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REVIEW

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# Insulin delivery and nocturnal glucose control in children and adolescents with type 1 diabetes

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**ABSTRACT**

**Introduction**: Nocturnal glucose control remains challenging in children and adolescents with type 1 diabetes due to highly variable overnight insulin requirements. The issue may be addressed by glucose responsive insulin delivery based on real-time continuous glucose measurements.

**Areas covered**: This review outlines recent developments of glucose responsive insulin delivery systems from a paediatric perspective. We cover threshold-based suspend application, predictive low glucose suspend, and more advanced single hormone and dual-hormone closed-loop systems. Approaches are evaluated in relation to nocturnal glucose control particularly during outpatient randomised controlled trials.

**Expert opinion**: Significant progress translating research from controlled clinical centre settings to free-living unsupervised home studies have been achieved over the past decade. Nocturnal glycaemic control can be improved whilst reducing the risk of hypoglycaemia with closed-loop systems. Following the US regulatory approval of the first hybrid closed-loop system in non-paediatric population, large multinational closed-loop clinical trials and pivotal studies including paediatric populations are underway or in preparation to facilitate the use of closed-loop systems in clinical practice.

## 1. Introduction

Tight glycemic control through intensive insulin therapy and frequent monitoring of blood glucose is the therapy goal in the management of type 1 diabetes to avoid short- and long-term disease-related complications [1,2].

The night period, in particular, remains challenging with over 50% of severe hypoglycemic episodes occurring during sleep in children and adolescents [3]. An assembly of aggravating factors including reduced frequency of blood glucose self-monitoring, blunted sympathoadrenal response to falling blood glucose concentration, reduced hypoglycemia awareness, and reduced warning symptoms and arousal from sleep explain the propensity to nocturnal hypoglycemia [4]. Children and adolescents may be more likely to experience hypoglycemic seizures at nighttime [3]. Fear of hypoglycemia is the major barrier to therapy intensification [3], being also a major source of stress and anxiety for families and caregivers [5], affecting quality of life and psychological well-being of the young and families, and leading to suboptimal glucose control [6].

Typically, nighttime is the longest interprandial interval and therefore basal insulin rather than prandial insulin plays a significant role in overnight maintenance of normoglycemia. Though considerable advances have been made over the past two decades regarding new basal insulin analog formulations which show a flatter and more reproducible action compared to previously used NPH insulins [7,8], pharmacokinetics of currently available basal insulin formulations administered at supper or at bedtime still fall short of desired outcomes. Nocturnal hypoglycemia and hyperglycemia continue to be an issue mainly due to a considerable within-night and between-night variability of insulin requirements [9] of unclear ethology and not accounted for by the diurnal variations and other factors [10,11].

More flexible ways of insulin delivery such as a continuous subcutaneous infusion of fast acting insulin analogs into the subcutaneous tissue at variably adjustable half-hourly to hourly rates via an insulin pump are increasingly popular particularly in the pediatric population [12]. Minimally invasive real-time continuous glucose monitoring complements advances in insulin delivery and is progressing toward accurate, insulin-dosing approved, factory calibrated systems [13]. However, data from systematic reviews and meta-analysis on effectiveness of insulin pump therapy and continuous glucose monitoring have been mixed, particularly in the pediatric population [14–16]. Clinical benefits of continuous glucose monitoring including combined use of insulin pump are conditioned on high regular use [16,17]. Although insulin pump therapy and continuous glucose monitoring may be beneficial in terms of glycemic control, quality of life, and hypoglycemia [12], the majority of young people with type 1 diabetes still do not meet treatment targets especially among adolescents [18,19]. The complexity of self-managing insulin therapy and the inherent unpredictability and variability of glucose levels remain a significant barrier.

A concerted effort is underway to develop autonomous automated glucose responsive insulin delivery systems, broadly referred to as artificial pancreas or closed-loop systems. Threshold-based suspend and predictive low glucose management insulin pump therapy are the first commercial predecessors of closed-loop technology [20,21] followed by the first hybrid closed-loop system approved for the non-pediatric population [22].

## 2. Aims and methods

We assess glucose responsive insulin delivery systems from the viewpoint of nocturnal glucose control in children and adolescents with type 1 diabetes. We discuss clinical and psychosocial outcomes summarizing current closed-loop studies in the pediatric and adolescent populations.

We reviewed published literature on the effectiveness of threshold-based and predictive low glucose insulin suspend as well as on the topic of closed-loop technology with respect to overnight glycemic control. We focused on randomized controlled trials (RCT) in outpatient settings including pediatric and adolescent populations (Table 1).

## 3. Glucose responsive suspension of insulin delivery

Automated suspension of insulin delivery at low sensor glucose levels or when low glucose levels are predicted represent the simplest embodiments of glucose responsive modulation of insulin delivery (Table 2). Both applications, the threshold-based insulin suspend and the predictive low glucose suspend constitute enhancements of sensor-augmented pump therapy, and are precursors of closed-loop systems. The suspend technologies address the issue of hypoglycemia but are unable to counteract rising glucose levels and hyperglycemia.

