Pharmacological Research 195 (2023) 106882

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

New therapies towards a better glycemic control in youths with type 1 diabetes

Roque Cardona-Hernandez [a,1], Klemen Dôvc [b,c,1], Torben Biester [d,2], Laya Ekhlaspour [e], Maddalena Macedoni [f], Martin Tauschmann [g], Chiara Mameli [f,h,*]

[a] Division of Pediatric Endocrinology. Hospital Sant Joan de Déu, Barcelona, Spain
[b] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[c] Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, University Children's Hospital, Ljubljana, Slovenia
[d] AUF DER BULT, Diabetes Center for Children and Adolescents, Hannover, Germany
[e] Department of Pediatrics, Division of Endocrinology. University of California, San Francisco, CA, United States
[f] Department of Pediatrics, V. Buzzi Children's Hospital, Milan, Italy
[g] Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria
[h] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Type 1 diabetes
Youths
Children
Technology
Automated insulin delivery
Time in range

ABSTRACT

Type 1 diabetes (T1D) is the most frequent form of diabetes in pediatric age, affecting more than 1.5 million people younger than age 20 years worldwide. Early and intensive control of diabetes provides continued protection against both microvascular and macrovascular complications, enhances growth, and ensures normal pubertal development. In the absence of definitive reversal therapy for this disease, achieving and maintaining the recommended glycemic targets is crucial. In the last 30 years, enormous progress has been made using technology to better treat T1D. In spite of this progress, the majority of children, adolescents and young adults do not reach the recommended targets for glycemic control and assume a considerable burden each day. The development of promising new therapeutic advances, such as more physiologic insulin analogues, pioneering diabetes technology including continuous glucose monitoring and closed loop systems as well as new adjuvant drugs, anticipate a new paradigm in T1D management over the next few years. This review presents insights into current management of T1D in youths.

1. Introduction

Type 1 diabetes (T1D) is the most common form of diabetes in childhood and adolescence, accounting for more than 90% of cases. Its incidence is increasing worldwide by an average of 3–4% per year [1], despite wide global variation [2]. In 2021, there were approximately 8.4

Abbreviations: ADA, American Diabetes Association; AHCL, Advanced hybrid closed-loop; AID, Automatic insulin delivery; AUC, area under the curve; BMI, body mass index; CSII, continuous subcutaneous insulin infusion pumps; CGM, Continuous glucose monitoring; DCCT, Diabetes Control and Complications Trial; DKA, diabetes ketoacidosis; DIY, Do-It-yourself; EDIC, The Epidemiology of Diabetes Interventions and Complications; FDA, Food and Drug Administration; FGP, Fastig Plasma Glucose; EMPA, Empaglifocin; euDKA, euglycemic diabetes ketoacidosis; FLAIR, Fuzzy Logic Automated Insulin Regulation; Gla-100, Insulin glargine 100 U/mL; Gla-300, Insulin glargine 300 U/mL; HCL, hybrid closed loop; HCPs, Healthcare professionals; HbA1c, Glycated hemoglobin A1c; IAsp, Insulin aspart; ICF, insulin correction factor; ICR, insulin-to-carbohydrate ratio; IOB, insulin on board; isCGM, Intermittently scanned continuous glucose monitoring; ISPAD, International Society for Pediatric and Adolescent Diabetes; LDL, low density lipoprotein; LGS, Low Glucose Suspension; MDI, multiple daily injections; MPC, Model Predictive Controller; NPH, Neutral Protamine Hagedorn; PDM, personal diabetes manager; PID, Proportional Integrative Derivative; PLGS, Predicted low glucose suspension; RCT, Randomized Clinical Trial; rtCGM, Real-Time continuous glucose monitoring; SAP, Sensor-augmented pump; SGLTi, sodium-glucose cotransporter inhibitors; ST, standard therapy; TAR, Time above range; TBR, Time below range; TDI, total daily insulin; TIR, Time in range; T1D, type 1 diabetes; URLi, Ultra rapid lispro.

* Correspondence to: Department of Pediatrics, V. Buzzi Children's Hospital, Univerisity of Milan, Via Lodovico Castelvetro, 32, 20154 Milan, Lombardia, Italy.
E-mail address: chiara.mameli@unimi.it (C. Mameli).
[1] Roque Cardona-Hernandez and Klemen Dovc have contributed equally to this manuscript and both have the same consideration as first author.
[2] ORCID 0000–0001-8051–5562

https://doi.org/10.1016/j.phrs.2023.106882
Received 13 February 2023; Received in revised form 10 July 2023; Accepted 2 August 2023
Available online 3 August 2023

million (95% uncertainty interval 8·1–8·8) individuals worldwide with T1D: of these 1.5 million (18%) were younger than age 20 years [3].

Prolonged exposure to hyperglycemia may result in micro and macrovascular disease [4]. The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) established solid evidence as to the importance of intensive insulin treatment to achieve near-normal glycemic levels and avoid long-term complications [4,5]. Moreover, the EDIC study, introduced the concept of *metabolic memory* consisting on the influence that high blood glucose level during the first years of T1D may have in the development of future long-term complications describing the beneficial impact of early intensive insulin treatment on preventing these complications many years later [5–7]. Nevertheless, the majority of children and adolescents with T1D do not achieve recommended glycemic targets. In a global registry-based study from the period 2017–2019, only 37% of children and adolescents were able to attain the former International Society for Pediatric and Adolescent Diabetes (ISPAD) glycated hemoglobin A1c (HbA1c) recommended target of < 7.5% (58 mmol/-mol) while only 21% attained the current ISPAD and American Diabetes Association (ADA) HbA1c target < 7.0% (53 mmol/mol) [8].

Growth, hormonal and pubertal status, unpredictable eating patterns, dynamic lifestyles, unscheduled physical activity and fear of hypoglycemia [9] may be key factors influencing difficulties reaching recommended targets in children and adolescents. Over the last few years, the development of promising new advances in therapies, such as more physiologic insulin analogues, pioneering diabetes technology including continuous glucose monitoring (CGM) and Automated Insulin Delivery (AID) systems as well as new adjuvant drugs, anticipate a new paradigm in diabetes management.

2. The era of time in range

For the past 30 years, glucose management has primarily been assessed with the HbA1c, a generally recognized and reliable biomarker that reflects long-term average glucose level [10–15]. Current international guidelines recommend that for the majority of children and nonpregnant adults HbA1c should be < 53 mmol/mol (7%) or even < 47.5 mmol/mol (6.5%) if this can be achieved safely [16]. While HbA1c realistically represents the average glycemic control in retrospect, it has limited utility for assessing short-term outcomes and day-to-day glucose fluctuations. Importantly, it lacks information about acute complications, such as severe hypoglycemia or diabetic ketoacidosis that are, together with the fear of hypoglycemia, important barriers impeding diabetes care optimization [17,18]. CGM, either real-time (rtCGM) or intermittently scanned (isCGM), effectively addresses these barriers: data derived from CGM present a more comprehensive glucose control picture than HbA1c alone [19].

In 2017, an international consensus recommended standardized CGM reporting and defined outcomes definitions with a core set of ten CGM metrics for standardized reports [19].

The consensus suggested easy-to-understand TIR targets, along with TBR and TAR targets for routine management of type 1 and type 2 diabetes and for type 1 diabetes complicated by pregnancy. Targets should be individualized and ligned with personal necessities and circumstances. Each incremental 5% improvement in TIR is associated with clinically significant benefit.

The principal goal for all children and adults with T1D is to maintain:

1. **70% of TIR** (70–180 mg/dL / 3.9–10 mmol/L) = *16 h 48 min per day*,
2. while at the same time minimizing both TBR and TAR:
3. **< 4% of TBR** (< 70 mg/dL / 3.9 mmol/L) = *1 h per day*, and
4. **< 25% of TAR** (> 180 mg/dL / 10 mmol/L) = *6 h per day*

To unify and improve diabetes-related outcomes and quality of life with our routine clinical care, we need to constantly improve the presentation and usage of provided CGM data. Improvement in diabtes care using the new metrics will only be achived if it is understood and broadly adoption by individuals with diabetes and health care professionals.

3. Pharmacological approach

3.1. Insulin therapy

After the discovery of insulin in 1921 and its first use in humans in 1922, a broad spectrum of treatment choices for children and adolescents with T1D has been developed with the aim to mimic as closely as possible normal physiological patterns. Before 2018, insulin formulations for the pediatric population included: rapid-acting analogs (such as insulin aspart, glulisine and lispro), regular insulin, Neutral Protamine Hagedorn insulin (NPH) and basal long-acting analogs (glargine, detemir and degludec) [20]. Since 2018, a new basal long-acting insulin analog (insulin glargine 300 U/mL - Toujeo®) and two new ultra-rapid acting analogues (faster aspart 100 u/mL - Fiasp® and ultra-rapid lispro - Lyumjev®) have been developed and approved for the pediatric population. An inhaled insulin formulation (technosphere insulin - Afrezza®) has been approved for adult use. Table 1 shows the baseline characteristics of the phase 3 trials and independent studies on pediatric patients using new insulin formulations.

a) Long-acting analogues

3.1.1. Insulin glargine 300 U/mL

Insulin glargine 300 U/mL (Gla-300) is a second-generation long-acting basal insulin analogue. It has a more stable and prolonged pharmacokinetic/pharmacodynamic profile than insulin glargine 100 U/mL (Gla-100) with a duration of glucose-lowering activity exceeding 24 h. This fact reflects that the injection volume is reduced and constitutes itself as a smaller subcutaneous depot which leads to a slower and more prolonged insulin release and absorption profile. These important characteristics may reduce glycemic fluctuations and confer flexibility around the time of administration [21].

