Evolving Pharmacotherapeutic Strategies for Type 1 Diabetes Mellitus

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Despite pharmacotherapeutic advancements in the management of type 1 diabetes mellitus during the past several decades, patients struggle to achieve glycemic goals. Additionally, hypoglycemia, especially in extremes of age, decreases quality of life. The lack of optimal glycemic control and risk for hypoglycemia are multifactorial. Nevertheless, endeavors aiming to develop pharmacotherapeutic options with enhanced pharmacokinetic, pharmacodynamic, and clinical profiles continue. This review article discusses recent ventures in 3 categories of insulin, non-insulin, and glucagon products.

ABBREVIATIONS AUC, area under serum concentration-time curve; C_{max} , maximum concentration; C-peptide, insulin connecting peptide; DAPA, dapagliflozin; DKA, diabetic ketoacidosis; DM, diabetes mellitus; faster aspart, faster-acting insulin aspart; FDA, US Food & Drug Administration; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; RCT, randomized controlled trial; SGLT2, sodium glucose cotransporter 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

KEYWORDS diabetes; glucagon; insulin; non-insulin; pediatrics; type 1 diabetes mellitus

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Introduction

Diabetic ketoacidosis (DKA) at diagnosis, hyperglycemia, plasma glucose variability, and severe hypoglycemia have been associated with negative neurocognitive and neurodevelopmental effects in the pediatric population.^{1–3} Nonetheless, the rates of achieving a hemoglobin A1c (HbA1c) of <7.5% in 2- to 5-year-old, 6- to 12-year-old, and 13- to 17-year-old children and adolescents were 22%, 20%, and 16% according to the type 1 diabetes (T1D) Exchange registry data for the 2013–2014 period.⁴ Although there are different factors contributing to a failure to achieve target HbA1c, recent pharmaceutical advancements may offer better therapeutic options for the management of pediatric diabetes mellitus (DM). The development of newer insulin analogs allows flexibility in dose administration time. Additionally, some studies have evaluated the use of non-insulin glycemic control agents in the pediatric T1DM population. Moreover, new formulations of glucagon aim at easing the management of severe hypoglycemic events. This article reviews the available data on the abovementioned therapeutic options in 3 categories of insulin, non-insulin, and glucagon products.

Insulins

Insulin Degludec. Insulin degludec (IDeg) is an ultra–long-acting insulin approved by the US Food & Drug Administration (FDA) for children with T1DM, age 1 year and older.⁵ It is formulated as 100 and 200 units/

mL disposable pens (Table 1). After injection, the insulin dihexamers form multihexamer chains in the subcutaneous tissue that slowly dissociate and allow a stable release of insulin monomers into circulation, extending the action of this basal insulin to more than 40 hours.⁶

A single-center, randomized, double-blind, crossover trial evaluated the area under the serum concentration-time curve (AUC) and maximum concentration (C_{max}) for IDeg and insulin glargine (IGlar) following a single dose of 0.4 units/kg on 2 separate dosing visits.⁷ This study was conducted with 37 T1DM patients divided into 3 age categories of children (6–11 years), adolescents (12–17 years), and adults (18–65 years). Although direct comparisons between IDeg and IGlar were not made, the AUC and C_{max} for IDeg were higher in children and adolescents compared with adults. Nonetheless, statistical significance was only observed for the AUC of IDeg when comparing adolescents with adults (1.33; 95% CI, 1.08–1.64). IDeg was detectable in the 72-hour blood sample following a single dose in all the study patients. No severe hypoglycemia was reported, and hypoglycemic episodes were slightly more common following the IGlar dose.

A randomized, crossover study of 18 Japanese children with T1DM, ages 7 to 14 years, looked at the safety and efficacy of IGlar compared with IDeg as part of a basal bolus regimen for 24 weeks (Table 2).⁶ Nocturnal hypoglycemia with IDeg significantly decreased at 12 and 24 weeks, respectively. There were no significant differences in nocturnal hypoglycemia in the IGlar

Table 1. New Insulin Products

Brand (Generic)	FDA Approval	Available Concentration(s)	Units per Vial	Units per Pen	Pens per Box	Stability Duration (Once Opened)
Tresiba ⁵ (insulin degludec)	≥1 yr of age	100 units/mL, 200 units/mL	N/A	U-100 FlexTouch: 300 units U-200 FlexTouch: 600 units	U-100: 5 pens U-200: 3 pens	56 days
Ryzodeg 70/30 ^{*9} (insulin degludec/aspart)	≥1 yr of age	100 units/mL	N/A	U-100 FlexTouch: 300 units	5 pens	28 days
Basaglar ¹² (insulin glargine)	≥6 yr of age [†]	100 units/mL	N/A	U-100 KwikPen: 300 units	5 pens	28 days
Toujeo ¹⁴ (insulin glargine)	Not approved [‡]	300 units/mL	N/A	U-300 SoloStar: 450 units	3 and 5 pens	42 days
Fiasp ¹⁷ (insulin aspart)	Not approved [§]	100 units/mL	10-mL vial: 1000 units	U-100 FlexTouch: 300 units	5 pens	28 days

FDA, Food and Drug Administration

^{*} Not commercially available.[†] FDA approval for Lantus is also for use in children ages ≥6 yr with T1DM.[‡] Lacks pediatric data.[§] Pediatric data limited to 1 pharmacokinetic study.

group compared with baseline (2 ± 0.5). Additionally, this study showed a non-inferiority in glycemic control based on finger stick blood glucose and HbA1c levels, after changing from IGLar to IDeg. This study's small subject size limits adequate assessment for safety and the incidence of adverse effects.

