown to be able to keep blood glucose in a near-normal glucose range. The technologies were, however, unavailable by these times to allow ambulatory implementation. While portable insulin pumps were gradually developed from the 1980s, mostly using subcutaneous (SC) insulin infusion, the lack of reliable glucose sensors allowing wearable CGM remained the bottle-neck for further progression toward an outpatient use of AID systems.

The availability of sufficiently safe and accurate SC glucose sensors from 1999 opened the door for a renewal of the AID concept for diabetes care [12]. Meanwhile, modeling of glucose metabolism and insulin action led to the development of simulation platforms that allowed the design and the assessment of closed-loop algorithms through in silico trials in which virtual patients with diabetes could be submitted to insulin infusion according to glucose evolution [13]. Attempts were initially performed to develop and investigate in patients with diabetes sophisticated fully implanted closed-loop systems which combined IV glucose sensing via implanted long-term sensors placed through jugular or subclavian access and intra-peritoneal (IP) insulin delivery from implanted pumps [14]. The rationale for this initial choice was based upon the expected fast glucose sensing and insulin action thanks to the respective IV and IP routes. Using PD algorithms derived from earlier experiments with bedside AP systems, or secondarily newly designed proportional-integral-derivative (PID) algorithms to take into account the observed internal delays of glucose sensing inherent to the implanted sensors and the somewhat delayed insulin action of IP insulin compared to IV insulin, closed-loop glucose control could be reported in 48-h hospital trials with up to

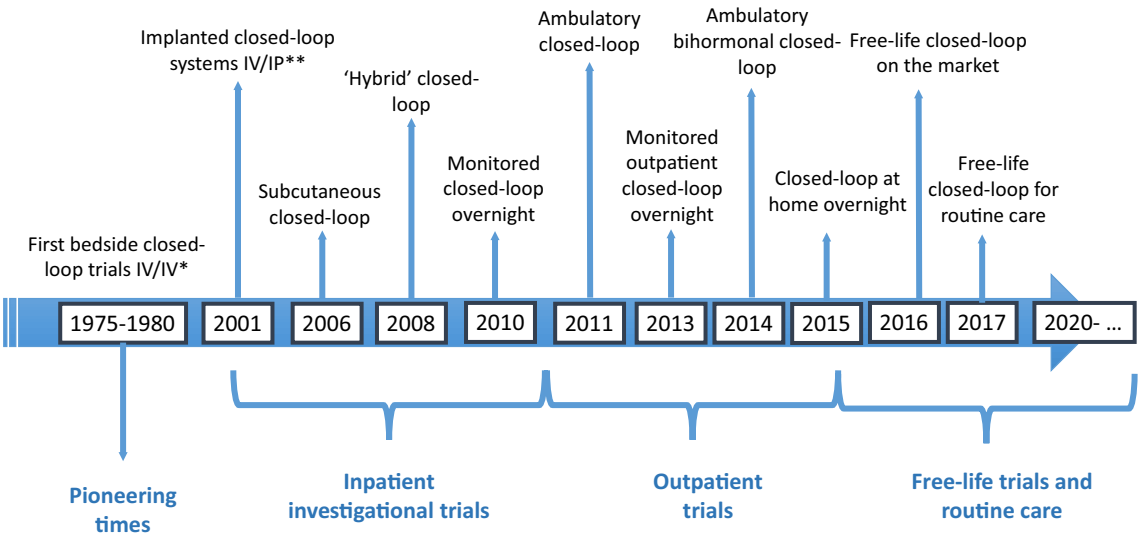

Fig. 1 The closed-loop saga: 45-year history from early prototypes to systems available for routine care

91.7% time spent in 80–240 mg/dl glucose range [15]. The invasiveness and limited lifetime of implanted IV sensors led to a move to SC sensors connected to IP-insulin pumps which allowed keeping glucose in 80–180 mg/dl range for 76.5% of time in hospital trials under a hybrid closed-loop design including priming pre-meal bolus [16]. Nevertheless, the limited extension of IP insulin use worldwide compared to the broadly adopted continuous subcutaneous insulin infusion (CSII) from wearable pumps drove the research efforts toward the privileged SC sensing-SC infusion combination, supported by funding from the Juvenile Diabetes Research Foundation (JDRF) from 2006, US National Institute of Health (NIH) from 2009 and European Union (EU) from 2010.

Implementation of CSII and SC CGM for investigations of AID systems in a controlled setting

While ADICOL experience [17] with simulated SC glucose sensing and newly designed model predictive control (MPC) algorithms which took into account delays of SC sensing and SC insulin action had shown the feasibility of a semi-closed-loop insulin delivery (i.e., closed-loop control between meals and prandial insulin bolus), the first full-closed-loop 30-h inpatient clinical experiment with actual SC sensing, SC insulin infusion and a PID algorithm was reported by Steil et al. in a landmark paper in 2006 [18]. Glucose was kept for 75% of time in 70–180 mg/dl range, but time spent below 60 mg/dl was not reduced under closed-loop glucose control. Indeed, full-closed-loop insulin delivery at meal-times resulted in early blood glucose spikes followed by late post-meal hypoglycemia due to the delayed action of SC infused insulin in response to the increase in blood glucose levels following meal intakes. This phenomenon could be prevented by manually ordered pre-meal bolus as shown by Weinzimer et al. [19]. Hence, further developments of AP systems using SC glucose sensing and SC insulin infusion have followed this hybrid configuration of closed-loop, also called semi-closed-loop, which includes meal announcement so that meal intakes are preceded by an insulin bolus computed according the carbohydrate component of the meal, the pre-meal blood glucose level and the estimated 'insulin on board' according to insulin infusion rate [20].