On February 2015 the U.S. Food and Drug Administration (FDA) approved glargine 300 IU/mL (Toujeo®) for the treatment of T1D in adults [22,23]. On November 2019, approval was expanded to children aged > 6 years This indication was supported by the phase 3 Edition Junior trial [ClinicalTrials.gov Identifier: NCT02735044] [24].

a) Fast-acting analogues

3.1.2. Faster aspart

Fast-acting insulin aspart 100 u/mL (faster aspart) is a formulation of insulin aspart (IAsp) with two added excipients, L-arginine and niacinamide. These excipients ensure a formulation stability as well as an accelerated initial absorption after the subcutaneous administration. Accelerated absorption results from more rapid monomer formation from the stable insulin hexamers [25]. A trial investigating the pharmacological properties of faster aspart vs IAsp in children, adolescents and adults with T1D demonstrated that, after injection, consistently across all age groups, the mean serum IAsp concentration-time profiles were shifted to the left for faster aspart vs IAsp. Onset of appearance occurred approximately twice as fast and early exposure was greater for faster aspart vs IAsp, with no treatment differences in total exposure or maximum concentration (Cmax). Two-hour post-meal plasma glucose excursion in children was reduced for faster aspart vs IAsp [26]. On January 2020, the FDA expanded the use of Fiasp, in children as young as 2 years to treat diabetes (the treatment had already been approved for use in adults in September 2017, and for use in insulin pumps in October 2019). Approval followed the review of data from the Onset 7 clinical trial [27], a 26-week, phase 3, multicenter, randomized, double-blind, parallel-group study that was conducted in subjects with T1D aged

Table 1
Baseline characteristics of the phase 3 trials and independent studies on pediatric patients using new insulin.

Autor/Company and year [Ref]	Country	Study design	Population -age range	Study period	Treatment prior study enrollment	Main outcomes	Follow up
Danne T, 2020 [29]	Multicentre	RCT	N = 463; aged 6–17 y	2016–2018	MDI	To compare efficacy and safety of insulin Gla-300 VS Gla-100 in children and adolescents with T1D	6 m + 6 m safety extension period
Al Hayek AA, 2022 [30]	Saudi Arabia	OS	N = 86; aged 14–40 y (n = 26 ≤ 20 y).	2021	MDI	To compare efficacy, safety and patient-reported satisfaction of insulin Gla-300 VS insulin Gla-100 in adolescents and young adults with T1D	3 m
Bode BW, 2019 [33]	Multicentre	RCT	N = 777; aged 1–17 y	2016–2018	MDI	To compare efficacy and safety of faster aspart VS IAsp (both while on basal insulin degludec) in children and adolescents with T1D	6 m
Costa C, 2022 [35]	Portugal	RS	N = 60; aged 3–19 y	2019–2020	N = 47 on CSII; n = 13 on MDI	To compare efficacy of faster aspart VS other rapid-acting insulin analogues in children and adolescents with T1D.	3 m
González de Buitrago Amigo J, 2020 [36]	Spain	OS	N = 32; aged 7–17 y	2019	CSII (MiniMed640G)	To compare efficacy and safety of faster aspart VS IAsp in children and adolescents with T1D on CSII	3 m
Eli Lilly and Company, "PRONTO-Peds" trial [42]	Multicentre	RCT	N = 716; aged 1–17 y	2019–2021	MDI	To compare efficacy and safety of URLi VS Humalog in children and adolescents with T1D.	6 m
Mannkind Corporation, "Afrezza INHALE-1″ Study in Pediatrics [44]	USA	RCT	N (estimated) = 264; aged 4–17 y	2021-ongoing	MDI	To compare efficacy and safety of Afrezza VS rapid-acting insulin analogues plus basal insulin in children and adolescents with T1D or T2D.	6 m + 6 m safety and efficacy extension period

RCT: Randomized Controlled Trial; OS: Observational Study; RS: Retrospective Study; N: number; Y: years; M: months; MDI: Multiple Daily Injections; CSII: Continuous Subcutaneous Insulin Infusion; insulin Gla-300: insulin glargine 300 U/mL; insulin Gla-100: insulin glargine 100 U/mL; IAsp: Insulin Aspart; URLi: Ultra Rapid Lispro insulin; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes.

1–17 years. The current trial showed that mealtime and postmeal faster aspart were both noninferior to IAsp in terms of HbA1c control (with a statistically significant difference in favour of mealtime faster aspart vs mealtime IAsp). Since 2019, two "real-world" studies have been published to provide such data on the pediatric population [28,29]. Costa el al [28]. conducted a retrospective analysis in Portugal with 60 pediatric patients (n = 47 on CSII; n = 13 on MDI) with T1D that assessed the impact on the metabolic control, after changing their rapid-acting insulin analogue to Fiasp. Another trial conducted in Spain [29] analysed the efficacy of faster aspart vs insulin aspart in 32 children and adolescents with T1D on CSII treatment with predicted low glucose suspension (PLGS) (Medtronic MiniMed640G®). The study covered a three months periods and the results did not differ from those reported by Costa C et al. [28]. Although data in the pediatric age are still limited, these studies suggest that faster aspart is a mealtime and postmeal effective and safe option in children and adolescents with T1D both on MDI and CSII. While the ISPAD guidelines [20] recommend bolus insulin administration at least 15–20 min before meals, this can be challenging in younger children, during acute illness and in adolescents. Faster aspart, according to the current evidence, allows insulin administration within the first 20 min after starting a meal, and thus may confere benefits to avoid these barriers.

3.1.3. Ultra-rapid insulin lispro

Ultra rapid lispro (URLi) is a novel insulin lispro formulation containing two locally acting excipients: treprostinil, a prostacyclin analogue that induces local vasodilation, and citrate that increases vascular permeability, thereby accelerating insulin lispro absoprtion at the injection site [30,31]. In a euglycaemic clamp study comparing URLi to lispro in adult patients with T1D [32], URLi demonstrated earlier insulin action and a shorter duration of action therefore matching more closely to physiological insulin secretion. The onset of appearance of insulin lispro in serum was 6 min faster with URLi, leading to a sevenfold higher insulin exposure during the first 15 min after the injection. In addition, exposure 3-hours post injection was 39–41% lower, with an exposure duration reduction by 72–74 min in comparison with lispro. A corresponding shift was observed in the pharmacodynamic profile. The onset of insulin action was 11–12 min earlier with URLi, and insulin action was threefold greater over the first 30 min postdose. Late insulin action beyond 4 h postdose was reduced by 44–54% with a duration of action reduced by 34–44 min compared with lispro.On June 2020, the FDA approved the use of ultra-rapid insulin lispro 100 and 200 units/mL (Lyumjev®) for the treatment of adults with T1D and type 2 diabetes on multiple daily injection. Approval was based on data from two phase 3 randomized controlled trials comparing URLi with lispro in people with T1D (the PRONTO-T1D trial) [33] and type 2 diabetes (the PRONTO-T2D trial) [34]. Expanded approval for administration via CSII was accomplished in August 2021. The EU approved pediatric use in December 2022 for children aged >1 year

3.2. Adjuvant therapies

Today there is still a life expectancy gap between individuals living with and without diabetes. In addition to glycemic control, cardiovascular risk factors have also been associated with this fact. The need for improvement or prevention of concomitant diseases i.e obesity, heart and kidney failure or microvascular disease in individuals with T1D from childhood is of prime importance t. Controlling the metabolic state of people with T1D by adjuvant pharmacological measures without increasing risk of (further) weight gain, as with insulin, has been discussed in the past [35]. Nevertheless, despite all efforts, the risk of these individuals, for cardiovascular disease, in particular remains elevated compared with to non-type 1 diabetes individuals. Follow-up of the participants in the DCCT study stresses this unambiguous association: the group of patients who significantly gained weight in the course of intensified insulin therapy had a particularly high incidence of cardiovascular events [36]. Swedish registry shows how smoking, systolic blood pressure, LDL cholesterol (LDL: low density lipoprotein), glycated hemoglobin or albuminuria also influence the mortality risk in T1D [35]. The consequences of increasing weight are: increasing insulin resistance, increasing insulin dosages, rising blood pressure levels and reduced mobility. Although, for people without T1D but with significant overweight, physical activity is a "simple" and low side-effect means of weight control, frequent hypoglycemia during and/or after exercise,

requiring correction with carbohydrates (and thus calories.), ris a source of frustration and demotivation.

3.2.1. Options for adjuvant pharmacotherapy

On average, optimized insulin adjustment can achieve glycemic control on target in only half of those affected. Improving this by adjuvant pharmacological measures is an obvious target. There are several approaches to address this issue. Table 2 shows an overview on investigated substances. None of these are currently approved for adjunctive use in pediatric T1D.

a) Pamlintide

Pramlintide is an injectable amylin analogue approved only in the US for the treatment of T1D and type 2 diabetes [37]. Amylin is a neuroendocrine hormone that inhibits glucagon secretion and contributes to reducing postprandial glucose variability, for T1D, amylin deficiency is described in T1D [38]. In T1D, pramlintide has been shown to improve postprandial glucose levels but also causes postprandial hypoglycemia [39]. Therefore, the clinical use has been limited.

b) GLP-1 analogues

Two Phase III trials in adult populations (ADJUNCT ONE and ADJUNCT TWO) investigate liraglutide, a well-known GLP-1 analogue used in type 2 diabetes treatment as an adjunct to insulin. In both trials, it reduced body weight and Hba1c and was well-tolerated. Main side effects were elevated serum ketones without acidosis and more hypoglycemic events. Other trials showed similar effects [40] Accordingly the use of GLP1-analogues in T1D patients -at least in those with obesity- continues [41] Notably other trials e.g using exenatide found no benefits [42].

c) SGLTi

The most promising approach currently appears to be the class of *SGLTi*, which allow an insulin independent approach for glucose lowering by stopping the tubular re-absorption of glucose from primary urine [43]. Different SGLTi have been investigated as adjunctive therapy for people with T1D. Having proven success in treatment of type 2 diabetes [44] and being beneficial for the risk factors mentioned above [45], investigating these drugs also in T1D is feasible and expeected effects will not be not specific to treat type 2 diabetes but may dispay as a "class effect". All SGLTi provide an insulin-independent approach to lower serum glucose by inhibition of tubular reabsorption from primary urine. Most are SGLT2-inhibitors, but also combined SGLT1 and 2 inhibitors are also under investigation [46]. Several T1D trials have shown a 2–4 mmol/mol (0.2–0.4%) HbA1c improvement without an inherent risk of hypoglycemia, a moderate improvement in body weight (2–3 kg) and systolic blood pressure (3–4 mmHg decrease) [47–52], while comparability between studies is difficult due to endpoints and treatment schemes. A corresponding approval as an adjuvant therapy option is not currently available for acarbose or for metformin, SGLT-2 inhibitors (SGLTi) or GLP-1 receptor agonists. The (still) sparse data indicate a favorable effect on HbA1c levels, body weight, and daily insulin levels [53] concerning side effect of SGLTi is the side effect of so called euglycemic ketoacidosis (euDKA) [54]. Due to the renal glucose excretion, a high blood glucose can not provide an alert signal, the only way to discriminate acute illness without insulin deficiency in measurement of serum ketones [55]. Although a consensus statement recommended the use of SGLTi in T1D only when prescribed by experts [56], the concern of euDKA led to an actual withdrawal of dapagliflozins T1D approval [57], removing from the market the only SGLTi on the market available for T1D. No approvals have been issued by regulatory agencies for the pediatric population.

