Insulin-delivery methods for children and adolescents with type 1 diabetes

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Ther Adv Endocrinol Metab

2020, Vol. 11: 1–13

DOI: 10.1177/2042018820906016

***Abstract*:** Efforts directed toward restoring normal metabolic levels by mimicking the physiological insulin secretion, thereby ensuring safety, efficacy, minimal invasiveness and conveniences, are of great significance in the management of type 1 diabetes among children and adolescents. Regardless of the various technologies being discovered in addressing invasiveness and enhancing medication adherence in the management of type 1 diabetes, yet limited success had been observed among children and adolescents. The multiple daily subcutaneous insulin injections route using vial and syringe, and occasionally insulin pens, remain the most predictable route for insulin administration among children and adolescents. However, this route has been associated with compromised patient compliance, fear of injections and unacceptability, resulting in poor glycemic control, which promote the demand for alternative routes of insulin administration. Alternative routes for delivering insulin are being investigated in children and adolescents with type 1 diabetes; these include the hybrid closed-loop 'artificial pancreas' system, oral, inhalation, intranasal routes, and others. This review article explores the current advances in insulin-delivery methods that address the needs of children and adolescents in the treatment of type 1 diabetes.

Keywords: adolescents, artificial pancreas, children, insulin delivery, nasal insulin, type 1 diabetes

Received: 20 July 2019; revised manuscript accepted: 17 January 2020.

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Introduction

Type 1 diabetes mellitus is characterized by impaired insulin secretion. According to the World Health Organization report, 422 million people are diagnosed with diabetes, globally.[1] The International Diabetes Federation reports an estimated 1.11 million children and adolescents aged <20 years have type 1 diabetes, with 132,600 new cases diagnosed annually from children and adolescents of the age group <20 years, worldwide, in 2017.[2] Moreover, the overall annual incidence of type 1 diabetes among children and adolescents has been estimated at around 3%.[2] Therefore, treatment of diabetes among children remains one among the global health priorities.

About 14% of children achieve the glycated hemoglobin (HbA_{1c}) target of $<7.5\%$ compared with 30% of adults (HbA_{1c} target of $<7.0\%$).[3] Challenges relating to the poor treatment outcomes among children and adolescents with type 1 diabetes have contributed, including noncompliances and nocturnal hypoglycemic episodes, and a very close parental/guardian supervision is very much needed.[3–5] However, improved and novel technologies including the use of insulin pens, insulin pumps, sensor-augumented pumps (SAPs) and artificial pancreas system improve the safety, effectiveness, and adherence to insulin regimen among children and adolescents with type 1 diabetes.[6–13] In addition, automated modulating insulin-delivery systems according to the measured glucose levels under minimal supervision are particularly needed in alleviating the insulin delivery challenges.[3,7] This necessitates the need for reviewing advanced technologies

addressing challenges associated with insulin delivery systems among children and adolescents with type 1 diabetes.

Nevertheless, vial-and-syringe method has been a conventional effective insulin treatment method among children and adolescents with type 1 diabetes to control HbA_{1c} levels.[14] However, maintaining good glycemic control in children and adolescents might be affected by inaccurate dosing, pain, fear of injection (needle phobia), acceptability, and inconveniences, as far as the standard vial-and-syringe-delivery method is concerned.[4,14,15] These drawbacks promoted the necessity for alternative insulin delivery methods such as insulin pens, insulin pumps, closed-loop 'artificial pancreas' systems, and other insulin delivery routes including oral, inhalation, and nasal routes.[8,9,11,16–20] This review article explores the current advances in the insulin delivery methods that address the needs of children and adolescents in the treatment of type 1 diabetes.

Materials and methods

The search terms 'vial and syringes,' 'insulin pen,' 'insulin pump,' 'hybrid closed loop,' 'oral insulin,' 'nasal insulin,' 'inhaled insulin,' 'type 1 diabetes,' 'children,' 'adolescents,' and other acronyms were used in combination with the Boolean operators as described by Boell and Cecez-Kecmanovic[21] in identifying articles that were included in this review. Two authors (ZZ and WL) independently searched for the relevant articles written in English language up to June 2019 in the Ovid Medline, PubMed, and Google scholar electronic databases. Furthermore, the searches were supplemented through scanning citations for the relevant articles.

