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Dual-hormone artificial pancreas for management of type 1 diabetes: Recent progress and future directions

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Abstract

Over the last few years, technological advances have led to tremendous improvement in the management of type 1 diabetes (T1D). Artificial pancreas systems have been shown to improve glucose control compared with conventional insulin pump therapy. However, clinically significant hypoglycemic and hyperglycemic episodes still occur with the artificial pancreas. Postprandial glucose excursions and exercise-induced hypoglycemia represent major hurdles in improving glucose control and glucose variability in many patients with T1D. In this regard, dual-hormone artificial pancreas systems delivering other hormones in addition to insulin (glucagon or amylin) may better reproduce the physiology of the endocrine pancreas and have been suggested as an alternative tool to overcome these limitations in clinical practice. In addition, novel ultra-rapid-acting insulin analogs with a more physiological time–action profile are currently under investigation for use in artificial pancreas devices, aiming to address the unmet need for further improvements in postprandial glucose control. This review article aims to discuss the current progress and future outlook in the development of novel ultra-rapid insulin analogs and dual-

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AUTHOR CONTRIBUTIONS

Marco Infante conceived the manuscript, did the first literature search, and wrote the initial draft of the manuscript. All the remaining authors (David A. Baidal, Michael R. Rickels, Andrea Fabbri, Jay S. Skyler, Rodolfo Alejandro, and Camillo Ricordi) did additional literature search and drafted sections of the manuscript. Marco Infante combined the drafts and prepared the figures and the table. All the remaining authors (David A. Baidal, Michael R. Rickels, Andrea Fabbri, Jay S. Skyler, Rodolfo Alejandro, and Camillo Ricordi) subsequently revised and supervised the final manuscript.

hormone closed-loop systems, which offer the next steps to fully closing the loop in the artificial pancreas.

Keywords

amylin; closed-loop control; dual-hormone artificial pancreas; glucagon; multihormone artificial pancreas; pramlintide; T1D; triple-hormone artificial pancreas; type 1 diabetes; ultra-rapid insulin

1 | INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the immune-mediated destruction of insulin-secreting pancreatic β-cells, which ultimately results in lifelong dependence on exogenous insulin.[1] While progress is continuously being made toward the development of targeted immunotherapies[2,3] and β-cell replacement approaches,[4] advances in diabetes technology are also working toward easing the disease burden in patients with T1D.[5,6] Over the last few years, technological advances have had a major impact on the management of T1D, leading to remarkable improvements in insulin pump therapy (also known as CSII or continuous subcutaneous insulin infusion), continuous glucose monitors, and closed-loop systems that combine pumps and glucose sensors for algorithm-driven automation of insulin delivery.[6–11] The artificial pancreas (also referred to as “closed-loop automated insulin delivery system”) enables automated glucose management in patients with T1D. This system requires the interaction of three distinct and wirelessly interconnected device components, namely:

- A real-time continuous glucose monitoring (rt-CGM) sensor inserted in the subcutaneous space, which measures glucose concentrations in the interstitial fluid approximately every 5 minutes and wirelessly sends information about glucose readings to a control algorithm device (CAD) via a transmitter.
- A CAD (eg, a compatible receiver, a PC, a tablet, a smartphone, or the pump itself) which hosts a control algorithm (dosing algorithm) that computes the correct amount of insulin to deliver via the insulin pump and automatically adjusts the insulin infusion rate in real time based on current and predicted sensor glucose levels, aiming to maintain blood glucose levels within a specific target range.
- An insulin pump directed by the dosing algorithm, which delivers insulin via a subcutaneous cannula.[12–14]

Figure 1 illustrates the different components of an insulin-only single-hormone artificial pancreas system and how they are interconnected and work together. Currently available closed-loop systems are defined as “hybrid” because they automate basal insulin infusion rates (with or without automation of correction boluses, depending on the specific type of current commercial systems), but they still require patient intervention to insert the exact amount of carbohydrates ingested per each meal (carbohydrate counting-based meal announcement) and trigger mealtime insulin boluses. User input is required for mealtime boluses as delays in subcutaneous insulin absorption of currently available insulin analogs

limit the possibility of fully automated insulin delivery[14,15] using sensor glucose informed meal detection.[16] Besides being able to adjust basal insulin infusion rates, artificial pancreas systems can temporarily suspend insulin delivery by predicting impending hypoglycemia through predictive low-glucose suspend (PLGS) algorithms.[12] Nonetheless, in some cases, patients need to trigger correctional insulin boluses based on confirmatory blood glucose testing and treat hypoglycemia with oral carbohydrate when predictive suspension of insulin delivery fails to prevent the development of hypoglycemia. Figure 2 illustrates the daily report from a commercially available hybrid closed-loop automated insulin delivery system.

Mechanical problems with insulin delivery,[17] the delay and variability of insulin absorption from the subcutaneous space,[18,19] and variability of insulin action[20] represent key challenges to closed-loop control of blood glucose, particularly in the context of perturbations in glucose homeostasis introduced by meals, exercise and illnesses. The accuracy of continuous interstitial fluid glucose sensing is another critical determinant of the efficacy of current and emerging closed-loop systems. An important determinant of glucose sensor accuracy is the physiological time lag of glucose transport from the vascular to the interstitial space. Basu et al showed that the delay of glucose appearance from the vascular to the interstitial space is less than 10 minutes in both healthy subjects[21] and T1D individuals,[22] thereby implying that this time lag does not represent a relevant obstacle to the accuracy of interstitial glucose sensing and to the efficacy of closed-loop control systems for T1D. In most circumstances (especially in outpatient care settings), a 5-minute time lag of glucose from intravascular to interstitial compartment is negligible, as there is a comparable or greater lag in the pharmacokinetics of insulin analogs. However, traditional central laboratory devices, blood gas analyzers, and/or capillary point-of-care testing via glucometers still remain the most widely used and reliable tools for testing blood glucose under specific circumstances, such as acute and critical care settings.[23,24] Other minor limitations of some CGM devices that need to be overcome include the interference with certain substances and medications,[25,26] the need for fingerstick test calibration,[25] compression artifacts, as well as pairing and connectivity issues causing transient disconnection and interruption of communication between the sensor transmitter and the receiver.[27]

Given these preliminary remarks, current artificial pancreas devices lack fully automated insulin delivery and only partly resemble the physiology of endogenous insulin secretion. In order to overcome these major challenges to the development of an artificial pancreas that fully reproduces the physiology of the endocrine pancreas, novel approaches under investigation include: (a) the use of more physiological insulin delivery routes (eg, intraperitoneal) and ultra-rapid-acting insulin analogs that have enhanced absorption from subcutaneous tissue,[28,29] (b) the need for automated delivery of other hormones in addition to insulin that may better address postprandial hyperglycemia and interprandial hypoglycemia (amylin and glucagon, respectively),[8,30] and (c) the integration of such systems with advanced technologies enabling automated detection of several physiological variables capable of affecting glucose concentrations, such as meal timing and composition, exercise, stress, illnesses, sleep, and circadian variations in insulin sensitivity.[8,16,31–34] Yet, the advent of such technologies will take time for the development of robust control

algorithms and multivariable adaptive systems able to collect and elaborate information from wearable devices other than glucose sensors.[31,35]

Randomized controlled trials and meta-analyses have shown that artificial pancreas systems increase the time spent in target glucose range, reduce time spent in hyper- and hypoglycemia, reduce glycated hemoglobin (HbA1c), decrease mean glucose levels and glucose variability, and improve diabetes-specific positive well-being and quality of life compared with conventional insulin pump therapy and sensor-augmented pumps equipped only with low-glucose suspend feature enabling automated suspension of insulin delivery at a threshold glucose level.[5,13,36–45] Nonetheless, clinically significant hypoglycemic and hyperglycemic episodes still occur with the artificial pancreas.[13,36,46] Therefore, one of the main goals of research focused on technology for the management of T1D is to develop an artificial pancreas potentially capable of leading to near-normal glucose levels accompanied by a percentage of time spent in target glucose range as high as possible, with low glucose variability and without the occurrence of clinically significant hypoglycemic or hyperglycemic episodes. In this context, the development of novel ultra-rapid insulin analogs and advanced dual-hormone artificial pancreas systems delivering insulin in conjunction with glucagon or amylin may significantly help minimize glucose excursions and improve glucose control in clinical settings.[29,30] The aim of this review article is to discuss the current status and future prospects of ultra-rapid-acting insulin analogs and dual-hormone artificial pancreas systems, which represent pivotal steps to better reproduce the physiology of the endocrine pancreas and to ultimately close the loop in the artificial pancreas, thereby assisting in achieving near-normal glucose levels and low glucose variability in patients with T1D. In particular, this article attempts to delineate under what clinical contexts dual-hormone artificial pancreas systems may be advantageous over insulin-alone artificial pancreas systems in patients with T1D.

