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The challenges of Achieving Postprandial Glucose Control using Closed-Loop Systems in Patients with Type 1 Diabetes

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Abstract

For patients with type 1 diabetes, closed-loop delivery systems (CLS) combining an insulin pump, a glucose sensor and a dosing algorithm allowing a dynamic hormonal infusion have been shown to improve glucose control when compared to conventional therapy. Yet, reducing glucose excursion as well as simplification of prandial insulin doses remains a challenge. The objective of this literature review is to examine current meal-time strategies in the context of automated delivery systems in adults and children with type 1 diabetes. Current challenges and considerations for post-meal glucose control will also be discussed. Despite promising results with meal detection, the fully automated CLS has yet failed to provide comparable glucose control to CLS with carbohydrate-matched bolus in the post-meal period. The latter strategy has been efficient to control post-meal glucose using different algorithms and in various settings; yet, at the cost of meal carbohydrate counting burden for patients. Further improvements in meal detection algorithms or simplified meal priming boluses may represent interesting avenues. The greatest challenges remain in regards to the pharmacokinetic and –dynamic profiles of available rapid insulins as well as sensor accuracy and lag-time. New and upcoming faster acting insulins could provide important benefits. Multi-hormone CLS (eg, dual-hormone combining insulin with

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glucagon or pramlintide) and adjunctive therapy (eg, GLP-1 and SGLT2 inhibitors) also represent promising options. Meal glucose control with the artificial pancreas remains an important challenge for which the optimal strategy is still to be determined.

INTRODUCTION

Type 1 diabetes (T1D) requires life-long insulin replacement therapy with continuous health care support to achieve optimal blood glucose (BG) control, defined as glycated hemoglobin (HbA1c) <7%, and reduce the risk of long-term diabetes-related complications.^{1,2} Despite remarkable advances in diabetes treatment, patients continue to struggle in achieving glycemic targets, with an average HbA1c remaining >8.0% and a high frequency of severe and non-severe hypoglycemia events.^{3,4} Self-management in T1D involves multiple day-to-day tasks including, but not limited to, insulin dose adjustments, self-monitoring of BG, hypoglycemia management and carbohydrate (CHO) counting. These tasks can be challenging^{5,6} and compliance is often limited.^{7,8}

Closed-loop automated insulin delivery systems (CLS), also called “artificial pancreas”, are one of the most promising therapies for T1D, with the first system recently approved by the Food and Drug Administration (FDA) in the United States.⁹ CLS could help reduce the burden associated with day-to-day self-management while improving glucose control by reducing both hypo and hyperglycemia.¹⁰ In this system, insulin only (single-hormone CLS) or insulin and a second drug, typically glucagon (dual-hormone CLS), infusion rates are regulated based on algorithm-generated recommendations relying on continuous glucose monitoring systems (CGMS) readings. The efficacy of the CLS approach over conventional continuous subcutaneous insulin infusion (CSII) therapy to regulate glucose levels in patients with T1D has been demonstrated in several studies. Overall glycemic control has been improved with single-hormone and dual-hormone versions of the artificial pancreas compared with CSII therapy: the artificial pancreas is improving glucose time in target range (between 4.0 and 10.0 mmol/L in most studies), reducing blood glucose variability, reducing time in hypoglycemia (with better results during night-time), and reducing the time in hyperglycemia in most studies.^{11–17} However, one of the main challenges that remains with CLS is postprandial glucose control.

With CLS, several strategies have been proposed to control post-meal glucose excursions: 1) CLS with a classical CHO content matched meal bolus announcement implemented by the patient, also called hybrid CLS; 2) CLS with a meal announcement strategy that is completely or partially independent of the CHO meal content (simplified meal bolus); 3) a fully automated CLS with no meal announcement. Although a fully automated CLS approach would be optimal to alleviate the burden associated with meal glucose control, it should be achieved without compromising glucose control. In the meantime, several simplified strategies are currently developed and tested.

The objective of this literature review is to examine current strategies for simplification of meal glucose control in the context of closed-loop insulin delivery with or without adjunct therapy in adults and children with T1D. Considerations for effective post-meal glucose control and current challenges will also be discussed.

