Bringing closed-loop home: recent advances in closed-loop insulin delivery

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Purpose of review
To highlight the recent advances in closed-loop research, the development and progress towards utilizing closed loop outside of the clinical research setting and at patients’ homes.

Recent findings
In spite of the modern insulin therapy in type 1 diabetes, hypoglycaemia is still a major limiting factor. This often leads to suboptimal glycaemic control and risk of diabetes complications. Closed loop has been shown to improve glycaemic control whilst avoiding hypoglycaemia. Incremental progress has been made in this field, from the use of automated systems and bihormonal closed-loop systems in clinical research facility settings under close supervision to the use of ambulatory closed-loop prototype at patients’ homes in free-living conditions. Different population of patients with type 1 diabetes and control algorithm approaches have been studied, assessing the efficacy and safety. Transitional and home studies present different challenges at achieving better glycaemic outcome with closed loop. Improved glucose sensor reliability may accelerate the clinical use and faster insulin analogues increase the clinical utility.

Summary
Results and experience with closed-loop insulin delivery have been encouraging, leading the way for future improvements and development in the field, to make closed loop suitable for use in clinical practice.

Keywords
algorithm, ambulatory, automated, closed-loop, home studies

INTRODUCTION
The ultimate goal of diabetes therapy is to maintain normoglycaemia and avoid diabetes-related complications. Glycaemic control with insulin therapy in type 1 diabetes is influenced by insulin-dependent factors such as insulin kinetics, dosage and timing of insulin delivery [1,2], as well as physiological factors, such as effects of circadian rhythm and illness on insulin sensitivity [3–6]. Unfortunately, one of the known risks of tightening glycaemic control with insulin is hypoglycaemia [7]. The complexities of managing insulin therapy in daily life can, therefore, be overwhelming for some patients with type 1 diabetes, resulting in suboptimal control. Utilization of real-time continuous glucose monitoring (CGM) and modern continuous subcutaneous insulin infusion (CSII) therapy has been reported to improve the overall glycaemic control [8,9,10]. However, studies have shown that the benefits of these devices are limited to certain age groups and those who are motivated [11–13]. Closed-loop insulin delivery, also known as the artificial pancreas, may potentially be beneficial in improving the glycaemic control in type 1 diabetes, until a biological cure can be found.

Closed-loop systems deliver insulin in a continued glucose-responsive manner by coupling subcutaneous CGM and subcutaneous insulin pump delivery [14]. This novel approach differs from the conventional pump therapy by the use of a control algorithm, which autonomously directs insulin delivery based on real-time sensor glucose levels. Significant advances have been made in this field over the last 2 years. Closed-loop systems have progressed from manual input, in which researchers...
KEY POINTS

- Hypoglycaemia remains a significant risk of conventional insulin therapy in type 1 diabetes.
- Closed-loop system utilizes a control algorithm that directs insulin delivery in a glucose-responsive manner by coupling continuous glucose monitoring with insulin pump delivery.
- In controlled research facility settings, closed-loop systems are superior to conventional insulin pump therapy at improving the glycaemic control, whilst reducing the risk of hypoglycaemia.
- Closed-loop use outside of hospital settings is feasible, demonstrating safety and usability in transitional studies.
- Home studies are currently underway to assess closed-loop safety and performance during longer periods of unregulated daily activities.

provide manual data input to the algorithm [15,16*,17], to automated systems as early prototypes or aimed for home use [18,19**,20,21**]. Control algorithms and sensor glucose performance can be tested in in-silico environments, accelerating progression to clinical studies and avoiding the need for preclinical animal testing [22,23]. Presently, several technological, pharmacological and physiological hurdles still remain. Amongst them are the delayed pharmacokinetics of current rapid-acting insulin analogues to reach its maximum glucose-lowering capacity [24], the occasional large glucose-sensing errors caused by incorrect calibration or sensor drift [25*], and to a minor extent the physiological time lag between plasma and interstitial glucose levels because of the transport of glucose from blood to the interstitial fluid, which may contribute to sensor deviation and inaccuracy [26].

Initial closed-loop studies performed under close supervision in clinical research facilities (CRFs) are ‘proof of concept’ studies, assessing the safety and efficacy. More recently, ‘transitional’ studies have brought closed loop from controlled research environments to out-of-hospital settings, assessing the usability and reliability as well [19**,21**,27**]. Although close monitoring and supervision is still needed in transitional studies, it is nevertheless a first step towards patients using closed loop under free-living conditions, which may eventually lead to closed-loop use in standard clinical practice. Progress is currently underway with longer duration unsupervised closed-loop studies at patients’ homes. This review article highlights the developments and advances made over the last 2 years, as well as the future direction of this field.