2 | ULTRA-RAPID INSULIN ANALOGS FOR ARTIFICIAL PANCREAS SYSTEMS

Since the last 25 years, rapid-acting insulin analogs (lispro, aspart and glulisine) characterized by a faster time–action profile (faster onset of effect and shorter duration of action) and a more physiological profile compared with regular insulin have become available for insulin pump use.[29] Faster onset and offset of insulin action are highly desirable features in order to prevent early postprandial hyperglycemia (through greater early suppression of hepatic glucose production and higher stimulation of glucose disappearance)[47] and late postprandial hypoglycemia, which represent relevant barriers to improvement in glucose control.[48]

However, rapid-acting insulin analogs administered subcutaneously display a relatively slow onset of action (10–15 min), with the time to maximal glucose excursion of 40–60 minutes and a prolonged duration of action (approximately 3–5 h).[49,50] Moreover, subcutaneous absorption kinetics of rapid-acting insulin administered as a bolus may be delayed in patients with T1D, particularly among pump users.[51,52] More recently, novel insulin analogs (also known as “ultra-rapid-acting insulin analogs”) with improved

pharmacokinetic and pharmacodynamic features have been developed. Compared with rapid-acting insulin analogs, ultra-rapid-acting insulin analogs display an accelerated absorption after subcutaneous administration, a faster onset-of-action and a shorter duration of action, resulting in a more physiological time–action insulin profile.[53,54] The faster onset of action of ultra-rapid-acting insulin analogs allows insulin dosing to more precisely match a meal (dosing can occur at the start of the meal or even during the meal), thereby lessening the postprandial spike in blood glucose levels, reducing protracted insulin exposure and consequently lowering the risk of late postprandial hypoglycemia.[53] When used in closed-loop systems, ultra-rapid-acting insulin analogs can also allow for more rapid adaptation to changing glucose levels. Hence, ultra-rapid-acting insulin analogs better mimic the physiological prandial insulin secretion pattern and offer a valid therapeutic option to prevent or mitigate postprandial glucose excursions compared with rapid-acting analogs.

In light of these considerations, ultra-rapid-acting insulin analogs may be preferred over rapid-acting insulin analogs in selected subgroups of T1D patients, such as: (a) patients who fail to reduce postprandial glucose excursions and to achieve glycemic targets despite intensification of basal-bolus insulin therapy, (b) patients who experience frequent episodes of late postprandial hypoglycemia, (c) patients who are willing to inject prandial insulin boluses after starting the meal rather than at the start of the meal, (d) patients with marked post-breakfast hyperglycemia due to the dawn phenomenon, and/or (e) patients who intermittently or regularly consume meals with a high content of refined carbohydrates.[54] Nevertheless, future studies are needed to establish which patients would benefit most from the use of these newer ultra-rapid-acting insulin analogs compared with those who would not receive a significant clinical benefit.

It is also worth outlining that ultra-rapid-acting insulin analogs should be cautiously used in some instances in which the more physiological time–action profile of these analogs may not always be advantageous. Although there is still paucity of clinical data concerning the use of ultra-rapid insulin analogs in different “real-life” clinical scenarios, there may be a need for caution with their use due to the possible risk of early postprandial hypoglycemia under certain circumstances or in selected conditions, including: (a) initiation of exercise shortly after mealtime insulin injection; (b) consumption of low-glycemic index foods or high-fat and high-fiber meals and/or presence of diabetic gastroparesis, in which ultra-rapid onset of insulin action and delayed gastric emptying may concurrently contribute to increase the risk of early postprandial hypoglycemia.[48] In such circumstances, a careful adjustment of prandial insulin dose and/or a cautious evaluation of the optimal prandial timing of bolus dosing (eg, delayed, postmeal bolus administration) may be required to mitigate the risk of early postprandial hypoglycemia and concurrently prevent late postprandial hyperglycemia.

2.1 | Ultra-rapid aspart

A new ultra-rapid formulation of insulin aspart has entered the market after FDA approval in 2017.[53] This formulation has been developed to achieve a faster initial absorption after subcutaneous administration. In particular, ultra-rapid aspart contains two additional excipients (L-arginine and niacinamide) that ensure formulation stability and allow for accelerated initial absorption from subcutaneous tissue compared with previously

developed rapid-acting analogs.[48,53,55] Niacinamide increases the initial abundance of insulin aspart monomers and mediates a transient local vasodilatory effect to enhance insulin absorption after subcutaneous administration, while the amino acid L-arginine serves as a stabilizing agent.[54,56] Ultra-rapid aspart displays overall left shifts of the pharmacokinetic/pharmacodynamic profiles compared with insulin aspart, resulting in earlier onset of action (approximately 5–6 min faster onset of action), doubling in early exposure, up to 2.5-fold higher initial glucose-lowering effect within the first 30 minutes, along with an earlier offset of exposure and effect.[53,55,57] Similar findings have also been confirmed in CSII setting[58–60] and hybrid closed-loop setting,[61] suggesting that faster aspart better reproduces the physiological prandial insulin secretion and action profile observed in healthy individuals. Insulin aspart and ultra-rapid aspart also exhibit comparable compatibility with insulin pumps, with no observations of microscopically confirmed occlusions of the infusion set over a 6-week period.[62] A double-blind, parallel-group, 16-week randomized trial conducted in 472 adults with T1D using CSII therapy demonstrated that ultra-rapid aspart was superior to aspart in reducing 30-, 60-, and 120-minute postprandial glucose increments.[59] In 2019, FDA has therefore approved ultra-rapid aspart for use in insulin pumps in adults with T1D based on its noninferiority to insulin aspart.[59]

A recent randomized, open-label, crossover trial with two 7-week treatment periods compared ultra-rapid aspart versus insulin aspart in 40 T1D adults using a hybrid closed-loop system.[61] This study demonstrated that ultra-rapid aspart is safe and effective when used in a hybrid closed-loop system, leading to a higher percentage of time spent in the 70–180 mg/dL glucose range (+1.81%, equivalent to 26 min/day) and to a greater reduction in 1-hour postprandial glucose increase during the standardized mixed meal test compared with insulin aspart.[61]

2.2 | Ultra-rapid lispro

The use of a newly developed ultra-rapid formulation of insulin lispro has been investigated in patients with T1D and type 2 diabetes (T2D).[63,64] Compared with insulin lispro, this new formulation consists of two additional excipients, the prostacyclin analog treprostinil and sodium citrate, which are aimed to accelerate insulin absorption by promoting local vasodilation and increasing vascular permeability at the injection site, respectively.[54,65] A recent randomized, double-blind, four-period, crossover study conducted in 68 patients with T1D undergoing a standardized test meal compared pharmacokinetics and glucodynamics of ultra-rapid lispro, insulin lispro, insulin aspart and ultra-rapid aspart after subcutaneous insulin administration.[66] Ultra-rapid lispro displayed the fastest insulin absorption, the greatest early insulin exposure, the greatest reduction in late insulin exposure, and the shortest duration of exposure compared with all other insulin analogs. Ultra-rapid lispro also led to the greatest numeric postprandial glucose-lowering effect compared with all insulins tested, along with a statistically significant improvement in postprandial glucose excursions during the first 5 hours compared with insulin lispro and insulin aspart. Overall, early postprandial glucose profile following ultra-rapid lispro administration more closely matched that observed in 12 healthy subjects who received the same test meal during the first 2 hours postmeal. Hypoglycemic events during the test meal occurred at similar

frequencies for all the insulins tested, and ultra-rapid insulin lispro administration resulted in the lowest number of hypoglycemic events during the test meal assessment.[66]