### 3.1. Threshold-based insulin suspend

Threshold-based suspend allows insulin delivery to be automatically suspended for up to 2 h when sensor glucose falls below a preset sensor glucose threshold. Children may benefit most, in particular overnight, given a higher risk of nocturnal asymptomatic hypoglycemia [44].

The Medtronic Paradigm Veo (Medtronic Diabetes, Northridge, CA, USA) was the first commercial pump implementing threshold-based insulin suspend and was released in 2009. A revised version was approved in the USA in 2013 (MiniMed 530G; Medtronic Diabetes, Northridge, CA, USA).

The evidence from multicenter randomized controlled [20,23], (Table 1, and nonrandomized studies [45] including children and adolescents in real-life settings is that automated insulin suspension is safe and reduces the frequency and duration of overall and nocturnal hypoglycemic episodes compared to insulin pump therapy [23] or sensor augmented pump therapy [20,45]. The threshold-based suspend feature was shown to reduce the percentage of time spent with blood glucose levels in the hypoglycemic range overnight [20,23], and to reduce the overall risk of severe and moderate hypoglycemia in those with highest risk, including those with impaired hypoglycemia awareness and the highest frequency of severe hypoglycemia [23].

Periodic insulin suspension over up to 2 h did not result in elevated glucose concentration as indicated by similar average glucose levels and HbA1c levels over a period of 3-6 months compared to insulin pump therapy and sensor augmented pump therapy [20,23].

### 3.2. Predictive low glucose insulin suspend

Insulin delivery systems with predictive low glucose suspend utilize algorithms to discontinue insulin delivery when hypoglycemia is predicted. The predictive low glucose suspend feature was first introduced into clinical practice in Australia and Europe early 2015 (MiniMed 640G pump; Medtronic Diabetes, Northridge, CA, USA).

We identified two randomized controlled trials assessing the effectiveness and safety of overnight use of predictive low glucose suspend in outpatient home settings in children aged 1-14years [24] and adolescents and adults aged 15-45years [25]. An algorithm different from that used by 640G pump was used. One randomized trial assessed the incidence of hypoglycemia in children and adolescents aged 8-18 years using day-and-night predictive low glucose suspend using 640G pump [46].

The two overnight studies adopted a parallel design using conventional sensor augmented pump therapy as comparator over 42 nights. Predictive low glucose suspend reduced the frequency of nocturnal hypoglycemia by 25 and 36%, respectively. Median time with glucose levels less than 3.9 mmol/l was reduced in excess of 50%, and prolonged nocturnal hypoglycemia, defined by glucose readings below 3.3 mmol/l for more than 2 h, was reduced more than threefold. Mean overnight glucose and morning blood glucose results levels were higher with predictive low glucose suspend without increasing morning ketosis.

Table 1. Overnight glucose control in outpatient randomized controlled trials of glucose-responsive insulin delivery systems in pediatric and adolescent populations.