An international, treat-to-target, randomized controlled trial (RCT), including 350 patients ages 1 to 17 years with T1DM and an HbA1c $\leq 11\%$, compared IDeg to insulin detemir (IDet), both given with prandial insulin aspart (IAsp), for 26 weeks, followed by a 26-week extension (Table 2).⁸ Looking at the primary outcome, HbA1c after 26 weeks, non-inferiority was confirmed, although it was 0.15% lower in the IDet group. At the conclusion of the extension phase, week 52, the HbA1c was 7.9% in the IDet group and 7.8% in the IDeg group. Throughout the study, basal insulin requirements changed minimally in the IDeg group but increased by 38% in the IDet group. Hyperglycemia with ketosis was reduced in the IDeg group compared with the IDet group by 0.41 events per exposure year (95% CI, 0.22–0.78). Furthermore, the IDeg group had more confirmed or severe hypoglycemia and less nocturnal hypoglycemia compared with the IDet group, although these differences were not statistically significant. The authors discussed that this contrast was due to the lack of bolus and basal dose reduction when the patients' basal insulin regimen had changed to IDeg in the beginning of the trial. They further argued that in most cases of severe hypoglycemia, bolus insulin was the last insulin administered.

IDeg is a non-inferior option compared with IGLar and IDet. More robust studies are needed to assess whether it provides superior outcomes or an improved

safety profile compared with other long-acting insulins. In patients who have difficulty administering long-acting insulin at a consistent time each day, use of IDeg can be advantageous because of its longer duration of action and more stable pharmacokinetics.

IDeg and IAsp Combination. This combination product, consisting of 70% IDeg and 30% IAsp, is approved for management of DM in children ages 1 year and older (Table 1).⁹ A phase 1, non-randomized trial investigated the pharmacokinetic exposure to IDeg/IAsp in 38 T1DM patients ages 6 to 65 years.¹⁰ The patients received 0.5 units/kg IDeg/IAsp before the first meal of the day after at least a 10-hour fasting period. No differences were observed in lowering plasma glucose levels between the age groups (children, adolescents, and adults). After a single dose administration, the AUC of IAsp from 0 to 12 hours and the C_{max} were both higher with statistical significance in children compared with adults (1.69; 95% CI, 1.02–2.80; and 1.66; 95% CI, 1.10–2.51, respectively). However, the only statistically significant difference with IDeg was a higher C_{max} observed after a single dose of IDeg in children compared with adults (1.38; 95% CI, 1.09–1.76). The study authors stated that a higher IAsp AUC and C_{max} in children compared with adults were not observed in a different study where free serum IAsp was measured, whereas in this study total serum IAsp was measured.

A phase 3, randomized, open-label trial has evaluated the safety and efficacy of once-daily IDeg/IAsp with IAsp for remaining meals versus IDet with meal-time IAsp (Table 2).¹¹ This trial observed 362 children and adolescents ages 1 to 17 years with T1DM and looked at changes in baseline HbA1c after 16 weeks. The researchers also looked at other factors, such as

Table 2. Insulin Studies Clinical Outcomes

	Urakami et al ⁶	Thalange et al ⁸	NCT01835431 ¹¹	Russell-Jones et al ²⁰
Number of patients	18	350	360	1143
Age, yr	7–14	1–17	1–17	Adults
Insulins compared	IDeg and IGLar	IDeg and IGLar	IDeg/IAsp and IDet	Mealtime faster aspart, mealtime IAsp, and 20 min postmeal faster aspart
Duration of trial	24 wk, crossover	26 wk plus an extension phase to 52 wk	16 wk	26 wk
Percent change in HbA1c	IDeg: $7.8 \pm 0.3 \rightarrow 7.8 \pm 0.2$ IGlar: $7.7 \pm 0.3 \rightarrow 7.8 \pm 0.2$	IDeg: -0.27 IDet: -0.22	IDeg/IAsp: -0.3 ± 1.0 IDet: -0.3 ± 0.9	Mealtime faster aspart: -0.3 Mealtime IAsp: -0.2 Postmeal faster aspart: -0.1
Difference in nocturnal hypoglycemia	IDeg: $2 \pm 0.5 \rightarrow 0 \pm 0.5$ per mo IGlar: $2 \pm 0.5 \rightarrow 2 \pm 0.4$ per mo	IDeg: 6 events per exposure year IDet: 7.6 events per exposure year	IDeg/IAsp: 316 episodes IDet: 291 episodes	N/A
Other Outcomes	No statistically significant differences were observed in FBG, long-acting insulin need (units/kg/day), or total hypoglycemic events.	IDet group long-acting insulin requirements increased by 0.15 units/kg by the end of the trial. No change in the IDeg group. Hyperglycemia with ketosis reduced by 0.41 events per year in the IDeg group.	Number of hyperglycemic events where patient looks/feels ill: 599 with IDeg/IAsp and 449 with IDet.	Statistically significant lower postprandial plasma glucose with mealtime faster aspart compared with mealtime IAsp.