Current insulin-delivery methods for children and aldolescents with type 1 diabetes

Vial and syringe

The standard injection (SIs) using vial and syringe is considered as effective means of delivering insulin among children and adolescents with type 1 diabetes. Several modifications of modern syringes for insulin-delivery dates back to the early 19th century.[22] However, invasiveness and needle phobia have been associated with patients compliance, resulting in higher HbA_{1c} levels and infrequent blood glucose monitoring among children and adolescents with type 1 diabetes.[4,15]

Insulin pens

Inaccuracy and inconvenience are the common challenges of the vial and syringe in setting up the insulin dose for many patients, including children and adolescents.[14] These drawbacks of the vial and syringe led to manufacturing of insulin pens. The unveiling of NovoPen® (NovoNordisk A/S, Bagsvaerd, Denmark) in the mid-1980s by Novo Nordisk established another platform in diabetes treatment regimes as an alternative to the vial-and-syringe method.[23,24] Over the past 30 years after launching Novopen®, there have been several modifications by various pharmaceutical industries. Insulin pens are more accurate, user friendly (with less fear of injections), and associated with low pain when used with short and fine needles.[8,9,24–26]

NovoPen Echo® (NovoNordisk A/S, Bagsvaerd, Denmark) has merged two features, memory function, and half-unit increments dosing. It is a user-friendly, long-lasting insulin pen tailored for the pediatric population.[24] The REMIND study evaluated the safety, usefulness of memory function, and users' preferences of the NovoPen Echo® insulin pen in children and adolescents with type 1 diabetes ($n = 315$) aged 2–18 years from Canada, Finland, Israel, and Sweden. The study found that 99% of the patients reported the device was easy to read for the last-dose amount, and the vast majority of the patients were impressed by the safety, appearance, and user friendliness of the device.[6] Likewise, the number of patients achieving 558 mmol/mol (7.5%) HbA_{1c} decreased from 23.4% to 17.8% while the mean HbA_{1c} levels increased by 2.7%.[6] Moreover, Olsen and colleagues[9] assessed the usefulness, functionality, and attitudes towards the NovoPen Echo® against NovoPen® (NovoNordisk A/S, Bagsvaerd, Denmark) Junior and HumaPen® Luxura™ (Eli Lilly and Company, Indianapolis, IN, USA) HD in children and adolescents aged 7–18 years who received insulin treatment for less than 6 months in Germany, France, and Canada. They found that NovoPen Echo® was easy to set up, adjust, and inject insulin, and it was also more acceptable to children and adolescents, their parents, and healthcare practitioners than other pen devices (NovoPen® Junior and HumaPen® Luxura™ HD).[9,27] However, HumaPen® Luxura™ HD might be useful to children with

type 1 diabetes who need precise half-unit increment dosing.[26,28]

Another insulin pen, JuniorSTAR® (Sanofi-Aventis, Paris, France), is a reusable insulin pen with half-unit increments developed for meeting the needs for young people with diabetes.[8] Another evaluation study on the usefulness of the JuniorSTAR® insulin pen in young people (2–18 years) with type 1 diabetes involving both patients/parents and nurses found that ⩾87% of study participants ($n = 167$) agreed that it was easy to read and dial back when setting the dose, which help patients achieve high dosing accuracy in young people with type 1 diabetes.[8] Therefore, the use of JuniorSTAR® by both young people with type 1 diabetes and their caregivers was considered more convenient and highly suitable for young people's lifestyle.

The InPen® (Companion Medical, San Diego, CA, USA) system is a first US Food and Drug Administration (FDA)-approved smart pen for insulin management; it was launched in 2017 and uses Bluetooth® technology. It could help children and their caregivers in constant tracking, monitoring, and calculating the required amount of insulin therapy, particularly because of its simple design and the half-unit adjustments needed by most children with diabetes.[29,30]

Injection ports

In addressing the invasiveness and needle phobia of SI, an insulin injection port called i-Port Advance® (Medtronic, Northridge, CA, USA) was developed in order to improve medication adherence.[31] The i-Port Advance® rises to about 9.3 mm above the skin when applied, with a flexible cannula either 6 mm or 9 mm long for delivery of medication.[31] Very limited information exists on suitability of i-Port Advance® in children and adolescents with type 1 diabetes. However, regular use of the i-Port Advance® has been reported to improve patients' compliance, reduce the chances of being hospitalized and finally, leading to rare hypoglycemic events, with a nonsignificant 0.73/100 reduction in HbA_{1c} levels among patients with diabetes with mean age 14.96 ± 8.95 years.[32] Meanwhile, the I-Port® device (Patton Medical Devices, Austin, Texas, USA) was recommended for children and adolescents with type 1 diabetes in home and healthcare settings.[33] Blevins and coworkers reported that I-Port® may be used for the administration of multiple insulin doses using a single I-Port® device, and concluded it was a feasible alternative to SI.[33] In that context, both i-Port Advance® and I-Port® devices may be helpful in reducing needle phobia, and effectively achieving glycemic control among children and adolescents needing insulin therapy.