| Reference | Study population Range or mean age ±SD (years) | N | Study setting | Comparator | Duration of intervention | Hypoglycemia | Overnight glucose control Time in range | Average glucose |
|---|---|---|---|---|---|---|---|---|
| **Threshold-based insulin suspend** | | | | | | | | |
| Ly et al. [23] (Sep 2013) | 4–50 | 95 | At home | Insulin pump | Day-and-night 6 months | % of time with sensor glucose <3.9 mmol/l: median 11.8 vs. 4.4% (p < 0.001) | N/A | N/A |
| Bergenstal et al. [20] (Jul 2013) | 16–70 | 247 | At home | SAP | Day-and-night 3 months | AUC for nocturnal hypoglycemic events: mean 54.4 vs. 87.0 mmol/l × minutes; TS vs. SAP (p < 0.001) % of time with sensor glucose <3.9 mmol/l: 6.0 vs. 10.0%, TS vs. SAP (p < 0.001) | % of time in range (3.9–10.0 mmol/l): 64.7 vs. 62.2%, SAP+TS vs. SAP (p = n.s.) | N/A |
| **Predictive low glucose insulin suspend** | | | | | | | | |
| Battelino et al. [46] (Mar 2017) | 8–18 | 96 | At home | SAP | Day-and-night 2 weeks | Nr of events <3.6 mmol/l (minimum 20 min duration): mean 1.5 vs. 2.8, PLGS vs. SAP (p = 0.025) | N/A | N/A |
| Buckingham et al. [24] (Jul 2015) | 4–10 | 36 | At home | SAP | Overnight 42 nights | % of time with sensor glucose <3.9 mmol/l: 4– median 3.1 vs. 6.2%, PLGS vs. SAP (p < 0.001) | % of time in range (3.9–10.0 mmol/l): mean 63 vs. 63%, PLGS vs. SAP (p = 0.50) | Mean sensor glucose: 8.9 vs. 8.5 mmol/l, PLGS vs. SAP (p = 0.004) |
| Buckingham et al. [24] (Jul 2015) | 11–14 | 45 | At home | SAP | Overnight 42 nights | % of time with sensor glucose <3.9 mmol/l: median 4.6 vs. 10.1%, PLGS vs. SAP(p < 0.001) | % of time in range (3.9–10.0 mmol/l): mean 66 vs. 64%, PLGS vs. SAP (p = 0.10) | Mean sensor glucose: 8.4 vs. 8.0 mmol/l, PLGS vs. SAP (p < 0.001) |
| Maahs et al. (Jul 2014) [25] | 15–45 | 45 | At home | SAP | Overnight 42 nights | % of nights in which ≥1 sensor glucose values ≤3.3 mmol/l occurred: 21 vs. 33%, PLGS vs. SAP (odds ratio 0.52; p < 0.001) time with sensor glucose <3.3 mmol/l per night: median 7 vs. 23 min, PLGS vs. SAP (p < 0.001) | % of time in range (3.9–10.0 mmol/l): median 82 vs. 75%, PLGS vs. SAP (p < 0.001) | Mean sensor glucose: 7.3 vs. 6.9 mmol/l, PLGS vs. SAP (p < 0.001) Morning blood glucose>10 mmol/l: 27% of nights vs. 21% of nights, PLGS vs. SAP (p < 0.001) |
| **Single-hormone closed loop** | | | | | | | | |
| Spaic et al. [26] (Mar 2017) | 15–45 years | 30 | At home | PLGS | Overnight 42 nights | % of time with sensor glucose <3.9 mmol/l: median 1.1 vs. 1.0%, CL vs. PLGS (p = 0.75) | % of time in range (3.9–10.0 mmol/l)*: mean 78 vs. 71%, CL vs. PLGS (p < 0.001) | Mean sensor glucose: 7.9 vs. 8.4 mmol/l, CL vs. PLGS (p < 0.001) Mean morning blood glucose: 7.9 vs. 9.0 mmol/l, CL vs. PLGS (p < 0.001) |
| Nimri et al. [27] (Dec 2016) | 19.5 ± 10.0 | 75 | At home | SAP | Overnight 4 nights | % of time with sensor glucose <3.9 mmol/l: median 2.1 vs. 2.6%, CL vs. SAP (p = 0.004) | % of time in range (3.9–7.8 mmol/l): median 61.1 vs. 47.6%, CL vs. SAP (p = 0.001) | % of nights in which mean glucose levels were within 90–140 mg/dl: median 75% vs. 50%, CL vs. SAP (p = 0.008) Mean sensor glucose: 7.3 vs. 7.8 mmol/l (p = 0.334) |
| Sharifi et al. [28] (Dec 2016) | 15.2 ± 1.6 | 12 | At home | SAP+TS | Overnight 4 nights | % of time with sensor glucose <4.0 mmol/l: median 0.0 vs. 1.8%, CL vs. SAP+TS (p = 0.01) | % of time in range (4.0 – 8.0 mmol/l): 61.7 vs. 64.9%, CL vs. SAP+TS (p = 0.62) | Mean sensor glucose: 7.8 vs.7.0 mmol/l, CL vs. SAP+TS (p = 0.04) |
| Tauschmann et al. [29] (Nov 2016) | 14.6 ± 3.1 | 12 | At home | SAP | Day-and-night 21 days | % of time with sensor glucose <3.9mmol/l: median 2.5% vs. 3.9%, CL vs. SAP (p = 0.70) | % of time in range (3.9 to 8.0 mmol/l): mean 54.4% vs. 33.4%, CL vs. SAP (p < 0.001) | Mean sensor glucose: 8.2 mmol/l vs. 9.8mmol/l, CL vs. SAP (p = 0.002) |
| Ly et al. [30] (Aug 2016) | 17.9 ± 5.5 | 33 | Diabetes Camp | SAP | Day-and-nigh 5 days | % of time with sensor glucose <3.9 mmol/l: mean 1.4% vs. 4.2%, CL vs. SAP (p = 0.007) | % of time in target range (3.9 o 10.0 mmol/l): mean 90.3 vs. 67.2%, CL vs. SAP (p < 0.001) | Mean sensor glucose: 8.2 o 9.8mmol/l, CL vs. SAP (p = 0.002) |

(Continued)

Table 1. (Continued).