Similar findings have recently been confirmed by a phase 1, double-blind, randomized crossover study conducted in 31 Japanese patients with T1D who received a single subcutaneous dose of ultra-rapid lispro or insulin lispro before undergoing a euglycemic clamp procedure.[65] Authors showed that ultra-rapid lispro administration resulted in accelerated insulin absorption, faster early insulin action, reduced late exposure, and overall shorter duration of action compared with insulin lispro.[65]

The phase 3, 26-week randomized trial PRONTO-T1D assessed the safety and efficacy of ultra-rapid lispro compared with insulin lispro in 1222 adults with T1D who were also treated with basal insulin glargine or degludec.[63] The primary endpoint was HbA1c change from baseline after 26 weeks of treatment. This study showed that ultra-rapid lispro is able to provide a noninferior HbA1c reduction from baseline, along with superior postprandial glucose control and a similar safety profile compared with insulin lispro. Mealtime ultra-rapid lispro significantly reduced 1- and 2-hours postprandial glucose excursions during the mixed meal tolerance test (MMTT) compared with insulin lispro. Mealtime ultra-rapid lispro also led to a 37% significantly lower hypoglycemia rate in the late postprandial period (>4 h after meals) compared with insulin lispro.[63] Similar findings have also been confirmed in the phase 3, PRONTO-T2D trial conducted in patients with T2D.[64] A randomized, crossover, double-blind study recently showed that ultra-rapid lispro, compared with insulin lispro, accelerated insulin absorption, reduced late exposure and early postprandial glucose following a test meal also in children and adolescents with T1D.[67]

A subset of 269 participants enrolled in the PRONTO-T1D study were also evaluated through blinded CGM worn for up 14 days prior to baseline and at the 26-week primary endpoint.[68] Ultra-rapid lispro administration at the start of the meal resulted in improved postprandial glucose control, increased daytime time in glucose range 71–180 mg/dL, and decreased nighttime time in hypoglycemia ≤70 mg/dL compared with mealtime insulin lispro, although both groups showed similar HbA1c after 26 weeks of treatment.[68] The phase 3, 12-week, double-blind, crossover PRONTO-pump study conducted in 49 T1D adults on CSII therapy has recently demonstrated that ultra-rapid lispro is compatible with insulin pump use and has a safety profile similar to insulin lispro.[69] Moreover, a double-blind, randomized crossover study compared the pharmacokinetics and pharmacodynamics of ultra-rapid lispro and insulin lispro in 24 adult T1D patients on insulin pump therapy who underwent a MMTT.[70] In keeping with the aforementioned findings, ultra-rapid lispro administration via insulin pump displayed a faster insulin absorption and a reduced time to early half-maximal drug concentration compared with insulin lispro, with no differences observed in the number or severity of hypoglycemic episodes or local tolerability between the two insulin formulations. Ultra-rapid lispro administration via CSII was also associated with trends toward lower postprandial glucose excursion during the entire MMTT.[70] On June 15 2020, FDA has approved ultra-rapid lispro for treatment of adult patients with diabetes, based on data coming from PRONTO-T1D and PRONTO-T2D trials.

2.3 | Ultra-rapid biochaperone lispro

Also, a new ultra-rapid biochaperone formulation of the rapid-acting insulin analog lispro, which has been specifically designed for a faster subcutaneous insulin absorption and time–action profile,[29] is currently being evaluated in clinical trials. Ultra-rapid biochaperone lispro contains the novel oligomeric excipient BioChaperone 222 (BC222, a modified oligosaccharide) and citrate. Citrate increases vascular permeability at the injection site, whereas BC222 forms a physical complex with insulin lispro in the subcutaneous tissue protecting it from enzymatic degradation and promoting insulin hexamer dissociation and monomer absorption into the bloodstream.[54,71,72] A 14-day, phase 1, double-blind, randomized crossover study conducted in 36 patients with T1D on multiple daily injection insulin therapy showed that ultra-rapid biochaperone lispro, compared with insulin lispro, resulted in faster insulin absorption and significant reductions in 1- to 2-hours postprandial glucose excursions after individualized solid mixed meal tests.[72] Another phase 1, double-blind, randomized crossover trial conducted in 43 patients with T1D using an insulin pump and undergoing a euglycemic clamp procedure showed that the use of ultra-rapid biochaperone lispro was associated with faster-on and faster-off pharmacodynamics compared with insulin aspart, along with a higher early and a lower late exposure than both insulin aspart and ultra-rapid aspart.[71] More important, a phase 3 clinical trial is currently ongoing (ClinicalTrials.gov Identifier: NCT03262116),[73] aiming to compare the pharmacokinetic/pharmacodynamic profile and the effects on glucose control of ultra-rapid biochaperone lispro and first-generation rapid-acting insulin analogs (lispro and aspart) in adults with T1D using an automated insulin delivery system.

3 | DUAL-HORMONE ARTIFICIAL PANCREAS SYSTEMS

Dual-hormone artificial pancreas systems deliver other hormones in addition to insulin, attempting to mimic the normal physiology of glucose control more closely than first-generation, insulin-only closed-loop systems (Figure 3). To date, dual-hormone artificial pancreas devices delivering glucagon or amylin are currently being investigated in clinical trials and have not yet been approved for use in clinical practice.

3.1 | Insulin plus glucagon delivery

Dual-hormone artificial pancreas systems delivering insulin plus glucagon have been suggested as a valid alternative to single-hormone (insulin-alone) closed-loop systems in order to further improve glucose control by reducing clinically significant hyperglycemic and hypoglycemic episodes in T1D patients.[30,74–76] The rationale for the use of an artificial pancreas with insulin plus glucagon is based on the fact that T1D is also associated with a coexisting α-cell dysfunction and with an impaired α-cell glucagon secretion in response to hypoglycemia,[77] which already occurs shortly after the onset of disease[78,79] and is linked to several factors, including loss of paracrine signal from β cells,[80] early sympathetic islet neuropathy,[81] and downregulated expression of multiple genes and transcription factors critical for α-cell identity.[82] Dependence on exogenous insulin and impaired α-cell response to hypoglycemia predispose T1D patients to experience hypoglycemic episodes. Subjects with T1D also exhibit a blunted rise in glucagon concentrations during exercise,[83] potentially resulting in lowered ability to stimulate endogenous glucose production—which

is aimed to match the increased rate of glucose disposal in skeletal muscles during exercise —and subsequent increased risk of exercise-induced hypoglycemia.

Rapid-acting insulin analogs administered subcutaneously have a duration of action of approximately 3–5 hours.[49] Therefore, insulin will still be detectable in the plasma for a certain period after suspension of subcutaneous delivery, limiting the efficacy of suspension of insulin delivery for prevention of hypoglycemia during activities or under circumstances that can cause a rapid decline in blood glucose levels (eg, continuous aerobic exercise). In addition, increased insulin mobilization from subcutaneous depots at the insulin infusion sites may also occur during exercise,[83] as a likely consequence of the increased subcutaneous adipose tissue blood flow.[84]

Conversely, subcutaneous glucagon is rapidly absorbed, displaying an onset of action of 5 minutes, and a time to peak plasma concentrations of 10–20 minutes.[85,86] Because of such differences in the pharmacokinetics of insulin and glucagon, delivering glucagon when hypoglycemia occurs or is predicted may offer a more effective strategy to prevent hypoglycemia in comparison with suspension of subcutaneous insulin during closed-loop operation, particularly under circumstances of rapidly dropping blood glucose levels, such as during aerobic exercise.[87,88] Small doses of subcutaneous glucagon lead to a rapid and remarkable increase in blood glucose levels in a dose-dependent manner.[86] In fact, it has been shown that mini-dose glucagon (150 μg) administered subcutaneously effectively treats hypoglycemia (<70 mg/dL) in an outpatient setting,[89] prevents exercise-induced hypoglycemia, and results in less postintervention hyperglycemia compared with carbohydrate ingestion during 45 minutes of aerobic activity in individuals with T1D.[52]

