

The Evolution of Insulin Administration in Type 1 Diabetes

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Abstract

Insulin has been utilized in the treatment of type 1 diabetes (T1D) for 100 years. While there is still no cure for T1D, insulin administration has undergone a remarkable evolution which has contributed to improvements in quality of life and life expectancy in individuals with T1D. The advent of faster-acting and longer-acting insulins allowed for the implementation of insulin regimens more closely resembling normal insulin physiology. These improvements afforded better glycemic control, which is crucial for limiting microvascular complications and improving T1D outcomes. Suspension of insulin delivery in response to actual and forecasted hypoglycemia has improved quality of life and mitigated hypoglycemia without compromising glycemic control. Advances in continuous glucose monitoring (CGM) and insulin pumps, efforts to model glucose and insulin kinetics, and the application of control theory to T1D have made the automation of insulin delivery a reality. This review will summarize the past, present, and future of insulin administration in T1D.

Keywords

Type 1 Diabetes (T1D), Insulin, Hybrid-Closed Loop, Hypoglycemia

1. Introduction

The discovery, purification, and subsequent demonstration that insulin administration could reduce blood and urine glucose levels and reverse ketoacidosis in individuals with type 1 diabetes (T1D) ultimately changed T1D from a terminal disease into a manageable chronic illness [1] [2]. One hundred years later, there have been significant improvements in T1D outcomes, but there is still no cure for T1D. These improvements were directly facilitated by advancements in insu-

lin delivery (**Figure 1**). Results from the Diabetes Control and Complications Trial (DCCT) were reported in 1993 and illustrated that intensive insulin therapy, using three or more insulin injections or insulin pump therapy, was effective at reducing long-term complications of diabetes [3]. As a result, life expectancy for individuals with T1D has improved substantially, although is still on average 8 years less than someone without T1D [4] [5].

The DCCT also demonstrated that achieving tighter glycemic targets in adolescents and adults is limited by insulin-induced hypoglycemia [6] [7] [8]. Younger children are likely at an even higher risk of hypoglycemia [9]. Additionally, hypoglycemia and fear of hypoglycemia are barriers to exercise, which itself has glycemic and cardiovascular benefits and reduces mortality [10]-[15]. In the thirty years following the initial DCCT reports, iatrogenic hypoglycemia is still the main limiting factor in achieving normoglycemia in individuals with T1D [16].

Insulin is safely and effectively administered for therapeutic use via intravenous, subcutaneous and inhaled routes [17] [18]. Intravenous insulin is reserved for use in treatment of diabetic ketoacidosis, during major surgery, and in critical illness [19] [20] [21]. Intraperitoneal insulin using implantable pumps or percutaneous port systems is indicated when subcutaneous or inhaled routes are not possible or effective, although this is not widely available outside of Europe [22] [23]. Intramuscular injections should be avoided due to their propensity to precipitate severe hypoglycemia [24] [25]. Oral insulin is currently therapeutically ineffective due to enzymatic degradation by the gut [26]. It continues to be explored for a potential role in delaying or preventing T1D by inducing immune tolerance [27] [28] [29] [30].

2. Updates to Injectable Insulin

The first insulin injections were subcutaneous injections of animal-derived insulin and given to prevent severe metabolic decompensation associated with insulinopenia [1]. The goal of insulin therapy has progressed from preventing coma and death to achieving near-normal glucose levels. This has required modifications to insulin's structure and concentration, which were undertaken almost immediately after therapeutic use of insulin had begun [31]. Modifications to prolong the duration of insulin action were made as early as the 1930s and continue today [32] [33]. Purification processes continued to improve; semi-synthetic insulin, which was less immunogenic than pure animal insulin, was developed in the early 1980s [34]. Recombinant DNA (rDNA) human insulin became a reality shortly after, which resulted in a purer, less immunogenic product and enabled large scale production [35]. Modifications to create rapid acting analog formulations became available in the 1990s and continue to be improved upon today [36].

Basal-bolus therapy is standard-of-care in T1D and can be achieved using regular human insulin or rapid-acting insulin analogs (lispro, aspart, glulisine)