Table 2
Available drugs for adjuvant therapy.

Substance (class)	Effects		Approved for T1D
	+	-	
Acarbose	Reduction of postprandial glycemia without HbA1c effect		No
GLP1-RA	Reduced HbA1c, reduced body weight	Hypoglycemia and ketosis	No
Metformin	Reduced body weight and low-density cholesterol	Usual side effects of substance in T2D	No
Pramlintide	Less postprandial variability	Nausea, postprandial hypoglycemia	Only in US
SGLTi	Reduced HbA1c, insulin dose, reduced body weight	Risk for euDKA	No (dapaglifolzin had a limited approval in EU, but currently it was withdrawn)

RCT: Randomized Controlled Trial; HbA1c: glycated haemoglobin; euDKA: euglucemic diabetic ketoacidosis; US: United States; EU: European Union

4. Automated insulin delivery system

4.1. Terminology and algorithm controllers

"Automated insulin delivery" (AID) system, also known as an artificial pancreas or as "closed-loop system" describe the combination of an insulin pump (to deliver insulin) a glucose sensor (to measure interstitial fluid glucose level) and a controller algorithm that adjusts insulin delivery (up and down) in response to real-time sensor glucose levels and other inputs, such as meal intake [58]. Several types of algorithms have been developed and any particular system is not necessarily restricted to a single algorithm as combinations of two or more algorithms within the same system are also plausible [58,59].

According to the recent "Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association on Automated Insulin Delivery" [60] the terminology around AID systems includes the following terms:

Sensor-augmented pump (SAP): Insulin pump with use of a CGM either on a separate device or displayed directly on the pump. These systems allow for viewing of the sensor data, but insulin delivery is not altered on the basis of sensor glucose values.

Low glucose suspend (LGS) or predictive low glucose suspend (PLGS): Insulin pump system that suspends insulin delivery for actual hypoglycaemia due to sensor glucose value (LGS) or for predicted hypoglycaemia (PLGS).

Hybrid AID (also known as hybrid closed loop -HCL-): Insulin pump system that automatically increases or decreases basal insulin delivery in response to sensor glucose values; user still needs to dose prandial insulin manually. Advanced hybrid AID systems are also available now. These next-generation systems not only adjust basal insulin delivery but also delivers automatic correction boluses. However, they still require the person with diabetes to dose prandial insulin.

Full AID: AID system that automatically adjusts all insulin delivery, including prandial insulin.

DIY AID (also known as Loop, OPEN APS, Android APS): 'Do-it-yourself' AID system using a commercially available CGM system and insulin pump, plus an open-source algorithm; currently is approved only by FDA.

Artificial pancreas: This term was often used in the past as a synonym for AID, but the AP does not consider the exocrine functions of the pancreas.

Bihormonal (bionic pancreas) AID systems that incorporate two hormones (insulin and glucagon); insulin and pramlintide are also being studied.

Table 3 showed the pivotal and age expansion studies for

Table 3
Pivotal and age expansion studies for commercialized AID systems.

AUTHOR / PUBLICATION	DEVICE	STUDY DESIGN	STUDY DURATION	STUDY POPULATION	HbA1c AT BASELINE	RESULTADOS
Garg SK et al. Diabetes Technol Ther 2017 [82]	Medtronic 670 G™	Non-randomized One single arm	3 months	Adolescents > 14 y (n = 30) Adults (n = 94)	Adolescents 7.7% Adults 7.3%	Adolescents: • TIR ↑ from 60% to 67% • TBR ↓ from 4.3% to 2.8% • Adults: • TIR ↑ from 69% to 74% • TBR ↓ from 6.4% to 3.4%
Tauschmann M et al. Lancet 2018 [132	CamAPS FX™	RCT Parallel groups CL vs SAP	3 weeks	n = 24 children (2–7 years)	7.4%	For both groups • TIR: 70–72% • TBR: 4.5–4.7%
Forlenza GP et al. Diabetes Technol Ther 2019 [145]	Medtronic 670 G™	Non-randomized One single arm	3 months	n = 105 children (7–13 years)	7.9%	• TIR ↑ from 56% to 65% • TBR ↓ from 4.7% to 3.0%
Brown SA et al. NEJM 2019 [110]	Tandem Control IQ™	RCT Parallel groups Control IQ vs SAP	6 months	n = 168 adults and adolescents > 14 years	7.4%	Control-IQ vs SAP: • TIR ↑: 71% vs 59% • • TBR ↓: 1.6% vs 2.3%
Breton MD et al. NEJM 2020 [115]	Tandem Control IQ™	RCT Parallel groups Control IQ vs SAP	4 months	n = 101 children (6–13 years)	7.6–7.9%	Control-IQ vs SAP: • TIR ↑: 67% vs 55% • TBR ↔: 1.6% vs 1.8%
Sherr JL et al. Diabetes Technol Ther 2020 [146]	OmniPod 5	Non-randomized (Safety and performance)	96 h	Children (n = 15), Adolescents 6–18 y (n = 10) Adults 18–65 y (n = 11)	Children 8.0% Adolescents 8.4% Adults 7.4%	Adults (ST vs CL) • TIR ↑: from 68% to 73% • TBR ↓: from 3.2% to 1.7% • Adolescents (ST vs CL) • TIR ↑: from 60% to 59% • TBR ↓: 2.8% vs 2.4% • Children (ST vs CL) • TIR ↑: from 54% to 69% • TBR ↓: from 2.2% to 1.9%
Bergenstal RM et al. Lancet 2021 [90]	Medtronic 780 G™	RCT Cross-over ACHL vs 670 G	3 months	n = 113 adolescents and young adults (14–29 years)	7.9%	AHCL vs 670 G: • TIR ↑: 67% vs 63% • TBR ↔: 2.1% vs 2.1%
Ekhlaspour L et al. Diabetes Technol Ther 2021 [119]	Control-IQ	Non-randomized (Safety and performance)	48 h	n = 12 Children 2–5 years	7.3%	• TIR ↑ from 63% to 71% • TBR ↓ from 3.7% to 1.5%
Forlenza G et al. Diabetes Technol Ther 2021 [147]	OmniPod 5	Non randomized (one single-arm)	28 days	18 adults and 18 children (aged 6–70 years)	Children 7.8% Adults 7.1%	1. Children in 3 days 130 mg/dl target: 61% 2. Children in 3 days 140 mg/dl target 64.8% 3. Children in 3 days 150 mg/dl target 53.5% 4. Children in 5-days free-choice target 64.9% 5. Adults in 3 days 130 mg/dl target 75.1% 6. Adults in 3 days 140 mg/dl target 67.6% 7. Adults in 3 days 150 mg/dl target 63.7% 8. Adults in 5-days free-choice target 72.5% VS 1. Children in 14-days ST 51% 2. Adults in 14-days ST 65%
Brown S et al. Diabetes Care 2021 [148]	OmniPod 5	RCT CL vs SAP	3 months	235 participants (aged 6–70 years) - Children in 3 months HCL (n. 111) - Adults in 3 months HCL (n. 124)	Children 7.8% Adults 7.1%	CL vs ST Children • TIR 52% vs 68% • TBR 2.3% vs 0.8% Adults • TIR 65% vs 74% • TBR 3.4% vs 1.4%

(*continued on next page*)

Table 3 (*continued*)

AUTHOR / PUBLICATION	DEVICE	STUDY DESIGN	STUDY DURATION	STUDY POPULATION	HbA1c AT BASELINE	RESULTADOS
Ware J et al. NEJM 2022 [138]	CamAPS FX™	Randomized CL vs SAP	16 weeks	n = 44 Children 1–7 y	7.3%	• TBR = 4.9 vs 4.5% • TIR ↑ 71.6 vs 62.9%
Sherr JL et al. Diabetes Care 2022 [149]	OmniPod 5	Non randomized (one-single arm)	13 weeks	N = 80 Children 2–5.9 y	7.4%	• ↑ TIR: From 57% to 68% • ↓ TBR: From 3.4% to 2.4%

RCT: Randomized Controlled Trial; CL: closed loop; SAP: sensor-augmented pump; AHCL: Advanced Hybrid Closed loop; ST: Standard Therapy

commercialized AID systems.

4.2. MINIMED 780 G

The second-generation AID system 780 G system developed by Medtronic, USA (also advanced hybrid closed-loop – AHCL) includes an MD-Logic artificial pancreas algorithm to adjust automatic insulin infusion. The algorithm includes adjustable target glucose, automated correction boluses, and an updated controller that includes a modified integral action and new controller gains, a modified insulin feedback module, a modified adaptation method that ensures a more robust personalization of the therapy and increases time in AID, and a meal detection module that, if triggered, can potentially let the system deliver more aggressive automated- correction boluses [61–63]. Since October 2021, the system has been available with the non-adjunctive Guardian™ 4 sensor, which does not require calibration.