FBG, fasting blood glucose; HbA1c, hemoglobin A1c; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IGLar, insulin glargine

number of hyperglycemic and nocturnal hypoglycemic episodes. The HbA1c changed from baseline by an average of 0.3% in both the IDeg/IAsp and IDet groups. One of the reported secondary outcomes was number of hyperglycemic episodes where the patient felt ill. The occurrence of this adverse outcome was 33% higher in the IDeg/IAsp group. To the knowledge of the authors, the results of this study are not published yet.

Mixed insulin products are not ideal for glycemic control in T1DM because of required insulin dosing flexibility with the use of carbohydrate and correction ratios. Nonetheless, in certain situations (non-adherence, not following a carbohydrate ratio) this might be an alternative therapy option. It is worth mention that this product (Ryzodeg 70/30, Novo Nordisk Inc, Plainsboro, NJ) is not commercially available despite receiving FDA approval more than 2 years ago.

Insulin Glargine. Basaglar. Basaglar (Eli Lilly and Company, Indianapolis, IN) is an IGLar that is dosed once a day and approved for use in T1DM children ages 6 years and older.¹² It is formulated as a 100 units/mL injection pen (Table 1). Compared with other IGLar products, Basaglar appears to have the lowest average

wholesale price at the present time.

A phase 3, multicenter, open-label RCT in adult patients with T1DM compared Basaglar and Lantus (Sanofi-Aventis US LLC, Bridgewater, NJ).¹³ The primary end point for this trial was the difference in HbA1c change from baseline to 24 weeks between the 2 groups. The results showed similar efficacy of glucose-lowering effects with Basaglar, with an average decrease in HbA1c from baseline of 0.35%, compared with 0.46% with Lantus, meeting FDA non-inferiority criteria.

Toujeo. Not FDA-approved for use in children, Toujeo (Sanofi-Aventis US) is formulated as 300 units/mL compared with the other IGLar products, which are 100 units/mL (Table 1).¹⁴ Although similar in mechanism of action, this product has a slower onset of action compared with Lantus in adults: 6 hours compared with 3 to 4 hours, respectively.

A randomized, open-label phase 3 study comparing the safety and efficacy of Toujeo with Lantus in children and adolescents (ages 6–17 years) with T1DM is currently recruiting participants.¹⁵ This trial is measuring HbA1c levels at 26 weeks from baseline when comparing the efficacy of the 2 insulin therapies. Ad-

ditionally, a 6-month extension period is intended for further evaluation of hypoglycemia, hyperglycemia with ketosis, and adverse events.

Faster-Acting Insulins. It is difficult to dose fast-acting insulins prior to a meal in children because the child may not finish the meal. To mitigate this problem, dividing the mealtime insulin dose to 2 injections, 1 before the meal and 1 at the completion of the meal, would be a potential but unpopular approach. Therefore, development of faster-acting insulins could allow insulin administration after completion of a meal.

The fate of BioChaperone, ultrarapid insulin lispro, is unknown after a collaboration between Eli Lilly and Adocia, the French developer of this molecular delivery system, was dissolved in January 2017.¹⁶ Despite the setback with the ultrarapid insulin lispro, a faster-acting insulin aspart (Fiasp, Novo Nordisk) has received FDA approval for the control of T1DM and T2DM in adults (Table 1).¹⁷ The faster-acting insulin aspart (faster aspart), formulated with L-arginine and niacinamide as added excipients, provides a more stable formulation with faster initial absorption after administration.¹⁸ According to the labeling, faster aspart should be administered at the beginning of the meal or within 20 minutes after starting a meal, and IAsp should be administered 5 to 10 minutes before a meal.^{17,19} Russell-Jones et al²⁰ evaluated faster aspart in adults during a 26-week, randomized, multicenter trial (Table 2). The 1143 participants were randomized to double-blind mealtime (0–2 minutes before a meal) faster aspart or IAsp, or open-label postmeal (20 minutes after starting a meal) faster aspart. After 26 weeks, the HbA1c was decreased from 7.6% to 7.5%, 7.4%, and 7.3% with postmeal faster aspart, mealtime IAsp, and mealtime faster aspart, respectively. Furthermore, at week 26 postmeal plasma glucose was lower with statistical significance at 60 and 120 minutes when comparing mealtime faster aspart to mealtime IAsp and at 60 minutes when comparing mealtime IAsp to postmeal faster aspart. The results of this study, of adult participants, suggest that postmeal administration of faster aspart can yield similar glyce-mic control compared with mealtime administration of IAsp or faster aspart. It should be noted that in this study IAsp was administered 0 to 2 minutes before a meal, whereas the recommended administration time per package insert is 5 to 10 minutes before a meal.