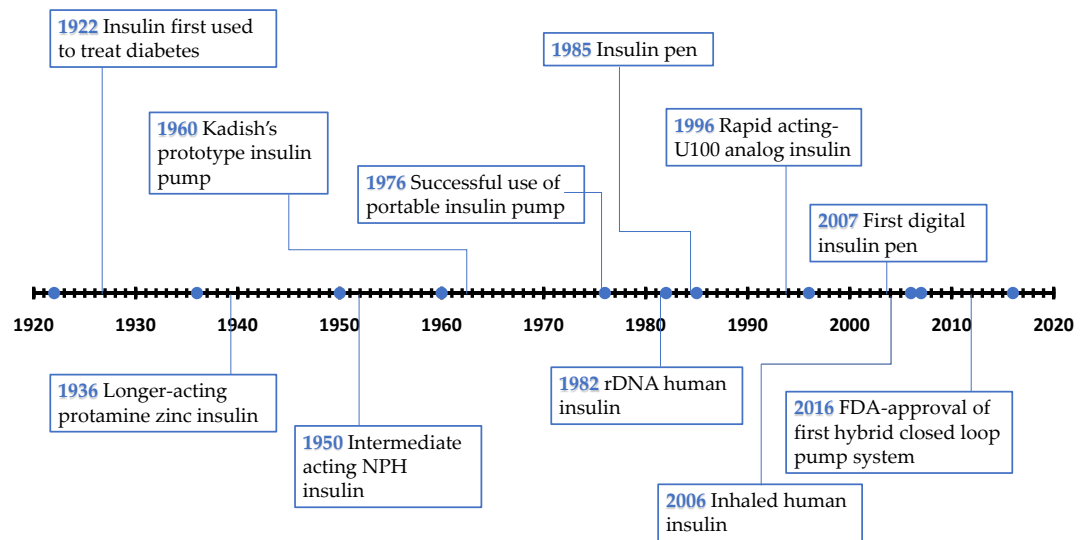


Figure 1. Timeline of important advancements in insulin delivery.

for prandial coverage [37] [38]. Rapid-acting analogs are generally preferred for prandial insulin in multiple daily injection (MDI) regimens as they offer a reduction in hypoglycemia alongside decreased post-prandial blood glucose (BG) [39] [40] [41] [42] [43]. They have an onset of action in 15 to 20 minutes and peak action in 1 - 2 hours [44] [45] [46] [47] [48]. Their pharmacokinetics allow for increased dosing flexibility over older regimens. Additionally, they can be used in traditional insulin pump therapy and hybrid-closed loop (HCL) therapy, described in further detail in sections 3 and 5. The standard U-100 concentrations are available in vials, cartridges, and pre-filled insulin pens [44] [45] [46]. A concentrated form of rapid acting insulin (lispro U-200) exists and can be prescribed as pre-filled pens only [49]. The main benefit of concentrated lispro, which is bioequivalent to U-100 lispro, is the ability to deliver lower volumes of insulin [50]. Lower injected volumes may decrease injection site pain [51].

Basal insulin therapy has undergone a similarly impressive transformation. Neutral protamine Hagedorn (NPH) insulin, lente and ultralente as basal insulin therapy have been improved upon with peakless long and ultra-long-acting basal insulins (detemir, glargine, degludec, discussed in the following paragraph). Adult data demonstrates better glucose control with less hypoglycemia on basal-bolus regimens using the previously discussed rapid-acting analogs with newer long-acting insulin analogs compared to NPH insulin/regular human insulin [52] [53]. Injection regimens with NPH and/or regular human insulin are still used in T1D and have the benefit of decreasing the injection burden and can be employed in situations where children do not have adequate supervision to inject insulin midday [38] [54].

Glargine is an rDNA insulin with modifications made to the amino acid structure that shift the isoelectric point, causing it to precipitate in tissue after injection and extending its duration of action to 24 hours [55]. It comes in both U-100 and U-300 concentrations, with the U-300 concentration demonstrating

even longer duration of action and a more even glucodynamic profile compared to U-100 [56]. As such, U-100 and U-300 glargine are not bioequivalent and a direct unit-per-unit conversion may not apply [57]. Detemir is also a modified rDNA insulin with an additional chemical modification (acylation) that allows it to bind to albumin, prolonging its absorption [58]. Smaller doses of detemir appear to last about 20 hours, with higher doses (0.6 to 1.6 U/kg) lasting about 24 hours in adults with T2D [59]. Insulin degludec (Tresiba, NovoNordisk, Bagsvaerd, Denmark) is a new, ultra-long-acting basal insulin with a glucose lowering effect lasting 42 hours after injection [60]. It is also an rDNA insulin with both amino acid substitutions and a chemical modification (acylation via glutamic acid linker) [61]. When compared to insulin glargine, degludec has comparable efficacy but demonstrates less nocturnal hypoglycemia in adults [62] [63]. Nocturnal hypoglycemia and hyperglycemia with ketosis are significantly reduced in pediatric patients when comparing degludec to detemir [64]. Degludec is available in U-100 and U-200 concentrations, which are bioequivalent [65].