Following the first trials that showed the feasibility of closed-loop insulin delivery by SC glucose sensing and SC insulin delivery, the primary concern became the prevention of hypoglycemia while using these systems since a failure on this matter would prevent any progression toward outpatient use of AID. Because nocturnal hypoglycemia is especially fearful in young T1D patients, Hovorka et al. assessed for the first time in children and adolescents how an AID system using an MPC algorithm could reduce the risk of hypoglycemia at night while improving time spent in a near-normal glucose range compared to CSII [21]. In their seminal paper which cumulated three randomized control trials, these authors reported in a pooled analysis an increase of % time spent in the target range (70–145 mg/dl) from 40 to 60% while % time spent below 70 mg/dl was reduced by half from 4.1 to 2.1%. Similar results were reported by Kovatchev et al. in adult T1D patients who were investigated for night-time control using another combination of SC glucose monitoring system, SC insulin pump and MPC algorithm [22].

Meanwhile, the Boston University group assessed the feasibility of an AID system which combined SC glucose monitoring and both SC insulin and SC glucagon infusions, driven by an MPC algorithm and a PD algorithm, respectively [23]. While glucose was kept for 68% of time in 70–180 mg/dl target range with minimal time spent in hypoglycemia (0.7%) during 51 h, the percent time in target overnight reached 93%. These results suggested a potential additional benefit of glucagon infusion for minimizing hypoglycemia at the cost of a more cumbersome system due to the need of wearing two infusion pumps and changing glucagon solution daily because of its poor physical stability.

In order to further reduce the risk of hypoglycemia while keeping single-hormone (insulin) infusion, the concept of a safety supervising module working in addition to the range control algorithm was brought by the international AP study group [24]. This modular control-to-range algorithm was assessed during 22-h admissions in two randomized control studies versus CSII, showing its ability to keep glucose between 70 and 180 mg/dl for 97% of time and between 80 and 140 mg/dl for 77% of time with a reduction by 2.7-fold of time spent below 70 mg/dl and reduced overnight glucose variability [25]. Moreover, these investigations reported for the first time the ability of closed-loop control to reduce significantly mean blood glucose level without increasing hypoglycemia in hospital-setting.

The safety of closed-loop systems for glucose control at night-time was further confirmed by the DREAM group which used an MD-Logic algorithm based on fuzzy logic design, i.e., on the estimated risks of hyper-or hypoglycemia according to physician and patient experiences without any pre-established equations linking glucose level to insulin delivery [26]. This algorithm was run on a laptop which received inputs from continuous SC glucose sensing and sent outputs to a SC insulin infusion pump. Children hosted in diabetes camps showed reduced occurrence of hypoglycemic events and time spent in hypoglycemia overnight when using the AID system compared to CSII during two nights submitted to each option in randomized order.

Beside extending the study period over 24 h, the EU-funded 'AP at home' consortium randomly assessed in 48 adult T1D patients two MPC algorithms compared to

patient use of a sensor-augmented pump (SAP) about their ability to keep blood glucose in 70–180 mg/dl range [27]. While time in target range was similar with the two AID options and SAP (close to 60% over 24 h), the AID systems appeared as safer since % time spent with blood glucose below 70 mg/dl was 2 and 2.1% vs. 6.4% with SAP. From this demonstrated and confirmed safety of various closed-loop systems, a move to experiments in a less controlled environment was considered. These so-called transitional trials aimed at demonstrating the feasibility, the safety and the efficacy of closed-loop systems in home-like conditions. A key-element of feasibility was the availability of a wearable platform able to run the control algorithm and to offer an easy-to-understand interface to the patient that allows monitoring of AID functioning.

Assessment of closed-loop systems in home-like setting

Following the DREAM study mentioned above, several studies have been performed in diabetes camps, mostly in children and adolescents with T1D in order to assess the safety and the efficacy of closed-loop systems while the patients were hosted in a less protected environment than in a Clinical Research Centre. Closed loop was active either overnight only or day and night during periods of 5–6 days. Systems with insulin use only showed similar percent time in target range under closed-loop vs. SAP overnight [28] or vs. SAP with threshold low glucose suspend during day and night [29]. A bi-hormonal system (insulin and glucagon) showed lower mean sensor glucose and percent time with glucose below 60 or 70 mg/dl when compared to patient use of an insulin pump [30].

The first report of 'true' outpatient AP use was published by the Universities of Montpellier and Padova after a patient at each site had spent 28 h in near free-life conditions (sleeping in a hotel, taking meals in restaurants, walking in town…) with glucose control obtained from a wearable closed-loop system in which CGM device and insulin pump were connected to the Diabetes Assistant (DiAs) device, based on a smartphone hosting a patient interface and running an MPC algorithm [31]. This pilot outpatient study was extended to more numerous patients and confirmed the feasibility of outpatient closed-loop although still limited to 28 h [32]. Hence, the first outpatient randomized control trial testing overnight closed-loop control vs. SAP during 40 h was performed and showed reduced risk and occurrence of hypoglycemia with the closed-loop system [33]. Using a similar system also based on DiAs wearable platform compared to SAP during the dinner and overnight time frame, two studies reported increased percent time in target range (70–180 mg/dl) with combined reductions of percent time below and above this range under closed-loop control [34] and reduced fasting blood glucose level [35]