A randomized, double-blind, crossover, pharmacokinetic trial in children, adolescents, and adults with T1DM studied faster aspart, and whether it provides faster onset and greater early exposure over IAsp.¹⁸ A total of 38 patients, ages 6 to 64 years, received 0.2 units/kg immediately before a standardized meal. The results of this study showed a 5- to 7-minute faster onset of insulin appearance in blood with the faster-acting insulin aspart compared with IAsp. Glucose levels 2 hours after the meal were lower with the faster aspart administration and were statistically significant only

among children (–27.0 mg/dL; 95% CI, –50.2 to –3.6 mg/dL). The outcomes of this study show that faster-acting insulin aspart has the potential to improve postprandial glycemia in children. However, phase 2 and 3 RCTs evaluating the safety and efficacy of this product in pediatric population are needed.

Non-insulins

An increase in growth hormone and gonadal steroid secretions during puberty can contribute to insulin resistance.^{21,22} This phenomenon is reported in adolescents with T1DM as well, leading to an increase in insulin dose (units/kg) for achieving glycemic control.^{23,24} Increased insulin requirement has been correlated with the presence of multiple risk factors for cardiovascular diseases in young adults.²⁵ Furthermore, the SEARCH for Diabetes in Youth study found that 12% of T1DM patients younger than 20 years were obese, and 22.1% were overweight.²⁶ Obesity in T1DM is also associated with greater atherosclerotic burden.²⁷ Studies have evaluated the efficacy and safety of adjunctive therapies for overcoming insulin resistance and improving glycemic control in pediatric patients with T1DM.

Metformin. Metformin is currently the most commonly reported adjuvant medication for T1DM in both the T1D Exchange registry in the United States and the Diabetes Patient Documentation registry in Germany and Austria, with frequencies of use of 3.5% and 1.3%, respectively.²⁸ Approved as an oral medication for the management of T2DM, metformin works by increasing insulin sensitivity and uptake of glucose in muscle tissue and by reducing hepatic glucose output.²⁹ Similarly to the adult population, abdominal pain, diarrhea, nausea, and vomiting are the most common adverse effects associated with the use of metformin in pediatrics.³⁰

Studies of metformin in T1DM patients have resulted in conflicting results, with some seeing significant improvements in HbA1c and others unable to reproduce those results. A systematic review and meta-analysis of 6 RCTs, which included 325 patients with a mean age of 15 years, found no statistically significant difference in HbA1c when adding metformin to insulin compared with placebo (–0.05%; 95% CI, –0.19% to 0.29%).³¹ The authors concluded there was a need for further safety studies with larger RCTs because they determined a trend toward more severe hypoglycemic and DKA events among the metformin arms of the trials analyzed. Because hypoglycemia is a barrier to optimal glycemic control, it was also suggested to include a measurement of health-related quality of life in future studies to determine clinical significance. Adverse events seen in these RCTs are reported in Table 3.

Overweight and obese patients have been of special interest when analyzing metformin's effect on HbA1c. In the Diabetes Patient Documentation registry, patients with T1DM taking metformin were found to have worse metabolic control, more likely to have a higher

Table 3. Summary of Metformin Studies

	Libman et al ³³	Nadeau et al ³⁴	Nwosu et al ³⁵	Hamilton et al ³⁶	Sarnblad et al ³⁷	Urakami et al ³⁸
Number of patients	140	74	28	27	26	9
Age, yr	12.1– 9.6	13–20	10–20	12–17	16.9 ± 1.6	15.1–22.0
Metformin dose	1000 mg twice/day	500 mg twice/day	1000 mg/day	<50 kg: 500 mg twice/day; 50–75 kg: 1500 mg/day; ≥75kg: 1000 mg twice/day	1000 mg twice/day	500–750 mg twice/day
Duration of trial	6 mo	6 mo	12 mo	3 mo	3 mo	12 mo
Change in HbA1c, %						
Baseline	8.8	9.5 ± 1.3	–0.72 ± 2.06 from baseline	–0.3 ± 0.7 from baseline*	9.6 ± 1	9.5 ± 1.2
End of study	9	9.2 ± 1.2			8.7 ± 1.5†	8.4 ± 1.2‡
Change in total daily dose of insulin						
Baseline	1.1 units/kg/day	1.21 ± 0.24 units/kg/day	–0.31 units/kg/day vs. placebo	–0.14 ± 0.1 units/kg/day	1.1 ± 0.3 units/kg/day	74 ± 31.2 units/day
End of study	0.9 units/kg/day§	1.12 ± 0.21 units/kg/day			1.1 ± 0.3 units/kg/day	67.3 ± 29.1 units/day†
Change in BMI, kg/m ²						
Baseline	94th %	23.5 ± 3.0	28.0 ± 5.4	–0.05 ± 1.0	23.5	24.2 ± 1.8
End of study	93rd %¶	23.5 ± 2.4	28.8 ± 3.1		23.3	23.5 ± 1.8†
Incidence of adverse effects						
GI events metformin	50	NR	NR	6	2	2 mild
GI events placebo	24	NR	NR	5	5	NR
DKA metformin	3	0	2	0	0	0
DKA placebo	2	0	0	0	0	NR
Severe hypoglycemia metformin	5	0	1	3	0	0
Severe hypoglycemia placebo	0	0	0	1	0	NR