The Fuzzy Logic Automated Insulin Regulation (FLAIR) study directly compared the Medtronic 670 G with the investigational version of the 780 G system in adolescents and young adults with T1D [64]. This was a multinational randomized crossover trial, including 113 individuals with T1D aged 14–29 years. Daytime time above range (primary endpoint) was reduced by 3% with Minimed 780 G use (34% vs. 37%, $P < 0.0001$), without increasing hypoglycemia (co-primary endpoint). Consequently, TIR was improved (67% with 780 G compared to 64% with 670 G use, $P < 0.0001$). Noteworthy, the 780 G system was associated with fewer system alerts, reduced Auto Mode exits and increased time spent in Auto Mode (86% vs 75%) [64].

The efficacy of Minimed 780 G was confirmed also in a real-world data analysis from 12,780 users, achieving a TIR of 73.9% (participants <15 years) and 76.5% (participants >15 years) [65].

Evaluating patient-reported outcome measures and psychosocial outcomes, several studies demonstrated improved quality of life, decreased fear of hypoglycemia, less emotional distress, and reduced burden of disease management with the use of Minimed 780 G [66–68]. In cost-effectiveness studies, 780 G use was shown to likely be cost-effective, by improving glycemic control and reducing hypoglycemia incidence, and was associated with gains in life expectancy and improvements in quality of life due to fewer and delayed diabetes-related complications [69,70].

4.3. Tandem control-IQ

The t:slim X2 insulin pump system with Control-IQ technology (developed by Tandem Diabetes Care, San Diego, CA) and an integrated factory-calibrated CGM (Dexcom® G6) is a HCL system that uses an algorithm that automatically adjusts insulin delivery based on the CGM data. The Control IQ closed-loop system improves glycemic outcomes using an MPC algorithm that includes a hypoglycemia safety module, basal rate modulation as well as automated corrections and more intensified control overnight using a lower target range (112.5–120 mg). The user still needs to enter the amount of the meal carbohydrate content into the bolus calculator [71].

A large multicenter NIH-sponsored clinical trial led to FDA approval of the t:slim X2 with the Control IQ closed loop system in December 2019. 168 participants (age 14–17 years) with Type 1D participated in a six-month study. TIR increased significantly 71% in Control IQ arm vs. 59% in control arm. There was a significant reduction in hypoglycemia (1.6% vs.2.3%) [72]. The sub-analysis of the adolescents and young adults in this trial (63 participants) who all completed the study showed Control IQ improved TIR by 13% vs. 1% in the usual care arm by reducing the time with hyperglycemia. Baseline HbA1c in this subgroup was 8.1% [73]. To compare the glycemic outcomes with the use of Basal IQ (the predictive low glucose suspend feature of the t:slim X2 insulin pump) with Control IQ, after six months of control IQ use 109 participants were randomized to either continue using Control IQ or Basal IQ. While in the Basal IQ arm TIR decreased from 70% to 60% over 13 weeks, in the Control IQ arm TIR remained comparable (70% vs. 68%). Time < 54 mg/dL was similar and showed reduction from baseline on both systems [74]. Following the pivotal trial in adolescents and adults, another large randomized clinical trial testing the safety and efficacy of the control IQ system was conducted in children between aged 6 and 13 years . 101 children completed a 16-week randomized trial. The system was effective and safe in the younger age group. Mean TIR increased from 53% at baseline to 67% in the Control IQ arm and from 51% to 55% in the standard treatment arm. The median time with hypoglycemia was low in both groups since most control arm patients used a low glucose suspend system [75]. The extension phase of the study showed that the use of the system in youth improves glycemic outcomes starting day one and remains effective through week 28. The increase in TIR from baseline 53 ± 17% persisted and was stable throughout the study to 67 ± 10% during the RCT and at 66 ± 10% through the 12 weeks post-RCT [76]. In this trial, baseline TIR was associated with lower TIR on closed loop. However, lower baseline TIR was also associated with greater improvement in TIR on closed loop. Active involvement and user-initiated boluses are essential for the higher TIR [77].

In order to expand the use of the system to a wider age range, Control IQ system was tested in a small group of older patients (mean age 68.7 years old). The system improved the glycemic control compared with SAP. TIR increased from 70% to 80%, and time below 70 mg/dl was decreased to 0.8% [78].

Recently a large multicenter study testing the Control IQ in children 2–5 y old has been published. Similarly to previous pivotal studies in the control IQ arm TIR improved significantly during the study period (from 56.7 ± 18.0% to 69.3 ± 11.1% and in the standard care arm from 54.9 ± 14.7% to 55.9 ± 12.6%) i The researchers observed similar treatment effects (favoring the closed-loop system) on the percentage of time that the glucose level was above 250 mg/dl, on the mean glucose level and on the HbA1c level with no significant between-group difference in the percentage of time that the glucose level was below 70 mg/dl. The authors reported two cases of severe hypoglycemia in the closed-loop group and one case in the standard-care group as well as one case of DKA occurred in the closed-loop group [79].

Psychosocial Impact. To asses user experience with technology and the system's impact on quality of life, during the large scale, outpatient, long-term clinical trials of the Control IQ system patient Reported Outcomes (PROs) were assessed through several questionnaires were completed at baseline, 3, and 6 months. The Fear of hypoglycemia decreased significantly after six months of HCL compared with the usual care arm, and the use of the system was not accompanied by a high level of burden, which is as important as the improvement in glycemic

outcomes [80]. In the 28-week study of the younger patients (age 6–13 years), the PRO outcomes improved non-significantly from baseline to week 16 and were sustained at week 28. However, the sleep scores for parents improved between baseline and 16 weeks were sustained in both arms [81].

Real-world studies. Following a few years on the market, several real-world studies have been published. Messer and team studied the glycemic outcomes during routine care of 191 children (median age 14 years) who were transitioned to Control IQ. Glycemic outcomes (TIR and hemoglobin A1C) significantly improved during the transition while percent time using the Control-IQ feature was 86.4% at six months, and < 4% of the cohort discontinued use [82].

4.4. Camdiab camaps FX

CamAPS FX (CamDiab, Cambridge, UK) is the first commercially available HCL mobile phone application (app). CamAPS FX utilizes a control algorithm developed at the University of Cambridge over more than a decade of research led by Professor Roman Hovorka. CamAPS FX has been commercialized by CamDiab (Cambridge, UK), a University spin-out company [83]. The CamAPS FX app, classified as a medical device, resides on an unlocked smartphone communicating wirelessly with a compatible insulin pump and glucose sensor. By design, the app is configured to be interoperable with multiple devices. At present, the app communicates with the Dana RS and Dana-I pumps (Sooil, Seoul, South Korea), mylife YpsoPump (Ypsomed, Burgdorf, Switzerland) and the Dexcom G6® sensor (Dexcom, San Diego, CA, USA), but will communicate with additional pumps and CGM systems in the future (e.g. Abbott's FreeStyle Libre 3) [58,84]. In March 2020, the CamAPS FX app received CE mark in the European Union and United Kingdom. The CamAPS FX system has the broadest approval of all currently commercially available closed loop system in terms of age (1 year and older), intended use population (including pregnant women with T1D), and compatible insulin formulations (including ultra-rapid insulin analogues). The algorithm is available as an app, and the first one working with two different insulin pumps and two different glucose sensors.

The CamAPS FX app is a HCL system, manual triggering of insulin boosts at mealtime is still required. The Cambridge control algorithm is based on the model predictive control paradigm. The treat-to-target algorithm calculates a new insulin infusion rate using a compartment model of glucose kinetics that describes the effect of rapid-acting insulin and meal carbohydrate content on glucose levels [85]. The algorithm continuously adjusts insulin delivery to achieve a default glucose target of 5.8 mmol/l (104 mg/dl) and adapts to a particular user based on total daily insulin requirements, day-to-day prandial and diurnal patterns [86]. The CamAPS FX is initialized with the participant's weight, and the total daily insulin dose only, insulin sensitivity and active insulin time are automatically calculated and adjusted. Unlike with other closed loop systems, no warm-up phase required. Insulin delivery is modulated by the adaptive control algorithm every 8–12 min [85]. In the CamAPs FX app, the user has the option to set glucose targets very individually, both in terms of the actual level (between 4.4 mmol/L and 11 mmol/l), as well as the time periods for the scope of various targets. Additionally, two features called "ease-off" and "boost" modes are available in the app that decrease and increase insulin delivery rates, respectively. Ease-Off mode can be activated during exercise or when glucose levels tend to be too low., while boost mode can be activated during periods of inactivity or increased food intake. The Cambridge algorithm has been extensively evaluated in RCTs over the past decade, beginning with controlled laboratory conditions, followed by short to medium free-living unsupervised outpatient studies to larger-scale, multicenter pivotal clinical trials [85,87,88].

In a randomized controlled multicenter trial across the United Kingdom and United States AID use was compared to pump therapy in 86 sub-optimally controlled (baseline HbA1c >58 mmol/mol [7.5%]) children, adolescents and adults aged 6–65 years, AID use increased time in target range over 12 weeks compared with sensor-augmented pump therapy by 10.8% points (95% CI 8.2–13.5; p < 0·0001) [87]. Time spent in hypoglycemia was lower in the AID group than the control group and HbA1c also improved with HCL use. Furthermore, the use of ultra-rapid insulin analogues was successfully tested with the CamAPS FX closed loop system, with advantages in terms of reducing hypoglycemia [89].

Other unique advantages of the Cambridge algorithm are available safety and efficacy studies in two very vulnerable populations: pregnant women and very young children with T1D. Following a pilot trial showing feasibility and safety of HCL insulin delivery in children aged 1–7 years with T1D using the Cambridge algorithm [90], the CamAPS FX HCL system was compared to SAP therapy in a multinational, multicenter, randomized, two-period, crossover trial including 74 very young children (mean (± SD) age: 5.6 ± 1.6 years, baseline glycated hemoglobin: 7.3 ± 0.7) [91]. Use of the CamAPs FX system significantly increased time in target range by 8.7% points compared with the SAP during the 16-week treatment periods. The difference in the glycated hemoglobin level was − 0.4% points. The time spent in a hypoglycemic state was similar with the two treatments.