| Reference | Study population Range or mean age ±SD (years) | N | Study setting | Comparator | Duration of intervention | Overnight glucose control Hypoglycemia | Time in range | Average glucose |
|---|---|---|---|---|---|---|---|---|
| Tauschmann et al. [31] (Jun 2016) | 15.4 ± 2.6 | 12 | At home | SAP | Day-and-night 1 week | % of time with sensor glucose <3.9 mmol/l: median 2.3 vs. 1.1%, CL vs. SAP | % of time in target range (3.9–8.0 mmol/l): median 63 vs. 40%, CL vs. SAP | Mean sensor glucose: 7.8 vs. 9.7 mmol/l, CL vs. SAP |
| Ly et al. [32] (Jun 2016) | 15.9 ± 2.5 | 21 | Diabetes camp | SAP | Overnight Up to 6 days | % of time with sensor glucose <3.9 mmol/l: mean 5.4 vs. 19.5%, CL vs. SAP ($p = 0.001$) | % of time in range (3.9–8.3 mmol/l): mean 66.4 vs. 50.6%, CL vs. SAP ($p = 0.004$) % of time in range (3.9–10.0 mmol/l): mean 79.9 vs. 60.0%, CL vs. SAP ($p < 0.001$) | Median sensor glucose: 7.3 vs. 7.1, CL vs. SAP ($p = 0.65$) |
| Del Favero et al. [33] (Jun 2016) | 7.6 ± 1.2 | 30 | Diabetes camp | SAP | Day-and-night 3 days | % of time with sensor glucose <3.9 mmol/l: median 0.0% vs. 2.2%, CL vs. SAP ($p = 0.002$) | % of time in range (3.9–10mmol/l): 56.0 vs. 59.7%, CL vs. SAP ($p = 0.430$) | Mean sensor glucose: 8.3 vs. 9.6 mmol/l, CL vs. SAP ($p = 0.002$) |
| Thabit et al. [34] (Sep 2015) | 12.0 ± 3.4 | 25 | At home | SAP | Overnight 12 weeks | % of time with sensor glucose <3.9 mmol/l: median 2.2 vs. 3.5%, CL vs. SAP ($p = 0.70$) | % of time in range (3.9–8mmol/l)*: mean 59.7 vs. 34.4%, CL vs. SAP ($p = 0.004$) | Mean sensor glucose: 8.1 vs. 9.8 mmol/l, CL vs. SAP ($p < 0.001$) |
| Ly et al. [35] (Jul 2015) | 18.6 ± 3.7 | 21 | Diabetes camp | SAP+TS | Day-and-night 6 days | % of time with sensor glucose <3.9mmol/l: mean 1.7 vs. 4.2%, CL vs. SAP+TS ($p = 0.14$) | % of time in target (3.9–8.3 mmol/l): mean 59.8 vs. 51.7%, CL vs. SAP+TS ($p = 0.42$) % of time in range (3.9–10.0 mmol/l): mean 79.9 vs. 68.2%, CL vs. SAP+TS ($p = 0.11$) | Mean sensor glucose: 8.1 vs. 8.3 mmol/l, CL vs. SAP+TS ($p = 0.75$) |
| Nimri et al. [36] (Nov 2014) | 21.2 ± 8.9 | 24 | At home | SAP | Overnight 6 weeks | % of time below 3.9 mmol/l: median 2.5% vs. 5.2%, CL vs. SAP ($p = 0.02$) | % of time in target range (3.9–7.8 mmol/l): median 47.4 vs. 36.4%, CL vs. SAP ($p = 0.003$) % of time in target range (3.9–10.0 mmol/l): median 72.9 vs. 58.7%, CL vs. SAP ($p = 0.001$) | Mean sensor glucose: 8.2 vs. 9.0 mmol/l, CL vs. SAP ($p = 0.008$) |
| Ly et al. [37] (Aug 2014) | 15.3 ± 2.9 | 20 | Diabetes camp | SAP | Overnight 5 – 6 days | Number of nights with ≥1 event <3.9 mmol/l: 11 vs. 21, CL vs. SAP ($p = 0.110$). | % of time in sensor target range (3.9–8.3 mmol/l): median 62% vs. 55%, CL vs. SAP ($p = 0.233$) | Mean sensor glucose: 8.2 vs. 8.1 mmol/l, CL vs. SAP ($p = 0.89$) |
| Hovorka et al. [38] (May 2014) | 15.6 ± 2.1 | 16 | At home | SAP | Overnight 3 weeks | % of time below 3.9mmol/l: median 1.4 vs. 0.9, CL vs. SAP ($p = 0.13$) | % of time in range (3.9–8mmol/l): median 68% vs. 46%, CL vs. SAP ($p < 0.001$) | Mean glucose: 7.6 vs. 8.4 mmol/l, CL vs. SAP ($p < 0.001$) |
| Phillip et al. [39] (Feb 2013) | 13.8 ± 1.8 | 56 | Diabetes camp | SAP | One night | Number of hypoglycemic events (sensor glucose <3.5mmol/l for ≥ 10 consecutive minutes): median 7 vs. 22, CL vs. SAP ($p = 0.003$) | % of time in range (3.9–7.8 mmol/l): median 4.4 vs. 2.8 h, CL vs. SAP | Median glucose: 7.0 vs. 7.8 mmol/l, CL vs. SAP |
| **Dual-hormone closed-loop** | | | | | | | | |
| Haidar et al. [40] (Jan 2016) | 33 ± 17 | 28 | At home | Single-hormone, insulin pump | Overnight 2 nights | % of time with sensor glucose <4.0 mmol/l: median 1% (dual-hormone CL) vs. 5% (single-hormone CL) vs. 14% (insulin pump); (dual-hormone CL vs. insulin pump: $p = 0.005$; dual-hormone CL vs. single hormone: $p = 0.34$; single-hormone CL vs. insulin pump: $p = 0.004$) | % of time in range (4.0–8.0 mmol/l): median 81% (dual-hormone CL) vs. 76% (single-hormone CL) vs. 47% (insulin pump); (dual-hormone CL vs. insulin pump: $p < 0.001$; dual-hormone CL vs. single hormone: $p = 0.5$; single-hormone CL vs. insulin pump: $p < 0.001$) | Mean sensor glucose: 6.2 (dual-hormone CL) vs. 6.2 (single-hormone CL) vs. 6.7 mmol/l (insulin pump); (dual-hormone CL vs. insulin pump: $p = 0.57$; dual-hormone CL vs. single hormone: $p = 0.32$; single-hormone CL vs. insulin pump: $p = 0.12$) |
| Russell et al. [41] (Mar 2016) | 9.8 ± 1.6 | 19 | Diabetes camp | Insulin pump | Day-and-night 5 days | % of time with sensor glucose <3.3 mmol/l: mean 0.6 vs. 2.8%, CL vs. pump ($p < 0.001$) | % of time in range (3.9–10.0 mmol/l): 91.9 vs. 58.8%, CL vs. pump ($p < 0.001$) | Median sensor glucose: 6.8 vs. 9.4 mmol/l, CL vs. pump ($p < 0.0001$) |