POSTPRANDIAL GLUCOSE CONTROL

Controlling postprandial glucose excursions is identified as a key component to achieve recommended HbA1c.^{2,18} The 2-h post-meal glucose target in individuals with T1D is between 5 and 10 mmol/L in most patients.^{2,19} CHO content of meals is the main determinant of postprandial glucose excursion.^{20,21} Consequently, in conventional T1D therapy, prandial insulin doses depend on the CHO content of each ingested meal: before each food intake, patients need to estimate the CHO content of their food (CHO counting) and to deliver insulin boluses proportional to the CHO content, based on their individualized insulin-to-CHO ratios.² Precision of CHO counting is associated with better glycemic control.²² However, it is also a challenging task for patients.⁶ Average error in CHO counting is approximately 20%, with most patients underestimating their meal content while poor CHO counting precision has been shown to be associated with increased glycemic variability and time in hyperglycemia.⁵ Moreover, in addition to CHO content, post-meal glucose concentrations are also influenced by many other factors that are discussed below. Several tools are available to patients and some Web or telephone-based applications are being developed to help patients estimate more accurately the CHO content of their meals and administer the appropriate insulin bolus. For example, GoCARB is a computerized application providing CHO content estimations based on pictures of meals which shows great potential to improve postprandial glucose control in T1D with or without CLS.^{23,24} Any technology or strategy that would alleviate the burden of CHO counting could not only improve overall glycemic control but patients' life quality as well. Patients with T1D have expressed their interest towards a device that would help minimize their disease burden and simplify their day-to-day management.^{6,25} CLS offers the perspective of CHO counting alleviation or simplification; yet, it should not be achieved at the expense of effective postprandial glucose control.

CLOSED-LOOP SYSTEMS (CLS)

Hybrid CLS

Hybrid CLS, or CLS with CHO-matched meal bolus implemented by the patient has been widely studied and tested by several research groups. After nearly a decade of inpatient controlled studies, beginning in 2006 with the CLS study by Steil et al.²⁶, the first outpatient automated CLS study was conducted in 2014 using the DiAs platform²⁷ followed by several automated and outpatient studies.^{16,28–30} Most CLS studies have used a pre-meal manual insulin bolus, usually matched to the CHO content of the meals (hybrid CLS). These studies typically demonstrate that hybrid CLS, as compared to CSII, increases time in target range, reduces time in hypoglycemia, and improves BG control overnight. The largest outpatient study so far included 33 adults and 25 children, and lasted 12 weeks.³¹ In this study, the hybrid CLS, as compared with sensor-augmented pump therapy, improved time in target range for glucose levels while reducing mean glycemia and time spent in hypoglycemia.³¹ However, even with the hybrid CLS in which preprandial glucose values are generally improved, postprandial glucose control remains suboptimal. CLS generally maintains glucose levels in-target for 70–75% of the time¹⁰ with the remaining time spent outside target mostly due to post-meal hyperglycemia. A strategy using sliding mode reference

conditioning (SMRC) combined with hybrid CLS could improve postprandial glucose control but larger outpatient studies remain needed.³² Again, an important limitation of a hybrid CLS is the persistent need for CHO counting.

Also, do-it-yourself (DIY) CLS is undergoing rapid development (eg. OpenApps). These systems are hybrid CLS with various meal announcement strategies including for example, an “eating soon mode” or “meals with high fat or protein content”. However, these systems are associated with numerous challenges including the multiple variations of approaches and the low availability of validation studies.³³

Fully automated CLS

A fully automated CLS is entirely reactive and no meal or physical activity information would be fed manually into the algorithm. As such, it offers the advantage of relieving the patient from intervening. Few groups have investigated the potential of a fully automated CLS in patients with T1D (Table 1). Most of the fully automated CLS studies have been conducted in small numbers of participants, in inpatient setting, and using single-hormone systems. Two main challenges emerged with the fully automated strategy: 1) significant postprandial hyperglycemic excursions; and 2) late postprandial hypoglycemia.

Despite finding no difference in mean glucose between CSII and CLS, Steil et al.²⁶ observed important postprandial glycemic excursions and suggested adding an insulin feedback mechanism to resolve this issue. Ruiz et al. compared a proportional-integral-derivative (PID) controller with insulin feedback to a PID controller only.³⁴ Insulin feedback reduced time spent in hypoglycemia, but did not improve post-meal BG excursions or area under the curve.³⁴ Two groups have studied dual-hormone CLS (insulin and glucagon) in the context of fully automated control. In the study by El-Khatib et al.³⁵, adjustments for insulin pharmacokinetic (PK) parameters allowed to prevent late postprandial hypoglycemia, but at the expense of an increase in average BG. In addition, this strategy led to prolonged postprandial glucose excursions and it was thus modified by the group who adopted meal priming boluses based on meal type and size in their following trials.^{16,36} Van Bon et al. showed in a first pilot study the feasibility of their fully automated CLS for post-meal glucose control by achieving comparable glucose control to CSII.³⁷ Yet, late postprandial hypoglycemia was induced in 50% of the participants.³⁷ They tested their system in outpatient settings, in which they reduced their median glucose and increased percentage of time spent in target range, but still had higher percentage of time in hypoglycemia³⁸ and no difference for postprandial median glucose as compared with CSII.³⁹ The latter studies only compared fully automated CLS to CSII while some compared fully automated CLS with hybrid CLS using patient driven administration of meal boluses. For example, Weinzimer et al. showed an important reduction in daytime plasma glucose levels and postprandial peak glucose levels with the addition of a partial meal priming bolus in comparison with their fully automated CLS.⁴⁰ This group was also the only one to test a fully automated system combining insulin and pramlintide as discussed below (adjunctive therapy)⁴¹, a combination that needs to be further explored.