Preliminary evidence shows that dual-hormone artificial pancreas (insulin and glucagon) is not superior to single-hormone (insulin alone) artificial pancreas in reducing nocturnal hypoglycemia in patients with T1D, suggesting that single-hormone system may be sufficient in counteracting slow overnight declines in glucose levels.[30,75,90,91] However, a potential effect of glucagon (infused subcutaneously through dual-hormone artificial pancreas systems) on lowering nocturnal hypoglycemia risk cannot be excluded. A randomized crossover trial demonstrated greater efficacy of dual-hormone artificial pancreas versus single-hormone system in reducing nocturnal hypoglycemia among children and adolescents with T1D attending a diabetes camp and participating in higher-than-usual levels of daytime physical activity.[92]

Larger and longer studies are warranted to better establish the role of dual-hormone artificial pancreas delivering insulin plus glucagon in improving nocturnal glucose control following different daytime activities mimicking real-life glucose excursions (eg, continuous moderate to high-intensity aerobic exercise, high-carbohydrate and/or high-fat meals, etc). Further studies are also needed in order to evaluate whether using glucagon in dual-hormone artificial pancreas systems is able to lead to better glucose control and time in range by allowing more aggressive insulin delivery and relying on glucagon to treat hypoglycemia. Nonetheless, the addition of glucagon to a dual-hormone artificial pancreas system does not completely abrogate the risk of hypoglycemia, particularly in the presence of high circulating insulin concentrations or if glucagon delivery fails.[93,94] Indeed, another aspect

worth mentioning is that insulin and glucagon absorption rates are positively correlated under closed-loop conditions, with slower absorption of insulin being associated with slower absorption of glucagon regardless of body composition (percentage of body fat, percentage of fat in the abdominal area, and total mass of abdominal fat).[85] It has also been shown that the efficacy of glucagon in preventing hypoglycemia depends upon circulating plasma insulin levels and insulin infusion rates: glucagon is more effective in raising blood glucose levels in the presence of low/moderate circulating insulin levels or lower insulin infusion rates, whereas it is less effective in the presence of high circulating insulin levels or high insulin infusion rates during closed-loop operation.[93,95,96] This phenomenon depends on the fact that the insulin-to-glucagon ratio regulates hepatic gluconeogenesis and glycogenolysis, thus determining the overall hepatic glucose output (eg, higher levels of this ratio results in a reduced hepatic glucose production).[88,97,98]

Due to the high cost and the significant complexity of dual-hormone artificial pancreas systems delivering insulin and glucagon, such devices may not be suitable for all users but could be particularly beneficial for selected T1D individuals, such as athletes experiencing frequent episodes of exercise-induced hypoglycemia, subjects with a recent history of severe hypoglycemia, or subjects suffering from hypoglycemia unawareness and/or recurrent severe hypoglycemic episodes. Therefore, long-term studies conducted in such high-risk populations are required to evaluate the efficacy of dual-hormone artificial pancreas with insulin plus glucagon in preventing or reducing hypoglycemia and potentially hypoglycemia unawareness by reversing the hypoglycemia-associated autonomic failure.[30,99] Additionally, glucagon may play a beneficial role in preventing weight gain or even in promoting weight loss through its effects on inducing central satiety, reducing caloric intake and increasing energy expenditure.[100] In this regard, glucagon delivery in T1D may be particularly advantageous given the growing prevalence of subjects with T1D who are overweight or obese.[101]

Yet, possible risks, limitations and disadvantages of incorporating glucagon into dual-hormone artificial pancreas systems also exist (Table 1). Different aspects pertinent to T1D pathophysiology and eating behaviors of T1D patients should be taken into account, namely reduced glycogen stores, decreased glycogen synthesis and breakdown, along with blunted hepatic glucose production in response to glucagon occurring particularly in subjects eating low-carbohydrate diets or consuming significant amounts of alcohol.[94] There is also concern that repeated small doses of glucagon in subjects with T1D may lead to hepatic glycogen depletion and subsequent impaired response to glucagon after chronic use.[88] However, a study involving 11 adult subjects with well-controlled T1D showed that hepatic glycogen stores (assessed by magnetic resonance spectroscopy) and the hyperglycemic response to glucagon administration were maintained after receiving multiple doses of glucagon (eight doses of subcutaneously administered glucagon at a dose of 2 μg/kg, for a total mean dose of 1126 μg over 16 h).[102] This finding supports the safety of repeated glucagon delivery in the setting of dual-hormone closed-loop systems, although there is a need for additional data on the safety profile of long-term low-dose glucagon administration.[88] Other concerns that have been raised regarding the use of glucagon in bihormonal artificial pancreas systems include the potential development of glucagon resistance or tachyphylaxis over time as well as the risk of occlusion of glucagon-delivering catheters. Yet, the latter risk will likely be

low with future improvements of infusion sets and with the availability of novel stable liquid formulations of glucagon or glucagon analogs.

Up to now, several studies demonstrated that automated closed-loop systems delivering insulin plus glucagon are able to reduce the frequency of hypoglycemia (including hypoglycemia occurring during and after exercise), time spent in hypoglycemic range, and the need for carbohydrate treatment compared with closed-loop systems delivering insulin alone in different settings (eg, home-use setting, diabetes camp setting, continuous moderate-intensity aerobic exercise sessions).[30,87,92,103–109]

One of the most relevant limitations of dual-hormone artificial pancreas systems delivering insulin plus glucagon relies on the fact that commercially available glucagon formulations are not stable in liquid form and are not suitable for continuous pump use. Since native glucagon is a highly unstable peptide, which tends to form β-pleated sheets of amyloid-like fibrils in aqueous solution,[110,111] glucagon cartridges for pump use need to be replaced every 8–24 hours with freshly reconstituted glucagon. To overcome the issue of chemical and physical stability of glucagon, in recent years, several pharmaceutical companies have been focusing on the development of novel alternative and stable liquid glucagon (or glucagon analog) formulations,[109,112] which will potentially be available for continuous pump use in dual-hormone artificial pancreas systems in the near future.[111]

With this regard, a recent 76-hours, open-label, crossover, randomized controlled trial enrolled 23 adults with T1D to assess the efficacy and feasibility of a dual-hormone closed-loop system delivering insulin and a novel liquid stable glucagon formulation in an outpatient setting with structured aerobic exercise.[109] The dual-hormone closed-loop system was compared with an insulin-only single-hormone closed-loop system and with an insulin-only PLGS system. Dual-hormone and single-hormone systems used an automated exercise detection algorithm. Dual-hormone closed-loop system was also equipped with a hypoglycemia-prediction algorithm aimed to deliver a minidose of glucagon in response to predicted hypoglycemia (<70 mg/dL) during the exercise period. The use of a novel liquid stable glucagon formulation abrogated the need for pump reservoir changes every 24 hours. The primary endpoint was percentage time in hypoglycemia (<70 mg/dL) from the start of aerobic exercise (45 minutes of aerobic exercise) to 4 hours after the start of exercise. For the in-clinic exercise period (from the start of exercise to 4 hours after the start of exercise), the dual-hormone closed-loop system significantly reduced the percentage time in hypoglycemia compared with insulin-only single-hormone closed-loop system (0.0% vs. 8.3%, respectively). During the same period, the dual-hormone closed-loop system significantly reduced the need for rescue carbohydrate treatments compared with both single-hormone and PLGS systems. Nevertheless, the reduction in the percentage time in hypoglycemia achieved with the dual-hormone system during the in-clinic exercise period came at the cost of a significantly increased percentage time in hyperglycemia (>180 mg/dL) compared with both single-hormone and PLGS systems (dual-hormone system: 20.8% vs. single-hormone system: 6.3% vs. PLGS system: 4.2%). Across the entire study duration, the percentage of time in hypoglycemia (<70 mg/dL) was significantly lower for the dual-hormone system compared with both single-hormone and PLGS systems (0.5% vs. 1.3% and 1.5%, respectively). For the entire study duration, the percentage of time