Home studies with AID systems

Overnight use for 6 weeks at home in adults and adolescents has been initially assessed in a randomized crossover study against SAP by Nimri et al. who reported a significant reduction of percent time with glucose below 70 mg/dl and an increased percent time in the glucose target range of 70–180 mg/dl [36]. Improved percent time in 70–180 mg/dl glucose range was confirmed with an overnight use of AP for 4 weeks in a multicenter study reported by Thabit et al. [37]. The 'AP at home' consortium assessed closed-loop control by a wearable AID system including the DiAs platform during dinner and nighttime vs. SAP during 2 months and reported a significant increase of percent time in 70–180 mg/dl glucose range associated with combined reductions of percent time spent below and above this range [38]. Moreover, this study showed for the first time a reduction of HbA1c with prolonged use of closed-loop in free life. Interestingly, glucose control on day and night was also significantly improved although closed-loop was not active during daytime. A one-month extension of this study with 24-h active closed-loop showed a further benefit on glucose variability [39]. Meanwhile, a multicenter prospective trial including sequential 2-week periods with SAP, followed by overnight AP and then full-day AP reported similar improvements vs. SAP when AP was active [40]. Moving from overnight to 24-h AP only further reduced time spent below 70 mg/dl during day and night. This observation points to the limits of the hybrid AID option in which meal management is close to that of a patient using a simpler bolus calculator. Hence improving glucose control during day-time by closed-loop vs. SAP is difficult to achieve. An extension of this trial investigated 24/7 closed-loop use up to 6 months and reported the sustained improvement of median time in target glucose range which was 77% against 66% at baseline [41]. Median time spent below 3.9 mmol/l remained significantly lower at 1.3% vs. 4.1% at baseline. Mean HbA1c levels moved from 7.2 to 7.0%, with a significant relationship between use of closed-loop mode and improvement of HbA1c level. Interestingly, glucose control was similar day and night although the patients perceived the benefit mainly at night-time. This study extension showed the feasibility of long-term closed-loop use. Nevertheless, the patients complained about the cumbersome wearable devices in everyday life.

Another long outpatient AID experience was reported for 12 weeks in adult, children and adolescents [42]. In this study, closed-loop was active day and night in adults and overnight only in children and adolescents, and randomly compared to SAP according to a crossover design. Percent of

Fig. 2 Currently available closed-loop systems for routine care. **a** The Medtronic MiniMed 780G system, combining a MiniMed 780G insulin pump with embedded SmartGuard algorithm and the connected Enlite glucose sensor and transmitter, **b** the Tandem Control-IQ system, combining the Tandem t:slim X2 insulin pump hosting the Control-IQ algorithm and the Dexcom G6 glucose sensor and transmitter, **c** the CamAPS FX application, hosted in an Android smartphone which receives Dexcom G6 glucose sensor and transmitter signal and tunes insulin infusion from a Dana insulin pump, **d** the Diabeloop DBLG1 system, combining a Kaleido insulin pump, the Dexcom G6 glucose sensor and transmitter et a terminal hosting the algorithm with wireless connection to the Dexcom G6 glucose sensor and the insulin pump and used as patient interface and for data remote transfer

time in the target range (70–180 mg/dl in adults; 70–145 mg/dl in children and adolescents) while using AP was significantly higher both in the adults study: 67.7% vs. 56.8%, and in the children/adolescents study: 59.7 vs. 34.4%. Similarly to previous studies, the improvement of glucose control by closed-loop was mostly due to tighter control during the night-time period.

Availability of AID systems for daily care of T1D

At the EASD meeting in September 2016, the results of a 3-month prospective 24/7 closed-loop study involving 124 patients were presented [43]. While the patients used the Medtronic MiniMed 670G (Medtronic Diabetes, Northridge, CA, USA) system, including an insulin pump with embedded control algorithm wirelessly connected to a CGM, with a median percent time of 87.2 in closed-loop mode, sensor glucose moved from 66.7 at baseline to 72.2% for the 3 months in the 70–180 mg/dl target range and mean HbA1c level decreased from 7.4 to 6.9%. Over 12 389 patient-days, no episodes of severe hypoglycemia or ketoacidosis were observed. These robust safety data led to the FDA approval of this system for clinical use in the therapy of T1D, which represents a milestone in the development of closed-loop insulin delivery. The detailed results of this study were reported a few months later [44].

Following this first approved AID system for routine care of T1D, the next step was to get a similar validation of other developed AID systems (Fig. 2). To reach this goal, the US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded 4 research programs by early 2017 aiming at the collection of data necessary to bring AID technology to T1D patients. Besides, other AID systems have been developed by industry [45], start-ups [46, 47] and academic centers worldwide [48].

The follow-up of users of the Medtronic 670G system in routine care was the first one to be reported. While a significant correlation was found between the use of the automated (Auto) mode and HbA1c levels, it appeared that many patients stopped using the Auto Mode with time: 28% after 3 months, 34% after 6 months, 35% at 9 months and 33% at 1 year [49]. Reasons for stopping the utilization of the Auto Mode included sensor issues in 62%, problems obtaining supplies in 12%, hypoglycemia fear in 12%, multiple daily injection preference in 8%, and sports in 8%. A more recently reported study investigated the glucose control in

the patients who went on using the 670G system for 1 year and the patient-reported outcomes (PROs) through questionnaires [50]. Mean percent time in target range (70–180 mg/dL) was 66% at baseline, and 74% and 68% at 6 and 12 months, respectively, for those who completed their CGM data. Related to PROs, fear of hypoglycemia decreased by 6 and 11 points, respectively, from baseline to 12 months. More than half of the patients reported issues with sleep interruption at night due to alarms, and 40% did not like frequent exits from Auto Mode.