Insulin pumps

Unlike insulin pens, physiological delivery of insulin is considered crucial in the management of type 1 diabetes in children and adolescents. Continuous subcutaneous insulin fusion (CSII) or insulin-pump therapy is coupled by a small, portable electronic pump for infusing insulin at a slow basal rate, considered ideal for titrating doses of insulin in children and adolescents to avoid hypoglycemia.[14,29] Several insulin pumps are now available with built-in features; blood-glucose monitoring (BGM) and continuous-glucose-monitoring (CGM) systems for infusing insulin in patients with type 1 diabetes (Table 2). However, these insulin pumps can be mutually and inclusively used with children and adolescents with type 1 diabetes, except MiniMed™ 670G (Medtronic, Northridge, CA, USA), which is recommended for children aged 7 years and above.

Several studies have shown the effectiveness of CSII against multiple daily injection (MDI) in children and adolescents.[10,13,16,57] A cross-sectional study by Szypowska and colleagues[13] compared the metabolic control in 16,570 children with type 1 diabetes aged between 0 and 18 years of age that were treated with CSII *versus* MDI in 46 SWEET centres. This study reported the adjusted HbA_{1c} levels and daily insulin intake {CSII: 7.7 (7–8.5)%, [60.7 (53–69) mmol/mol] *versus* MDI: 8.0 (7.2–9.1)%, [63.9 (55–76) mmol/mol], $p < 0.0001$} and [CSII: 0.83 (0.66–1.02) U/kg/d *versus* MDI: 0.9 (0.7–1.13) U/kg/d, $p < 0.0001$] were significantly reduced in children in the CSII group than MDI group, respectively.[13]

However, in a meta-analysis performed to evaluate the effectiveness of CSII against MDI in children with type 1 diabetes, there was a significant reduction in HbA_{1c} levels for CSII compared with MDI ($p = 0.007$ and $p = 0.006$, respectively).[10,57] Similarly, a transatlantic study involving 54,410 children and adolescents with type 1 diabetes aged under 18 years from three pediatric registries

Table 1. Comparison of popular insulin pens for use in children and adolescents with type 1 diabetes.[14]

Device	Manufacturer	Cartridge design	Memory function	Dose increments (units)	Recommended age (in years)	Reference
AutoPen®	Owen Mumford, Oxford, UK	Reusable	No	1.0	–	Owen Mumford Ltd[34]
NovoPen Echo®	Novo Nordisk A/S, Bagsværd, Denmark	Reusable	Yes	0.5	–	Novo Nordisk A/S[35]
Novolog® Flexpen®	Novo Nordisk A/S, Bagsværd, Denmark	Disposable	No	1.0	–	Novo Nordisk A/S[36]
Tresiba FlexTouch®	Novo Nordisk A/S, Bagsværd, Denmark	Reusable	No	1.0, 2.0	1+	Novo Nordisk A/S[37]
Levemir FlexTouch	Novo Nordisk A/S, Bagsværd, Denmark	Disposable	No	1.0	2+	Novo Nordisk A/S[38]
Humalog® Junior KwikPen®	Eli Lilly and Company, Indianapolis, IN, USA	Disposable	No	0.5	–	Eli Lilly and Company[39]
HumaPen® Luxura™ HD	Eli Lilly and Company, Indianapolis, IN, USA	Disposable	No	0.5	–	Eli Lilly and Company[40]
Basaglar® KwikPen®	Eli Lilly and Company, Indianapolis, IN, USA	Reusable	No	1.0	6+	Eli Lilly and Company[41]
JuniorSTAR®	Sanofi-Aventis, Paris, France	Reusable	No	0.5	–	Sanofi-Aventis[42]
Lantus® SoloSTAR®	Sanofi-Aventis, Paris, France	Disposable	No	1.0	6+	Sanofi-Aventis[43]
Admelog® SoloSTAR®	Sanofi-Aventis, Paris, France	Disposable	No	1.0	3+	Sanofi-Aventis[44]
Apidra® SoloSTAR®	Sanofi-Aventis, Paris, France	Disposable	No	1.0	4+	Sanofi-Aventis[45]

combined [the US T1D (type 1 diabetes) Exchange, the English-Welsh National Pediatric Diabetes Audit and the German–Austrian Prospective Diabetes Follow-up Registry] reported unadjusted HbA_{1c} levels in CSII users $8.0 \pm 1.2\%$ (64 ± 13.3 mmol/mol) were considerably lower than MDI users $8.5 \pm 1.7\%$ (69 ± 18.7 mmol/mol), $p < 0.001$.[11] Nevertheless, girls were more likely to use CSII pump therapy compared with boys [odds ratio (OR): 1.22, 95% confidence interval (CI): 1.17–1.27].[11] Despite insulin pumps improving insulin effectiveness, they have been reported to increase the incidence of ketoacidosis in children and adolescents with type 1 diabetes approximately six times more in the CSII group than in the MDI group.[16]