(Continued)

Table 1. (Continued).

| Reference | Study population<br>Range or mean age ±SD (years) | N | Study setting | Comparator | Duration of intervention | Overnight glucose control<br>Hypoglycemia | Time in range | Average glucose |
|---|---|---|---|---|---|---|---|---|
| Haidar et al. [42] (Aug 2015) | 13.3 ± 2.3 | 33 | Diabetes camp | Single-hormone insulin pump | Overnight 3 days | % of time with sensor glucose <4.0 mmol/l:<br>median 0% (dual-hormone CL) vs. 3.1% (single-hormone CL) vs. 3.4% (insulin pump); dual-hormone CL vs. insulin pump: $p = 0.0048$; dual-hormone CL vs. single hormone: $p = 0.032$; single-hormone CL vs. insulin pump: $p = 0.32$ | % of time in range (4.0–8.0mmol/l):-<br>median 63% (dualhormone CL) vs. 55% (single-hormone CL) vs. 29% (insulin pump); dual-hormone CL vs. insulin pump: $p < 0.0001$; dual-hormone CL vs. single hormone: $p = 0.032$; single-hormone CL vs. insulin pump: $p = 0.0001$ | Mean sensor glucose:<br>7.7 (dual-hormone CL) vs. 8.1 (single-hormone CL) vs. 9.3 mmol/l (insulin pump); dual-hormone CL vs. insulin pump: $p < 0.001$; dual-hormone CL vs. single hormone: $p = 0.066$; single-hormone CL vs. insulin pump: $p = 0.0093$ |
| Russell et al. [43] (Jun 2014) | 16 ± 3 years | 32 | Diabetes camp | Insulin pump | Day-and-night 5 days | % of time with sensor glucose <3.9 mmol/l: mean 2.6 vs. 4.0%, CL vs. pump ($p = 0.16$) | % of time in range (4.0 to 10.0 mmol/l): mean 86.9 vs. 66.7%, CL vs. pump ($p < 0.001$) | Mean sensor glucose: 6.9 vs. 8.7 mmol/l, CL vs. pump ($p < 0.001$) |

CL: closed loop; TS: threshold-based insulin suspend; PLGS: predictive low glucose suspension; N.S.: not significant; N/A: not applicable, data not published; SAP: sensor-augmented insulin pump therapy.

**Table 2.** Glucose responsive insulin delivery approaches and current status.

| Approach | Nature of glucose-responsive modulation of insulin delivery | Status |
|---|---|---|
| Threshold-based insulin suspend | Suspension of preset insulin delivery at low glucose threshold | Post-marketing studies |
| Predictive low glucose suspend | Suspension of preset insulin delivery when hypoglycemia is predicted | Post-marketing studies |
| Single-hormone closed loop | Graduated and continuous modulation of insulin delivery to reduce hypo- and hyperglycemic excursions | Clinical trials in home settings<br>Pivotal studies<br>Post-marketing studies (planned) |
| Dual-hormone closed loop | Graduated and continuous modulation of insulin to reduce hypo and hyperglycemic excursions; coadministration of glucagon or other hormone | Clinical trials in monitored home settings<br>Pivotal trials (planned) |

In a pooled analysis of the two above-mentioned trials, Calhoun et al. reported that predictive low glucose suspend appears to be beneficial with regard to reduction of nocturnal hypoglycemia irrespective of patient level factors such as age, gender, HbA1c, diabetes duration, total daily insulin dose, and night-level factors such as bedtime blood glucose, bedtime snack, insulin on board, exercise intensity, and hypoglycemia frequency during preceding day [47].

Results from a 2-week day-and-night home trial suggest that the use of predictive low glucose suspend feature is associated with a significantly reduced number hypoglycemic events including significant reductions during the day and overnight [46]. Mean morning glucose levels were not statistically different between the groups. However, overall percentage of time spent with sensor readings greater than 7.8 mmol/l was significantly increased [46].

## 3.3. Closed-loop insulin delivery

Closed-loop approaches are more elaborate than insulin suspension and expand on the concept of glucose responsive insulin delivery by using a control algorithm that automatically increases and decreases insulin delivery, and in some instances other hormones including glucagon, below and above the preset pump regimen (Table 2).