Due to the observed and perceived limitations of the 670G system, Medtronic launched an advanced hybrid closed-loop (AHCL) system with automated basal (Auto Basal) and automated bolus correction (Auto Correction) which has been commercialized as the Medtronic 780G system. This AHCL system was first compared to sensor-augmented pump therapy with predictive low glucose in a dual-center, randomized, open-label, two-sequence crossover study in AID–naive participants with T1D (aged 7–80 years) including two study phases of 4 weeks. Auto Mode was active 96.4% of the time during AHCL study phase. TIR was superior by 12.5%, while TBR was significantly reduced with AHCL with a higher improvement when AHCL target was set at 100 mg/dl vs. 120 mg/dl [51]. A second reported investigation of this AID system showed that time spent in closed loop averaged 94.9% ± 5.4% and involved only 1.2 ± 0.8 exits per week. Compared with sensor-augmented pump ± predictive low glucose management or Auto Basal, AHCL reduced HbA1c levels from 7.5% ± 0.8% to 7.0% ± 0.5%, TIR increased from 68.8% ± 10.5% to 74.5% ± 6.9%, and TBR reduced from 3.3% ± 2.9% to 2.3% ± 1.7%. The 100 mg/dL target for closed-loop control increased TIR to 75.4%, which was further optimized at a lower active insulin time of 2 h, without increasing TBR. There were no severe hypoglycemic or diabetic ketoacidosis events during the study phase [52]. In a randomized, open-label, two-period crossover trial comparing the AHCL system to the Medtronic 670G system (HCL) over two 12-week periods of closed-loop use, glucose monitoring satisfaction subscales for emotional burden and behavioral burden improved significantly over time with use of AHCL versus HCL and co-occurred with glycemic improvements with a reduced percent time above 180 mg/dL during the day and no change in % time less than 54 mg/dL across 24 h [53], and greater time in Auto Mode. [54].

The second AID system which became widely available for routine care of T1D was the system based upon a Tandem t:slim X2 insulin pump (Tandem, San Diego, CA, USA) hosting the Control-IQ algorithm connected to the Dexcom G6 CGM (Dexcom, San Diego, CA, USA). A pivotal 6-month randomized, multicenter trial comparing this AID system to a sensor-augmented pump showed a mean adjusted difference of 11 percentage points of TIR favoring the AID system [55]. TBR and HbA1c levels were also significantly better with the AID system. A pre-specified sub-analysis of outcomes in adolescents and young adults aged 14–24 years old who participated in this trial showed improved TIR and reduced hypoglycemia [56]. PROs which were assessed during this trial showed a significantly improved Hypoglycemia Fear Survey Behavior subscale with the AID system, while the participants using it reported high benefit and low burden with closed-loop control [57]. During an extension of this study, the participants who used the Control-IQ AID system during the study were randomized to go on with it or switch to a predictive low glucose suspend algorithm (PLGS, Basal-IQ) hosted by the same insulin pump and connected to the same CGM [58]. Switching to PLGS reduced TIR and increased HbA1c toward the pre-closed-loop control values, while hypoglycemia remained similarly reduced with both algorithms. After the Control-IQ AID system had been launched for routine care, a retrospective one-year real-world analysis of its use showed the same glycemic improvements as in the randomized controlled trial in a broad age range of people with different types of diabetes [59].

Interestingly, the Control-IQ AID system has been similarly investigated in T1D children aged 6–13 years in a 16-week, multicenter, randomized, open-label, parallel-group trial. Compared to a SAP, a mean adjusted difference of 11 percentage points favoring the AID system was reported. The median percentage of time that the system was in the closed-loop mode was 93% [60]. An extended 12-week use of the AID system showed the sustainability of the improvement of glucose control [61]. The Control-IQ AID system was also investigated to assess its safety and efficacy while used 24/7 versus only evening and night (E/N) for 18 weeks, and on extended 24/7 use for 18 more weeks, in free-living children with type 1 diabetes aged 6–12 years. AID was active 94.1% and 51.1% of the time in the 24/7 and E/N modes, respectively. TIR from baseline increased more in the 24/7 versus the E/N mode: + 14.4% vs. + 9.6%. Mean percentage TBR was similarly reduced, from 4.2% and 4.6% to 2.7%. TIR increased through the whole range of baseline levels and always more with 24/7 use. The results were maintained during the extension phase in those initially on 24/7 use and improved in those with initial E/N use up to those with 24/7 use [62].