Aside from improving glycemic control, the focus of the recently published CLOUD study was on the preservation of beta cell function following HCL initiation within 6 weeks of diabetes onset [92]. In this multicenter, open-label, parallel-group, randomized trial, 10–17 year-old children and adolescents were randomized within 21 days after a diagnosis of T1D to receive HCL therapy or standard insulin therapy (control) for 24 months. A total of 97 participants (mean±SD age, 12 ± 2 years) underwent randomization. The AUC for the C-peptide level at 12 months (primary end point) did not differ significantly between the two groups, nor did the AUC for C-peptide level at 24 months. However, HbA1c levels in the HCL group were significantly lower at 12 (−0,4%) and at 24 months (−1,0%) compared with standard therapy (ST).

4.5. Omnipod 5 automated glucose control system

The current Omnipod 5® Automated Glucose Control System Powered by Horizon (Omnipod 5 system) is the third single-hormone HCL system to reach the marketplace, approved by FDA in January 2022, CE marked in Europe September 2022. The Omnipod 5 system is the only wearable, tubeless and waterproof insulin pump, referred to as a "Pod", that is worn directly on the body and it is replaced every programmed 72 h in connection with an AID system. The Pod contains the insulin cartridge and a MPC algorithm that wirelessy receives, interstitial glucose data measured by CGM (Dexcom® sensor), every 5 min. The algorithm processes the CGM data and it engages the Pod to deliver insulin micro-boluses every 5 min. A personal diabetes manager (PDM) or the app running on a special device are used to activate the pod, to switch to the automated mode, to program pump settings: glucose target, basal insulin scheme, insulin on board (IOB), the insulin-to-carbohydrate ratio (ICR) and the insulin correction factor (ICF) for the bolus calculator function) and to deliver insulin boluses. In the Omnipod 5 System the automated basal doses are calculated on the estimated total daily insulin (TDI) dose from the last pod change (3 days). In contrast with other systems, it does not provide auto-correction bolus, but the glucose target is adjustable between 100 and 150 mg/dl with the possibility to program up to eight different targets during the day. The system is approved for age >2 or with a minimum insulin requirement of 6 U/day [93,94].

In 2020, Sherr et al. tested the Ominipod 5 System (HCL) in 36 youths and adults with T1D, during 96-h of free-living conditions, characterized by unrestricted meals and daily physical activity, in a supervised hotel/rental home[146]. Regardless of age, TIR was higher during the supervised setting compared with the following 7-days outpatient ST phase, reaching a statistical significance for both adolescents and children (HCL 79% ± 12.6% vs ST 60.6% ± 13.4% in adolescents and HCL 69.2% ± 13.5% vs ST 54.9% ± 12.9% in children).

This improvement was even more pronounced during the overnight period (23:00–07:00 h) with an increased absolute difference in TIR of 8.4% in adults, 23.3% in adolescents and 20.4% in children. In particular, children experienced an important reduction of time spent in hyperglycemia (>180 mg/dl) during the overnight period, corresponding to an absolute reduction of 18.8%. Adolescents, experienced a higher reduction in time spent in hyperglycemia, both > 180 mg/dl and > 250 mg/dl during the day, with an absolute decrease of 16.5% and 8.5% respectively. In youths, no differences were found in time spent in hypoglycemia (< 70 mg/dl) although at the overnight period, adolescents had an absolute decrease of TBR of 5.2% when using HCL. On the other hand, adults using HCL benefited of a significant reduction in TBR both < 70 mg/dl (absolute decrease of 3.2%) and < 54% (absolute decrease of 1%).

The first outpatient, prospective clinical study to assess the safety and efficacy of the Omnipod 5 System, testing different glucose targets during 14-day HCL phase, in children (age 6–13.9 years) and adults (14–70 years) with T1D demonstrated that the system performed well at different targets [95]. Compared to the previous 14-day ST phase TIR was significantly higher in children during the following target periods: 5-day free-choice, 72-h 130 mg/dl and 140 mg/dl . In adults, these differences were present only when the target was set at 130 mg/dl. Moreover, despite the use of the higher glucose target, TAR (>180 g/dl) was not significantly different from the ST phase. Informed by these promising results, despite the small size (only 36 subjects) and short duration of the study, a pivotal, multicenter, prospective, single-arm trial, including 235 subjects (111 children) was performed.

A recent single-arm study tested the HCL system in 80 very young children (aged 2–5.9 years) [96]. Primary outcomes were the evaluation of HbA1c and TIR during 13-week of HCL study phase compared with 14-day of ST phase. The system resulted safe with a good performance in very young children. HbA1c significantly decreased from 7.4 ± 1% at baseline to 6.9 ± 0.7% at the end of the study while TIR increased from 57.2 ± 15.3% to 68.1 ± 9% with higher increase during overnight period (from 58.2% to 81.0%). In addition, the percentage of children achieving HbA1c < 7.0%, TIR> 60% and TIR> 70% was respectively 54% (31% at the baseline), 83% and 44% (18% at the baseline). Regarding the safety outcomes, TBR< 70 mg/dL declined by median 0.27% and TAR > 180 mg/dl decreased by 9.9 ± 10.5%.

4.6. Combining new technologies and new pharmacological approach

Current commercially available AID systems require users to manually enter prandial insulin boluses and signal exercise while automatically modulating insulin delivery. Fully AID systems (fully closed-loop), which obviate the need for carbohydrate counting and manually initiated prandial boluses, are under development at present, but the benefits in reduced user burden come at the expense of glycemic control [97]. A fully automated AID system that eliminates the need for carbohydrate counting or meal announcement is highly anticipated for T1D and the use of faster insulin analogs within the AID system or adjunctive therapies may make this approach more feasible in the future and is being increasingly investigated [89,98,99]. Table 4 presents some of the key studies evaluating AID glucose control with added adjunctive non-insulin therapeutics.

The GLP1-RA liraglutide was added as a 1.8 mg dosage once daily to 22 out of 44 overweight or obese T1D people with insulin pump therapy (CSII) for a duration of 26 weeks in a double-blind randomized protocol. While no difference in blinded CGM was found at the beginning, TIR increased significantly in the intervention group compared to placebo (57%vs. 45%; p = 0.044). While HbA1c did not decrease in the intervention group, a difference was found compared with the control arm. The total insulin dose was reduced by 16% (p = 0.008) in the lira arm. Mean body weight was reduced by 6.3 kg (p < 0.001) compared with placebo [100].

There are currently few AID studies combined AID studies combined with non-insulin drugs are currently rare (Table 4), in the past some proof-of-concept-studies were done with small number of patients but promising results [101–103] with pramlintide and GLP1_RA. This newly dual approach with empagliflozin (EMPA) in an AID setting was used by Haidar et al. [104]. Counting carbohydrates and entering them correctly into the AID device led to a 14% higher postprandial glycemic control measured by TIR in this study. In this study EMPA added to AID had the potential reduce the need for carbohydrate counting but it does not allow for the elimination of meal announcement. The same group found the need for full carb counting reduced when using pramlintide in a special AID algorithm. In outpatient setting, there was no difference in TIR (70% ± 11%, 70% ± 13%) between meal announcement and full carb counting. Only placebo use during AID use and meal announcement only had a lower TIR (60% ± 13%) using Faster Aspart insulin in all arms [105]. A former publication from this group showed superiority of Fiasp when using a Pramlintide Co-AID-System [104].

A small single-dose randomized control trial in adolescents and young adults with type 1 diabetes using dapaglifolozin as an add-on a full closed-loop with two liquid meal challenges showed a similar improvement of 18% TIR in the intervention group compared to placebo over 24 h (68% ± 6% vs. 50% ± 13%; P < 0.001) [41]. This improvement was seen also during fasting at night, where AID systems work best, (6.2 ± 0.7 vs. 7.3 ± 1.7 mmol/L; P = 0.003). As observed in the other SGLTi plus AID trial, daytime postprandial glucose peaks were still observed using full AID setting with and without SGLTi. In this full closed loop setting, ketone levels tended to increase with SGLTi prior to the meal challenges but returned to normal levels within 30 min after the intake of oral carbohydrates and resulting automated insulin delivery.

Garcia-Tirado et al. [106] compared the use of EMPA versus no use in an AID or a PLGM setting. In both types of technical treatment, the intervention group had a significant higher TIR compared to no EMPA while the AID arm had a higher TIR also without the drug (PLGM 80% vs. 63%, +16.5%; p < 0.001; AID 81% vs 71% +9.9% p = 0.04) But also

Table 4
Current Studies Combining non-insulin pharmaceuticals and AID.

Author	Drug	Study	Participants	Duration	TIR outcome
Haidar 2020 [157]	Pramlintide	Open-label crossover RCT	28 adults	3 sequences	+ 10% vs AID only
Tsoukas 2021 [158]	Pramlintide	three-way, randomized, blinded, crossover design	7 adults	12 days	no difference between meal + announcement and full carb counting + placebo; + 10% compared to placebo and only meal announcement
Biester 2020 [162]	Dapagliflozin	Double-blind cross-over RCT	15 adolescents and 15 young adults	Single dose	+ 18%
Garcia-Tirado 2022 [159]	Empagliflozin	Open-label cross-over in HCL and PLGS RCT	34 adults	8 weeks	AID + 9.9% PLGS + 16.5%
Haidar 2022 [160]	Empagliflozin	2 × 2 factorial RCT placebo, crossover	24 adults	4 weeks	AID+ 7.2% SAP + 17.5%

RCT: Randomized Controlled Trial; AID: Automated Insulin Delivery; SAP: sensor-augmented pump; PLGS: predicted low glucose system

in this "protected" setting of a clinical trial one euDKA occurred.