Updates to subcutaneous insulin—even faster onset

Rapid-acting insulin analogs, as discussed above, provide significant improvement in insulin delivery, however they are still too slow in onset to match the physiologic insulin secretion pattern in individuals without T1D. They must be taken well in advance of eating to have maximal impact on post-prandial hyperglycemia, which is difficult especially for young children [66]. Faster-acting aspart (Fiasp, NovoNordisk, Bagsvaerd, Denmark), a modified version of aspart, has more rapid onset in the circulation with greater glucose lowering effects during the first 2 hours than traditional aspart [66]. It was approved by the FDA in 2017 for adult use and subsequently was approved for adult use in insulin pumps in 2019 [67]. It has been demonstrated safe and effective in children with T1D [68] and was expanded to pediatric use in 2020 [69]. Ultra-rapid lispro (Lyumjev, Eli Lilly, Indiana, US), a modified version of lispro, has a similarly shifted pharmacokinetic and glucodynamic profile [70]. Ultra-rapid lispro was FDA approved for adults in June 2020 [71]. A phase III trial is expected to conclude in mid 2021 for pediatrics (NCT03740919). Compatibility with insulin pumps has been demonstrated [72], but it is not approved for use in insulin pumps at the time of submitting this paper.

Insulin Pens

Insulin pens were first introduced in 1987 and partially address quality of life and diabetes outcome-related barriers to insulin delivery with vial and syringe (including convenience, dosage, pain, and hypoglycemia) [73]. Insulin pens contain pre-filled insulin, and a pen needle is attached for each injection. Accurate doses of insulin can be easily measured using a dial. The first digital insulin pen, the HumaPen Memoir, debuted in 2007 and allowed recall of the date, time, and recent insulin dosages [74]. The first smart insulin pen (InPen; Companion Medical Inc., San Diego, CA) launched in the US ten years later and syncs to a smartphone application. The application can be programmed with insulin-to-carbo-

hydrate (I:C) ratios, insulin sensitivity factors (ISF), BG targets, and duration of insulin action (DIA) which culminate in dosage suggestions similar to pump bolus calculators. Residual bolus insulin is tracked and accounted for to mitigate insulin stacking. Fixed dosing and meal-estimation can be used in place of I:C ratios in the dose calculator settings. Settings can be varied by time of day [75].

3. Traditional “Open Loop” Insulin Pumps

MDI remains the predominant mode of insulin delivery worldwide, although continuous subcutaneous infusion (CSII) via insulin pump continues to increase and varies widely by age and population [76] [77] [78]. Insulin pumps fall into two broad categories of medical devices: conventional pumps and patch pumps. Conventional pumps have a housing (which contains the insulin, electronics, pump and battery), a subcutaneous catheter, and tubing which connects the insulin pump to the catheter [79]. Patch pumps are worn on the skin and house the insulin and pump mechanisms in a small contained device [79] [80]. Both types of traditional pumps are based on an open-loop insulin delivery system, with no automation of insulin delivery based on BG levels. As such, traditional pumps can be used with or without continuous glucose monitoring (CGM) [80]. An excellent historical review of insulin pumps is provided by Alsaleh *et al.* [80].

Current traditional insulin pumps allow for settings to be programmed by the provider/user and have built-in bolus calculators, which have demonstrated improvements in glycemic control and patient satisfaction [81] [82]. Programmable settings are similar to the InPen discussed in Section 2 and include insulin-to-carbohydrate (I:C) ratio(s), basal rate(s), duration of insulin action/insulin action time(s) (DIA), insulin sensitivity factor(s) (ISF), and correction target(s) [83] [84] [85] [86]. These settings can be varied throughout the day to account for changes in insulin needs and insulin sensitivity. In traditional pump therapy, DIA is used to calculate the remaining insulin on board at any given time after a bolus [83] [84] [85]. These settings can improve safety in insulin delivery and can help mitigate insulin stacking, which could lead to hypoglycemia. These settings are used to some degree in the various automated insulin delivery systems, which are discussed in sections 5 and 7.

Typical insulin pumps use only rapid-acting or faster-acting rapid-acting insulin. CSII may modestly reduce HbA1c without sufficient evidence to infer improvements in glycemic outcomes such as hypoglycemia when compared to MDI [87]. Several studies cite quality of life improvements on CSII therapy [88] [89] [90]. Additional benefits to CSII include the ability to use extended, dual, or square-wave boluses to more closely mimic absorption of mixed macronutrient content meals [91]. While diabetic ketoacidosis (DKA) is of theoretical concern on CSII given the sole use of rapid-acting insulin, recent studies do not demonstrate significant differences in rates of DKA between CSII and MDI. This risk estimate is limited due to risk of bias in most clinical studies [92] [93]. Real-world data also do not favor increases in DKA in CSII users but may reflect CSII pre-

scribing practices [78].