in range (70–180 mg/dL) achieved with the dual-hormone system was comparable to that achieved with the single-hormone system (71.0% vs. 72.6%) and significantly higher than that achieved with the PLGS system (71.0% vs. 63.4%). However, the use of a dual-hormone system was also associated with a significantly higher percentage time in hyperglycemia (>180 mg/dL) compared with the use of a single-hormone system for the entire study duration (28.2% vs. 25.1%, respectively). Four participants experienced nausea related to glucagon during the dual-hormone system arm, and three of them withdrew from the study due to this complaint.[109] Castellanos et al[113] recently conducted an open-label, random-order, crossover, home-use trial to evaluate the function and safety of an advanced dual-chamber pump artificial pancreas (the iLet bionic pancreas) capable of combined subcutaneous delivery of insulin and dasiglucagon for autonomous bihormonal treatment of T1D. The authors used the novel soluble and chemically stable glucagon analog dasiglucagon, which is available in a ready-to-use aqueous solution (without need for reconstitution) and has already proven to have a good safety and efficacy profile for the treatment of severe hypoglycemia in patients with T1D.[114,115] Apart from the pump, the iLet bionic pancreas includes an integrated CGM sensor and mathematical dosing algorithms aimed to automatically deliver insulin and dasiglucagon based on glucose readings received by the sensor. Ten adults with T1D used for 7 days the iLet bionic pancreas in both its insulin-only and bihormonal configurations. The mean CGM glucose and time in range (70–180 mg/dL) were 149 ± 13 mg/dL and 72 ± 8%, respectively, in the insulin-only period, and 139 ± 11 mg/dL and 79 ± 9%, respectively, in the bihormonal period. The median percentage of time with CGM glucose <54 mg/dL was 0.6% in the insulin-only period and 0.2% in the bihormonal periods, respectively. The mean total daily dose of dasiglucagon was 0.35 mg/day[113] and was comparable to that of freshly reconstituted human glucagon used in previous bihormonal artificial pancreas trials.[105] Importantly, the use of a single, prefilled dasiglucagon cartridge for 7 days was not associated with infusion site reactions or occlusions, thus supporting the practicality for this liquid formulation in clinical use.[113] These findings support testing the use of dasiglucagon in much larger and longer bihormonal artificial pancreas trials. Additional novel, liquid glucagon preparations that are currently available for testing in dual-hormone artificial pancreas systems include a biochaperone glucagon and nonaqueous soluble glucagon.[112,116]

Overall, the aforementioned studies only demonstrated the short-term safety and efficacy of dual-hormone artificial pancreas systems delivering insulin plus glucagon. Future studies of appropriate size and duration are needed to: (a) establish the safety profile of long-term low-dose glucagon administration (the known safety profile of glucagon is mainly based on short-term high-dose administration) and (b) to assess the long-term efficacy of dual-hormone artificial pancreas systems with insulin and glucagon in preventing or reducing exercise-induced hypoglycemia without the need for rescue carbohydrate treatments or changes in insulin infusion rates and without increasing the percentage time spent in hyperglycemia.[88] Similarly, it would be worth investigating whether optimization of glucagon dose and timing (ie, adapting the preexercise glucagon according to the individual risk of subsequent hypoglycemia rather than using a fixed amount of minidose glucagon) may minimize hyperglycemia and glucagon-related gastrointestinal side effects, such as nausea and vomiting. It is tempting to speculate that dual-hormone artificial pancreas

systems delivering ultra-rapid-acting insulin analogs plus glucagon may be advantageous for athletes with T1D experiencing recurrent episodes of exercise-induced hypoglycemia. These remarks may also apply to non-athlete subjects with T1D, for whom fear of hypoglycemia, deterioration of glucose control, insufficient time, lack of motivation and general scarcity of knowledge around exercise management represent strong barriers to incorporating regular physical activity into daily life.[117,118]

3.2 | Insulin plus amylin (pramlintide) delivery

Another investigational approach to multihormone closed-loop control in patients with T1D includes the administration of insulin in combination with the amylin analog pramlintide. Amylin (also called islet amyloid polypeptide or IAPP) is a 37-amino acid peptide hormone that is cosecreted with insulin by pancreatic β-cells in response to meals, at a level of about 1% that of insulin.[119] Notably, amylin plays an important role in glucose homeostasis, promoting satiety, slowing gastric emptying and suppressing glucagon secretion in the postprandial period, thereby reducing postprandial glucose excursions and preventing excessive caloric intake.[120–123]

In T1D, autoimmune β-cell destruction also leads to a deficiency in amylin secretion that parallels insulin deficiency.[120,121,124] In this regard, T1D can be considered as a two-hormone deficiency disorder.[123] Coupled to insulin deficiency and failure of glucagon suppression in the postprandial period (due to the loss of paracrine inhibition by insulin released from the neighboring β-cells),[98,125] amylin deficiency represents another cause of postprandial hyperglucagonemia, poor postprandial glucose control and high glucose variability in patients with T1D.[124] Hence, coreplacement with insulin plus pramlintide by continuous infusion systems may represent a more physiological hormone replacement therapy in T1D as well as a promising strategy to overcome the limitations observed with insulin replacement therapy alone and to improve the efficacy of insulin treatments.[123] During closed-loop operation, the action of pramlintide to slow gastric emptying and glucose appearance at mealtime would also permit algorithms and insulin additional time to react to postprandial glucose excursions.[126] In healthy subjects, insulin is secreted by pancreatic β-cells into the hepatic portal vein and undergoes first pass-metabolism in the liver; thus, insulin levels are several times higher in the liver compared with peripheral tissues. Of note, pancreatic insulin secretion leads to an insulin gradient at the liver compared with the rest of the body (approximately 3:1). The hepatoportal insulin gradient is crucial for the normal control of glucose metabolism during both fasting and feeding states. The physiological 3:1 insulin ratio that exists between the liver and the rest of the body is always lost when insulin is administered via a peripheral route (eg, subcutaneous, peripheral vein, intranasally, inhalation), causing arterial hyperinsulinemia as well as impaired regulation of hepatic glucose production and whole-body glucose uptake.[127] Therefore, in subjects with T1D, subcutaneously administered (exogenous) insulin does not maintain circulating insulin concentrations and does not suppress hepatic glucose production to the same extent as endogenous insulin does through its physiological secretory route (the hepatic portal vein), resulting in greater postprandial glycogen mobilization from the liver. This phenomenon occurs because the suppressive effects of insulin on hepatic glucose production are primarily mediated by its direct actions on hepatocytes, whereas the indirect

effects exerted by insulin on nonhepatic tissues (suppression of lipolysis, α-cell glucagon secretion and glucogenic amino acid output from skeletal muscle) are likely to play a minor role in the regulation of hepatic glucose output.[127–131]

In this view, the addition of amylin analogs to insulin in diabetic patients may help to reduce daily insulin requirements and/or improve the efficacy of insulin therapy by virtue of amylin's dose-dependent ability to suppress postprandial glucagon secretion.[132] Pramlintide is a synthetic, stable, nonfibrillating, and soluble injectable analog of human amylin approved by the FDA as an adjunctive treatment to insulin therapy in patients with T1D and T2D.[133–135] Mealtime injections of pramlintide have been shown to improve glucose and metabolic control in patients with T1D by suppressing postprandial glucagon secretion and reducing the magnitude of postprandial glucose excursions.[134,136–140] Despite these potential benefits, the use of pramlintide as an injectable antidiabetic medication has remained infrequent from the time of its approval in 2005[141] due to some reasons, including (a) the need for administration of insulin and pramlintide as separate injections and (b) the possible occurrence of side effects, such as nausea (although it is often self-limiting after initial dosing) and postprandial hypoglycemia, which can occur particularly if prandial insulin dosing is not correctly adjusted.[123]

Two studies conducted in adolescent and young adults with T1D on insulin-alone closed-loop systems showed that the addition of pramlintide (administered by separate mealtime subcutaneous injections) was able to mitigate postprandial blood glucose excursions by delaying and reducing the peak increment in postprandial plasma glucose levels.[142,143] However, the need for separate subcutaneous pramlintide injections with each meal in addition to insulin injections still represents a serious barrier to patient adherence and acceptance for a long-term period.