Recently, Haidar et al. [107] evaluated the use of AID with EMPA to AID without empagliflozin and to SAP with or without EMPA in a 2 × 2 factorial placebo-controlled crossover RCT. The results of this study show that EMPA (25 mg/day) add-on therapy to AID systems significantly increased TIR compared to placebo (paired difference 7.2% towards AID+placebo and 17.5% towards SAP+placebo, $P < 0.0001$ for both comparisons), with no diabetic ketoacidosis or severe hypoglycemia events occurred during the study period. Notably, higher ketone concentrations were more common in EMPA groups compared to placebo. Further investigations are needed on a broader scale and with a longer study duration to fully assess the potential of SGLT2 inhibitors in conjunction with modern AID systems.

Although the automated insulin dosing might reduce the risk of an absolute insulin deficit by regulating the insulin, euDKA was previously described with AID [108]. Considering this risk for ketoacidosis when using SGLTi, a combined sensor measuring glucose and ketones in the subcutaneous tissue, which was announced by companies, might be an option to mitigate the risk on euDKA once this data is implemented into AID algorithms [109]. In addition, prevention of euDKA is possible today with the regular measurement of ß-hydroxybutyrate in serum.

5. Conclusions

Diabetes does not have a definitive cure today. Moreover, its management still offers evident limitations with most children, adolescents and young adults not reaching the recommended targets for glycemic control and assuming a considerable burden each day. Nevertheless, promising new advances in therapies, including more physiologic insulin analogues, pioneering diabetes technology and new adjuvant drugs anticipate a new paradigm in diabetes management for the next few years and a better horizon for children and adolescents living with diabetes.

CRediT authorship contribution statement

RCH, KD, CM: conceptualization. RCH, TB, LE, MM, MT: writing. CM reviewed and edited the manuscript.

Declaration of Competing Interest

CM and MM declared no conflict of interest.

Acknowledgements

We thank Giulia Maria Smylie for her help in writing this manuscript.

References

[1] E.J. Mayer-Davis, J.M. Lawrence, D. Dabelea, J. Divers, S. Isom, L. Dolan, et al., Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012, N. Engl. J. Med 376 (15) (2017) 1419–1429.
[2] D. Magliano, E.J. Boyko. IDF diabetes atlas, 10th ed., International Diabetes Federation, Brussels, 2021.
[3] G.A. Gregory, T.I.G. Robinson, S.E. Linklater, F. Wang, S. Colagiuri, C. de Beaufort, et al., Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study, Lancet Diabetes Endocrinol. 10 (10) (2022) 741–760.
[4] DCCT Group. Diabetes Control and Complications Trial Research Group, D. M. Nathan, S. Genuth, et al., The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, N. Engl. J. Med 329 (14) (1993) 977–986. Available from: https://www.nejm.org/doi/10.1056/NEJM199309303291401?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov.
[5] D.M. Nathan, M. Bayless, P. Cleary, S. Genuth, R. Gubitosi-Klug, J.M. Lachin, et al., Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions, Diabetes 62 (12) (2013) 3976–3986.
[6] Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the epidemiology of diabetes interventions and complications (EDIC) study, JAMA 290 (16) (2003) 2159.
[7] N.H. White, W. Sun, P.A. Cleary, W.V. Tamborlane, R.P. Danis, D.P. Hainsworth, et al., Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents, Diabetes 59 (5) (2010) 1244–1253.
[8] R. Cardona-Hernandez, A. Schwandt, H. Alkandari, H. Bratke, A. Chobot, N. Coles, et al., Glycemic outcome associated with insulin pump and glucose sensor use in children and adolescents with type 1 diabetes. Data from the international pediatric registry SWEET, Diabetes Care (2021) dc201674.
[9] J. Lawton, N. Waugh, K.D. Barnard, K. Noyes, J. Harden, J. Stephen, et al., Challenges of optimizing glycaemic control in children with Type 1 diabetes: a qualitative study of parents' experiences and views, Diabet. Med 32 (8) (2015) 1063–1070.
[10] The DCCT Research Group, Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: diabetes control and complications trial, J. Pedia 125 (2) (1994) 177–188.
[11] M. Lind, A.M. Svensson, M. Kosiborod, S. Gudbjörnsdottir, A. Pivodic, H. Wedel, et al., Glycemic control and excess mortality in type 1 diabetes, N. Engl. J. Med 371 (21) (2014) 1972–1982.
[12] D.S. Schade, G.M. Lorenzi, B.H. Braffett, X. Gao, K.E. Bainbridge, A. Barnie, et al., Hearing impairment and type 1 diabetes in the diabetes Control and complications trial/ epidemiology of diabetes interventions and complications (DCCT/EDIC) cohort, Diabetes Care 41 (12) (2018) 2495–2501.
[13] M.A. Atkinson, G.S. Eisenbarth, A.W. Michels, Type 1 diabetes, Lancet 383 (9911) (2014) 69–82.
[14] J.W.Y. Yau, S.L. Rogers, R. Kawasaki, E.L. Lamoureux, J.W. Kowalski, T. Bek, et al., Global prevalence and major risk factors of diabetic retinopathy, Diabetes Care 35 (3) (2012) 556–564.
[15] D.E. Goldstein, Is glycosylated hemoglobin clinically useful? N. Engl. J. Med 310 (6) (1984) 384–385.
[16] American Diabetes Association, 6. Glycemic targets: standards of medical care in diabetes—2022, Diabetes Care 45 (Supplement_1) (2022) S83–S96.
[17] B.A.W. Beyond A1C Writing Group, Need for regulatory change to incorporate beyond a1c glycemic metrics, Diabetes Care 41 (6) (2018) e92–e94.
[18] A.S. Runge, L. Kennedy, A.S. Brown, A.E. Dove, B.J. Levine, S.P. Koontz, et al., Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes, Clin. Diabetes 36 (2) (2018) 112–119.
[19] T. Danne, R. Nimri, T. Battelino, R.M. Bergenstal, K.L. Close, J.H. DeVries, et al., International consensus on use of continuous glucose monitoring, Diabetes Care 40 (12) (2017) 1631–1640.
[20] T. Danne, M. Phillip, B.A. Buckingham, P. Jarosz-Chobot, B. Saboo, T. Urakami, et al., ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes, Pedia Diabetes 19 (2018) 115–135.
[21] H.A. Blair, G.M. Keating, Insulin glargine 300 U/mL: a review in diabetes mellitus, Drugs 76 (3) (2016) 363–374.
[22] P.D. Home, R.M. Bergenstal, G.B. Bolli, M. Ziemen, M. Rojeski, M. Espinasse, et al., New insulin glargine 300 units/ml versus glargine 100 units/ml in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4), Diabetes Care 38 (12) (2015) 2217–2225.
[23] M. Matsuhisa, M. Koyama, X. Cheng, Y. Takahashi, M.C. Riddle, G.B. Bolli, et al., New insulin glargine 300 U/mL versus glargine 100 U/mL in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1), Diabetes Obes. Metab. 18 (4) (2016) 375–383.
[24] T. Danne, W.V. Tamborlane, O.A. Malievsky, D.R. Franco, T. Kawamura, M. Demissie, et al., Efficacy and safety of insulin glargine 300 units/ml (Gla-300) versus insulin glargine 100 units/mL (Gla-100) in children and adolescents (6–17 years) with type 1 diabetes: results of the EDITION JUNIOR randomized controlled trial, Diabetes Care 43 (7) (2020) 1512–1519.
[25] H. Haahr, T. Heise, Fast-acting insulin aspart: a review of its pharmacokinetic and pharmacodynamic properties and the clinical consequences, Clin. Pharm. 59 (2) (2020) 155–172.
[26] M. Fath, T. Danne, T. Biester, L. Erichsen, O. Kordonouri, H. Haahr, Faster-acting insulin aspart provides faster onset and greater early exposure vs insulin aspart in children and adolescents with type 1 diabetes mellitus: FATH et al. Pedia Diabetes 18 (8) (2017) 903–910.
[27] B.W. Bode, V. Iotova, M. Kovarenko, L.M. Laffel, P.V. Rao, S. Deenadayalan, et al., Efficacy and safety of fast-acting insulin aspart compared with insulin aspart, both in combination with insulin degludec, in children and adolescents with type 1 diabetes: the onset 7 trial, Diabetes Care 42 (7) (2019) 1255–1262.
[28] C. Costa, M.I. Linhares, F. Bastos, R. Cardoso, I. Dinis, A.P. Santos, et al., Effect of ultra-rapid insulin aspart on glycemic control in children with type 1 diabetes: the experience of a Portuguese tertiary centre, Diabetol. Int 13 (3) (2022) 531–537.
[29] J. González de Buitrago Amigo, A. González García, P. Díaz Fernández, M. Fernández Llamas, M.L. Tejado Bravo, J.M. de Nicolás Jiménez, et al., The impact of "faster aspart" on blood glucose control in children and adolescents with type 1 diabetes treated using a sensor-augmented insulin pump, Pedia Engl. Ed. 95 (5) (2021) 321–329.
[30] E. Pratt, J. Leohr, C. Heilmann, J. Johnson, W. Landschulz, Treprostinil causes local vasodilation, is well tolerated, and results in faster absorption of insulin lispro (abstract 975-P), Diabetes 66Suppl (2017) 1A253.