STUDIES IN CLINICAL RESEARCH FACILITY

Formative evaluation in CRFs is important to assess the safety and efficacy of closed-loop prototypes in a controlled environment. The following section outlines the recent findings from CRF-based closed-loop studies in the paediatric and adult patients with type 1 diabetes.

Closed-loop studies in the paediatric age group

Children with type 1 diabetes are vulnerable to the adverse effects of neuroglycopenia, an extreme example being hypoglycaemia-related seizures at night [28]. By linking CGM readings to insulin delivery, closed-loop insulin delivery can potentially limit the exposure to overnight hypoglycaemia in this vulnerable group. The first randomized crossover manual closed-loop study in adolescents with type 1 diabetes by our group established that improved blood glucose control with minimal hypoglycaemia was possible using closed loop, compared with conventional pump therapy [29].

Automated closed-loop systems currently demonstrate similar safety and efficacy overnight. In a multicentre study, an automated closed-loop with feedback control algorithm was compared with conventional CSII on two sequential nights [30]. Closed loop significantly increased the time spent in near-normal sensor glucose range (3.5–7.8 mmol/l = 63–140 mg/dl) by more than three-fold. Closed loop also led to significantly less glucose variability overnight ($P < 0.001$). Despite the lower mean overnight glucose levels, no nocturnal hypoglycaemia events occurred during closed loop. In a recent overnight closed-loop study of very young type 1 diabetes children (<7 years old), no difference in time within the target glucose levels was observed [31*]. However, closed loop reduced the time spent overnight with hyperglycaemia ($\geq 16.7 \text{ mmol/l}$ or $300 \text{ mg/dl}$, 0.18 vs. 1.3 h; $P = 0.035$) without causing further hypoglycaemia.

Accuracy and reliability of glucose sensors during closed loop are important [25*,32]. Wearing additional CGM sensors has been considered as a possible mitigation against sensor performance failure. In a recent study, patients wore two CGM sensors during closed loop [20]. A fault detection system evaluated the signal deviations between the two sensors. Larger deviations, which are of particular concern, will prompt the patient to perform a
blood glucose calibration. Compared with conventional CSII, closed-loop systems significantly improved the CGM sensor time in target (3.9–8.0 mmol/l ≤70–144 mg/dl) from 46.7% to 84.5% \((P < 0.0001)\), with less hypoglycaemia \((<3.3 \text{ mmol/l or } 59 \text{ mg/dl, } 0.9 \text{ vs. } 3\% ; P < 0.0001)\). However, the use of the additional sensor did not improve sensor accuracy when compared with the reference plasma glucose.

Exercise is known to cause significant perturbation of glycaemia in type 1 diabetes [33]. A potential benefit of closed-loop systems is to reduce the risk of nocturnal hypoglycaemia following daytime exercise. In a randomized controlled study, the frequency of nocturnal hypoglycaemia following an afternoon exercise (60 min of brisk walk on treadmill) was reduced from eight events during conventional CSII to one during closed loop [34]. A greater portion overnight was also spent with normoglycaemia whilst on closed loop. Currently, however, daytime use of closed-loop systems during meals and exercise remains challenging. A 36-h hybrid closed-loop study was recently performed in adolescents with type 1 diabetes [35]. During the study, prandial insulin bolus was given before main meals, and participants underwent two sessions of moderate unannounced exercise. In comparison with conventional CSII, closed-loop systems increased the time spent in glucose target range by 35% and improved the mean plasma glucose levels. Hypoglycaemia events related to exercise persisted during closed loop (9 vs. 10 occasions). This highlights the limitations faced by the current closed-loop systems in relation to the delay in action of current subcutaneous insulin analogues.

**Closed-loop studies in adults**

As a result of the inherent lag of sensor glucose readings relative to the plasma glucose levels following meals and the delay in insulin analogue absorption and action, immediate postprandial hyperglycaemia and late postprandial hypoglycaemia are amongst the challenges faced by closed loop during mealtimes. Two control algorithm approaches were recently studied, in which information regarding meal composition and times were unannounced to both algorithms, and no premeal insulin boluses were given [36]. The authors reported comparable postprandial glycaemic excursions \((114\pm 28 \text{ vs. } 114 \pm 47 \text{ mg/dl})\), with notable reduction in the risk of hypoglycaemia in one of the study arms using an enhanced control approach \((8 \text{ vs. } 0 \text{ events})\). Although the study number was small \((n = 4)\) and no control arm available, it nevertheless highlights that with further optimization of control algorithms, improved outcomes can be obtained.