Despite promising results for some CLS and for meal detection algorithms⁴³, there is still a need for robust, outpatient, randomized trials to demonstrate the efficacy of fully automated

CLS to control postprandial glucose levels. Patients' acceptance of a fully automated CLS needs to be examined. Its potential to improve quality of life is probable but should be obtained while aiming concomitantly for an optimal glucose control.

CLS with simplified meal bolus

Additional strategies have been tested in combination with CLS in order to reduce or avoid the need for CHO counting (Table 2). In a pilot project, a prandial bolus based on body weight (0.047U of insulin per kg) was compared with a CHO-matched bolus within the context of dual-hormone CLS.⁵¹ This weight based meal bolus resulted in prolonged glycemic excursion and it is unlikely to provide an acceptable postprandial glucose control. In a subsequent inpatient trial, the efficacy of dual-hormone CLS combined with a CHO-matched bolus was compared to dual-hormone CLS combined with a meal bolus based on semi-quantitative CHO content assessment: patient's current insulin-to-CHO ratio and meal category (regular meal or large meal).⁵² The simplified strategy tested yielded an overall comparable mean blood glucose with, however, higher postprandial glucose excursions compared to CHO-matched bolus after meals with >90g of CHO.⁵² In a following outpatient study, additional meal categories were created and the efficacy of the simplified bolus strategy was compared to CHO-matched boluses in the context of single and dual-hormone CLS.⁵³ No difference was observed for any outcome between the simplified strategy and the CHO-matched boluses using both CLS systems. However, increased time in hypoglycemia was observed with the simplified strategy compared to CSII. The potential benefits of the simplified strategy are: 1) the patient would only have to evaluate the size of the meal in terms of CHO (e.g. snack, regular, large or very large), a far simpler evaluation than the current CHO counting strategy; 2) simplified partial bolus can still be individualized for each patient and for each meal. However, these studies have tested the strategy in rather small samples. Adaptive meal-priming boluses have been developed and used in a first study by El-Khatib et al. in 2014.⁵⁴ With this strategy, patients have to select a meal (breakfast, lunch or dinner), and then select a meal size: typical, more than usual, less than typical or a small bite.^{16,36} The meal-priming bolus administered corresponds to 75% of the average prandial insulin provided for previous meals of the same size and at the same time of day. This approach preserves the benefits of meal announcement to improve the overall CLS performance while largely relieving the burden associated with CHO counting. The latest outpatient automated studies using this strategy have demonstrated the merits of this approach to improve glucose control in both adults and children.^{16,36}

In the current context, informing the algorithm of a meal is probably a needed compromise. By announcing a meal, the system is better prepared to handle rapid changes in BG. Simplified meal priming approaches still require some CHO content or meal size assessment, but at a far simpler level than CHO counting. The risks of meal misclassification and the impact of associated human errors will need to be examined in future long-term outpatient trials. With this strategy and with hybrid CLS, the risks of hypoglycemia and hyperglycemia associated with meal announcement in the event of a missed meal or a changed meal (addition or subtraction of a significant amount of macronutrients), which can typically happen in children for example, will remain a challenge, as it is with current CSII

or MDI treatment. Consequences and strategies to mitigate this risk will need to be addressed in the context of CLS.

CHALLENGES AND TECHNICAL ISSUES

In the following section, challenges and issues pertaining both to CLS components and human factor error or influence will be discussed. Current main technical issues regarding CLS components include limitations due to current insulin pharmacodynamics (PD) and PK. Other factors also intervene with CLS efficacy to control postprandial glucose excursions including sensor accuracy and delays, the impact of other nutrients and their absorption, variations in insulin sensitivity, patients' behaviors (eg, sensor calibration, additional boluses, overriding the system, etc.), addition of adjunct therapy allowing to counteract insulin (eg, glucagon), modifying gastric emptying (eg, pramlintide or GLP-1-analogs) or glucose renal excretion (eg, SGLT2-inhibitors).