BMI, body mass index; DKA, diabetic ketoacidosis; GI, gastrointestinal; HbA1c, hemoglobin A1c; NR, not reported

* p < 0.05 compared to change in placebo.

† p < 0.05 compared to baseline.

‡ p < 0.01 compared to baseline.

§ p < 0.001 compared to change in placebo.

¶ p = 0.004 compared to change in placebo.

body mass index, and were more likely to be classified as obese.³² A subgroup of 285 patients taking metformin were followed for 1.4 years and compared to a matched control, and researchers saw significant changes in body mass index and reduction in insulin doses, but no significant changes in HbA1c. Some other metformin studies have also not shown HbA1c-lowering benefits (Table 3) but have demonstrated other positive outcomes, such as reduced waist circumference, decreased total daily dose of insulin, and improved insulin sensitivity.^{33–35}

On the contrary, some studies have demonstrated HbA1c-lowering benefits with the use of metformin in adolescents with T1DM (Table 3).^{36–38} These studies had a smaller number of participants compared with the studies discussed earlier. Additionally, differences in baseline characteristics between metformin and placebo groups were noted in 2 of these studies. In 1 study the HbA1c was higher in the metformin group by 0.7%, and in the other the insulin sensitivity was lower in the metformin group by 0.5 mg/m²/min at baseline. Besides HbA1c improvements with metformin, reduction in daily insulin requirements, fasting glucose levels, and body mass index were among additional positive outcomes.

Glucagon-Like Peptide-1 Agonists. Glucagon-like peptide-1 (GLP-1) agonists act in the gut to induce insulin secretion in the presence of glucose and inhibit gastric acid secretion and gastric emptying. This mechanism is thought to help reduce postprandial glucose excursions.³⁹ By acting to suppress appetite, GLP-1 agonists have shown promise as an effective adjunct therapy to insulin in T2DM patients for weight loss in addition to improvements in HbA1c.⁴⁰ Common adverse effects are gastrointestinal related and often transient.⁴¹ Acute pancreatitis has been reported with the use of these agents, so they should be used with caution in patients with a history of pancreatitis. Moreover, thyroid parafollicular cell hyperplasia, adenomas, and medullary thyroid carcinomas have been seen in mice studies, but not in humans. Because of this finding, they are contraindicated in patients with a personal or family history of medullary thyroid carcinoma.

The role of GLP-1 agonists in the management of patients with T1DM is being examined as more evidence of the effectiveness of these agents surfaces. Studies are ongoing in both adult and pediatric populations. The T1D Exchange registry reported a 0.91% use frequency for these agents, second to metformin as adjuvant therapy in T1DM patients.²⁸

An RCT in adults with T1DM, both with and without partial β -cell function, demonstrated a significant decrease in total daily dose of insulin needed when taking concurrent liraglutide, -0.19 units/kg/day ($p < 0.001$) in the insulin connecting peptide (C-peptide)-positive group and -0.13 units/kg/day ($p < 0.05$) in the C-peptide-negative group.⁴² This study did not report any significant changes in postprandial blood glucose

or HbA1c. Another multinational study looking at the efficacy and safety of liraglutide in 831 patients with T1DM found statistically significant decreases in HbA1c in patients randomized at doses of 0.6, 1.2, and 1.8 mg compared with placebo, with mean differences of -0.24% ($p = 0.0011$), -0.23% ($p = 0.0021$), and -0.35% ($p < 0.001$), respectively.⁴³ A statistically significant weight reduction was also observed in the patients on liraglutide (1.8 mg, -5.1 kg; 1.2 mg, -4.0 kg; 0.6 mg, -2.5 kg). Evaluating adverse events, documented symptomatic hypoglycemia (typical symptoms of hypoglycemia plus a measured plasma glucose of ≤ 70 mg/dL) was higher with statistical significance only in the 1.2 mg group (estimated rate ratio, 1.33; 95% CI, 1.07–1.67).