Others have evaluated closed-loop performance at achieving different ranges of glucose levels. Utilizing two different control algorithm approaches at preventing extremes of glycaemic excursions, known as control to range (CTR), investigators reported incremental improvements in glycaemic outcomes when an enhanced CTR approach was compared with standard CTR, with decrements in hypoglycaemia risk [37]. Several closed-loop algorithms are currently being studied, but few have been compared to each other. A recent multicentre study compared two model predictive control (MPC) algorithms and conventional CSII with each other in 48 adult patients with type 1 diabetes [17]. Each patient had three 24-h study visits, in which blood glucose was controlled using conventional CSII, an MPC algorithm from the University of Cambridge, and an MPC algorithm resulting from a multinational collaboration (University of Pavia, Italy, and University of Virginia and University of California at Santa Barbara). Although the time spent in target glucose range was comparable in all three study arms, an almost three-fold reduction of the time spent in hypoglycaemia was observed during closed loop. This was achieved by a lower rate of insulin delivery and measured plasma insulin levels in both closed-loop algorithms. The glycaemic outcomes between the two MPC algorithms were comparable, with less insulin delivered by the Cambridge algorithm. However, sensor overreading during the study necessitated appropriate adjustments to the control algorithm to avoid insulin overdelivery and may have caused suboptimal performance of both closed-loop arms. This highlights a further need for improvements in sensor accuracy.

**Bihormonal close-loop system**

Closed-loop insulin delivery has been shown to be superior to conventional insulin pump therapy in improving the glycaemic control, whilst reducing the risk of hypoglycaemia. The risk of hypoglycaemia is still present primarily because of delayed insulin kinetics. To mitigate against this further, dual-hormone (also known as bihormonal) closed-loop systems are under investigation, combining the delivery of insulin with subcutaneous glucagon [38]. In the longest bihormonal closed-loop study to date, participants spent 51-h in a CRF, with high carbohydrate meals accompanied by meal-priming dose and structured exercise to evoke glycaemic perturbations [39]. Although participant numbers were small and there was no control arm, hypoglycaemia (plasma glucose <3.9 mmol/l = 70 mg/dl)
occurred rarely (0.7% of the 576 h of closed-loop control). Overnight, closed loop was able to maintain plasma glucose between 3.9 and 10.0 mmol/l (i.e., 70–180 mg/day) over 90% of the time, in spite of the exercise period during the day.

Recently, a randomized crossover controlled study of a bihormonal closed-loop system was performed in 15 adults with type 1 diabetes [16\textsuperscript{*}]. Patients stayed overnight in the CRF for 15 h, during which they exercised for 30 min and had an evening meal. The bihormonal system improved the overall proportion of time [70.7 (interquartile range = IQR 46.4–88.4) vs. 57.3% (IQR 25.2–71.8); \(P = 0.003\)] within the target range (4.0–10.0 mmol/l between hours of 16:00 and 23:00, and 4.0–8.0 mmol/l between hours of 23:00 and 07:00). Despite no differences in the amount of insulin delivered, no episodes of hypoglycaemia (<4.0 mmol/l = 72 mg/dl) were observed during closed loop (0.0 vs. 10.2%). As a result of the sensor under-reading, however, no improvements in the time spent above the target glucose range or mean plasma glucose levels were reported.

Apart from the issues related to sensor accuracy and reliability, other limitations to bihormonal closed-loop systems are currently present. An additional pump device is currently needed for glucagon delivery, contributing to ‘device burden’ to patients [16\textsuperscript{*}, 39\textsuperscript{*}]. Current glucagon aqueous solution preparation is not stable for extended pump use; it forms amyloid fibrils hours after reconstitution, leading to the formation of insoluble gels which can occlude pump catheters [40]. Studies are underway to prevent glucagon fibrillation, that is, using alkaline pH medium, and reducing its biodegradability, thus making it more feasible for bihormonal closed-loop use [41].