Two main categories of control algorithms have been employed, the proportional-integral-derivative (PID) controller [48,49], and the model predictive controller (MPC) [50]. Other approaches include controllers based on fuzzy logic ('MD logic') [51] or a combination of MPC and PID for insulin and glucagon codelivery [52]. Bi-hormonal or dual-hormone systems have emerged which deliver both insulin and glucagon, or another hormone [53].

Studies of closed-loop insulin delivery have evolved from small pilots undertaken in laboratory settings over single night, to larger trials in outpatient settings such as diabetes camps and hotels for over up to 6 days, to medium-term multicenter unsupervised studies in home settings of up to 6-month duration.

Most prototypes of closed-loop systems follow a hybrid approach characterized by manual delivery of prandial insulin. Figure 1 depicts a hybrid closed-loop prototype applied in home unsupervised studies. In September 2016, the FDA approved the first hybrid closed-loop system (MiniMed 670G pump, Medtronic, Northridge, CA) based on safety outcomes of a nonrandomized pivotal trial including 124 adolescents and adults [22,55].

Henceforth, we discuss randomized controlled closed-loop trials in outpatient settings including children and adolescents. The focus is on overnight glycemic control (Table 1) adopting single- and dual-hormone closed-loop delivery.



**Figure 1.** Closed-loop system prototype [54]. (a) FlorenceM closed-loop system comprises a continuous glucose monitoring transmitter with Enlite 3 sensor, an insulin pump (modified 640G pump) integrated with the continuous glucose monitoring receiver and a mobile phone running the control algorithm. (b) A photo of a participant (obtained with consent) using the closed-loop system.

### 3.3.1. Single-hormone closed-loop insulin delivery
#### 3.3.1.1. Transitional outpatient settings. Many transitional outpatient studies have been performed in camp settings among children and adolescents (Table 1). Whilst participants are studied in a 'real-world' surroundings, monitoring by medical and research personnel allows interventions to take place in case of safety concerns or system malfunctions to underpin safety aspects. Hypoglycemia is a well-recognized complication at diabetes camps often attributed to increased exercise and dietary alterations [56]. Thus, camp settings provide a challenge testbed for closed-loop systems. Given the higher hypoglycemia burden, studies in camp environments are more likely to show benefits with respect to hypoglycemia reduction.

In one of the first outpatient studies adopting a multicenter randomized design, an MD-logic control algorithm was evaluated over a single night in 56 children and adolescents in a diabetes camp and compared to sensor augmented pump therapy [39]. The number of hypoglycemia events with sensor glucose values below 3.5 mmol/l was significantly reduced during closed-loop use with comparable median glucose levels during the two interventions.

The use of a closed-loop system with an MPC control algorithm in a diabetes camp in children and adolescents over 5–6 nights significantly reduced the time spent in hypoglycemia overnight (<2.8, <3.3, and <3.9 mmol/l) but did not improve time spent in the target range from 3.9 to 8.3 mmol/l nor mean glucose levels compared to sensor augmented pump therapy as per intention-to-treat analysis [37]. Using a similar system day-and-night in a diabetes camp over 5–6 days in adolescents with type 1 diabetes, the percentage of time spent with sensor readings below 3.9 mmol/l overnight was significantly reduced with the closed-loop system compared to sensor augmented pump therapy, as were mean overnight glucose and time spent in hyperglycemic glucose ranges, while overnight time in target between 3.9 and 10.0 mmol/l was increased [30].

Comparing the use of a closed-loop system utilizing a modified PID controller [57] with sensor augmented pump therapy at a diabetes camp in 21 children and adolescents for up to six nights, nocturnal hypoglycemia was reduced and overnight time spent in the target range 3.9-8.3mmol/l was greater with closed-loop [32]. Using the same algorithm in a fully integrated hybrid day-and-night closed-loop system in 21 adolescents and young adults in a diabetes camp over up to 6 days, there was no additional benefit with regard to nocturnal hypoglycemia, time in target range and mean overnight glucose when compared with sensor augmented pump therapy combined with low glucose suspension [35].

Focusing on younger children, Del Favero et al. conducted a camp trial in children aged 5–9 years [33]. A hybrid closed-loop system was compared against sensor augmented pump therapy over 3 days. Closed-loop use resulted in a significant reduction of nocturnal time spent with sensor glucose readings below 3.9 mmol/l. Time in range overnight was similar between interventions, but mean overnight glucose was higher with closed-loop.

#### 3.3.1.2. Home studies of closed-loop insulin delivery. Home studies accurately mimic anticipated use of closed-loop systems in clinical practice. Evaluations without supervision or close remote monitoring represent the ultimate challenge in providing unequivocal assessment of closed-loop performance under free-living conditions.

Overnight closed-loop insulin delivery with remote monitoring was tested in 24 participants including adolescents for 6 weeks using the MD-logic algorithm applying sensor augmented pump therapy as comparator [36]. The use of overnight closed-loop resulted in a significant reduction of time spent hypoglycemia by nearly twofold and increased time spent within target range by 14 percentage points. Similar results were observed in a multicenter, multinational study using the MD-logic system in 75 patients aged 10–54 years over four consecutive nights with sensor augmented pump therapy as a comparator [27].