The closed-loop algorithm developed by the University of Cambridge (Cambridge, UK) has also been investigated in view of reaching a commercially available AID system. In a first open-label, randomized, crossover study, the FlorenceD2A closed-loop system using this algorithm was compared to usual pump therapy for 4-week periods in free-living adults with well controlled T1D [63]. TIR was 10.5 percentage points higher during closed-loop delivery compared with usual pump therapy, while TBR was reduced by 65% and time below 2.8 mmol/l by 76%. No episodes of serious hypoglycemia or other serious adverse

events occurred. The Cambridge MPC algorithm was then investigated while hosted in a smartphone and using a modified Medtronic 640G pump connected to an Enlite 3 glucose sensor [64]. In an open-label, multicenter, multinational, single-period, parallel randomized controlled trial, including adults and children above 6 years of age, the closed-loop system was compared to a SAP therapy in T1D patients with suboptimal control for 12 weeks. TIR was significantly higher in the closed-loop group with a mean difference in change 10.8 percentage points. Reductions in HbA1c percentages were significantly greater in the closed-loop group compared with the control group with a mean difference in change of 0.36%. The time spent with glucose concentrations below 3.9 mmol/l and above 10.0 mmol/l was shorter in the closed-loop group than in the control group.

Moreover, the Cambridge algorithm was shown to be safe and effective in very young children aged 1–7 years [65]. In a recently reported multicenter, randomized, crossover trial, including T1D children 1 to 7 years of age, the closed-loop system was compared with SAP therapy in two 16-week periods [66]. The TIR was 8.7 percentage points higher during the closed-loop period than during the control period. The mean adjusted difference in the percentage of time spent in a hyperglycemic state was -8.5 percentage points and the difference in the HbA1c level was -0.4 percentage points with the closed-loop, while the time spent in hypoglycemia was similar with the two treatments.

The cumulated investigational data using the Cambridge MPC algorithm led to the CamAPS FX (CamDiab, Cambridge, U.K.) hybrid closed-loop app hosting the algorithm on an Android smartphone. It is approved in the European Union for use in children ≥ 1 year and adults (including during pregnancy) with T1D. The interoperable CamAPS FX app receives glucose data from Dexcom G6 CGM and connects to the Dana Diabecare RS and DANA-I Sooil (Sooil, Seoul, South Korea) insulin pump to direct glucose-responsive insulin delivery every 8–12 min, includes a bolus calculator allowing discrete bolusing, and streams data in real time to cloud-based diabetes data repositories (Diasend/Glooko, Gothenburg, Sweden). A recent public announcement declared that CamAPS FX app is expected to be used either with the Dexcom G6 CGM or the FreeStyle Libre 3 CGM (Abbott Diabetes Care, Alameda, CA, USA) and the mylife Ypsomed insulin pump (Ypsomed, Liederbach, Germany).

The Diabeloop closed-loop system DBLG1 (Diabeloop, Grenoble, France) is the fourth AID system currently available in Europe. The DBLG1 system, which combines an algorithm based on machine-learning within a physiological framework with an expert system and self-learning algorithms, is a hybrid closed-loop device that requires the patient to record carbohydrate intake semi-quantitatively, and intensity and duration of planned physical activities. The used CGM is the Dexcom G6 which sends the glucose signal to a hand-held terminal which hosts the control algorithm. This algorithm controls a Kaleido insulin pump (ViCentra, Utrecht, Netherlands) that replaces the initially selected Cellnovo pump [67]. In a multicenter, open-label, randomized, crossover trial, over two periods of 12 weeks comparing the DBLG1 system to a SAP therapy, TIR was significantly higher in the DBLG1 group with a mean difference of 9.2%, while TBR was significantly lower than with the sensor-assisted pump with a mean difference of –2.4%. A post hoc analysis of this trial investigated the efficacy of the DBLG1 system in controlling the hypoglycemia induced by physical activity in real-life conditions. TBR was not significantly different between days with and without physical activity, regardless of its intensity or duration [68]. In a study where patients were exposed to real-life challenging situations (gastronomic dinners or sustained physical exercise), time spent overnight in the tight range of 4.4 to 7.8 mmol/l was longer with the DBLG1 compared to an open-loop, while time spent during the day in the range of 3.9–10.0 mmol/l was also longer [69]. In a real-life setting enrolling 25 T1D patients, at 6-month follow-up, the mean HbA1c decreased from 7.9 to 7.1% and TIR 70–180 mg/dl increased from 53 to 69.7%, while TBR decreased from 2.4 to 1.3%, and time < 54 mg/dl decreased from 0.32 to 0.24%. No serious adverse event was reported during the study [70]. Of note, the Diabeloop algorithm has been recently used with the AccuChek Insight insulin pump (Roche Diabetes Care, Mannheim, Germany) and the Dexcom G6 CGM with similar performance on glucose control in free life in close to 1000 patients.

Perspectives

The last decade has shown dramatic advances in the performance of clinical trials with AID systems which clearly document the feasibility of this mode of therapy for patients with T1D in real-world conditions, its ability to improve time spent in close-to-normal glucose range with a reduction of risk of hypoglycemia and a predominant efficacy for glucose control at night. Systematic reviews tell that outpatients using AID systems spend 60–70% of time in a glucose range of 70–180 mg/dl [71, 72]. These results were obtained in rather selected patients who presented an average HbA1c level between 7 and 8%, were compliant to care and were not prone to harmful glucose deviations (ketoacidosis or severe hypoglycemia). Nevertheless, recently reported experiences with AID systems in real-world for periods up to one year in numerous less selected patients show in most cases sustained benefits close to those obtained in clinical trials.

Expected improvements of AID systems include a move toward full-closed-loop systems that will not need meal

announcements and systems with more discrete appearance. Reported trials with faster-acting insulin analogues did not show any significant improvements in glucose control [73, 74]. Fully automated AID system with automatic prandial dosing have shown safety and feasibility and some benefits on glucose control in case of omission of meal announcement [75]. The recently reported clinical trial of Omnipod 5 system which includes the Omnipod tubeless insulin pump (Insulet Corporation, Acton, MA, USA) has shown in a single-arm, multicenter, prospective study improvements in HbA1c levels, TIR and TBR in adults and children [76].