Participants are currently being recruited for an observational study to determine whether liraglutide can decrease the mean weekly blood glucose in T1DM patients ages 15 to 21 years.⁴⁴ Liraglutide will be given at a dose of 0.6 mg daily for 7 days, and blood glucose will be measured on a continuous glucose monitor. The study will also evaluate changes in the total daily insulin dose, episodes of hypoglycemia, and amylase levels.

Another study is currently enrolling patients with an early diagnosis of T1DM (no symptoms, oral glucose tolerance test–based diagnosis) to determine whether liraglutide will improve insulin secretion by measuring the serum C-peptide AUC during a 2-hour mixed-meal tolerance test.⁴⁵ Patients ages 10 to 30 years will be included. Evaluation of safety will include monitoring serum and urine amylase, serum lipase, and serum calcitonin levels, hypoglycemic episodes, and gastrointestinal side effects during the 26-week treatment period and 26-week follow-up period.

Exenatide has also been studied in a trial where adolescents were included. A 3-phase, double-blinded RCT of 8 T1DM adolescent patients ages 13 to 22 years compared a prebreakfast bolus insulin and a 12-ounce standard liquid meal phase with 2 treatment phases, where the same patients were given a 20% less bolus insulin plus exenatide (1.25 and 2.5 mcg) before the liquid meal.⁴⁶ The study found both doses of exenatide to be effective at reducing postprandial hyperglycemia and delaying gastric emptying compared with insulin monotherapy. Three incidences of nausea were reported with exenatide. In addition to the small sample size, another limitation to this study is that the results of the study are reported with limited details.

A randomized, open-label, crossover trial is currently recruiting patients ages 12 to 18 years with a recent diagnosis (past 3 months) of T1DM to determine how exenatide compares to insulin monotherapy at reducing postprandial hyperglycemia.⁴⁷ Participants will undergo each intervention in a random order at separate visits: exenatide 1.25 mcg subcutaneous plus long-acting insulin, long-acting plus short-acting insulins, and long-acting insulin alone. The investigators intend to compare the patients to healthy matched controls. The

effects on exenatide on postprandial glucagon and gastric emptying will also be evaluated.

Dipeptidyl Peptidase IV Inhibitors. By competitively inhibiting the enzyme responsible for the metabolism of GLP-1, the dipeptidyl peptidase IV inhibitors produce effects similar to those of the GLP-1 agonists.⁴⁸ Delayed gastric emptying is not seen in the dipeptidyl peptidase IV inhibitors, which would suggest less appetite suppression compared with GLP-1 agents.^{49,50} Adult studies of sitagliptin in T1DM have shown some promise in reducing total daily insulin dose.^{51,52} Both studies were limited in sample size and duration. In one of the studies, investigators saw a large Hawthorne effect during a crossover design study, as seen by a significant decrease in the HbA1c in both the treatment and placebo groups.⁵¹ There were no serious hypoglycemic events reported during this study, but patients on sitagliptin spent more time (0.2 ± 0.1 hour; $p = 0.08$) with lower blood glucose (<56 mg/dL), suggesting the need for further evaluation of hypoglycemia.

Sodium Glucose Cotransporter 2 Inhibitors. Sodium glucose cotransporter 2 (SGLT2) inhibitors reduce reabsorption of glucose in the proximal tubules of the kidney.⁵³ T1D Exchange registry data indicated that 0.63% of patients were prescribed these agents as adjuvant treatment.²⁸ Possible adverse events include genital mycotic infections, urinary tract infections, and hypovolemia and hypotension due to osmotic diuresis. In 2015, the FDA issued a warning regarding a potential risk for DKA, urosepsis, and pyelonephritis. In this communication, the FDA cited 73 reports of DKA, between March 2013 and May 2015, in T1DM or T2DM patients treated with a SGLT2 inhibitor.⁵⁴ Moreover, the link between SGLT2 inhibitors and euglycemic DKA has been discussed in multiple case reports and publications in the past few years.^{55–58} It is speculated that increased renal glucose clearance mediated by use of SGLT2 inhibitors coupled with decreased insulin use to avoid hypoglycemia can lead to lipolysis as the source of energy, and consequently development of euglycemic DKA.^{55,56}

A phase 1, single-center, double-blind, placebo-controlled, crossover study of 33 patients ages 12 to 21 years with T1DM for ≥ 12 months stratified the patients by baseline HbA1c to 1 of 2 treatment arms: 10 mg of dapagliflozin (DAPA) or placebo.⁵⁹ While maintaining plasma glucose levels between 160 and 220 mg/dL with infusion pumps of insulin and glucose, patients underwent a 10-hour fasting period followed by 10 mg of DAPA or placebo. A standardized liquid mixed meal was administered 6 and 12 hours after dosing. Patients continued to fast between the meals and until 24 hours after the DAPA or placebo dose. Total insulin doses, urine glucose excretion, and plasma β -hydroxybutyrate were tracked for 24 hours after dosing. The total insulin dose used in 24 hours was 13.6% lower with DAPA versus placebo (95% CI, -17.4% to -11.4%). Urine glucose ex-