Unsupervised free-living overnight use of a MPC algorithm driven closed-loop in adolescents over a period of 3 weeks showed significant improvements in time spent within target range by a median 15 percentage points, reduced mean glucose by a mean 0.8 mmol/l, and reduced the number of nights with glucose readings below 3.5 mmol/l compared to sensor augmented pump therapy [38]. A slightly revised version of this closed-loop system was tested in the longest randomized home study in children and adolescents to date. Over a period of 3 months, the overnight closed-loop application was compared to sensor augmented pump therapy during free-living conditions in 6-18-year youth [34]. Closed-loop improved the overnight time in target range between 3.9 and 8.0 mmol/l by 25 percentage points and reduced overnight mean glucose by 1.6 mmol/l. Extended benefits of overnight closed-loop use were seen over the full 24-h period including greater percentage of time in target range, lower mean glucose, and significantly reduced burden of hypoglycemia. Two recent day-and-night trials by the same group conducted in adolescents over one [31] and 3-week duration [29] demonstrated improved overnight time spent within target range compared to sensor augmented pump therapy and reduced mean overnight sensor glucose without increasing the risk of hypoglycemia.

The overnight application of a hybrid closed-loop system using a modified PID algorithm was compared to sensor augmented pump therapy with low-glucose suspend function over 4 consecutive nights in a study including 12 adolescents [28]. Closed-loop resulted in a reduced time spent with sensor readings below 3.9%; no difference in the percentage of time in the target range between 4.0 and 8.0 mmol/l was observed, but mean overnight glucose was slightly elevated during closed-loop use.

Recently, Spaic et al. compared predictive hyperglycemia and hypoglycemia minimization system with predictive low glucose suspend in the home setting in adolescents and adults over 42 nights [26]. The addition of the predictive hyperglycemia minimization component increased the time spent in the target range between 3.9 and 10.0 mmol/l, significantly reduced mean overnight and morning blood glucose levels, and performed equally well with respect to hypoglycemia outcomes.

### 3.3.2. Dual-hormone closed-loop insulin delivery

Dual-hormone closed-loop systems deliver subcutaneous glucagon or, infrequently, other hormone in addition to insulin when hypoglycemia is impending or predicted. The dual-hormone approach may alleviate the risk of hypoglycemia per se, or may be exploited to increase aggressiveness insulin delivery with anticipation that certain degree of insulin over-delivery may be counteracted by glucagon [53,58].

A dual-hormone closed-loop system was studied over 5 day-and-nights in adolescents in a diabetes camp using conventional insulin pump therapy as comparator [43]. Mean overnight sensor glucose was significantly reduced during the closed-loop use, the percentage of time spent with low sensor glucose readings was similar during the two interventions, and the percentage of time in target range was greater with closed loop. The dual-hormone system delivered on average 0.7 mg of subcutaneous glucagon per day. In another outpatient diabetes camp study, dual-hormone closed-loop was applied in preadolescent children aged 6–11 years over 5 day-and-nights [41]. Compared to conventional insulin pump therapy, mean overnight sensor glucose on days 2–5 was significantly reduced as was the time spent with sensor readings below 3.3 mmol/l during nights, and overnight time in range was greater during closed-loop application.

A different dual-hormone system applying insulin delivery in a fashion similar to that of a single-hormone closed-loop system and adding glucagon as a safety mitigation to reduce the risk of hypoglycemia was evaluated in children and adolescents in a diabetes camp over three consecutive nights [42]. Insulin-alone closed-loop and conventional pump therapy were comparators. The nocturnal time spent in hypoglycemia with the dual-hormone system was significantly reduced compared to insulin-alone closed-loop and insulin pump therapy. The number of hypoglycemia events overnight was reduced from 15 during nights with conventional pump therapy compared with four events with insulin-alone closed loop and none with the dual-hormone closed-loop. Mean glucagon delivery during dual-hormone closed-loop nights was 0·04 mg per night. A similar dual-hormone system was tested at home in adolescents and adults and compared to single-hormone closed-loop and conventional pump therapy over two consecutive nights [40]. Interventions were applied after a high carbohydrate/high fat meal and after exercise. The findings suggest that single- and dual-hormone closed-loop systems provide superior overnight glucose control compared to conventional pump therapy. However, the dual-hormone configuration did not lead to significant incremental benefit to single-hormone closed-loop with respect to overnight time in target glucose levels and time in hypoglycemia.

### 3.4. Quality of life and psychosocial aspects

The assessment of user feedback and experience is essential to inform the development of closed-loop prototypes and products, and clinical practice adoption [59].

In quantitative and qualitative psychosocial analyses of experiences of home trial participants, pediatric and adolescent users of overnight closed-loop and their parents reported benefits including reassurance/peace of mind, having 'time-off' from managing their diabetes, improved overnight control leading to improved daily functioning and diabetes control, and improved sleep [60,61]. The key negative themes related mainly to technical issues such as device connectivity and sensor calibration, intrusiveness of alarms, and size of the devices. Overall, children and adolescents reported a positive experience of the closed-loop technology with perceived benefits of a closed-loop system outweighing practical challenges [60,61].