4. Partial Automation Part 1—Hypoglycemia Mitigation. The Evolution of Low Glucose Suspend (LGS) and Predictive Low Glucose Suspend (PLGS)

Iatrogenic hypoglycemia continues to limit achievement of normoglycemia in T1D [16]. Additionally, fear of hypoglycemia is common in individuals with T1D and parents of children with T1D with significant impact on quality of life [94] and conflicting evidence on glycemic control [95] [96]. Integration of CGM with CSII allowed for low glucose alarms and subsequently the birth of sensor-augmented pump therapy (SAP) systems with low-glucose suspend (LGS). LGS systems suspend insulin delivery when the CGM-reported BG hits a pre-set hypoglycemia threshold. Basal insulin typically remains suspended for a maximum fixed time interval if no action is taken [97]. Studies of LGS demonstrated stable glycemic control with improvements in hypoglycemia [98] [99].

Introduction of algorithms used to forecast future hypoglycemia based on CGM trends and insulin-on-board led to predictive low glucose suspend (PLGS), including the MiniMed 640G (Medtronic, Northridge, California) and the Basal-IQ system (Tandem Inc., San Diego, California) [100] [101]. Basal insulin delivery is shut off when the predicted or actual CGM value reaches a pre-specified hypoglycemia threshold and may remain suspended for a fixed time interval (Basal-IQ, 640G), may stay suspended until the CGM glucose value starts to rise (Basal-IQ), or a future predicted BG is above a pre-specified threshold (Basal-IQ, 640G) depending on the system [100] [101]. PLGS demonstrates benefits over LGS, including less time spent < 70 mg/dL. PLGS also demonstrates reduction in fear of hypoglycemia and improvements in sleep quality while maintaining stable glycemic control [102].

5. Hybrid Closed Loop Systems

5.1. Commercially-Available Hybrid Closed Loop Systems (HCL)

Hybrid closed loop systems (HCL, also called artificial pancreas) are insulin delivery systems that automate insulin delivery in addition to augmenting or suspending insulin for actual or predicted hypoglycemia. They employ algorithms that integrate readings from CGM along with insulin-on-board (with other nuances, out of the scope of this article). The outcome is dynamic modulation of insulin administration to keep BG at a prespecified target or in a prespecified target range. HCL are not completely closed systems, as carbohydrates must still be counted and manually entered by the user. Each system uses a different algorithm running on a different device (*i.e.*, pump or cellphone) and employs different CGM(s). Each system thus has different adjustable settings and reasons for auto mode exits [103]. Commercially-available, soon-to-be-available, and do-it-yourself systems are summarized in **Table 1**. More details about do-it-yourself systems can be found in section 5.2.

Table 1. Summary of currently and soon-to-be available single hormone hybrid closed loop insulin delivery systems. HCL, hybrid closed loop; BG, blood glucose; CGM, continuous glucose monitor; I:C, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; DIA, duration of insulin action; iob, insulin on board; DIY, do-it-yourself; TDD, total daily dose.