Interestingly, a 24-hour inpatient study conducted in adults with T1D showed that continuous subcutaneous infusion of regular human insulin plus pramlintide (administered via separate infusion pumps in a fixed ratio consisting of 9 μg of pramlintide per unit of insulin) reduced glucose variability and postprandial glucose and glucagon increments, without occurrence of major hypoglycemic events.[144] Similar findings have recently been confirmed in a randomized crossover trial conducted in adults with T1D in inpatient settings for 24 hours.[145] A dual-hormone artificial pancreas delivering pramlintide in a basal-bolus, glucose-responsive manner and with a fixed ratio relative to insulin (6 μg of pramlintide per unit of insulin) was used to mimic a coformulation (of insulin and pramlintide) and reproducing the physiology of amylin secretion.[145] Artificial pancreas system delivering rapid-acting insulin and pramlintide has been shown to improve glucose control compared with a rapid-acting insulin-alone system by increasing time spent in target glucose range and reducing mean glucose level and glucose variability, without increasing hypoglycemia.[145] Higher treatment satisfaction was also reported by participants using the rapid-acting insulin-and-pramlintide artificial pancreas system compared to those on the rapid-acting insulin-alone system.[145] Gastrointestinal symptoms were reported more frequently with the rapid and regular insulin-and-pramlintide systems compared with the rapid insulin-alone system, although none of the symptoms were severe.[145] Notwithstanding, it is worth noting that all these studies were conducted over a 24-hour period and involved small groups

of patients with T1D. Larger and longer-term ambulatory studies are therefore needed to establish the safety and efficacy of dual-hormone artificial pancreas devices delivering insulin plus pramlintide in subjects with T1D.

Efforts to develop novel fixed-dose, stable coformulations of pramlintide and fast-acting insulin analogs are currently ongoing to leverage the beneficial effects of pramlintide on postprandial glucose without the need for additional injections.[146,147] The main challenge in developing stable coformulations of insulin and amylin analogs relies on the fact that insulin analogs and pramlintide are typically formulated at different pH levels (approximately 7.4 and 4, respectively).[126,148,149] Moreover, pharmacokinetics of the current pramlintide and insulin formulations are highly dissimilar due to different aggregation states of the proteins in the formulations, leading to distinct subcutaneous absorption behaviors of pramlintide and insulin.[148] When injected separately, pramlintide is more rapidly absorbed from subcutaneous tissue than rapid-acting insulin analogs and displays an almost immediate onset of action, peak action at approximately 20 minutes, and a total duration of action of about 90 minutes.[148] This ultimately results in the lack of pharmacokinetic overlap of pramlintide and insulin, which prevents the physiological mode of action and the synergistic effects of these two hormones in current dual-hormone replacement therapies.[148,150]

Maikawa et al[148] recently employed a simultaneous supramolecular, noncovalent PEGylation of rapid-acting insulin analogs and pramlintide by using CB[7]-PEG (cucurbit[7] uril-conjugated polyethylene glycol) to stabilize the two hormones in a coformulation. The authors demonstrated that this coformulation is stable at physiological pH (pH 7.4) and leads to a greater overlap between the pharmacokinetic profiles of insulin and pramlintide in a rat model and in a swine model of insulin-deficient diabetes. This overlap in insulin and pramlintide exposure profiles mainly occurred as a consequence of the extended pramlintide duration of action. Importantly, the increase in overlap between the pharmacokinetic curves of insulin and pramlintide was also associated with relevant metabolic implications in diabetic pigs. The coformulation better mimicked the physiological endogenous β-cell cosecretion of insulin and amylin by enhancing postprandial glucagon suppression compared with the clinical standard of separate insulin and pramlintide administrations.[148] Although awaiting future clinical translation, this newly developed coformulation of insulin and pramlintide may reduce the burdensome need for insulin and pramlintide administration as two separate injections and concurrently offer a valuable and more physiological dual-hormone replacement strategy capable of improving glucose control by virtue of its pronounced mealtime glucagon suppression ability.[148,150]

In this regard, two studies conducted in T1D subjects have recently investigated the pharmacokinetics and pharmacodynamics of ADO09, a novel stable coformulation of pramlintide and the rapid-acting A21G human insulin analog (the main circulating metabolite of insulin glargine)[151,152] formulated at acidic pH (pH 4).[153,154] A double-blind randomized crossover trial conducted in 21 T1D subjects compared premeal injection of ADO09 versus insulin aspart (both in combination with degludec as basal insulin) over 24 days.[153] Authors showed that the use of pramlintide-insulin coformulation significantly improved postprandial glucose during the MMTT and led to a significant increase in 24 hours-time in two different target glucose ranges (70–180 mg/dL and tight range 80–

140 mg/dL) compared with insulin aspart. Moreover, pramlintide-insulin coformulation use was associated with significantly lower prandial insulin doses compared to insulin aspart, along with a significant reduction in body weight from baseline.[153] Another double-blind randomized crossover meal test trial compared the safety, pharmacokinetics and pharmacodynamics of ADO09 with insulin lispro and separate subcutaneous injections of human insulin and pramlintide in 24 adults with T1D.[154] Fixed doses of 7.5 U insulin (all arms) and 45 μg pramlintide (pramlintide arms) were administered subcutaneously to participants immediately before the meal test. Compared with lispro, the ADO09 formulation led to a significant 97% reduction in postprandial blood glucose excursions within the first hour after the test meal, along with a significant decrease in postprandial glucagon levels during the first 2 hours and a significantly slower gastric emptying (as assessed by acetaminophen absorption kinetics). ADO09 showed a favorable tolerability profile and hypoglycemic events after dosing were rare. Notwithstanding, the insulin exposure from insulin lispro alone was higher in the first 2 hours compared with the insulin exposure from both treatments containing pramlintide, suggesting that the pharmacological pramlintide effects on postprandial glucagon secretion and gastric emptying outweigh the lower early insulin exposure.[154]

With regard to dual-hormone artificial pancreas devices, coformulations of insulin and pramlintide may help to overcome the need for the concomitant use of two separate continuous subcutaneous infusion systems and two separate infusion sites. In fact, these coformulations may be used in the same reservoir of conventional single-chamber insulin pumps of artificial pancreas devices (that are already on the market), thus providing a better strategy to reduce or prevent postprandial glucose excursions compared to more aggressive insulin delivery, which can lead to a higher risk of hypoglycemia. Furthermore, coformulations of insulin and pramlintide would potentially allow for the future development of dual-chamber pump artificial pancreas systems capable of concurrent delivery of insulin, pramlintide and glucagon (triple-hormone artificial pancreas), which may more closely mimic the physiology of the endocrine pancreas (Figure 3). In this regard, Majdpour et al[155] conducted a series of experiments in nine adults with T1D aiming to design and optimize a novel fully automated triple-hormone (insulin–pramlintide–glucagon) artificial pancreas that does not require meal input from the user and alleviates the burden of carbohydrate counting, while maintaining noninferior glucose control compared with insulin-alone hybrid artificial pancreas systems. Each participant underwent two 27-hour inpatient interventions: (a) an insulin-alone artificial pancreas intervention with carbohydrate counting (which served as a comparator) and (b) a fully automated multihormone artificial pancreas intervention. For the triple-hormone intervention, three separate infusion pumps were installed to deliver faster-acting insulin aspart, pramlintide and freshly reconstituted glucagon, respectively. The artificial pancreas system was iteratively enhanced between participants to reduce postprandial hyperglycemia and gastrointestinal symptoms and to prevent hypoglycemia. The baseline dosing algorithm for the triple-hormone artificial pancreas was a model predictive controller that administered pramlintide and insulin boluses when glucose levels crossed 9.0 mmol/L (threshold-triggered insulin and pramlintide boluses). Pramlintide and insulin were administered in a basal-bolus manner with a fixed ratio to mimic an insulin–pramlintide coformulation and the physiology of the endocrine

pancreas. Glucagon was administered as miniboluses in response to low glucose levels. The threshold-triggered insulin and pramlintide boluses appeared to achieve suboptimal postprandial glucose excursions as such boluses were administered 1–2 hours after meals. This resulted in prolonged postprandial hyperglycemia and increased risk of late postprandial hypoglycemia.[155] Since 25%–50% of a high-glycemic-load carbohydrate meal is absorbed within the first hour of meal consumption,[156,157] administering pramlintide more than 1 hour after the meal may be ineffective in slowing gastric emptying and lowering postprandial hyperglycemia as a large portion of the meal carbohydrate content has already been absorbed at that time. Similarly, administering late insulin boluses may increase the risk of late postprandial hypoglycemia. Therefore, investigators added a model-based meal-detection algorithm in order to detect meals 30–40 minutes after ingestion and trigger insulin and pramlintide boluses, rather than administering correction boluses when glucose levels were >9.0 mmol/L (>162 mg/dL). Investigators also modified the algorithm to no longer deliver glucagon, since the results from previous participants suggested that glucagon was only needed to prevent impending hypoglycemia resulting from late insulin and pramlintide boluses. When the meal detection algorithm was added, insulin and pramlintide were administered closer to mealtimes and this made the system more effective in improving postprandial glucose levels. Moreover, removing glucagon did not increase the time spent in hypoglycemia by participants.[155] However, the aforementioned approach used to optimize the fully automated artificial pancreas had some limitations. First, the study was conducted in an inpatient setting for only one day without vigorous exercise, which does not reflect real-life conditions. In addition, each change to the algorithm was driven by the results of two or three participants, which may not be generalizable to the general population.[155]