[31] M. Michael, C. Zhang, A. Siesky, A. Cox, A. Sperry, R. Hansen, Exploration of the mechanism of accelerated absorption for a novel insulin lispro formulation, Diabetes 66Suppl (2017) 1A250.
[32] H. Linnebjerg, Q. Zhang, E. LaBell, M.A. Dellva, D.E. Coutant, U. Hövelmann, et al., Pharmacokinetics and glucodynamics of ultra rapid lispro (URLi) versus Humalog® (Lispro) in younger adults and elderly patients with type 1 diabetes mellitus: a randomised controlled trial, Clin. Pharm. 59 (12) (2020) 1589–1599.
[33] L. Klaff, D. Cao, M.A. Dellva, J. Tobian, J. Miura, D. Dahl, et al., Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26–week PRONTO-T1D study, Diabetes Obes. Metab. 22 (10) (2020) 1799–1807.
[34] T. Blevins, Q. Zhang, J.P. Frias, H. Jinnouchi, A.M. Chang, Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D, Diabetes Care 43 (12) (2020) 2991–2998, 43:8.
[35] A. Rawshani, A. Rawshani, N. Sattar, S. Franzén, D.K. McGuire, B. Eliasson, et al., Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus, Circulation 139 (16) (2019) 1900–1912.
[36] J.Q. Purnell, B.H. Braffett, B. Zinman, R.A. Gubitosi-Klug, W. Sivitz, J.P. Bantle, et al., Impact of excessive weight gain on cardiovascular outcomes in type 1 diabetes: results from the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study, Diabetes Care 40 (12) (2017) 1756–1762.
[37] G.J. Ryan, L.J. Jobe, R. Martin, Pramlintide in the treatment of type 1 and type 2 diabetes mellitus, Clin. Ther. 27 (10) (2005) 1500–1512.
[38] C. Martin, The Physiology of Amylin and Insulin, Diabetes Educ. 32 (3_suppl) (2006) 101S–104S.
[39] M.C. Riddle, R. Nahra, J. Han, J. Castle, K. Hanavan, M. Hompesch, et al., Control of postprandial hyperglycemia in type 1 diabetes by 24-hour fixed-dose coadministration of pramlintide and regular human insulin: a randomized, two-way crossover study, Diabetes Care 41 (11) (2018) 2346–2352.
[40] Ghanim H., Batra M., Green K., Abuaysheh S., Hejna J., Makdissi A. Liraglutide treatment in overweight and obese patients with type 1 diabetes: A 26-week randomized controlled trial; mechanisms of weight loss. Diabetes Obes Metab 202022101742–52 [Internet]. Available from: https://dom-pubs-onlinelibrary-wiley-com.sire.ub.edu/doi/pdf/10.1111/dom.14090.
[41] Kobayati A., Haidar A., Tsoukas M.A. Glucagon-like peptide-1 receptor agonists as adjunctive treatment for type 1 diabetes: Renewed opportunities through tailored approaches? Diabetes Obes Metab 2022245769–87.
[42] N.J. Johansen, T.F. Dejgaard, A. Lund, C. Schlüntz, C.S. Frandsen, J.L. Forman, et al., Efficacy and safety of meal-time administration of short-acting exenatide for glycaemic control in type 1 diabetes (MAG1C): a randomised, double-blind, placebo-controlled trial, Lancet Diabetes Endocrinol. 8 (4) (2020) 313–324.
[43] E. Ferrannini, A. Solini, SGLT inhibition in T1DM — definite benefit with manageable risk, Nat. Rev. Endocrinol. 13 (12) (2017) 698–699.
[44] B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med 373 (22) (2015) 2117–2128.
[45] F. Zannad, J.P. Ferreira, S.J. Pocock, S.D. Anker, J. Butler, G. Filippatos, et al., SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials, Lancet 396 (10254) (2020) 819–829.
[46] T. Danne, T. Biester, O. Kordonouri, Combined SGLT1 and SGLT2 inhibitors and their role in diabetes care, Diabetes Technol. Ther. 20 (S2) (2018) S2-69–S2-77.
[47] S.K. Garg, R.R. Henry, P. Banks, J.B. Buse, M.J. Davies, G.R. Fulcher, et al., Effects of sotagliflozin added to insulin in patients with type 1 diabetes, N. Engl. J. Med 377 (24) (2017) 2337–2348.
[48] Henry R.R., Dandona P., Pettus J., Mudaliar S., Xu J., Hansen L. Dapagliflozin in patients with type 1 diabetes: A post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting beta-hydroxybutyrate levels in a phase IIa pilot study. Diabetes Obes Metab 2017196814–21.
[49] C. Mathieu, G. Rudofsky, M. Phillip, E. Araki, M. Lind, N. Arya, et al., Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT -2 study): 52–week results from a randomized controlled trial, Diabetes Obes. Metab. 22 (9) (2020) 1516–1526.
[50] P. Dandona, C. Mathieu, M. Phillip, L. Hansen, D. Tschöpe, F. Thorén, et al., Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study, Diabetes Care. 41 (12) (2018) 2552–2559.
[51] Biester T., Kordonouri O., Danne T. Beyond type 2 diabetes: sodium glucose co-transporter-inhibition in type 1 diabetes. Diabetes Obes Metab 201921 Suppl 253–61.
[52] J. Rosenstock, J. Marquard, L.M. Laffel, D. Neubacher, S. Kaspers, D.Z. Cherney, et al., Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials, Diabetes Care 41 (12) (2018) 2560–2569.
[53] A. Palanca, F. van Nes, F. Pardo, F.J. Ampudia Blasco, C. Mathieu, Real-world evidence of efficacy and safety of SGLT2 inhibitors as adjunctive therapy in adults with type 1 diabetes: a european two-center experience, Diabetes Care 45 (3) (2022) 650–658.
[54] A.L. Peters, E.O. Buschur, J.B. Buse, P. Cohan, J.C. Diner, I.B. Hirsch, Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium–glucose cotransporter 2 inhibition, Diabetes Care 38 (9) (2015) 1687–1693.
[55] S.K. Garg, A.L. Peters, J.B. Buse, T. Danne, Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatmentwith SGLT inhibitors: a STICH protocolstrategy for mitigating DKA, Diabetes TechnolTher. 20 (9) (2018) 571–575.
[56] T. Danne, S. Garg, A.L. Peters, J.B. Buse, C. Mathieu, J.H. Pettus, et al., International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (SGLT) inhibitors, Diabetes Care 42 (6) (2019) 1147–1154.
[57] T. Danne, F.J. Ampudia-Blasco, C. Mathieu, Diabetes and the WHO model list of essential medicines, Lancet Diabetes Endocrinol. 10 (1) (2022) 18–19.
[58] Boughton C.K., Hovorka R. New closed-loop insulin systems. Diabetologia [Internet]. 2021 Feb 6 [cited 2021 Jul 4]; Available from: http://link.springer.com/10.1007/s00125–021-05391-w.
[59] S. Trevitt, S. Simpson, A. Wood, Artificial pancreas device systems for the closed-loop control of type 1 diabetes: what systems are in development? J. Diabetes Sci. Technol. 10 (3) (2016) 714–723.
[60] J.L. Sherr, L. Heinemann, G.A. Fleming, R.M. Bergenstal, D. Bruttomesso, H. Hanaire, et al., Automated insulin delivery: benefits, challenges, and recommendations. A consensus report of the joint diabetes technology working group of the European Association for the Study of Diabetes and the American Diabetes Association, Diabetologia 66 (1) (2023) 3–22.
[61] M. Phillip, T. Battelino, E. Atlas, O. Kordonouri, N. Bratina, S. Miller, et al., Nocturnal glucose control with an artificial pancreas at a diabetes camp, N. Engl. J. Med 368 (9) (2013) 824–833.
[62] S. Weinzimer, R. Bailey, R.M. Bergenstal, R. Nimri, R.W. Beck, D. Schatz, et al., A comparison of post-prandial glucose control in the medtronic advanced hybrid closed-loop system vs 670G, Diabetes Technol. Ther. 24 (8) (2022) 1–10.
[63] K. Dovc, T. Battelino, R.W. Beck, J. Sibayan, R.J. Bailey, P. Calhoun, et al., Impact of temporary glycemic target use in the hybrid and advanced hybrid closed-loop systems, Diabetes Technol. Ther. (2022).
[64] R.M. Bergenstal, R. Nimri, R.W. Beck, A. Criego, L. Laffel, D. Schatz, et al., A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial, Lancet 397 (10270) (2021) 208–219.
[65] A. Arrieta, T. Battelino, A.E. Scaramuzza, J. Da Silva, J. Castañeda, T.L. Cordero, et al., Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12 870 real-world users, Diabetes Obes. Metab. 24 (7) (2022) 1370–1379.
[66] A. Gianini, J. Suklan, B. Skela-Savič, S. Klemencic, T. Battelino, K. Dovc, et al., Patient reported outcome measures in children and adolescents with type 1 diabetes using advanced hybrid closed loop insulin delivery, Open Access Edited (2022).
[67] M.B. Abraham, M. De Bock, G.J. Smith, J. Dart, J.M. Fairchild, B.R. King, et al., Effect of a hybrid closed-loop system on glycemic and psychosocial outcomes in children and adolescents with type 1 diabetes: a randomized clinical trial, JAMA Pedia (2021) 1–9.
[68] B. Matejko, A. Juza, B. Kieć-Wilk, K. Cyranka, S. Krzyżowska, X. Chen, et al., Transitioning of people with T1D from multiple daily injections and self-monitoring of blood glucose directly to MiniMed 780G advanced hybrid closed loop system: a two-center, randomized, controlled study, Diabetes Care 1 (2022) 8.
[69] J. Jendle, J. Pöhlmann, S. De Portu, J. Smith-Palmer, S. Roze, Cost-effectiveness analysis of the MiniMed 670G hybrid closed-loop system versus continuous subcutaneous insulin infusion for treatment of type 1 diabetes, Diabetes Technol. Ther. 21 (3) (2019) 110–118.
[70] J. Jendle, M.I. Buompensiere, A.L. Holm, S. de Portu, S.J.P. Malkin, O. Cohen, The cost-effectiveness of an advanced hybrid closed-loop system in people with type 1 diabetes: a health economic analysis in Sweden, Diabetes Ther. 12 (11) (2021) 2977–2991.
[71] C. Berget, S. Lange, L. Messer, G.P. Forlenza, A clinical review of the t:slim X2 insulin pump, Expert Opin. Drug Deliv. 17 (12) (2020) 1675–1687.
[72] S.A. Brown, B.P. Kovatchev, D. Raghinaru, J.W. Lum, B.A. Buckingham, Y. C. Kudva, et al., Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes, N. Engl. J. Med 381 (18) (2019) 1707–1717.
[73] E. Isganaitis, D. Raghinaru, L. Ambler-Osborn, J.E. Pinsker, B.A. Buckingham, R. P. Wadwa, et al., Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial, Diabetes Technol. Ther. 23 (5) (2021) 342–349.
[74] S.A. Brown, R.W. Beck, D. Raghinaru, B.A. Buckingham, L.M. Laffel, R.P. Wadwa, et al., Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial, Diabetes Care 43 (8) (2020) 1822–1828.
[75] M.D. Breton, L.G. Kanapka, R.W. Beck, L. Ekhlaspour, G.P. Forlenza, E. Cengiz, et al., A randomized trial of closed-loop control in children with type 1 diabetes, N. Engl. J. Med 383 (9) (2020) 836–845.
[76] L.G. Kanapka, P. Wadwa, M.D. Breton, K.J. Ruedy, L. Ekhlaspour, G.P. Forlenza, et al., Extended use of the control-IQ closed-loop control system in children with type 1, Diabetes 44 (2021) 6.
[77] M.J. Schoelwer, L.G. Kanapka, R.P. Wadwa, M.D. Breton, K.J. Ruedy, L. Ekhlaspour, et al., Predictors of time-in-range (70–180 mg/dL) achieved using a closed-loop control system, Diabetes Technol. Ther. 23 (7) (2021) 475–481.
[78] A. Bisio, L. Gonder-Frederick, R. McFadden, D. Cherñavvsky, M. Voelmle, M. Pajewski, et al., The impact of a recently approved automated insulin delivery system on glycemic, sleep, and psychosocial outcomes in older adults with type 1 diabetes: a pilot study, J. Diabetes Sci. Technol. 16 (3) (2022) 663–669.
[79] R.P. Wadwa, Z.W. Reed, B.A. Buckingham, M.D. DeBoer, L. Ekhlaspour, G. P. Forlenza, et al., Trial of hybrid closed-loop control in young children with type 1 diabetes, N. Engl. J. Med [Internet] (2023) [cited 2023 Jul 9];388(11):