Sensor-augmented pump

Another milestone in the management of type 1 diabetes in children and adolescents involves the integration of CGM and insulin-pump (or CSII) technologies. When CGM and CSII are coupled, it is sometimes referred to as a SAP. However, CGM and MDI can altogether be useful in optimizing metabolic levels.[29] A randomized controlled trial investigated the predictive low-glucose management (PLGM) of the MiniMedTM 640 (Medtronic, Watford, Hertfordshire, UK) device in reducing hypoglycemia rates in comparison with the SAP in 100 children and adolescents (aged 8–18 years) with type 1 diabetes who were clinically based at two sites, each from Israel and Slovenia. This study showed reduced

Table 2. Comparison of mostly popular insulin pumps that can be used in children and adolescents with type 1 diabetes.

Device	Manufacturer	Built-in feature	Bolus increment (units)	Basal increment (units)	Recommended age (in years)	Reference
MiniMed™ 670G	Medtronic, Northridge, CA, USA	Hybrid closed-loop system	0.025–0.1[a]	0.025–0.1[a]	7+	Medtronic MiniMed Inc[46]
MiniMed™ 630G	Medtronic, Northridge, CA, USA	CGM	0.025–0.1[a]	0.025–0.1[a]	–	Medtronic MiniMed Inc[47]
MiniMed™ 530G	Medtronic, Northridge, CA, USA	BGM and CGM	0.025–0.1[a]	0.025–0.1[a]	–	Medtronic MiniMed Inc[48]
MiniMed™ 640G	Medtronic, Watford, Hertfordshire, UK	BGM and CGM	0.025–0.1[a]	0.025–0.1[a]	–	Medtronic MiniMed Inc[49]
OmniPod® UST400	Insulet Cooperation, Billerica, MA, USA	BGM	0.05–1.0[b]	0.05	–	Insulet Corporation[50]
Dana Diabecare IIS	SOOIL Development Co., Ltd., Seoul, Korea	BGM	0.05–1.0[b]	0.01, 0.1	–	SOOIL Development Co., Ltd.[51]
Accu-Chek® Spirit	Roche Diabetes Care, Inc., Indianapolis, IN, USA	BGM	0.1–2.0[c]	0.01–0.1[d]	–	Roche Diabetes Care, Inc.[52]
Accu-Chek® Combo	Roche Diagnostics Ltd., Burgess Hill, West Sussex, UK	BGM	0.1–2.0[c]	0.01–0.1[d]	–	Roche Diagnostics Ltd.[53]
Accu-Chek® Insight	Roche Diagnostics Ltd., Burgess Hill, West Sussex, UK	BGM	0.01–2.0*	0.01	–	Roche Diagnostics Ltd.[54]
t:slim X2™	Tandem Diabetes Care Inc., San Diego, CA, USA	CGM	0.5–5.0[d]	0.1	6+	Tandem Diabetes Care Inc.[55]
t:slim G4™	Tandem Diabetes Care Inc., San Diego, CA, USA	CGM	0.5–5.0[e]	0.1	–	Tandem Diabetes Care Inc.[56]

All information gathered in this table was obtained from the reference manual of each specified insulin-pump device.
*No specific increments were stated in the manual.
Specific increments were:
[a]0.025, 0.05 and 0.1;
[b]0.05, 0.1, 0.5 and 1.0;
[c]0.1, 0.2, 0.5, 1.0 and 2.0;
[d]0.01, 0.05 and 0.1 and [e]0.5, 1.0, 2.0 and 5.0.
BGM, blood-glucose monitoring; CGM, continuous glucose monitoring.

hypoglycemic events at the expense of extended duration in moderate hypoglycemia below 3.6 mmol/l in the PLGM on relative to PLGM off (mean ± standard deviation: 4.4 ± 4.5 *versus* 7.4 ± 6.3, $p = 0.008$, respectively).[5]

Similarly, a home-based randomized crossover trial investigated the effectiveness and safety of integrated t:slim X2™ pump with Dexcom G5 sensor deploying PLGM against SAP therapy in adolescents, children, and adults with type 1 diabetes ($n = 103$, 6–72 years), and reported a significant hypoglycemia reduction using the t:slim X2™ Basal-IQ™ PLGM system.[17] In this context, a closed-loop insulin delivery system can reduce hypoglycemia risk, leading to improved metabolic control and reduced burden to children with type 1 diabetes.[5,17,18]

Table 3. Selected types of inhaled insulin and their actions.