Single Hormone HCL System	Compatible CGM(s)	BG target in standard automated modes	BG targets in activity modes	Method(s) of insulin adjustment	User-adjustable settings in automated mode	Settings that cannot be adjusted in automated mode	FDA-approved?	Insulin requirements for auto mode
MiniMed 670G	Guardian 3, calibration required	120 mg/dL	Exercise: 150 mg/dL	Basal modulation; pump may recommend bolus if BG \geq 150 mg/dL but user must accept. System calculates the TDD over the past 6 and uses this to inform the basal rates and ISF.	I:C ratio DIA	Basal rates Target (except for exercise) ISF	Yes, age 7+	8 U - 250 U TDD
MiniMed 770G	Guardian 3, calibration required	120 mg/dL	Exercise: 150 mg/dL	Basal modulation; pump may recommend bolus if BG \geq 150 mg/dL but user must accept. System calculates the TDD over the past 6 days and uses this to inform the basal rates and ISF.	I:C ratio DIA	Basal rates Target (except for exercise) ISF	Yes, age 2+	8 U - 250 U TDD
MiniMed 780G	Guardian 3, planned release of updated sensor requiring no calibration	100 mg/dL, can increase to 120 mg/dL	Exercise: 150 mg/dL	Basal modulation and automatic correction boluses q5 minutes. System calculates the TDD over the past 6 days at midnight and uses this to inform the basal rates and ISF.	I:C ratio DIA Target	Basal rates ISF	Not yet, (approved in Europe in June 2020); likely to start out at 7+	8 U - 250 U TDD
Tandem Control-IQ	Dexcom G6	112.5 mg/dL - 160 mg/dL; Correction target is 110 mg/dL	Sleep: 112.5 mg/dL - 120 mg/dL Exercise: 140 mg/dL - 160 mg/dL	Basal modulation of pre-set basal rates and automatic correction boluses q1 hour of 60% predicted need (correction boluses not administered in sleep mode).	I:C ratio ISF Basal rate TDD (this constrains the max basal rates) Target	DIA Correction target, can tighten range by running sleep	Yes, age 6+	10 U TDD minimum
CamAPS FX	Dexcom G6	Default is 104 mg/dL but is adjustable (80 - 200 mg/dL); can be varied by time of day	Boost: for periods of increased insulin needs (<i>i.e.</i> atypical food intake, stress, illness) Ease off: for when less insulin is needed (<i>i.e.</i> exercise); can be set in the future	Basal modulation	I:C ratio and ISF are used by the bolus calculator for meals and for user-initiated correction boluses in auto mode	Basal rates	No, but approved in UK/EU for age 1+	5 U - 350 U TDD; at least 10 kg
Omnipod 5	Dexcom G6	110 - 150 mg/dL in 10 mg/dL increments; can be varied by time of day	Hypoprotect: 150 mg/dL	Basal modulation. Autobasals are based on estimated and then actual TDD after initialization.	Target ISF, DIA (used for user-initiated correction boluses in auto mode, not autodelivered insulin)	Basal rates	Submitted	None mentioned
Tidepool Loop	Many	Likely to be adjustable	Likely to be adjustable	Basal modulation	I:C ratio ISF Basal rate Target	DIA	No	None studied, seeking FDA approval from DIY Loop studies
Loop	Many	Adjustable	Adjustable	Basal modulation of the pre-set basal rates. Autobolus branch gives automatic correction boluses.	I:C ratio ISF, Basal rate Target	DIA (you choose the model based on age and type of insulin you use, can be modified with code adjustments)	No-DIY	None studied
AndroidAPS	Many	Adjustable	Adjustable	Basal modulation of the pre-set basal rates. Orefl can give automated boluses.	I:C ratio ISF, Basal rate DIA, Target Advanced settings (max iob, autosensing, insulin curves, etc.)	N/A	No-DIY	None studied
OpenAPS	Many	Adjustable	Adjustable	Basal modulation of the pre-set basal rates. Orefl can give automated boluses.	I:C ratio ISF, Basal rate Basal rate DIA, Target Advanced settings (max iob, autosensing, insulin curves, etc.)	N/A	No-DIY	None studied

The first FDA-approved HCL system available was Minimed 670G (Medtronic, Northridge, California). When in auto mode, automated basal rates are modulated to achieve the preset target. The user/provider can adjust I:C ratios and DIA when in auto mode. The auto mode target is set at 120 mg/dL unless a temporary (exercise) target is set, which raises the target to 150 mg/dL. ISF is autosensed using historical data, so extraneous insulin entries and/or significant variability in insulin sensitivity may affect performance. The pump may recommend a user-initiated bolus if the BG is greater than or equal to 150 mg/dL. Users cannot employ square wave, dual wave, or other types of advanced boluses when in auto mode [84]. The 770G was approved last year with an expanded age indication and allowed for remote data visualization [104]. The 780G is not yet FDA approved but adds in autocorrective boluses with an updated algorithm. It is expected to work with an improved CGM that will only require calibration on the first day of use. The 780G features a default target of 100 mg/dL, with an option to increase to 120 mg/dL. All three MiniMed systems have demonstrated safety and efficacy [105] [106] [107]. Further improvements to hyperglycemia and TIR without increased hypoglycemia are noted when comparing the 780G to the 670G [105] [108]. Real world data from the 670G demonstrates that percentage of time spent in auto mode declined significantly over the first year with a main barrier to usage being CGM-related issues [109] [110].

The Tandem Control-IQ system (Tandem Inc., San Diego, California) has the ability to give automated correction boluses [111]. However, one still must bolus for meals. In normal Control-IQ mode, user/provider-set basal rates are adjusted to keep BGs in the target range of 112.5 - 160 mg/dL. Insulin delivery is suspended if BG is predicted to go below 70 mg/dL 30 minutes into the future or does go below 70 mg/dL. Automatic corrections are given if BG is predicted to be above 180 mg/dL in the next 30 minutes and are given up to once per hour using a correction target of 110 mg/dL. Sixty percent of the predicted insulin correction is administered with automatic correction boluses. The ISF can be adjusted by the user/provider—ISF, IOB, and TDD drive the algorithm's maximum insulin delivery rate calculation. Extended boluses can be set for 2 hours duration in Control-IQ mode. The user can enable activity modes (*i.e.*, sleep or exercise) which modify the BG target range. No automatic boluses are given during sleep mode [83]. Pivotal trials using Control-IQ demonstrated safety and efficacy as compared to SAP in children and adults, with significant improvements in TIR and HbA1c [111] [112]. Adults also saw decreased hypoglycemia [111]. Median percent time in automation remained over 90% at one year of real world use with this system [113].