The advent of robust meal-and exercise-detection algorithms may certainly offer next steps to developing fully automated triple-hormone artificial pancreas systems, although the use of such technologies will need to be investigated in larger and longer studies conducted in free-living outpatient conditions. Table 1 summarizes the established and potential benefits, risks and limitations of ultra-rapid-acting insulin analogs and dual-hormone artificial pancreas systems delivering insulin in conjunction with glucagon or pramlintide.

4 | CONCLUSION

Although several studies showed that current artificial pancreas devices are able to improve glucose control compared with conventional insulin pump therapy, the use of an artificial pancreas remains often associated with clinically significant hypoglycemic and hyperglycemic episodes. Indeed, postprandial glucose excursions (early postprandial hyperglycemia and late postprandial hypoglycemia) and exercise-induced hypoglycemia represent major hurdles in improving glucose control and glucose variability in many patients with T1D.[158,159] Moreover, current “hybrid” closed-loop systems still require several efforts and inputs from the user. The ultimate goal of T1D technology research is the fully automated control of blood glucose aimed to achieve near-normal glucose levels with low glucose variability, which would result in reduced risk of long-term diabetes complications accompanied by an unquestionable improvement in the quality of life for millions of people living with T1D worldwide. Hence, research is increasingly moving toward the development of fully automated artificial pancreas systems able to

automatically adjust basal insulin infusion rates and trigger the delivery of mealtime insulin boluses based on several physiological variables (meal timing and composition, duration and type of exercise, etc) and without the need for human intervention. Development of ultra-rapid-acting insulin analogs with a more physiological time–action profile, as well as subcutaneous delivery of glucagon and pramlintide in addition to insulin, represent important steps to fully closing the loop in artificial pancreas systems, better reproducing the physiology of the endocrine pancreas and addressing the unmet need for further improvements in postprandial and postexercise glucose control in several patients with T1D. With this regard, FDA has recently approved ultra-rapid insulin aspart for pump use, and clinical trials are currently investigating newly developed ultra-rapid formulations of insulin lispro for pump use.

Several short-term studies demonstrated the safety and efficacy of dual-hormone artificial pancreas systems delivering glucagon or pramlintide in addition to insulin in terms of prevention and/or reduction of exercise-induced hypoglycemia and postprandial glucose excursions in patients with T1D. Novel liquid glucagon products are now available with enhanced stability necessary for use in dual-hormone artificial pancreas systems, and novel coformulations of insulin and pramlintide are under investigation. Nevertheless, some limitations of dual-hormone artificial pancreas systems still remain to be addressed, including the issue of cost and supply of novel glucagon and amylin formulations, additional patient education, increased complexity in control algorithms, requirement of dual-chamber pumps coupled with two infusion sets and infusion sites, and frequent site rotation.

Based on the current evidence (mostly coming from short-term studies), selected subgroups of T1D patients who may benefit from the use of bihormonal artificial pancreas systems delivering glucagon or pramlintide in addition to insulin may include those experiencing repeated exercise-induced hypoglycemic episodes or frequent postprandial hyperglycemic episodes, respectively. Future studies will undoubtedly be crucial to better establish under what clinical contexts dual-hormone artificial pancreas systems might be advantageous over insulin-alone artificial pancreas systems in patients with T1D. In this regard, the next few years will be focused on the study of bihormonal artificial pancreas devices during a long-term period with the incorporation of novel stable glucagon liquid formulations, as well as on the development of coformulations of insulin and pramlintide which may allow for the development of dual-chamber pump artificial pancreas systems capable of combined subcutaneous delivery of insulin, glucagon and pramlintide (triple-hormone artificial pancreas). Such advances will certainly bring artificial pancreas systems a step closer to better mimicking the physiology of the endocrine pancreas, potentially alleviating the individual disease burden and improving the quality of life and clinical outcomes in subjects with T1D. In the meantime, research efforts will constantly move forward in the parallel race to find a biological cure for T1D based on safe and effective β-cell replacement approaches.

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CONFLICT OF INTEREST

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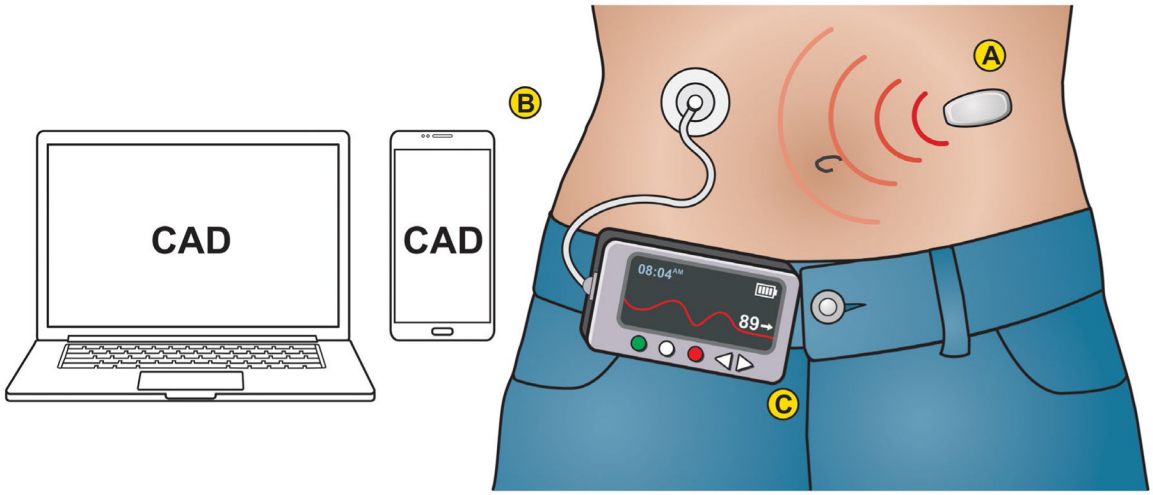

FIGURE 1.

Schematic diagram illustrating the automated insulin delivery in insulin-only single-hormone artificial pancreas systems. A real-time continuous glucose monitor sensor inserted in the subcutaneous space (A) measures interstitial glucose concentrations approximately every 5 minutes and wirelessly sends such information via a transmitter to a control algorithm device (CAD; B) hosting a control algorithm (dosing algorithm) that analyzes and processes glucose readings from the glucose sensor and subsequently calculates in real time the correct amount of insulin to deliver via the insulin pump (C). Then, the insulin pump, which communicates with the CAD, automatically delivers the correct insulin dose calculated by the algorithm via a subcutaneous cannula

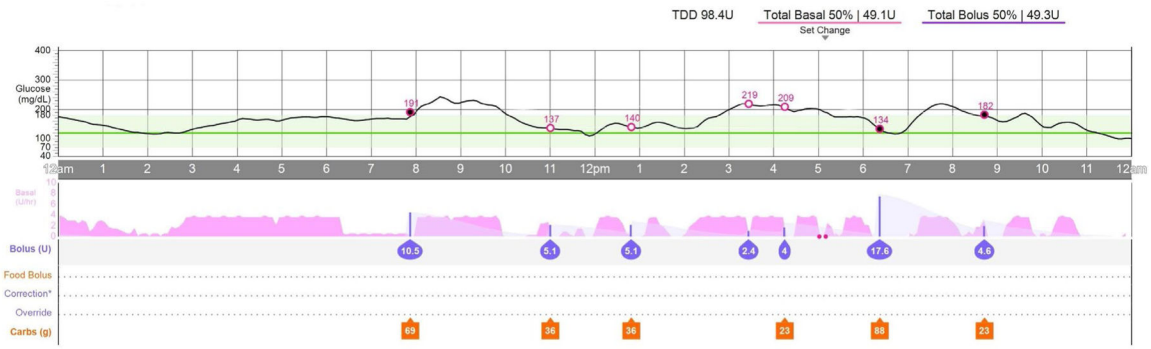

FIGURE 2.