991–1001. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2210834.
[80] Y.C. Kudva, L.M. Laffel, S.A. Brown, D. Raghinaru, J.E. Pinsker, L. Ekhlaspour, et al., Patient-reported outcomes in a randomized trial of closed-loop control: the pivotal international diabetes closed-loop trial, Diabetes Technol. Ther. 23 (10) (2021) 673–683.
[81] E.C. Cobry, L.G. Kanapka, E. Cengiz, L. Carria, L. Ekhlaspour, B.A. Buckingham, et al., Health-related quality of life and treatment satisfaction in parents and children with type 1 diabetes using closed-loop control, Diabetes Technol. Ther. 23 (6) (2021) 401–409.
[82] L.H. Messer, C. Berget, L. Pyle, T. Vigers, E. Cobry, K.A. Driscoll, et al., Real-world use of a new hybrid closed loop improves glycemic control in youth with type 1 diabetes, Diabetes Technol. Ther. 23 (12) (2021) 837–843.
[83] CamDiab Ltd. 25 Oct, 2022. https://camdiab.com/.
[84] Abbott, CamDiab and Ypsomed Unveil New Automated Insulin Delivery Partnership for People with Diabetes. 2022. https://abbott.mediaroom.com/2022–04-27-Abbott,-CamDiab-and-Ypsomed-Unveil-New-Automated-Insulin-Delivery-Partnership-for-People-with-Diabetes.
[85] R. Hovorka, Artificial pancreas project at cambridge 2013, Diabet. Med 32 (8) (2015) 987–992.
[86] M. Phillip, R. Nimri, R.M. Bergenstal, K. Barnard-Kelly, T. Danne, R. Hovorka, et al., Consensus recommendations for the use of automated insulin delivery (AID) technologies in clinical practice, Endocr. Rev. (2022).
[87] M. Tauschmann, H. Thabit, L. Bally, J.M. Allen, S. Hartnell, M.E. Wilinska, et al., Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial, Lancet 392 (10155) (2018) 1321–1329.
[88] Z.A. Stewart, M.E. Wilinska, S. Hartnell, R.C. Temple, G. Rayman, K.P. Stanley, et al., Closed-loop insulin delivery during pregnancy in women with type 1 diabetes, N. Engl. J. Med 375 (7) (2016) 644–654.
[89] C.K. Boughton, S. Hartnell, H. Thabit, T. Poettler, D. Herzig, M.E. Wilinska, et al., Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: a double-blind, multicentre, multinational, randomized, crossover study, Diabetes Obes. Metab. 23 (6) (2021) 1389–1396.
[90] M. Tauschmann, J.M. Allen, K. Nagl, M. Fritsch, J. Yong, E. Metcalfe, et al., Home use of day-and-night hybrid closed-loop insulin delivery in very young children: a multicenter, 3-week, randomized trial, Diabetes Care 42 (4) (2019) 594–600.
[91] J. Ware, J.M. Allen, C.K. Boughton, M.E. Wilinska, S. Hartnell, A. Thankamony, et al., Randomized trial of closed-loop control in very young children with type 1 diabetes, N. Engl. J. Med 386 (3) (2022) 209–219.
[92] C.K. Boughton, J.M. Allen, J. Ware, M.E. Wilinska, S. Hartnell, A. Thankamony, et al., Closed-loop therapy and preservation of c-peptide secretion in type 1 diabetes, N. Engl. J. Med 387 (10) (2022) 882–893.
[93] Insulet Corporation. Omnipod 5: User Guide. Action (MA): 2022. Available from: https://omnipod.com/sites/default/files/Omnipod-5_User-guide.pdf.
[94] C. Berget, J.L. Sherr, D.J. DeSalvo, R.S. Kingman, S.L. Stone, S.A. Brown, et al., Clinical implementation of the omnipod 5 automated insulin delivery system: key considerations for training and onboarding people with diabetes, Clin. Diabetes 40 (2) (2022) 168–184.
[95] G.P. Forlenza, B.A. Buckingham, S.A. Brown, B.W. Bode, C.J. Levy, A.B. Criego, et al., First outpatient evaluation of a tubeless automated insulin delivery system with customizable glucose targets in children and adults with type 1 diabetes, Diabetes Technol. Ther. 23 (6) (2021) 410–424.
[96] Sherr J.L., Bode B.W., Forlenza G.P., Laffel L., Schoelwer M.J., Buckingham B., et al. Safety and Glycemic Outcomes With a Tubeless Automated Insulin Delivery System in Very Young Children With Type 1 Diabetes: A Single-Arm Multicenter Clinical Trial. Diabetes Care 2022451907–1910.
[97] S.A. Weinzimer, G.M. Steil, K.L. Swan, J. Dziura, N. Kurtz, W.V. Tamborlane, Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 31 (5) (2008) 6.
[98] K. Dovc, C. Piona, G. Yeşiltepe Mutlu, N. Bratina, B. Jenko Bizjan, D. Lepej, et al., Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapy in type 1 diabetes: a double-blind randomized crossover trial, Diabetes Care 43 (1) (2020) 29–36.
[99] M.H. Lee, B. Paldus, S. Vogrin, D. Morrison, D.P. Zaharieva, J. Lu, et al., Fast-acting insulin aspart versus insulin aspart using a second-generation hybrid closed-loop system in adults with type 1 diabetes: a randomized, open-label, crossover trial, Diabetes Care 44 (10) (2021) 2371–2378.
[100] Dejgaard T.F., Schmidt S., Frandsen C.S., Vistisen D., Madsbad S., Andersen H.U., Nørgaard K. Liraglutide reduces hyperglycaemia and body weight in overweight, dysregulated insulin-pump-treated patients with type 1 diabetes: The Lira Pump trial-a randomized, double-blinded, placebo-controlled trial. Diabetes Obes Metab 2020224492–2020224500.
[101] J.L. Sherr, N.S. Patel, C.I. Michaud, M.M. Palau-Collazo, M.A. Van Name, W. V. Tamborlane, et al., Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide, Diabetes Care 39 (7) (2016) 1127–1134.
[102] V.S. Renukuntla, N. Ramchandani, J. Trast, M. Cantwell, R.A. Heptulla, Role of glucagon-like peptide-1 analogue versus amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm, J. Diabetes Sci. Technol. 8 (5) (2014) 1011–1017.
[103] J. Ilkowitz, R. Katikaneni, M. Cantwell, N. Ramchandani, R.A. Heptulla, Adjuvant liraglutide and insulin versus insulin monotherapy in the closedloop system in type 1 diabetes: a randomized open-labeled crossover design trial, Diabetes Sci. Technol. 10 (5) (2016) 1108–1114.
[104] A. Haidar, M.A. Tsoukas, S. Bernier-Twardy, J.F. Yale, J. Rutkowski, A. Bossy, et al., A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial, Diabetes Care 43 (3) (2020&;;) 597–606.
[105] Tsoukas M.A., Cohen E., Legault L., Von Oettingen J., Yale J.F., Odabassian M., et al. Alleviating carbohydrate counting with a FiASP-plus-pramlintide closed-loop delivery system (artificial pancreas): Feasibility and pilot studies. Diabetes Obes Metab 20212392090–8. 23(9):2090–2098.
[106] J. Garcia-Tirado, L. Farhy, R. Nass, L. Kollar, M. Clancy-Oliveri, R. Basu, et al., Automated insulin delivery with SGLT2i combination therapy in type 1 diabetes, Diabetes Technol. Ther. 24 (7) (2022) 461–470.
[107] A. Haidar, L.E. Lovblom, N. Cardinez, N. Gouchie-Provencher, A. Orszag, M. A. Tsoukas, et al., Empagliflozin add-on therapy to closed-loop insulin delivery in type 1 diabetes: a 2 × 2 factorial randomized crossover trial, Nat. Med 28 (6) (2022) 1269–1276.
[108] S. Singh, R.J. Rushakoff, A.B. Neinstein, A case report of diabetic ketoacidosis with combined use of a sodium glucose transporter 2 inhibitor and hybrid closed-loop insulin delivery, J. Diabetes Sci. Technol. 13 (3) (2019) 605–606.
[109] T. Biester, T. Danne, The role of sodium-glucose cotransporter inhibitors with AID systems in diabetes treatment: is continuous ketone monitoring the solution? Diabetes Technol. Ther. 24 (12) (2022) 925–928.