Omnipod (Insulet Corporation, Boston, Massachusetts) has completed their pivotal trial for the Omnipod 5 automated glucose control system (NCT04196140) in individuals aged 6 - 70. Data are pending FDA review, but currently available data demonstrate improvements in HbA1c and TIR in pediatric and adult participants, with adults also demonstrating a decreased time spent in hypoglycemia

[114]. Free-living trials have also demonstrated safety and efficacy of this system [115]. Benefits of this system include tubeless automated insulin delivery and adjustable BG targets that can be varied by time of day [116].

The CamAPS system is the only HCL system currently approved for use in pregnancy, receiving a CE mark for use in 2020 [117]. A thorough review of commercially available hybrid closed-loop systems in the UK provides additional details on the CamAPS FX system (CamDiab Ltd., Cambridge, UK) [118] [119] [120]. The DBLG1 system (Diabeloop, Grenoble, France) recently completed a real-world efficacy trial with promising results [121]. Additional details about the system can be found in the pilot study (Benhamou *et al.*) [122].

There are other HCL algorithms in development, both in academic and commercial settings. It is beyond the scope of this article to review them all in detail. Some of these include dual hormone (*i.e.*, insulin and glucagon) algorithms, which are briefly reviewed in section 7. Beta Bionic's iLet (Beta Bionics, Boston, Massachusetts, USA), which has single and dual hormone options has an ongoing phase 3 clinical trial (NCT04200313) for the insulin-only version of their pump, and enrolled adults and children age 6+. The SAFE-AP system is a single-hormone HCL controller that includes carbohydrate recommendations as an additional control input. This can be used with both announced and unannounced exercise and has been demonstrated to maintain BGs within target range after both unannounced and announced heavy physical activity. This algorithm is programmed to ensure that the counter-regulatory effect of the rescue carbohydrates does not trigger additional insulin release [123].

5.2. Do-It-Yourself (DIY) Hybrid Closed Loop Systems

Frustrated with the pace of discovery, unaffordability, and lack of customization, the #WeAreNotWaiting movement developed do-it-yourself artificial pancreas systems (DIYAPS) [124]. The three main DIYAPS systems include OpenAPS (algorithm runs on a small computer), AndroidAPS (algorithm runs on an android phone, same base algorithm as OpenAPS), and Loop (algorithm runs on an iPhone and uses a hardware radio bridge communication device). The FreeAPS branch of Loop, which offered some unique features, has been frozen as the developers work on a new DIYAPS called FreeAPS X [125]. Similar to the commercially-available systems, the algorithms collect and analyze data related to glucose, insulin, and carbohydrates to predict future glucose levels and automate insulin delivery in response. There are additional customizations and forked branches. A comprehensive review of these systems is provided by Kesavadev *et al.* [126]. At the of the time of article submission, over 2200 people worldwide were using DIYAPS [127].

The Loop Observational Study (NCT03838900) recently completed after enrolling 1212 participants using Loop. They collected device data via Tidepool (Tidepool Project, Palo Alto, California), HbA1c, self-reported adverse events, self-reported device issues, and psychosocial/user experience data. Interval data were

presented at the Advanced Technologies and Treatments for Diabetes meeting in 2020 on 873 Loop users. The baseline mean TIR for users was fairly high at 67% but improved significantly to 73% with corresponding reductions in HbA1c. They reported low baseline and follow up hypoglycemia rates with additional improvements in diabetes distress, fear of hypoglycemia, and sleep quality [128]. Tidepool has adapted the Loop app for commercial use as an interoperable glycemic controller, meaning their application will work across platforms with multiple insulin pumps and CGMs [129]. The 510(k) was submitted to FDA in December 2020 using data from the aforementioned Loop Observational Study [128]. In silico trials of the OpenAPS algorithm using University of Virginia's Padova T1D simulator demonstrated safety and efficacy, with optimal performance using the automated bolus version (oref1 algorithm) [130]. There are few randomized control trials evaluating DIYAPS, but an OpenAPS repository includes promising real-world data [127]. A randomized clinical trial of AndroidAPS (the CREATE trial), comparing this to SAP therapy is underway. An excellent review on outcomes of DIYAPS studies is provided by Jennings *et al.* [131].