The recent availability of stable glucagon (Xeris Pharmaceuticals, Chicago, IL, USA) and dasiglucagon (Zealand Pharma, Søborg, Denmark) formulations in solution is expected to renew the feasibility of dual-hormone closed-loop initiatives although demonstration of the safety of long-term infusion of these glucagon formulations will be needed.

A recent editorial points to the need of more physiological insulin delivery in order to avoid peripheral hyperinsulinism which may increase macrovascular complications. An insulin supply that is physiologically available to the hepatoportal circulation before release at lower levels into the peripheral circulation could fulfill this goal [77]. A non-randomized experience of sequential full-closed-loop trials using a MPC algorithm performed in hospital in the same patients using SC insulin delivery and IP insulin infusion through a DiaPort system (Roche Diabetes Care, Mannheim, Germany) has reported the significant improvement of TIR with IP insulin associated with significantly lower post-meal glucose excursions [78].

The move toward tubeless insulin pumps, fully automated systems with no need of meal announcements and possible implanted AID systems could fulfill patient requests of more convenient systems in daily life than the currently available portable systems [79]. Indeed, in contrast to the improved glucose control associated with AID use, technical difficulties, intrusiveness of alarms, and size of equipment have been reported by the patients who have been using AID systems as key negative aspects of this technology.

Ultimately, technology should allow moving from external devices to implantable 'artificial beta cells' comprising long-term implantable glucose sensors and implanted insulin pumps using the more physiological intra-peritoneal or intra-portal routes. Hence artificial organ option will compete with cell therapy as two different modes of cure for T1D.

Declarations

Conflict of interest The author reports serving on advisory boards for Abbott, Dexcom Inc, Insulet, Sanofi, Roche Diabetes Care, Novo Nordisk and Eli Lilly, and received research support from Dexcom Inc and Tandem.

Ethical approval Not applicable.

Informed consent Not applicable.

References

1. The Diabetes Control and Complications Trial Research Group (DCCT). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329:977–986
2. Nathan DM and for the DCCT/EDIC Research Group (2014) The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care 37:9–16
3. The DCCT Research Group (1991) Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 90:450–459
4. Ruan Y, Thabit H, Leelarathna L, Hartnell S, Willinska ME, Dellweg S et al (2016) Variability of insulin requirements over 12 weeks of closed-loop insulin delivery in adults with type 1 diabetes. Diabetes Care 39:830–832
5. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA et al (2019) State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. Diabetes Technol Ther 21:66–72
6. Renard E, Ikegami H, Daher Vianna AG, Pozzilli P, Brette S, Bosnyak Z et al (2021) The SAGE study: global observational analysis of glycaemic control, hypoglycaemia and diabetes management in T1DM. Diabetes Metab Res Rev 37:e3430
7. Cobelli C, Renard E, Kovatchev B (2011) Artificial pancreas: past, present, future. Diabetes 60:2672–2682
8. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W (1974) An artificial endocrine pancreas. Diabetes 23:389–396
9. Mirouze J, Selam JL, Pham TC, Cavadore D (1977) Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. Diabetologia 13:273–278
10. Shichiri M, Kawamori R, Yamasaki Y, Inoue M, Shigeta Y, Abe H (1978) Computer algorithm for the artificial pancreatic beta cell. Artif Organs 2(Suppl):247–250
11. Clemens AH, Chang PH, Myers RW. The development of Biostator, a glucose-controlled insulin infusion system (GCIIS). Horm Metab Res. 1977; Supplement: 23–33
12. Mastrototaro J (2000) The minimed continuous glucose monitoring system. Diabetes Technol Ther 2(Supplement 1):S13–S18
13. Kovatchev BP, Breton MD, Dalla Man C, Cobelli C (2009) In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol 3:44–55
14. Renard E (2002) Implantable closed loop glucose-sensing and insulin delivery: the future for insulin pump therapy. Curr Opin Pharmacol 2:708–716
15. Renard E, Costalat G, Chevassus H, Bringer J (2006) Artificial beta cell: clinical experience toward an implantable closed-loop insulin delivery system. Diabetes Metab 32:497–502
16. Renard E, Place J, Cantwell M, Chevassus H, Palerm CC (2010) Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery: feasibility study testing a new model for the artificial pancreas. Diabetes Care 33:121–127
17. Hovorka R, Chassin LJ, Wilinska ME, Canonico V, Akwi JA, Federici MO et al (2004) Closing the loop: the ADICOL experience. Diabetes Technol Ther 6:307–318

18. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF (2006) Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 55:3344–3350
19. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV (2008) Fully automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 31:934–939
20. Doyle FJ 3rd, Huyett LM, Lee JB, Zisser HC, Dassau E (2014) Closed-loop artificial pancreas systems: engineering the algorithms. Diabetes Care 37:1191–1197
21. Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D et al (2010) Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. The Lancet 375:743–751
22. Kovatchev B, Cobelli C, Renard E, Anderson S, Breton M, Patek S et al (2010) Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. J Diabetes Sci Technol 4:1374–1381
23. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER (2012) Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Diabetes Care 35:2148–2155
24. Patek SD, Magni L, Dassau E, Karvetski C, Toffanin C, De Nicolao G et al (2012) Modular closed-loop control of diabetes. IEEE Trans Biomedical Eng 29:2986–3000
25. Breton M, Farret A, Bruttomesso D, Anderson S, Magni L, Patek S et al (2012) Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes 61:2230–2237
26. Phillip M, Battelino T, Atlas E, Kordonouri O, Bratina N, Miller S et al (2013) Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 368:824–833
27. Luijf YM, Devries JH, Zwinderman K, Leelarathna L, Nodale M, Caldwell K et al (2013) Day and night closed-loop control in adults with type 1 diabetes mellitus: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. Diabetes Care 36:3882–3887
28. Ly TT, Breton MD, Keith-Hynes P, De Salvo D, Clinton P, Benassi K et al (2014) Overnight glucose control win automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes Care 37:2310–2316
29. Ly TT, Roy A, Grosman D, Shin J, Campbell A, Monirabbasi S et al (2015) Day and night closed-loop control using the integrated Medtronic hybrid closed-loop system in type 1 diabetes at diabetes camp. Diabetes Care 38:1205–1211
30. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG et al (2014) Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 371:313–325
31. Cobelli C, Renard E, Kovatchev BP, Keith-Hynes P, Ben Brahim N, Place J et al (2012) Pilot studies of wearable outpatient artificial pancreas in type 1 diabetes. Diabetes Care 35:e65–e67
32. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM et al (2013) Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 36:1851–1858
33. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM et al (2014) Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 37:1789–1796
34. Del Favero S, Place J, Kropff J, Keith-Hynes P, Visentin R, Monaro M et al (2015) Multicenter outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using modular model predictive control in adults with type 1 diabetes. Diabetes Obes Metab 17:468–476
35. Brown SA, Kovatchev BP, Breton MD, Anderson SM, Keith-Hynes P, Patek SD et al (2015) Multinight « bedside » closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther 17:203–209
36. Nimri R, Muller I, Atlas E, Miller S, Fogel A, Bratina N et al (2014) MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 37:3025–3032
37. Thabit H, Lubina-Solomon A, Stadler M, Leelarathna L, Walkinshaw E, Pernet A et al (2014) Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. Lancet Diabetes Endocrinol 2:701–709
38. Kropff J, Del Favero S, Place J, Toffanin C, Visentin R, Monaro M et al (2015) 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 3:939–947
39. Renard E, Farret A, Kropff J, Bruttomesso D, Messori M, Place J et al (2016) 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. Diabetes Care 39:1151–1160
40. Anderson SM, Raghinaru D, Pinsker JE, Boscari F, Renard E, Buckingham BA et al (2016) Multinational home use of closed-loop control is safe and effective. Diabetes Care 39:1143–1150
41. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME et al (2015) Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 373:2129–2140
42. Kovatchev B, Cheng P, Anderson SM, Pinsker JE, Boscari F, Buckingham BA et al (2017) Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. Diabetes Technol Ther 19:18–24
43. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV et al (2016) Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 316:1407–1408
44. Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS et al (2017) Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 19:155–163
45. Buckingham BA, Forlenza GP, Pinsker JE, Christiansen MP, Wadwa RP, Schneider J et al (2018) Safety and feasibility of the omnipod hybrid closed-loop system in adult, adolescent, and pediatric patients with type 1 diabetes using a personalized model predictive control algorithm. Diabetes Technol Ther 20:257–262
46. Benhamou PY, Huneker E, Franc S, Doron M, Charpentier G (2018) Customization of home closed-loop insulin delivery in adult patients with type 1 diabetes, assisted with structured remote monitoring: the pilot WP7 Diabeloop study. Acta Diabetol 55(6):549–556. https://doi.org/10.1007/s00592-018-1123-1
47. Blauw H, van Bon AC, Koops R, DeVries JH (2016) Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. Diabetes Obes Metabol 18(7):671–677. https://doi.org/10.1111/dom.12663
48. Abitbol A, Rabasa-Lhoret R, Messier V, Legault L, Smaoui M, Cohen N et al (2018) Overnight glucose control with dual- and single-hormone artificial pancreas in type 1 diabetes with hypoglycemia unawareness: a randomized controlled trial. Diabetes Technol Ther 20:189–196
49. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM (2019) One year clinical experience of the first commercial hybrid closed-loop system. Diabetes Care 42:2190–2196