cretion was significantly higher in the treatment versus placebo group, with a mean difference of 121.07 g/24 hr (143.44 vs. 22.37 g/24 hr). The possible risk for DKA was monitored with regular β -hydroxybutyrate plasma levels. The levels were different between the 2 groups, with statistical significance (0.17 ± 0.13 mmol/L with DAPA vs. 0.11 ± 0.08 mmol/L with placebo; $p < 0.0001$), but this average is considered mild and below levels associated with clinical DKA.^{60–62} Nonetheless, 5 episodes where the levels were ≥ 0.6 and <1.0 mmol were observed in the DAPA group, in contrast to 1 episode in the placebo group.⁵⁹ Authors stated that a limitation to this study is exclusion of patients younger than 12 years. Therefore, issues related to younger age, such as effects of the drug on developing nephrons and bone growth and increased risk of urinary tract infections when using diapers, could not be evaluated.

Other Agents. Alpha glucosidase inhibitors like acarbose are used in T2DM to inhibit digestion of disaccharides and monosaccharides and have been studied in adult T1DM with improvements in post-prandial glucose levels but not significant improvements to HbA1c.⁶³ Amylin analogues, such as pramlintide, suppress glucagon secretion and slow gastric emptying and have shown promise in reducing HbA1c in adult T1DM.⁶⁴ Limited pediatric studies have shown reductions in post-prandial hyperglycemia, decreases in HbA1c, body weight, and insulin doses with no severe hypoglycemia or DKA.⁶³ Besides the need for subcutaneous administration, a minimum required consumptions of 250 calories or 30 grams of carbohydrates with the dose and a 50% meal-time insulin dose reduction limit pramlintide compliance and usage in T1DM.^{63,65}

Glucagon

Exogenous glucagon is used as a life-saving measure for reversal of DM-associated severe hypoglycemia. Endogenously, pancreatic α cells and the liver are responsible for the production and release of glucagon in response to hypoglycemia. Glucagon stimulates glycogenolysis and gluconeogenesis, leading to a rise in serum glucose, which is critical for central nervous system function. The viability of this counterregulatory mechanism in T2DM is disputed, but it is known to become diminished early on in T1DM.^{66,67} That is why exogenous glucagon is used during a severe hypoglycemic episode, when the patient is not coherent enough to safely intake glucose through the oral route.

Exogenous glucagon is commercially available as a kit containing the glucagon powder for injection and water for reconstitution prior to parenteral administration. This product is traditionally considered unstable as a solution, and the unused portion should be discarded per package insert. In spite of that, it is used in bihormonal artificial pancreas studies for infusion pump delivery during 24 hours. The results of a recent pharmacokinetic study supported this practice by verifying

Table 4. Caregivers' Perception of Intranasal Glucagon Ease of Use

	Assessment of Ease of Use	
	Very Easy, % (n)	Easy, % (n)
Opening the kit	82 (27)	18 (6)
Instructions	67 (22)	18 (6)
Administering	61 (20)	33 (11)
Degree of satisfaction	67 (22)	24 (8)
Easy to teach others	88 (29)	12 (4)

the chemical and physical stability of the reconstituted product in a 24-hour period.⁶⁸

Although a life-saving measure, there are disadvantages to the glucagon powder for injection. Because of the need for reconstitution and parenteral administration, it requires training. The glucagon kit also features a diagram that depicts steps for preparation and administration. However, the stress of the situation for caregivers can add difficulty to this process. A study of 136 parents of teenagers and young children with DM found that 69% of the parents had difficulty handling the kit and preparing the dose, and as many as 30% did not administer an accurate dose. The mean time to administration was 2.5 minutes (0.5 to 12.5 minutes) for parents compared with 1.3 minutes for health care professionals.⁶⁹

To date, glucagon powder for injection remains the only available formulation, but new formulations are in the pipeline. In fact, the results of a pediatric phase 3 clinical study on a dry-powder intranasal formulation was made available in June 2017, and Eli Lilly announced submission of a new drug application for this product to FDA in July 2018.^{70,71} Intranasal delivery of glucagon has been studied since the early 1980s. These studies demonstrated intranasal glucagon's ability to increase blood sugar in healthy individuals and to reverse hypoglycemia in both children and adults with DM.⁷² Despite the success with these early studies, not much was published on intranasal glucagon in early 2000s. This might have been due to the limited market size for glucagon compared with insulin and other treatments for DM.⁷² Alternatively, issues surrounding the shelf-life of glucagon in solution form, the optimal delivery device, or finding the right promoter to enhance the absorption of glucagon (a larger molecule) may have slowed the efforts during that time period. In 2015, however, Eli Lilly acquired phase 3 intranasal glucagon from Locemia Solutions.