**TRANSITIONAL PHASE STUDIES: FIRST STEPS OUTSIDE**

The objective of transitional phase studies is to assess the feasibility of ambulatory closed-loop systems outside of hospital clinical research settings. These studies represent an ‘intermediate’ phase between the CRF and home. Although patients are studied in a ‘real-world’ environment outside the CRF, closed monitoring by medical and research personnel are still implemented. A smartphone-based closed-loop prototype was recently evaluated in a short-term transitional feasibility study, involving research groups from Italy, France and the USA [21\textsuperscript{*}]. Patients were studied and monitored for 42 h in a hybrid hospital–hotel setting in Italy and France, and an outpatient setting in the USA. The primary objective was to test the communication system reliability of the portable close-loop platform, which is hosted on a commercially available smartphone, with its other components in an outpatient setting. Together with the smartphone, each patient wore two Dexcom Seven Plus sensors (DexCom, San Diego, California, USA) and an Insulet OmniPod insulin pump (Bedford, Massachusetts, USA). Remote monitoring was implemented during the outpatient utilization of the study, with closed contact available to the research physicians at all times. Closed-loop operation was reported to be successful for 533.5 h, representing 97.7% of total possible time from the start to the end of the study for each patient. The study was not designed to test the algorithm performance and post hoc analyses of closed-loop vs. open-loop nights did not show any significant differences in the glycaemic control parameters.

A randomized crossover study in a diabetes youth camp was performed in three countries, utilizing a portable close-loop prototype known as the MD-Logic AP system [19\textsuperscript{**}]. In comparison to the transitional phase study described previously, the primary objective of this study was to assess the frequency and duration of nocturnal hypoglycaemia, as well as mean overnight glucose levels during closed loop. Fifty-six patients used closed loop for one night, and a sensor-augmented insulin pump on another night as control. Study clinicians monitored each patient’s glucose continuously overnight, utilizing a remote-monitoring system as well as hypoglycaemia alert alarm. On closed-loop nights, the number of episodes of hypoglycaemia with sensor glucose values below 3.5 mmol/l (63 mg/dl) was significantly reduced by 30%, compared with the control arm. The median glucose values overnight were not significantly different between closed-loop and control arms [7.0 (IQR 6.4–7.7) vs. 7.8 mmol/l (IQR 5.9–9.3)]. The number of interventions overnight requiring ‘rescue’ carbohydrate hydrates for hypoglycaemia by study clinicians was reportedly similar between the two arms.

This study showed that ambulatory use of closed-loop systems outside the CRF settings is feasible, albeit still dependent on the research clinicians providing remote monitoring and carbohydrate interventions when needed. The evaluation of only a single night on closed loop in the study also needs to be taken into perspective, as daily and overnight glycaemia fluctuations are commonplace in individuals with type 1 diabetes [42]. The next challenge is implementing closed loop at home under real-life uncontrolled conditions, whilst improving on the safety and usability elements.
BRINGING CLOSE-LOOP HOME

Several groups are currently assessing the closed-loop safety and performance during unregulated daily activities at home. As the overnight period has been the main concern for many patients and clinicians [28,43], this has been the initial focus of closed-loop home studies. In spite of the benefits of real-time CGM, benefits of real-time CGM devices on nocturnal hypoglycaemia remain limited, mainly because of the challenges of responding to glucose alarms overnight and applying proper intervention [44,45]. Thus, achieving persistent euglycaemia overnight at home in an autonomous manner will be of significant benefit.

An interim analysis of 15 patients (5 adults and 10 adolescents with type 1 diabetes) using the MD-Logic AP system with remote monitoring for four nights at home compared to conventional sensor-augmented pump therapy was recently published [46*]. The primary endpoint analyses, based on the CGM readings, demonstrated over a ten-fold reduction in the time spent below 3.9 mmol/l (70 mg/dl) on closed-loop compared with control nights per patient [3.8 (0–11.6) vs. 48.7 min (0.6–67.9); P = 0.0034], but with correcting for simultaneous use of glucose sensor to control glucose and measure outcome [47], the difference was reduced [7.6 (1.2–21.7) vs. 16.4 (2.6–107.4) min; \( P = \text{NS} \)]. No significant improvement was seen in the time spent overnight between 5.0 and 7.8 mmol/l (90–140 mg/dl).