Insulin	Formulation	Duration of action	Potential side effects	Stage of development	Recommended for children	Reference
Exubera®	Dry powder	5–6 h	Hypoglycemia, cough, sore throat	FDA approved, but off market	No	ModernMedicine Network[58]
Afrezza®	Dry powder	2–3 h	Hypoglycemia, cough, throat pain or irritation	FDA approved, available on the market	No	Klonoff[59]
AERx® iDMS	Liquid	5–6 h	Nocturnal hypoglycemia	Terminated phase III clinical trial	No	Wollmer *et al.*[60]

FDA, US Food and Drug Administration; iDMS, insulin diabetes management system.

Future approaches for delivering insulin in children and adolescents with type 1 diabetes

Inhaled-insulin devices

Regardless of the wide availability of various inhaled-insulin devices on the market, they have not been widely recommended for application in children and adolescents with type 1 diabetes. Inhaled-insulin devices have been associated with technical challenges for children and adolescents with type 1 diabetes, including safety and potential side effects, such as hypoglycemia, cough and throat pain despite their non-invasive route of administration (Table 3).

The first FDA-approved inhaled insulin, known as Exubera® (EXU), was approved in January 2006. Children and adolescents were, arguably, the group expected to benefit most from EXU by avoiding and minimizing injections.[61] EXU was not approved for children aged < 18 years. However, a study by White and coworkers[62] compared the effectiveness and safety of EXU against subcutaneous insulin (SCI) in children with type 1 diabetes aged 6–11 years, and reported an adjusted mean decrease in HbA_{1c} levels [EXU − SCI], −0.23 (95% CI: −0.49 to 0.03). Additionally, mild–moderate cough was 3.6 times higher in the EXU than SCI patients. In that context, EXU was shown to be effective in reducing plasma glucose levels in children with type 1 diabetes.[62] However, EXU was withdrawn from the market by Pfizer due to its poor market performance and unacceptability among patients and physicians.[22,63] As a result of this, a 12-month randomized, open-label phase III clinical trial [ClinicalTrials.gov identifier: NCT00479258] assessing safety and effectiveness of EXU in comparison with SCI therapy in type 1 diabetic children and adolescents (6–17 years old) was also terminated.[64]

Another promising inhaled-insulin device, Afrezza®, a monomeric inhaled-insulin developed by Mannkind Corporation, was the second inhaled-insulin device approved by the FDA in June 2014.[20,59] Nevertheless, Afrezza® was conditionally approved for rapid-acting inhaled insulin in improving postprandial (after meal) glycemic control in adults with either type 1 or type 2 diabetes but not in children.[20] However, Mannkind Corporation is running a phase II clinical trial in assessing the safety and tolerability of Afrezza® among children and adolescents aged 4–17-years old with type 1 diabetes [ClinicalTrials.gov identifier: NCT02527265].[65]

AERx® insulin diabetes management system (iDMS) is another inhaled-insulin device that generates liquid aerosol with consistent 2–3 µm-sized particles.[63] Unlike EXU and Afrezza® inhaled-insulin devices, very limited information exists concerning the safety and efficacy of the AERx® iDMS among adolescents and children with type 1 diabetes. However, a randomized, parallel clinical trial assessing the safety and effectiveness of AERx® iDMS with SCI therapy in patients with type 1 diabetes aged between 18 and 81-years old reported differences in HbA_{1c} levels (AERx® iDMS–SCI), 0.18% (95% CI: −0.04 to 0.39) while the fasting plasma glucose was significant lower in the AERx® iDMS group than the SCI group (9.2 mmol/l *versus* 11.7 mmol/l, $p < 0.001$).[63] Additionally, reduced percentage difference of the predicted lung diffusing capacity for carbon monoxide, using AERx® iDMS was −2.03%, $p = 0.04$, which occurred after 3 months and then

stabilized.[63] Furthermore, the findings from this clinical trial suggested that the effectiveness and safety of inhaled-insulin AERx® iDMS are comparable to the SCI Aspart, with further optimization among adults with type 1 diabetes. Conversely, a phase III clinical trial [ClinicalTrials.gov identifier: NCT00322257] comparing the effectiveness and safety of inhaled-insulin AERx® iDMS with SCI aspart, with each intervention grouped with insulin detemir among type 1 diabetic patients aged $\geqslant 18$ years, was terminated by Novo Nordisk A/S.[66] The development of inhaled-insulin AERx® iDMS was discontinued by Novo Nordisk A/S due to inability to provide significant clinical benefits over the modern insulin pen devices, and not for safety reasons.[63]