50. DuBose SN, Bauza C, Verdejo A, Beck RW, Bergenstal RM, Sherr J (2021) Real-world, patient-reported and clinic data from individuals with type 1 diabetes using the minimed 670g hybrid closed-loop system. Diabetes Technol Ther 23:791–798
51. Collyns OJ, Meier RA, Betts ZL, Chan DSH, Frampton C, Frewen CM et al (2021) Improved glycemic outcomes with medtronic minimed advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care 44:969–975
52. Carlson AL, Sherr JL, Shulman DI, Garg SK, Pop-Busui R, Bode BW, et al. Safety and glycemic outcomes during the minimed™ advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2021 Nov 16 Online ahead of print
53. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D et al (2021) A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet 397:208–219
54. Hood KK, Laffel LM, Danne T, Nimri R, Weinzimer SA, Sibayan J et al (2021) Lived experience of advanced hybrid closed-loop versus hybrid closed-loop: patient-reported outcomes and perspectives. Diabetes Technol Ther 23:857–861
55. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC et al (2019) Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 381:1707–1717
56. Isganaitis E, Raghinaru D, Ambler-Osborn L, Pinsker JE, Buckingham BA, Wadwa RP et al (2021) closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial. Diabetes Technol Ther 23:342–349
57. Kudva YC, Laffel LM, Brown SA, Raghinaru D, Pinsker JE, Ekhlaspour L et al (2021) Patient-reported outcomes in a randomized trial of closed-loop control: the pivotal international diabetes closed-loop trial. Diabetes Technol Ther 23:673–683
58. Brown SA, Beck RW, Raghinaru D, Buckingham BA, Laffel LM, Wadwa RP et al (2020) glycemic outcomes of use of CLC versus plgs in type 1 diabetes: a randomized controlled trial. Diabetes Care 43:1822–1828
59. Breton MD, Kovatchev BP (2021) One year real-world use of the control-iq advanced hybrid closed-loop technology. Diabetes Technol Ther 23:601–608
60. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L, Forlenza GP, Cengiz E et al (2020) A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med 383:836–845
61. Kanapka LG, Wadwa RP, Breton MD, Ruedy KJ, Ekhlaspour L, Forlenza GP et al (2021) extended use of the control-IQ closed-loop control system in children with type 1 diabetes. Diabetes Care 44:473–478
62. Renard E, Tubiana-Rufi N, Bonnemaison E, Coutant R, Dalla-Vale F, Bismuth E (2021) Outcomes of hybrid closed-loop insulin delivery activated 24/7 versus evening and night in free-living prepubertal children with type 1 diabetes: A multicentre, randomized clinical trial. Obes Metabol 24(3):511–521. https://doi.org/10.1111/dom.14605
63. Bally L, Thabit H, Kojzar H, Mader JK, Qerimi-Hyseni J, Hartnell S et al (2017) Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 5:261–270
64. Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME et al (2018) Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 392:1321–1329
65. Tauschmann M, Allen JM, Nagl K, Fritsch M, Yong J, Metcalfe E et al (2019) Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multicenter, 3-week. Random Trial Diabete Care 42:594–600
66. Ware J, Allen JM, Boughton CK, Wilinska ME, Hartnell S, Thankamony A et al (2022) Randomized trial of closed-loop control in very young children with type 1 diabetes. N Engl J Med 386:209–219
67. Benhamou PY, Franc S, Reznik Y, Thivolet C, Schaepelynck P, Renard E et al (2019) Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. Lancet Digit Health 1:e17–e25
68. Franc S, Benhamou PY, Borot S, Chaillous L, Delemer B, Doron M et al (2021) No more hypoglycaemia on days with physical activity and unrestricted diet when using a closed-loop system for 12 weeks: a post hoc secondary analysis of the multicentre, randomized controlled diabeloop WP7 trial. Diabetes Obes Metab 23:2170–2176
69. Hanaire H, Franc S, Borot S, Penfornis A, Benhamou PY, Schaepelynck P et al (2020) Efficacy of the diabeloop closed-loop system to improve glycaemic control in patients with type 1 diabetes exposed to gastronomic dinners or to sustained physical exercise. Diabetes Obes Metab 22:324–334
70. Amadou C, Franc S, Benhamou PY, Lablanche S, Huneker E, Charpentier G et al (2021) Diabeloop DBLG1 closed-loop system enables patients with type 1 diabetes to significantly improve their glycemic control in real-life situations without serious adverse events: 6-month follow-up. Diabetes Care 44:844–846
71. Thabit H, Hovorka R (2016) Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 59:1795–1805
72. Bekiari E, Kitsios K, Thabit H, Tauschmann M, Athanasiadou E, Karagiannis T et al (2018) Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 361:k1310
73. Bode B, Carlson A, Liu R, Hardy T, Bergenstal R, Boyd J et al (2021) Ultrarapid lispro demonstrates similar time in target range to lispro with a hybrid closed-loop system. Diabetes Technol Ther 23:828–836
74. Boughton CK, Hartnell S, Thabit H, Poettler T, Herzig D, Wilinska ME et al (2021) Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: a double-blind, multicentre, multinational, randomized, crossover study. Diabetes Obes Metab 23:1389–1396
75. Garcia-Tirado J, Diaz JL, Esquivel-Zuniga R, Koravi CLK, Corbett JP, Dawson M, et al. Advanced Closed-Loop Control System Improves Postprandial Glycemic Control Compared With a Hybrid Closed-Loop System Following Unannounced Meal. Diabetes Care. 2021; dc210932. Online ahead of print.
76. Brown SA, Forlenza GP, Bode BW, Pinsker JE, Levy CJ, Criego AB et al (2021) Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes. Diabetes Care 44:1630–1640
77. Levitsky LL (2022) Reducing Caretaker Burden, Protecting Young Brains and Bodies. N Engl J Med 386:285–286
78. Dassau E, Renard E, Place J, Farret A, Pelletier MJ, Lee J et al (2017) Intraperitoneal insulin delivery provides superior glycaemic regulation to subcutaneous insulin delivery in model predictive control-based fully-automated artificial pancreas in patients with type 1 diabetes: a pilot study. Diabetes Obes Metab 19:1698–1705
79. Barnard KD, Wysocki T, Thabit H, Evans ML, Amiel S, Heller S, Young A, Hovorka R (2015) Psychosocial aspects of closed- and open-loop insulin delivery: closing the loop in adults with Type 1

diabetes in the home setting. Diabet Med 32(5):601–608. https://doi.org/10.1111/dme.12706