These findings are in line with experiences from a study evaluating overnight predictive low glucose management systems at home settings where participants reported break from the daily burden of diabetes care [62]. In another overnight home trial, closed-loop application had a positive impact on hypoglycemia fear and other indices of health-related quality-of-life outcomes [63].

## 4. Conclusions

Nocturnal glucose control is a major concern for children and adolescents as well as parents and caregivers. Innovative technologies including automated glucose responsive insulin delivery has driven improvements in overnight glucose control over the past decade though further progress remains desirable.

Threshold-based suspend and predictive low glucose suspend applications are safe and effective in children and adolescents alleviating overnight hypoglycemia in hypoglycemia-prone individuals. These benefits might be achieved at the expense of mildly elevated overnight and morning mean glucose levels [24,25] and a slightly increased time in mild hyperglycemia depending on the algorithmic approach [24].

Single-hormone closed-loop systems may reduce nocturnal hypoglycemia whilst also increasing time glucose is within the normoglycemia range. Depending on control algorithm and the population, mean overnight glucose is lower [29,31,34,36,38], similar [27,32,35,37] or slightly elevated [28,33] than during control therapy.

Current findings support the use of a single-hormone closed-loop strategy for overnight glycemic control in the pediatric and adolescent populations [40]. The incremental benefit of glucagon for overnight glucose control *in situ*ations such as hypoglycemia unawareness, following overdosing of prandial insulin at dinner/bedtime, and prolonged exercise as observed, for example, in diabetes camp settings is to be observed but further developments need to take place and cost–benefit analyses to be carried out.

Participants of trials evaluating glucose responsive insulin delivery systems consistently express trust in the technology and reduced disease burden embracing the potential of these technologies to positively impact on quality of life.

In summary, results of up to several months closed-loop use in outpatient and home settings are promising and demonstrate the distinctive ability of such systems to improve overall nocturnal glucose control and reduce the risk of hypoglycemia, a feat unachievable with many other therapeutic modalities.

## 5. Expert opinion

Over the past decade, significant progress has been made translating research into glucose responsive insulin delivery from controlled clinical research center settings to free-living unsupervised home use. The approval of the first hybrid closed-loop system by the FDA marks a new era in the adoption of such systems in clinical practice. Multinational closed-loop clinical trials and pivotal studies are underway or in preparation including in adults and pediatric populations to support reimbursement and to delineate clinical effectiveness.

The first generation of commercial closed-loop systems will enable extensive data collection to take place to underpin further tuning and refinements. Overnight use, not burdened by meals and exercise, is of primary relevance given the documented benefits of closed-loop use compared to wake-time. Optimizing glucose control during rapid prandial and exercise-related glycemic fluctuations remains challenge. Ultra-rapid insulin analogs such as faster insulin aspart with an earlier onset of appearance and action [64] are likely to be beneficial. Adjunctive therapies including pramlintide and glucagon-like peptide-1 [65,66], inhaled insulin [67], or ancillary technologies such as site-warming [68] continue to be explored.

Dual-hormone systems with glucagon coadministration may further reduce the risk of hypoglycemia and/or provide additional improvements in glucose control. Technological and pharmacological challenges, currently being addressed, include unavailability of dual chamber pumps and instability of current glucagon preparation [69]. Safety and tolerability of chronic subcutaneous glucagon use is to be established. Practical challenges include increased complexity and cost.

Advances in continuous glucose monitoring are taking place. Factory-calibrated flash glucose monitoring can be applied for up to 2 weeks [70]. A long term up to 3-months implantable glucose sensors is available for use in clinical practice [71]. Single-port technologies combining glucose sensing at the site of insulin delivery are being tested [72,73].

Smaller and more user friendly devices will be particularly important for children [74]. At present, a multi-device architecture is often used. This complexity increases device burden, and the risk of communication and connectivity-related issues. As closed-loop devices may be vulnerable to cybersecurity threats, e.g. interference with wireless protocols and unauthorized data retrieval [75], implementation of secure communications protocols is of paramount importance. Fully integrated systems might overcome these issues.

So far, study participation has been limited to established pump users. This selection bias may diminish generalizability of study findings. Future studies are needed to investigate the application of closed-loop systems in pump naïve users. Other subgroups including very young children are to be enrolled so that safety, efficacy, and utility analysis can be assessed. Future research may include identifying sub-populations which may benefit most.

Cost-effectiveness of closed-loop is to be determined to support access and inform reimbursement decision-making. In addition to conventional endpoints such as glycated hemoglobin, quality of life is to be included to assess burden of disease management and hypoglycemia. A concert effort is underway to develop measures that more adequately capture the role of human and psychological factors play in the uptake and efficient use of closed-loop systems [76,77].

## Declaration of interest

M Tauschmann reports having received speaker honoraria from Novo Nordisk and Medtronic. R Hovoka reports having received speaker honoraria from Eli Lilly, Novo Nordisk and Astra Zeneca, serving on an advisory panel for Eli Lilly and Novo Nordisk, receiving license fees from BBraun and Medtronic; and having served as a consultant to BBraun. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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