Insulin PK/PD

Plasma glucose concentration typically rises within 10 minutes following food ingestion and it is expected to return to the pre-meal level within 2 to 3 hours, although nutrient absorption can continue for up to 5 to 6 hours post-meal.⁵⁵ Indeed, several factors discussed below can affect the rise in BG and nutrient absorption such as meal composition, meal timing and gastric emptying. In healthy individuals, insulin is secreted in response to meal consumption in a timely and synchronized manner to adequately control rising BG levels. This synchronized insulin response is lost due to the subcutaneous route of insulin replacement in T1D. The major challenge to control post-meal glucose control is thus the delayed PK/PD with subcutaneously administered insulin.⁵⁶ Rapid-acting insulin analogs (Lispro, Aspart and Glulisine) are used with CSII and in CLS, and the onset of these insulin preparations is between 10 and 15 minutes, with a peak action between 1 and 2 hours.² Even with the current rapid acting insulin analogs, the post-meal glucose absorption is much faster than insulin absorption through the subcutaneous tissue. This mismatch largely explains the inability of current CLS to control postprandial glucose excursions and the increased risk of late postprandial hypoglycemia in response to important reactive insulin infusion with fully automated CLS.^{40,45}

This time lag between fast acting insulin absorption and meal absorption has motivated research towards faster acting insulins.⁵⁷ Faster insulin Aspart (FiAsp) in which modified excipients allow faster absorption was shown to improve postprandial glucose profile (a reduction of approximately 1.2 mmol/L at 1-h and 0.7 mmol/L at 2-h).⁵⁸ The FiAsp's onset of appearance in the bloodstream is twice as fast as Aspart with an earlier onset of glucose lowering effects.^{59,60} This new insulin has not yet been tested in CLS, but will likely generate interest. Use of other avenues such as insulin combined with hyaluronidase to hasten insulin absorption could also represent promising alternatives for postprandial glucose improvement.^{61,62}

The intra-peritoneal insulin infusion route is technically challenging but advantageous in terms of pharmacokinetics for glucose regulation as compared to the subcutaneous route because insulin is delivered mainly in the portal vein rather than systemically, which is far

closer to normal physiology allowing a larger and direct effect on hepatic glucose production regulation.⁶³ Intra-peritoneal insulin infusion is associated with tight glucose control and a low hypoglycemia incidence.^{64,65} CLS with intraperitoneal insulin infusion from an implanted pump has been tested showing improved glucose control as compared with open-loop intraperitoneal insulin infusion.⁶⁶ Comparison of this strategy to subcutaneous CLS and in larger studies is warranted.

Sensor accuracy and delays

The accuracy and reliability of the CGMS is also of importance in CLS. These devices have considerably evolved over time, are increasingly accepted by patients and healthcare professionals, and shown to improve glycemic control in adult patients with T1D.⁶⁷ CGMS readings are measured in the interstitial fluid, which can differ from plasma BG due to the time delay needed to equilibrate glucose between the blood vessels and interstitial fluid compartments. The time delay can vary from 3 to 12 minutes and is highest when BG levels are rapidly changing such is the case post meals or during exercise.^{68,69} These sensor delays remain one of the main challenges faced by CLS algorithms and can affect the efficacy of the artificial pancreas in regards to meal. Other than time delays, CGMS performance can be influenced by calibration errors and delays from patients or from capillary glucose meter value.⁶⁸ Inaccuracies related to the device itself such as errors in signalling, noise filtering, or positional stability are additional variables.^{70,71} The accuracy of the CGMS has considerably improved⁷², however, errors can be challenging in study protocols; for example, sensor failure due to inaccuracy or loss of signal was reported in 28% of the experiments during the hybrid CLS safety trial by Zisser et al.⁷³ Over time, in a context of proper usage, particularly in relation to proper calibration⁷⁴, such as ideal timing and frequency, the performance of CGMS has improved significantly with the newer generations; the measurement error has been reduced to about 10% with most devices.⁷⁵ Nevertheless, CLS algorithms need to adequately account for the limitation of these devices (eg, a sensor underestimation of actual blood glucose will lead to increased postprandial glucose excursions) and patient education about optimal use of CGMS device is crucial to operate CLS safely and effectively.

Nutrient absorption and impact of other macronutrients

Several factors can impact glucose absorption such as gastric emptying, physical activity, alcohol consumptions and meal composition.² CHO of all types are pooled together for CHO counting, with the exception of dietary fibres which do not raise BG and sugar alcohols which are not fully absorbed, with both CHO types subtracted from total CHO.² However, post-meal glucose concentrations are also influenced by the type of CHO or more precisely, by the glycemic index of food consumed.^{76,77} Choosing food sources with a low glycemic index is recommended for individuals with T1D to help optimize glycemic control. Whether CLS efficacy is specifically affected by high glycemic load meals has not been studied. Recently, the protein and lipid content of meals have been suggested to impact postprandial glucose control, adding to the complexity of prandial insulin calculation.^{78–80} Meals rich in lipids would, for their part, result in a prolonged postprandial hyperglycemia extending from 2 to 4 hours after a meal. A study showed that the addition of 35g of fat to a meal significantly increased, by 2.3 mmol/L, the 5-h post-meal glycemia.⁷⁸ This prolonged