Daily report from MiniMed 670G hybrid closed-loop system. The upper portion of the report shows sensor glucose values (black line) over a 24-h period. Small black dots indicate confirmatory fingerstick blood glucose readings entered into the control algorithm device for glucose sensor calibration. The green shaded area shows the glucose range to 70–180 mg/dL (time in range). The lower portion of the report illustrates the automated basal insulin delivery (basal infusion rates are represented by pink waves) and insulin boluses. Purple bars represent insulin boluses, whereas the adjacent purple shaded waves represent active insulin (also referred to as “insulin on board,” defined as the insulin which is still active from previous bolus doses). Purple-filled circles indicate the exact bolus doses, whereas orange-filled boxes indicate the number of carbohydrates consumed per meal. Currently available hybrid closed-loop systems require patient intervention to insert the exact amount of carbohydrates ingested and trigger mealtime insulin boluses. TDD, total daily insulin dose

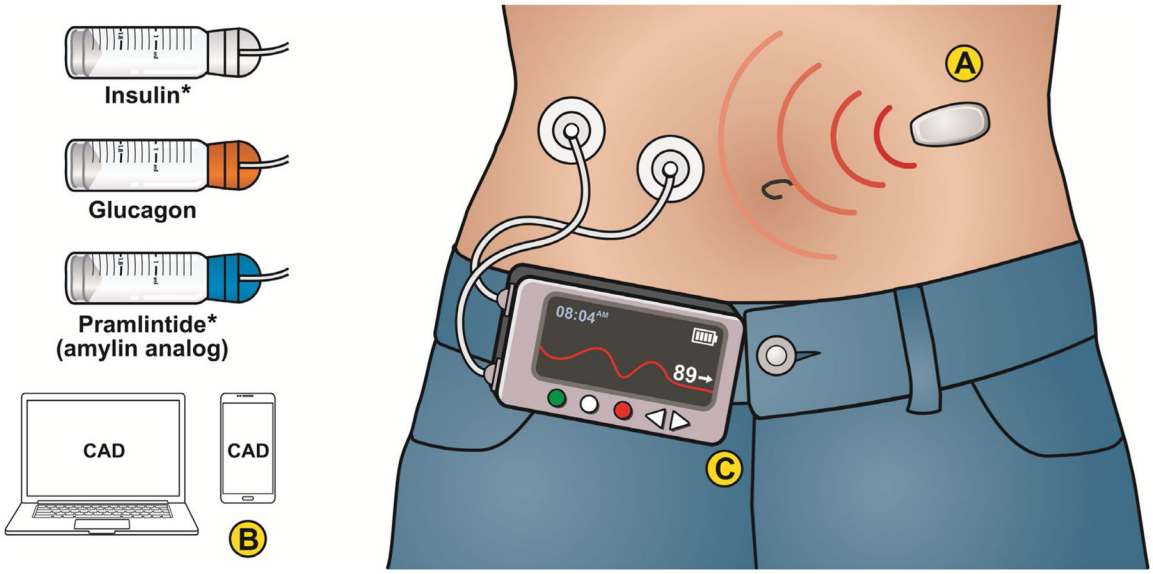

FIGURE 3.

Schematic diagram illustrating the concept of a dual-hormone artificial pancreas system. A dual-chamber pump is equipped with two infusion sets for subcutaneous infusion of insulin in conjunction with glucagon or pramlintide (an amylin analog). A real-time continuous glucose monitor sensor inserted in the subcutaneous space (A) transmits information about interstitial glucose measurements to a control algorithm device (CAD; B). The CAD hosts a control algorithm (dosing algorithm) that analyzes and processes glucose readings from the glucose sensor and communicates wirelessly with the dual-chamber pump (C), which automatically delivers insulin and glucagon or pramlintide based on glucose values. *Novel coformulations of insulin and pramlintide are currently under investigation and may allow for the development of dual-chamber pump artificial pancreas systems capable of combined subcutaneous delivery of insulin, glucagon and pramlintide (triple-hormone artificial pancreas)

TABLE 1

Established and potential benefits, risks and limitations of ultra-rapid-acting insulin analogs and dual-hormone artificial pancreas systems delivering insulin in conjunction with glucagon or pramlintide

Ultra-rapid insulin analogs	•	*Benefits*
	–	More physiological insulin time–action profile
	–	Reduction of early postprandial hyperglycemia
	–	Reduction of late postmeal hypoglycemia
	–	More rapid adaptation to changing glucose levels during closed-loop operation
	•	*Possible risks or limitations*
	–	Need for a cautious use under certain circumstances or in selected conditions due to the possible risk of early postprandial hypoglycemia (eg, initiation of exercise shortly after mealtime insulin injection, consumption of low-glycemic index foods, or high-fat and high-fiber meals, diabetic gastroparesis)
Glucagon (or glucagon analogs)	•	*Benefits*
	–	Reduced frequency and duration of hypoglycemia and exercise-induced hypoglycemia
	–	Reduced need for carbohydrate ingestion or rescue carbohydrate treatments and/or patient's interaction with the system
	–	Reduced postintervention hyperglycemia compared with carbohydrate ingestion during aerobic exercise
	–	Potential role in preventing weight gain or promoting weight loss by inducing central satiety, reducing caloric intake and increasing energy expenditure
	•	*Possible risks or limitations*
	–	Need for development of stable liquid formulations of glucagon or glucagon analogs (currently available glucagon formulations are not stable in liquid form and glucagon cartridges for pump use need to be replaced every 8–24 h with freshly reconstituted glucagon)
	–	Interindividual variability in hepatic glucose production in response to glucagon
	–	Potential hepatic glycogen depletion occurring after repeated glucagon delivery
	–	Potential risk for development of glucagon resistance or tachyphylaxis over time
	–	Reduced ability of glucagon to prevent hypoglycemia in the presence of high circulating insulin concentrations or defects in glucagon delivery from the pump reservoir
	–	Potential risk of increased percentage time spent in hyperglycemia (>180 mg/dL) during and after exercise
	–	Occurrence of glucagon-related side effects (nausea, vomiting, headache, erythema, and/or edema at the glucagon infusion site)
	–	Glucagon is contraindicated in patients with known hypersensitivity to the drug and in patients with known pheochromocytoma
	–	Additional patient education,[a] high cost,[a] increased complexity in control algorithms,[a] requirement of dual-chamber pumps coupled with two infusion sets and infusion sites,[a] frequent site rotation,[a] and risk of infusion set occlusion[a]
Pramlintide (amylin analog)	•	*Benefits*
	–	Reduced postprandial glucose excursions and glucose variability by slowing gastric emptying, promoting satiety and suppressing postprandial glucagon secretion and endogenous glucose production

- Delayed gastric emptying and glucose appearance at mealtime would permit algorithms and insulin additional time to react to postprandial glucose excursions during closed-loop operation

- *Possible risks or limitations*
  - Need for development of stable coformulations of insulin and pramlintide
  - Occurrence of nausea (often self-limiting after initial dosing)
  - Occurrence of postprandial hypoglycemia, particularly if prandial insulin dosing is not correctly adjusted
  - Pramlintide is contraindicated in patients with known hypersensitivity to the drug and in patients with hypoglycemia unawareness or confirmed gastroparesis
  - Additional patient education,[a] high cost,[a] increased complexity in control algorithms,[a] requirement of dual-chamber pumps coupled with two infusion sets and infusion sites,[a] frequent site rotation[a], and risk of infusion set occlusion[a]

[a]These limitations apply to dual-hormone artificial pancreas systems in general.