6. Technosphere Inhaled Insulin

Inhaled human insulin (Afrezza, Valencia, California) was approved in 2014 for adults with diabetes as an alternative prandial insulin. It follows Exubera (Pfizer, New York, NY, USA), which is an inhaled insulin approved in 2006. Production of Exubera was voluntarily discontinued shortly thereafter due to low sales [132]. Safety and pharmacokinetic studies of Afrezza in pediatric patients were recently completed in children aged 8 - 17 in two age cohorts (NCT02527625) but it is not yet approved for pediatric use. Afrezza comes in cartridges that can be dosed in 4-unit increments [133]. Multiple cartridges are required for doses exceeding 12U. Spirometry is required prior to initiation of therapy as it is contraindicated in patients with chronic lung disease. Afrezza has an onset of action of less than 15 minutes with a mean peak action of 50 minutes in adults [133]. The duration of action varies by dose, ranging from 90 minutes with smaller doses to 270 minutes at larger doses [133]. Individuals report improved satisfaction and quality of life using inhaled insulin as compared to injectable insulin [134] [135]. Inhaled insulin has been associated with lower weight gain in type 2 diabetes and less hypoglycemia compared to subcutaneous insulin but generally demonstrates lower glycemic efficacy compared to subcutaneous insulin therapy [136]. Studies using CGM to monitor glycemia in T1D using inhaled insulin are sparse as are long-term trials evaluating glycemia [18]. The most common pulmonary symptom associated with use of inhaled insulin is non-productive cough [136]. A recent study comparing pre-prandial doses of inhaled insulin versus subcutaneous CSII insulin boluses in conjunction with HCL therapy have demonstrated improvements in early glycemic excursions with utilization of inhaled insulin, consistent with its glucodynamic action. Additional research is needed to determine

efficacy, safety, and patient satisfaction of this inhaled/HCL combination insulin dose strategy [137].

7. The Future of Insulin Administration—Insulin Adjuncts, Additional Improvements to Insulin, Complete Closed Loop, Dual-Hormone Pumps

Sodium-glucose cotransporter (SGLT) inhibitors

SGLT-2 is present in the proximal tubule of the kidney, and SGLT-1 is present in both the kidneys and the intestine. SGLT inhibitors are a class of oral medication that eliminate glucose reabsorption in either or both of these transporters, which increases urinary glucose excretion, decreases intestinal glucose absorption, and as such decrease BG in an insulin-independent manner [138]. Results of the EASE, DEPICT, and in Tandem trials demonstrated that selective SGLT2 inhibitors are effective adjuncts for glucose lowering therapy in adults with T1D [139] [140] [141]. These trials also noted improved weight loss without hypoglycemia. The major concern in the use of SGLT inhibitors is euglycemic DKA, postulated to occur via a starvation mechanism [142]. Meta-analysis of SGLT inhibitors in T1D have similarly demonstrated efficacy, with primary adverse events being DKA and genital infections [143]. Continuous ketone monitoring would allow for safer utilization of SGLT agonists, facilitate the safe use of very-low carb diets, as well as provide adjunctive data to closed-loop algorithms. Microneedle technology employing a NAD-dependent dehydrogenase-based electrochemical biosensor has demonstrated the ability to detect real-time levels of β -hydroxybutyrate along with glucose and lactate [144].

Insulin updates

The most common cause of DKA is insulin non-adherence, and current insulin regimens are cumbersome [145]. Simplified treatment regimens have shown improvements in patient-reported outcomes in type 2 diabetes, but direct studies in T1D are difficult due to the necessity of insulin therapy [146]. Once-weekly insulin treatment with insulin icodec was demonstrated to be effective at lowering HbA1c levels in adults with type 2 diabetes [147]. Phase 3 trials of insulin icodec compared to degludec are being studied in adults with type 1 diabetes (NCT04848480). Weekly insulin for T1D may offer improvements in quality of life and decrease DKA due to insulin omission. The biggest weakness to weekly-dosed insulin is the inflexibility of dosing, which has major implications in active and growing individuals. This may make icodec of limited benefit for the pediatric population, who is likely to benefit most from simplifying insulin delivery.

Hybrid closed-loop and fully closed loop insulin pump therapy

Current rapid acting insulin formulations do not have fast enough onset to allow for completely successful total automation. Simple meal announcement without carbohydrate counting using insulin-only strategies may alleviate some of the mental burden of T1D and improve glycemic outcomes and quality of life.