hyperglycemia could be explained by the effect of lipids on gastric emptying, on insulin sensitivity, etc.⁷⁹ A similar observation was described for the impact of proteins on postprandial glucose control. Smart et al. showed a 2.6 mmol/L increase in glycemia 5 hours following a meal with the supplementation of 35g of protein to a 30 g CHO meal.⁷⁸ Using a CLS, Wolpert et al. showed that a high fat meal compared with a low-fat meal with similar protein and CHO content resulted in more insulin requirements and increased BG.⁸⁰ Accurate CHO counting is an essential aspect to manage postprandial BG levels in T1D²² and already constitutes a challenging task for most patients with T1D^{5,6}; thus, adding protein and lipid aspects to prandial insulin bolus calculations would considerably increase the complexity of post-meal glucose control for patients. In CLS, a meal bolus strategy that does not require proteins and lipids counting without compromising post-meal glucose control would greatly simplify patients' treatment. Since the time associated with lipids and proteins impact on postprandial BG is relatively long (approximately 5 hours), CLS is expected to have the time to adjust in response to changing BG levels. However, well-designed studies are needed to answer this important question.

Insulin sensitivity variations

Postprandial glucose control is also challenged by the considerable intra- and inter-individual variability in the metabolic effect of subcutaneous insulin infusion in patients with T1D.^{81,82} For the same body weight and age, insulin sensitivity can vary by up to 6-fold between individuals. Across daytime, a significant range of in-between meals insulin sensitivity also exists, with an increasing sensitivity from breakfast to lunch.⁸² In addition, within the same individual but across days, it is estimated that there is 31% variability in insulin sensitivity overnight and 17% variability during the day.⁸³ Patients' insulin-to-CHO ratios will thus often vary across the day.⁸⁴ Other factors also impact insulin sensitivity such as physical activity, physical or emotional stress, growth and hormonal fluctuations (puberty, pregnancy, menopause, menstrual cycle).² Next generation algorithms with adaptive properties are expected to account to some extent for these variabilities and individualize treatment through enhancement of its day-to-day learning process.

Behavioral challenges

Safe and adequate use of CLS is necessary to avoid compromising glucose control. Many outpatient studies have now been conducted without serious adverse events reported. The FDA has even approved the first system for commercialization. However, some safety issues will need to be addressed with patients. An entirely automated system has the potential in adults to improve quality of life by releasing patients from daily burdensome tasks. It could be particularly beneficial for patients with poor adherence to meal insulin-boluses as well as children and adolescents. In children, limitations for postprandial glucose control include, for example, unpredictable appetite, difficulty in foreseeing the beginning of food intake, limited communication and collaboration. For overnight glucose control, a CLS approach has been shown to be feasible and effective for hypoglycemia risk reduction.^{12,85,86} Yet, daytime CLS studies in young children are scarce. A recent study in a small number of young children showed decreased mean BG without increased hypoglycemia during a 68-h period as compared with conventional therapy with a CLS system adapted for young children.⁸⁷ Adolescence is also known as a difficult period for glucose control with

important physiological changes impacting insulin sensitivity⁸⁸ and a low-adherence to diabetes self-treatment plan⁸⁹, including omission^{90–92} or underestimation⁹³ of insulin boluses for meals and snacks. Omission of meal boluses appears to be common, with 65% of youths using CSII who would miss at least one meal-time bolus per week⁹¹. In most cases, adolescents would simply be unaware of missed boluses⁹¹; yet, it is also possible that insulin boluses were omitted to limit hypoglycemia risk or to control weight. A tendency in female adolescents to skip or reduce insulin doses for weight control purposes has been observed in several studies.^{94,95} The efficacy and safety of hybrid CLS control could thus be compromised in youths who voluntarily or accidentally omit boluses. One study demonstrated safety of CLS glucose control in the context of reduction or omission of meal bolus.⁹⁶ Following the bolus omission of a 55g of CHO lunch, hyperglycemia was not prevented despite an increased insulin infusion; yet, hypoglycemia risk was not increased in the 5.5-h postprandial period.⁹⁶ Following an unannounced snack and a reduced meal bolus, CLS also improved short-term glucose control as compared with usual care without increasing hypoglycemia risk in adolescents.⁹⁷ Thus, the safety of the system (hypoglycemia) appears to be preserved with bolus omission, yet postprandial glucose control (hyperglycemia) is impaired.