We recently evaluated the home use of unsupervised closed loop in a group of 16 adolescents with type 1 diabetes over 3 weeks compared to sensor-augmented pump therapy [48**]. Each patient used the closed loop overnight at home on their own, without any remote monitoring. They were provided with a 24-h telephone number to contact the study team in the event of any clinical or technical issues. Overnight closed loop was utilized on 311 nights (93%), turned on at 21:34 (20:37–22:35) and turned off at 07:37 (07:01–09:09) operating over 10.0 (8.7–11.6) hours. Closed loop significantly increased the time spent in glucose target range (3.9–8.0 mmol/l) by a median of 15% (\( P < 0.001 \)). Mean CGM glucose overnight was also reduced by 0.8 mmol/l (\( P < 0.001 \)). Time when glucose was below 70 mg/dl was less during both interventions, but nights with glucose below 63 mg/dl for at least 20 min were less frequent during closed loop (10 vs. 17%, \( P = 0.01 \)). Despite the lower total daily insulin doses by a median of 2.3 units, \( P = 0.009 \), overall 24-h glucose was reduced by a mean 0.5 mmol/l (\( P = 0.006 \)) during closed loop.

The feasibility of a portable bihormonal fully closed-loop system (no prandial boluses) was assessed in a randomized crossover 48-h home study [27**]. The median glucose levels, time spent in target range (3.9–10.0 mmol/l = 70–180 mg/dl) and below target range during closed loop, and conventional pump therapy were comparable in 11 out of 16 patients, but five patients could not be analysed because of the technical problems with the system. Median (IQR) glucose on the second day of closed-loop intervention was significantly reduced in the closed-loop arm [7.70 (2.29) vs. 8.84 mmol/l (0.87); \( P = 0.027 \)]; however, this came at the expense of greater time spent in the hypoglycaemia range [0.0 (11.0) vs. 2.8% (9.8); \( P = 0.0172 \)]. Insulin infusion by closed loop was higher compared with open loop during the first day [52.0 (29.0) vs. 34.7 IU (22.8); \( P = 0.001 \)], but was comparable on the second day [50.7 (39.9) vs. 37.6 IU (31.7); \( P = 0.1055 \)]. The daily glucagon dose during closed loop was comparable on both days [day 1 vs. day 2: 2.7 (2.0) vs. 1.7 mg (1.5)], and no differences in the oral carbohydrate rescue treatments were reported in both arms.

CONCLUSION

Improving the glycaemic control whilst reducing the risk of hypoglycaemia, especially at night, is achievable with closed loop. Recent results from the early transitional and home studies are encouraging, demonstrating that the roadmap for real-life clinical use in type 1 diabetes is making significant progress. Current closed-loop systems are still limited by factors such as CGM reliability and delay in insulin absorption; therefore, further developments in this field would improve outcomes. Harnessing the use of this technology may help reduce the burden and improve the quality of life of patients with this chronic condition.

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Conflicts of interest

H.T. reports no conflicts of interest. R.H. reports having received speaker honoraria from Minimed Medtronic, Lifescan, Eli Lilly, BBraun, and Novo Nordisk; serving on advisory panel for Animas, Minimed Medtronic, and Eli Lilly; receiving license fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun, Sanofi, and Profil, and patent applications.
REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest


A review article summarizing the currently available evidence from clinical studies of insulin pump therapy.

17. This is the randomized crossover crossover study of a biorhonal closed-loop system in a clinical research facility setting.
21. This is the first randomized crossover transitional study to demonstrate the efficacy of short-term overnight closed-loop use in diabetes camp to reduce the frequency of nocturnal hypo/hyperglycemia.
23. This study assesses the technical feasibility of an ambulatory closed-loop system in a transitional setting without changes to glucose control.

This study provides a method of assessing the suitability and safety of continuous glucose monitor in a closed-loop system by evaluating the frequency and duration of large sensor inaccurancy of two continuous glucose monitoring devices.

The first study to assess the feasibility of a biorhonal fully closed-loop system (no prandial boluses) in a home setting.
32. The use of closed loop in a very young paediatric cohort was demonstrated to be well tolerated and was able to decrease the risk of nocturnal hypo/hyperglycemia.

This study highlights the benefit of closed loop in reducing the risk of nocturnal hypoglycemia, even following antecedent exercise during the day.
37. The challenges of day and night closed-loop insulin delivery, especially during exercise and meal periods, are highlighted in this study.
40. Data from an international, multicentre, randomized, crossover, clinical research facility-based study is presented in this study.
43. Biorhoral closed-loop system was shown to reduce hypoglycaemia in a 44-h clinical research facility study, despite the challenges related to meals and exercise.


This study was an interim analysis of a short-term overnight closed-loop home study. It reports an improvement in the time spent with hypoglycaemia overnight compared with sensor-augmented pump therapy.


This is the first randomized crossover study to demonstrate the safety and efficacy of unsupervised overnight closed-loop use at home for 3 weeks, with reduction in nights with hypoglycaemia.