Use of faster-acting insulin analogs discussed above in HCL is underway [148] [149] [150] [151]. Faster acting insulins could potentially allow for simplification of meal bolusing or elimination of meal announcement all together [152]. DIY options (*i.e.* OpenAPS's advanced dosing features) already exist for unannounced meals [153]. Dual-hormone systems, discussed immediately below, may also make full automation possible.

Dual-hormone closed-loop therapy (insulin/glucagon)

The advent of liquid stable glucagon has enabled dual hormone (DH) closed-loop systems to become achievable [154] [155] [156]. Several research groups are working on automated DH algorithms and devices, which administer both insulin and glucagon [157] [158] [159] [160] [161]. Early feasibility studies show promise for both improved glycemic control as well as hypoglycemia mitigation over PLGS and HCL systems including in situations with a propensity to trigger hypoglycemia, such as exercise [162] [163]. In addition to hypoglycemia, DH algorithms show promise in eliminating precise carbohydrate counting although do seem to operate best when using simple meal announcements with estimated meal size [162]. Adverse outcomes of using micro-doses of glucagon primarily include nausea, vomiting, and headache [164].

Other dual-hormone options (pramlintide/insulin, GLP-1 agonists/insulin)

Pramlintide, an analogue of amylin, can be co-injected with insulin to delay gastric emptying and suppress glucagon secretion and has been demonstrated to improve post-prandial hyperglycemia in T1D. Pramlintide co-administration with rapid-acting insulin in HCL systems has been demonstrated to mitigate meal-related glycemic excursions [165]. Co-administration of faster-acting insulin aspart and pramlintide with only simple meal announcement demonstrated feasibility, and the results of the non-inferiority trial to HCL with standard carbohydrate counting completed in February 2020 (NCT02814123) [152]. Liraglutide, a GLP-1 agonist, may reduce post-prandial glucose excursions and HbA1c in T1D but also may increase hypoglycemia and ketosis [166] [167], making it unlikely to gain widespread use in T1D management.

Improvements for exercise

Management of T1D and exercise remains challenging due to increases in insulin sensitivity and increased insulin-independent glucose uptake into muscles which can persist long after the exercise has completed [168] [169] [170]. DH-closed loop systems discussed above show promise in mitigating early and late-onset exercise-induced hypoglycemia in T1D [157] [171] [172]. Incorporation of heart-rate detection, and lactate and ketone levels into closed-loop algorithms may also help overcome challenges associated with exercise and T1D [144] [173] [174] [175] [176].

8. Caveats

Despite significant advancements in insulin and related diabetes technology, a minority of patients with T1D are meeting the glycemic targets known to reduce complications [78]. Further work needs to be done to explore barriers to achieve-

ment of these goals, especially in the adolescent population who have seen worsening glycemic control despite increasing technology uptake [78].

Additionally, equity in diabetes care and care delivery needs to be addressed, as related variables are often absent from trials [92]. Despite an overall rise in insulin pump use (which is associated with improvements in quality of life), non-Hispanic Black youth, Hispanic youth, and American Indian/Alaskan Native youth are significantly less likely to be on insulin pump therapy independent of socioeconomic status [177]. CGM in conjunction with CSII, especially when accounting for PLGS and HCL functionality have demonstrated superiority in many studies and highlights the need to understand and address this inequity [178].

Addressing socioeconomic barriers will also be crucial as the management of T1D continues to evolve. The cost of insulin can be prohibitive [179]. Rapid acting analogs are cost-effective in the treatment of T1D however may be unattainable for uninsured patients [180] [181]. Heterogeneity exists in reimbursement for diabetes technology [182]. As such, patients and their families may have difficulties accessing more advanced diabetes features. Pre-existing gaps in diabetes care and outcomes are likely to widen [183] [184]. Advanced diabetes devices are difficult to learn, maintain and manage, and different educational frameworks will be needed to allow for a wide spectrum of users to achieve success. Mentorship programs and telehealth show promise in addressing health disparities in T1D [185] [186]. Further research in optimal education and care delivery are necessary as diabetes technology becomes more advanced.

9. Conclusion

Insulin administration has evolved dramatically over the last 100 years. However, with no imminent cure for T1D, further optimization of insulin delivery is necessary. Iatrogenic hypoglycemia is still therapeutically problematic and impairs quality of life. Automated insulin delivery shows great promise in helping patients achieve glycemic targets while mitigating hypoglycemia, but is not perfect nor universally accessible. Research is necessary to identify and rectify barriers to uptake and continued utilization of more advanced methods of insulin administration. More robust head-to-head comparisons of automated insulin delivery methods using representative populations in real-world conditions as well as pragmatic trials will facilitate further improvements and allow for a more patient-centered approach to T1D.

Supplementary Materials

NA

Author Contributions

CTP and MJT conceptualized and wrote the first draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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