Multi-hormone CLS and adjunctive therapies

Multi-hormone systems are identified, alongside insulin-only automated delivery systems, as the final steps towards CLS development by the Juvenile Diabetes Research Foundation (JDRF).⁹⁸ Dual-hormone approach has traditionally involved the addition of glucagon, although different systems are now testing the addition of pramlintide either with insulin only or with insulin and glucagon. Other adjunctive therapies used alongside advanced algorithms also have the potential to improve post-meal glucose control compared to current artificial pancreas systems, such as pramlintide, glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter-2 inhibitors (SGLT2-I). Each of these suggested additions to CLS has its own benefits, challenges and safety issues.

As previously discussed, Glucagon is delivered as intermittent mini-boluses which in association with meals could allow more aggressive insulin therapy and/or prevent and treat late postprandial hypoglycemia. It would allow more important insulin infusion in the early postprandial period while preventing late postprandial hypoglycemia. Despite a building evidence for an added benefit of glucagon incorporation in CLS^{38,45,99}, technical and safety issues related to its regular use still need to be circumvented.¹⁰⁰ Up till now, CLS studies use glucagon provided in the hypoglycemia emergency kit which necessitates immediate use after reconstitution and disposal of any left-over due to glucagon instability (degradation, fibrillation and risk of loss of potency with cytotoxicity).^{101,102} In CLS, it is being used in infusion pump sets for 24-h with good clinical efficacy and acceptable stability.¹⁰⁰ However, a regular use of glucagon requires the development of a glucagon formulation that can be stable for multiple days at ambient temperatures. Research efforts are advancing for that matter with new glucagon formulations and analogs being under development or testing in clinical settings.^{103,104} On the other hand, glucagon exerts diverse effects on many organs and systems raising questions about its potential additional benefits (eg, reducing satiety) but also safety in the context of chronic use.¹⁰⁰ While no major side effects have been reported

in the short-term clinical trials aside from mild nausea and occasional vomiting, glucagon safety in the setting of chronic use still need to be established.¹⁰⁰

Amylin is co-secreted from Beta cells with insulin in response to meals and acts on decreasing food intake, slowing gastric emptying and suppressing glucagon release.¹⁰⁵ Its stable equipotent analog, pramlintide, has been approved by the FDA for diabetes treatment since 2005. Due to its favorable effect on postprandial glucose¹⁰⁶, pramlintide has attracted researchers to test it in the setting of CLS for better glucose control. Two studies have so far tested premeal pramlintide (Amylin analog) injections to single-hormone CLS control without insulin boluses or meal announcement, showing reductions in time to peak postprandial BG and its excursion as well as in insulin dose administered by CLS post meals.^{41,107} In combined insulin/pramlintide therapy, the meal is extended allowing more time for adequate feedback to CLS to adjust insulin possibly improving glucose control. An ongoing study is investigating the effect of continuous pramlintide infusion using subcutaneous pumps in addition to insulin on overall glucose control (NCT02814123). Future studies will reveal if technical issues would arise with continuous pramlintide infusion through pumps. Potential side effects with pre-meal pramlintide use include nausea and an increased risk of hypoglycemia particularly in hypo-unaware patients.¹⁰⁸ These as well as any additional side effects will need to be closely monitored in CLS studies. The hope is for pramlintide to help fully closing the loop around meals or at least allowing for some meal priming without the need for accurate CHO counting.

Similar to pramlintide, GLP-1 constitutes an attractive adjunctive option to CLS. GLP-1 is an incretin secreted by intestinal cells in response to food intake and works on suppressing glucagon release, increasing insulin secretion (a mechanism not involved for patients with T1D) increasing satiety and delaying gastric emptying.¹⁰⁹ Several GLP-1 analogs are on the market and have been mainly used in patients with type 2 diabetes. Liraglutide (GLP-1 analog) addition as a once daily 1.2 mg injection to CLS improved overall glucose control (decreased by an average of 0.83 mmol/L) and postprandial BG excursions in comparison to insulin-only CLS control arm in 15 patients over 24-h.¹¹⁰ In a prior study, exenatide (another GLP-1 analog) was compared to pramlintide in CLS settings, both given as injections prior to lunch and dinner. An attenuation in postprandial BG and glucagon levels was significant with exenatide but not with pramlintide in 10 patients over 27-h.¹¹¹ Pramlintide was better tolerated than exenatide in terms of gastrointestinal side effects (four patients in exenatide versus one in pramlintide group), but no hypoglycemia episodes were reported in either arms.¹¹¹ Larger studies with adequate drug titration are needed to better characterize the added benefit of GLP-1 analogs.

Other potential oral adjunctive medications include Dipeptidyl peptidase-4 inhibitors such as sitagliptin that was recently shown to decrease BG after the first two meals in the setting of closed-loop insulin delivery over 25-h in 15 patients with no significant effect on glucagon levels.¹¹² SGLT2 inhibitors belong to a new class of oral anti-diabetic medications that act by increasing renal glucose excretion, and may potentially be combined with CLS to improve glucose control. However currently the use of this class is limited by an increased risk of ketoacidosis especially in patients with T1D. Adequately controlled large trials with all these promising additional hormones and adjunctive agents are highly needed and

expected to help in developing efficient feedback-only controllers to relieve patients from the burden of CHO counting.