Portal insulin delivery

The hepatic-directed vesicle (HDV) was developed by Diasome Pharmaceuticals Inc., Cleveland, Ohio, USA. It is a novel investigational insulin-delivery system with diameter < 150 nm, capable of carrying any commercially available insulin and a specific hepatocyte-targeting molecule remotely mimicking a portal vein insulin infusion and a non-invasive oral route.[67] Meanwhile, the study findings of the InSulin Liver Effect (ISLE-1) phase IIb, multicenter, randomized, double-blind clinical trial [ClinicalTrials.gov identifier: NCT02794155] investigated the safety and efficacy of the hepatic-directed vesicle insulin lispro (HDV-L) against insulin lispro (LIS) in patients with type 1 diabetes over a 26-week treatment period were a mean change in HbA_{1c} levels of 0.09% (95% CI: 20.18–0.35) from baseline.[68] Similarly, incidence rates of severe hypoglycemia among poorly controlled patients ($HbA_{1c} \geqslant 8.5\%$) and better-controlled patients ($HbA_{1c} < 8.5\%$) in HDV-L and LIS arms were (69 and 97, $p = 0.03$) *versus* (191 and 21, $p = 0.001$) events/100 person-years, respectively.[69] If the current trendline of the study findings continue in the upcoming phase III clinical trial, patients under insulin treatment would simultaneously achieve the target HbA_{1c} levels and reduce hypoglycemic risks.

Oral insulin delivery

Various developmental challenges have been associated with rendering effectiveness of the oral route for insulin delivery. These include poor epithelial permeability and enzymatic degradation of insulin in the gastrointestinal (GI) tract, leading to insufficient bioavailability of insulin.[70] The oral route is considered an appropriate, convenient and safe route for insulin administration in children and adolescents with type 1 diabetes.

Neither published evidence from clinical trials nor approved oral insulin therapy assessing the safety and effectiveness of oral insulin in the treatment of type 1 diabetes in adolescents and children is yet to be available. However, a pilot study conducted by Eldor and coworkers[19] reported the treatment effect of ORMD-0801 in the glucose reading frequencies > 200 mg/dl was associated with 24.4% reduction ($60.7 \pm 7.9\%$ against $45.4 \pm 4.9\%$ in pretreatment and in-treatment with ORMD-0801 respectively, $p = 0.023$) in patients with uncontrolled type 1 diabetes aged 27–50-years old [ClinicalTrials.gov identifier: NCT00867594]. In the Pre-POINT randomized clinical trial [ClinicalTrials.gov identifier: NCT02620553] assessing the effects of high-dose oral insulin (from Lilly Pharmaceuticals) on the immune response in children (2–7 years) highly susceptible for type 1 diabetes, the day-to-day oral dosage of 67.5 mg insulin triggered immune response without inducing hypoglycemia.[71] However, the phase III clinical trial could help determine the prevention effect of this oral insulin against islet autoimmunity and type 1 diabetes among children of the same age.[72]

Recently, Abramson and colleagues[70] developed an ingestible self-orienting millimeter-scale applicator (SOMA) system that directly engages with GI tissue for insulin delivery. *In vivo* studies in rats and pigs demonstrated the SOMA system to be safe and effective, of which the active insulin levels were comparable with those administered *via* the SCI route.[70] Nevertheless, novel approaches for oral insulin development in overcoming the GI tract's harsh conditions need to be apprehended.

Buccal insulin delivery

The buccal route of administration helps to bypass the GI degradation, thus enhance bioavailability of the delivered biomolecules. Oral-lyn® (developed by Generex Biotechnology Corp., Toronto, Canada) is a short-acting insulin (in liquid formulation) sprayed into the mouth using a proprietary RapidMist® device for management of type 1 and type 2 diabetes. Currently, there is no any ongoing

clinical trial of the Generex Oral-lyn® involving children and adolescents with type 1 diabetes. Nevertheless, the study findings of a 26-week open-label, randomized, active comparator phase III clinical trial [ClinicalTrials.gov identifier: NCT00668850] compared the Oral-lyn® against a regular human insulin therapy as measured by HbA_{1c} levels; the number of hypoglycemic episodes in patients with type 1 diabetes aged 18–75 years are not yet disclosed.[73] Recently, Generex Biotechnology Corp., announced reformulation of Altsulin® (microencapsulated sertoli cells) from its subsidiary ALTuCELL, Inc. for the treatment of type 1 diabetes.[74]