Eli Lilly's new intranasal glucagon is formulated as an intranasal powder delivered via a single actuation. The phase 2 pharmacokinetics and pharmacodynamics clinical trial for this product was conducted including 48 participants with T1DM in 3 age groups of 4 to 7 years, 8 to 11 years, and 12 to 16 years.⁷³ Participants in the 2 younger age groups were randomly assigned to receive a 2- or 3-mg dose of intranasal glucagon at 2

separate sessions or to receive a weight-based dose (0.5 vs. 1 mg) of intramuscular glucagon. Participants in the oldest age group received 3 mg of intranasal and 1 mg of intramuscular glucagon in a crossover manner. The primary outcome of a ≥ 25 mg/dL rise in blood glucose from nadir within 20 minutes of dosing was achieved in all participants regardless of the dose or route of delivery except in 1 instance, when the patient immediately blew his nose after intranasal delivery of glucagon. The authors did not statistically evaluate the difference of mean rise in plasma glucose after 20 minutes of glucagon administration between groups, but the values ranged from 41 to 77 mg/dL. Gastrointestinal adverse effects were more common with intramuscular compared with intranasal administration among participants younger than 12 years of age. On the contrary, headache or nasal adverse effects were more common with intranasal administration. The results of the phase 3 clinical trial are not published yet but are available on clinicaltrials.gov.⁷⁰ Similar to the phase 2 trial, the 26 participants had T1DM and were ages 4 to 16 years. Conducted as an open-label, single-arm, multicenter trial, the caregivers of all participants were trained for administration and provided with 4 doses of 3 mg of intranasal glucagon. The primary outcome was the number of participants awakening or returning to a normal status within 30 minutes following administration of the studied drug. This outcome was measured based on caregivers' responses to a set of questions. The primary outcome of interest was achieved 100% of the time for the 33 hypoglycemic events in 14 participants that were included for analysis. Most caregivers found intranasal administration of glucagon very easy, and 61% of the time it took them <30 seconds to administer the dose (Table 4). It is also reported that all participants experienced adverse events without any further specifications.

A few alternative novel methods of glucagon delivery are in development by Xeris Pharmaceuticals. In addition to completing a phase 3 clinical trial in pediatric participants using a glucagon pen for treatment of severe hypoglycemia, this pharmaceutical firm has 4 other glucagon products in various stages of development: a pen for treatment of moderate hypoglycemia, pump delivery for management of DM hypoglycemia or congenital hyperinsulinemia, and a bihormonal artificial

pancreas.⁷⁴ It is noteworthy that Xeris Pharmaceuticals has claimed that its glucagon solution has a 2-year shelf life without the need for refrigeration.

The results of the aforementioned phase 3 clinical trial of the glucagon pen are not yet available. However, this multicenter, open-label trial included participants ages 2 to 17 years. Following an insulin-induced hypoglycemia, subcutaneous doses of 0.5 and 1 mg were administered to participants ages 2 to 11 and 12 to 17 years, respectively. Evaluating changes in plasma glucose within the first 30 minutes after administration of the dose was the primary objective for this study.⁷⁴ Furthermore, all major insulin pump manufacturers have completed some preliminary clinical trials for glucagon use via a bihormonal bionic pancreas. Some of these studies are published and will be discussed in the next review of this series.

The future of glucagon delivery is advancing rapidly. Although not enough information is available for speculations, it is likely that intranasal glucagon will enter the market first, followed shortly by a glucagon pen. The glucagon pen may have the advantage of being studied in a younger patient population (age 2 vs. 4 years). It also has a 2-year shelf-life, although to the knowledge of the authors information on the shelf-life of intranasal glucagon is not available. Moreover, the introduction of a bihormonal bionic pancreas does not seem too far ahead and will be discussed in the next review of this series.

Summary

IDeg has shown non-inferiority in efficacy compared with the traditional treatments and may provide flexibility in dosing without compromising glucose control. To determine whether it has a better safety profile, more studies are required. The combination product of IDeg and IAsp has limited clinical applicability and has not entered the market despite receiving the FDA approval 2 years ago. The availability of multiple IGlir products provides the possibility for more economical choices and a more concentrated option for those requiring larger daily doses. Faster aspart could represent an improvement in bolus insulin for children, but data in children are currently limited to a pharmacokinetic study, where the 2-hour postmeal glucose was lower in the faster aspart group. Among non-insulin pharmacotherapy options for T1DM, metformin is the most commonly used according to patient registries from the United States, Germany, and Austria. The data from metformin studies are not quite congruent, although most studies found some beneficial effects from adjuvant use of metformin. Beyond metformin, pediatric data for the use of other non-insulin products are limited. However, it is noteworthy that studies are recruiting patients ages 10 and 12 years and older for the evaluation of liraglutide and exenatide, respectively, for the treatment of T1DM. Furthermore, the introduction of newer modes of glucagon

delivery in the near future can be expected, especially the intranasal formulation, which has completed phase 3 trials in both adults and pediatrics.

ARTICLE INFORMATION

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