Several technical issues related to multi-hormone systems will, however, need to be addressed before such systems are made available to patients. These issues include the added complexity of such a system, the additional pumps and catheters needed or the need for a dual-chamber pump, the more complex interactions that the algorithm needs to manage, the safety issues in the event of pump or catheter failure (eg, inability to deliver a glucagon bolus) and the necessity to develop stable and safe hormones (eg, glucagon, pramlintide) that can be used in a pump.

CONCLUSION

The hybrid artificial pancreas is now available to patients. Its efficacy is undisputed and patients have high expectations for this system. However, to be adopted by patients and clinicians, the device needs to improve glucose control as well as improve quality of life, or at least reduce some burden associated with diabetes management. Postprandial glucose excursions remain too large with most systems and need to be improved. These systems could lead to alleviation or simplification of CHO counting, however this benefit should not be detrimental to overall glucose control. The optimal meal strategy for insulin boluses is yet to be determined and several challenges still need to be tackled.

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Table 1

Fully automated closed-loop system studies

Reference	Study design and CLS type	Control arms	N	Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
Steil CM et al. 2006 ²⁶	Nonrandomized; single-hormone	CSII (3-day)	10 Adults	Inpatient	28 to 30-h	Individualized: average between 45 and 88g of CHO	-	No difference in mean glucose between CSII and CLS; 2-h postprandial glycemia is higher than target with CLS, especially after breakfast.
Weinzimer SA et al. 2008 ⁴⁰	Randomized; single-hormone	CLS + pre-meal priming bolus (25 to 50% of a CHO-matched bolus)	17 Adolescents (8 fully automated vs. 9 with meal priming bolus)	Inpatient	34-h	Unspecified	-	No difference in 24-h mean glucose levels and in night-time glucose levels; daytime plasma glucose levels and postprandial peak glucose levels were significantly reduced with CLS + pre-meal priming bolus compared with fully automated CLS
Atlas E et al. 2010 ⁴⁴	Uncontrolled; single-hormone	-	7 Adults	Inpatient	8-h or 24-h sessions	Three mixed meals of 17.5 to 70g of CHO	-	Mean peak postprandial glucose levels = 12.4 ± 1.2 mmol/L; 73% of time in target range (3.9 – 10.0 mmol/L) and 27% of time > 10.0 mmol/L.
El-Khatib FH et al. 2010 ⁴⁵	Uncontrolled; dual-hormone	-	11 Adults	Inpatient	27-h	Three meals, individualized (45–60% of kcal from CHO per meal)	-	Seventeen hypoglycemia episodes in 5 patients with slower insulin pharmacokinetic (PK) (0 episode in repeated experiment following adjustments of insulin PK parameter settings);

Reference	Study design and CLS type	Control arms	N	Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
								hyperglycemic excursion following each meal; following adjustments, average time spent in target range was 74% and 51% for the faster and the slower PK groups, respectively.
								2 Algorithms were tested: standard control to range (sCTR) and enhanced control to range (eCTR): both CLS significantly improved overall time between 3.9 and 10.0 mmol/L with no difference for overall time between 4.4 and 7.8 mmol/L compared with CSII; reduced hypoglycemic risk with sCTR and no difference with eCTR compared with CSII
Breton M et al. 2012 ⁴⁶	Randomized cross-over; single-hormone	CSII	11 Adolescents and 27 adults	Inpatient	22-h	Variable meal CHO content (1.08 ± 0.24g of CHO per kg of body weight)	30-min	
								Higher mean blood glucose with PID control compared to PID + IFB; no difference in post-meal BG excursions or area under the curve between both controllers; reduced hypoglycemic event occurrence with PID + IFB (0 event) compared to PID alone (8 events).
Ruiz JL et al. 2012 ³⁴	Nonrandomized; single-hormone	Proportional-integral-derivative (PID) + insulin feedback (IFB)	4 Adolescents or adults	Inpatient	24-h PID vs. 24-h PID + IFB	Variable CHO content (254 ± 42g for 3 meals) with identical meals on both days	-	
Weinzimer SA et al. 2012 ⁴¹	Randomized; single-hormone or insulin + pramlintide	CLS + pre-meal pramlintide injections (30µg)	8 Adolescents or adults	Inpatient	24-h CLS vs. 24-h CLS + pramlintide	Variable CHO-content (84 ± 26g / meal) with identical meals on both days	-	With fully automated CLS, 75% of sensor glucose values were within target range,