Nasal insulin delivery

Intranasal insulin-delivery route is more advantageous over the oral delivery route, as it has an ability to bypass GI peptidases, is non-invasive, painless, and no potential side effects have been associated with lung function.[75] However, inefficient permeability of large molecules across the nasal mucosa and rapid mucociliary clearance, resulting in varied bioavailability of the active insulin in systemic circulation, are the drawbacks of the intranasal insulin delivery.[75–77]

Currently, a PINIT randomized phase II clinical trial [ClinicalTrials.gov identifier: NCT03182322] is testing the immune effectiveness and safety of intranasal insulin (440 IU) treatment in islet-autoimmunity-negative children aged 1–7 years at high risk of having type 1 diabetes.[78] However, an active randomized controlled phase II clinical trial [ClinicalTrials.gov identifier: NCT00336674] has determined the prevention effect of intranasal insulin (440 IU) in children and young adults aged 4–30 years at risk of type 1 diabetes.[79] Both these clinical trials use nasal spray Pfeiffer actuators in administering the 440 IU intranasal insulin, which contains recombinant human insulin, benzalkonium chloride, glycerol, and water. However, the results from these phase II clinical trials are awaited.

Future closed-loop systems

An automated insulin-delivery system (also called closed loop, artificial pancreas) combines an algorithmic controller for subcutaneous estimation of the blood-glucose levels, computing and administering insulin dosing commands using an insulin pump. The MiniMed™ 670G system (Medtronic, Northridge, CA, USA) became the first hybrid closed-loop system to get FDA approval.[12] However, several other automated closed-loop insulin-delivery systems are either in clinical trials or under development.

Recently, Brown and coworkers[7] assessed the safety and efficacy of an automated insulin-delivery system that combines the t:slim X2™ insulin pump, Dexcom G6 CGM, coupled with a built-in Control-IQ™ algorithm among patients with type 1 diabetes aged 14–61 years ($n = 168$; 112 were assigned to the closed-loop group and 56 in the control group) in a 6-month, multicenter, randomized trial [ClinicalTrials.gov identifier: NCT03563313].[7] The study reported that the significant mean percentage difference of time (closed loop minus control) in the glucose target range of 80–180 mg/dl was 11% (95% CI: 9–14, $p < 0.001$).[7] After 6 months, the mean adjusted difference in glycated hemoglobin HbA_{1c} levels was −0.33% (95% CI: −0.53 to −0.13; $p = 0.001$).[7] Therefore, the greater percentage of time spent using the closed-loop system was strongly associated with the target glycemic range rather than the SAP. Yet, the study findings of the Control-IQ™ among patients with type 1 diabetes aged 14+ years had been submitted to the FDA for approval. In line with this, there is an ongoing clinical trial [ClinicalTrials.gov identifier: NCT03844789] assessing the safety and acceptance of the artificial pancreas, t:slim X2™, incorporating Dexcom G6 CGM, coupled with a built-in Control-IQ™ technology for improving blood-glucose levels among children with type 1 diabetes aged 6–13 years old.[80]

Nevertheless, an ongoing 6-month day-and-night open-label, multicenter, multinational, single-period, randomized, parallel-group clinical trial (DAN05) [ClinicalTrials.gov identifier: NCT02925299] assessing the efficacy, safety and usability of an automated closed-loop insulin delivery [FlorenceM in the US (MiniMed™ 640G insulin pump, Medtronic, CA, USA incorporating the Medtronic Guardian™ Sensor 3 CGM) and FlorenceX in the UK (Dana Diabecare® R insulin pump, SOOIL Development, Seoul, Korea, incorporating the Dexcom G6 CGM)] in comparison with the insulin-pump therapy by measuring HbA_{1c} levels for controlling the blood glucose among children and adolescents ($n = 130$) with type 1 diabetes aged 6–18 years old.[81,82] The DAN05 study is expected to be completed by

June 2020 and will measure both primary and secondary outomes. The primary outcome will involve the mean group differences in HbA_{1c} levels at baseline for the 6-month duration; while the secondary outcomes, such as the time spent between 70 mg/dl and 180 mg/dl (3.9–10.0 mmol/l) glucose target levels, and time spent above or below the glucose target, as measured by CGMs and other related CGM metrics, will be documented.[81,82]