Reference	Study design and CLS type	Control arms	N	Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
Dassau E et al. 2013 42	Uncontrolled; single-hormone	CSII (outpatient)	15 Adults (18 tests)	Inpatient	6.3-h (3.4 to 8.3-h)	30 ± 5 g of CHO	-	Average time in target (4.4 – 10.0 mmol/L) = 70%; no hypoglycemic event; improved blood glucose control as compared with outpatient CSII in uncontrolled conditions.
Mauseth R et al. 2013 47	Uncontrolled; single-Hormone	-	7 Adults	Inpatient	24-h	30g CHO breakfast and 60g CHO lunch	-	Mean blood glucose through experiment = 9.2 mmol/L with 65% of time spent in target range (3.9 – 10.0 mmol/L); 4h post-meal blood glucose was within target for 64% and 16% of the time following the 30 and 60g meals, respectively.
Turksoy K et al. 2013 48	Uncontrolled; single-hormone	-	3 Adults (7 tests)	Inpatient	32- or 60-h	8 meals, variable CHO content (30–115g)	Yes, variable duration	Glucose remained within target range (3.9 – 10.0 mmol/L) 62% of the time, and 56% of the time following meals.
Cameron F et al. 2014 49	Uncontrolled; single-hormone	-	2 Cohorts with distinctive algorithms; 4 and 6 Adults	Inpatient	32-h	Five meals of 0.8 to 1.2g CHO/kg bodyweight	Walking only	Results for the second cohort, following algorithm improvements: mean sensor glucose = 8.0 ± 2.4 mmol/L with 75%

Reference	Study design and CLS type	Control arms	N	Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
Blaauw H et al. 2016³⁹; Previous studies^{38,37,50}	Randomized cross-over; dual-hormone	CSII	10 Adults	Outpatient	72-h	Unspecified (uncontrolled)	Unspecified (Allowed)	<p>of sensor readings between 3.9 and 10.0 mmol/L; 9% of time spent >13.9 mmol/L after 3 hours postprandial; one hypoglycemic event.</p> <p>No difference in median glucose levels; increased time spent in target range (3.9 – 10.0 mmol/L) with the CLS compared with CSII; no difference for postprandial median glucose or time spent in hyperglycemia (>10.0 mmol/L) for breakfast and dinner but improved postprandial glucose control for lunch with CLS compared with CSII.</p>

CSII: continuous subcutaneous insulin infusion; CLS: closed-loop system; CHO: carbohydrate

Table 2

Hybrid closed-loop system studies with simplified meal bolus strategy

References	Study design and CLS type	Control Arms	Meal bolus description	N and Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
Body weight dependent bolus								
Haidar et al. 2014 ⁵¹	Randomized; dual-hormone	CHO-matched bolus	Based on body weight: 0.047 U/kg	12 Adults; Inpatient	2 x 5-h	75g CHO breakfast	-	Glucose values returned to pre-prandial levels after 5 h with the body weight dependent bolus and after 2 h with the CHO-matched bolus; 5-h incremental area under the curve and percentage of time above 10 mmol/L were lower after the CHO-matched bolus compared with the body weight dependent bolus.
Meal category announcement								
Gingras V et al. 2016 ⁵³	Randomized; single and dual-hormone	CHO-matched bolus and CSII	Based on semi-quantitative meal CHO content assessment: 1) snack <30g (bolus for 15g); 2) regular meal 30–60g (bolus for 35g); 3) large meal 60–90g (bolus for 65g); 4) very large meal >90g (bolus for 95g)	12 Adults; Outpatient	5 x 15-h	Uncontrolled	Uncontrolled	Similar mean glucose level and percentage of time in target range with the carbohydrate-matched boluses and simplified strategy using both single-hormone and dual-hormone CLS; increased time in hypoglycemia
Previous study ⁵²								

References	Study design and CLS type	Control Arms	Meal bolus description	N and Setting	Duration	Meals	Exercise	Main outcomes and postprandial outcomes
Russell SJ et al. 2016 ³⁶ Previous study ¹⁶	Randomized cross-over; dual-hormone	CSII	Meal type selection: breakfast, lunch or dinner; then, meal size selection: typical, more than usual, less than typical or small bite (individualized based on usual CHO intakes)	19 Children; Outpatient	2 x 5-d	Uncontrolled	Uncontrolled	with single and dual-hormone CLS and the simplified strategy compared with CSII. Lower mean sensor glucose was observed with CLS as compared with CSII; increased proportion of time within target range, including less time in hyperglycemia; lower proportion of time spent in hypoglycaemia in CLS compared with CSII; lower % of time with sensor glucose <3.3 mmol/L and lower number of episodes requiring treatment.

CSII: Continuous subcutaneous insulin infusion; CHO: Carbohydrate, CLS: Closed-loop system