Currently, MiniMed™ 670G is the only automated insulin-pump system available on the market which automatically adjusts basal insulin delivery depending on the CGM readings.[12] In June 2019, Medtronic launched a home-based study trial [ClinicalTrials.gov identifier: NCT03959423] to evaluate the safety of the MiniMed™ 780G, advanced hybrid closed-loop sytem for automated basal insulin delivery in adult and pediatric participants with type 1 diabetes aged 7–75 years ($n = 250$).[83] The primary outcomes, including change in HbA_{1c} levels, and mean difference in percentage of time spent between 70 mg/dl to 180 mg/dl from baseline to the end of a 3-month study period will be measured, while the number of hypoglycemic events and diabetic ketoacidosis experienced by participants as the secondary outcomes will also be evaluated.[83]

In a day-and-night, randomized crossover study trial [ClinicalTrials.gov identifier: NCT02105324] with an automated artificial pancreas, bihormonal bionic pancreas (giving both insulin and glucagon hormones) from Beta Bionics Inc., Boston, MA, USA against the conventional insulin-pump therapy in preadolescent children ($n = 19$, aged 6–11 years) with type 1 diabetes in a diabetes camp setting showed a significant lower mean of the measured CGM glucose levels and time percentage of measured CGM glucose levels < 3.3 mmol/l (7.6 ± 0.6 mmol/l *versus* 9.3 ± 1.7 mmol/l, $p = 0.00037$ and $1.2 \pm 1.1\%$ *versus* $2.8 \pm 1.2\%$, $p < 0.0001$) in the bionic pancreas period than the control period of 2–5 days, respectively.[3] These findings highlight the need for investigational studies having a long duration to fully understand the bionic pancreas potentials among children with type 1 diabetes in the real-world settings. Additionally, in a very recently completed day-and-night randomized crossover trial study [ClinicalTrials.gov identifier: NCT04112069] testing the safety and effectiveness of the 5-day insulin-only mode Gen3 iLet (iLet) bionic pancreas using a Dexcom G5 CGM against 5-day SAP therapy in children with type 1 diabetes and adolescents ($n = 20$, aged 6–17 years).[84] The prefindings showed that participants achieved good glycemic control with the mean CGM glucose levels and the mean percentage time-in-range target glucose levels (70–180 mg/dl) of 160 ± 27 mmol/l *versus* 163 ± 15 mmol/l; and $65 \pm 15\%$ *versus* $65 \pm 10\%$ for SAP and iLet groups, respectively.[85] Regardless of the improved glycemic control with low hypoglycemia levels, there were very few hyperglycemic events which led to the changes in the Gen4 iLet under development in improving its safety and usability in the pedriatic population.

Nevertheless, Abbott Diabetes Care Inc., from Alameda, CA, USA and Bigfoot Biomedical Inc., from Milpitas, CA, USA collaborated in the development of the smartloop™ automated insulin-delivery system that automatically measures a patient's blood-glucose levels every 15 min for up to 10 days.[86] The study findings from a clinical trial [ClinicalTrials.gov identifier: NCT02849288] completed in 2016 that assessed the safety and feasibility of the smartloop™ automated insulin-delivery system among patients aged 7+ years with type 1 diabetes are not yet disclosed.[87] However, the smartloop™ automated insulin-delivery system is expected to be available in the market after FDA approval.

Conclusion and future prospects

The search for alternative insulin-delivery methods that have minimal invasiveness, convenient, safe, effective, and tailored for children and adolescent patients are considered of great importance. Insulin pens remain the alternative delivery device in children and adolescents with diabetes, as they continue to improve insulin treatment adherence over the traditional means of insulin administration using vial and syringes. Further advances on hybrid closed-loop 'artificial pancreas' system should be strongly emphasized, as this system has already shown significant metabolic control among children and adolescents with diabetes. In future, pain-free and non-invasive smart fitted patches of microneedles might influence insulin injection compliance and reduce anxiety in children and adolescents with type 1 diabetes.

Funding

The authors disclose receipt of the following financial support for the research, authorship,

and/or publication of this article: The National Key Technology Research and Development Program (2015BAD05B02), the National Natural Science Foundation of China (51774128), the China of Postdoctoral Science Foundation (2016T90769, 2016M592456, 2015M580707), the Natural Science Foundation of Hunan Province of China (2018JJ4061, 2018JJ2090 and 2018JJ4009), the Key Program of Hunan Provincial Department of Science and Technology (2016NK2096), Huxiang Youth Talent Support Program (2015RS4051), the Scientific Research Fund of Hunan Provincial Education Department (17A055 and 18B290), Zhuzhou Key Science & Technology Program of Hunan Province (2017), and the Green Packaging and Security Special Research Fund of China Packaging Federation (2017ZBLY14).

Conflict of interest statement

The authors declare that there is no conflict of interest.

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