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REVIEW

Unmet Needs in the Treatment of Childhood Type 2 Diabetes: A Narrative Review

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ABSTRACT

Type 2 diabetes (T2D) in youth is a global health concern characterized by an increasing incidence and prevalence, especially among disadvantaged socioeconomic subgroups. Moreover, youth-onset T2D is more aggressive and causes earlier, more severe long-term cardio-renal complications compared with T2D in adults. The therapeutic options available are limited and often inadequate, partially due to the numerous challenges in implementing clinical trials for this vulnerable patient population. Over the last few years, a significant effort has been made to develop new effective drugs for children and adolescents with T2D. Specifically, a number of studies are currently generating new data to address the urgent unmet medical need for optimal management of this disease. This review describes the central features of youth-onset T2D and summarizes the available treatments and ongoing studies in pediatric patients.

Keywords: Adolescents; Childhood; Incidence; Management; Pediatric; Treatment; Type 2 diabetes; Youth-onset

Key Summary Points

Youth-onset of type 2 diabetes (T2D) is a global health issue.

Compared with adults, young patients with T2D have a faster progression of disease with more severe long-term cardiorenal complications.

Few therapeutic options are available, mostly due to the challenges of implementing clinical studies in youth-onset T2D , creating an urgent need for new therapies.

Various clinical trials are currently assessing potential new treatments to address the unmet need of optimal management of T2D in youth.

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INTRODUCTION

Between 2002 and 2012, the overall annual increase in the incidence of type 2 diabetes (T2D) in youth was 4.8%, with the highest values observed among non-Hispanic blacks (6.3%), Asian/Pacific Islanders (8.5%), and American Indians (8.9%), in contrast to 0.6% among non-Hispanic whites [1]. According to an analysis from 2009, in the US, among ~ 190,000 individuals aged < 20 years affected by diabetes, more than 20,000 had T2D [2]. In a systematic review of published studies that examined the incidence of youth-onset T2D (aged < 20 years) in a single year, Wu et al. estimated 41,600 new cases worldwide in 2021, with the highest numbers in China, India, and the United States of America (US) [3]. In the US, it is predicted that, if the increasing trends in incidence continue, the number of youths with T2D could rise to between 30,000 and 84,000 by 2050 [4]. Similar increases in the incidence of T2D in youths have also been shown in other countries; for example, a cohort study in Israel showed a rise in the incidence of youth-onset T2D from 0.63 per 100,000 individuals in 2008 to 3.41 per 100,000 individuals in 2019 [5].

The largest risk factor for T2D is obesity [6, 7], especially when left untreated [8]. Associated with an unhealthy diet [9] and a sedentary lifestyle [10], obesity escalates the pathogenesis of T2D by increasing insulin resistance [11, 12]. Evidence shows that T2D progresses more rapidly in younger patients, with yearly beta-cell function deterioration found to be 20–35% in youth with T2D[13] versus 7–11% in adults with T2D [14], despite similar disease durations. In addition, time to treatment failure was shorter in youth than in adult patients with T2D [15]. A retrospective real-world study of youth-onset T2D (15–-30 years) versus age-matched patients with type 1 diabetes (T1D) has shown that the development of nephropathy and neuropathy progressed faster in youth with T2D compared with youth with T1D, with a worse cardiovascular risk and mortality profile. A significant mortality excess (11% vs. 6.8%, $P = 0.03$) and increased risk of death [hazard ratio 2.0 (95% CI 1.2–3.2), $P = 0.003$] were noted [16]. This is supported by other studies demonstrating the higher risk of cardiovascular and kidney complications in youth with T2D versus T1D, which have been observed regardless of glycemic control [17–19].

The management of T2D in youth is particularly difficult given the complex social and environmental influences that can affect young people with T2D [20]. Treatment requires not only pharmacologic intervention but also psychosocial support from healthcare providers [21]. Multimodal intervention may be necessary to overcome the barriers to self-management and to address individual, family, and social processes [20].

METHODS

We searched PubMed with the following search terms: adolescents, childhood, incidence, management, pediatric, treatment, type 2 diabetes, and youth-onset. We then reviewed the titles and abstracts of the search results to identify any clinical trials that focused on treating T2D in youth. Additionally, we selected relevant trials from the ClinicalTrials.gov database (https://www.clinicaltrials.gov/) and assessed eligible recommendations and treatment guidelines from any relevant associations [for e.g., American Diabetes Association (ADA) [22], European Association for the Study of Diabetes (EASD) [23], and International Society for Pediatric and Adolescent Diabetes (ISPAD)] [24]. We also consulted the reference lists of the selected articles to include all relevant studies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT TREATMENTS AVAILABLE FOR YOUTH WITH T2D

Despite the significant increase in the prevalence of youth-onset T2D, the number of therapeutic options is limited, in part by the challenges associated with undertaking clinical

studies in this patient population [22]. These challenges include low numbers of participants, restrictive study eligibility criteria, and a small number of research sites worldwide with dedicated resources for youth T2D trials [23, 24]. The SEARCH for diabetes in youth study in the US highlighted these challenges, demonstrated that time from diagnosis to registration was more than twice as long in youth-onset T2D versus T1D clinical trials [25].

At present, metformin is the first-line treatment for the management of youth-onset T2D as indicated by international guidelines, i.e., ADA [26], EASD [27], and ISPAD [28]. When metformin does not provide adequate glycemic control, insulin is used as second-line treatment. Insulin is also recommended as the first choice when A1c is high (> 8.5%) [8] at diagnosis or in the presence of ketoacidosis [29]. The effects of oral metformin and injectable insulin in young people with T2D have been extensively evaluated in two trials—TODAY [30] and RISE Peds [31]. The TODAY trial showed that metformin was effective in providing glycemic control in only half of the participants, suggesting the need for additional therapies in youth-onset T2D [30]. In addition, both trials also demonstrated that neither metformin nor insulin could slow the progressive deterioration of beta-cell function [30, 31]. The longitudinal follow-up study to the TODAY trial—TODAY 2—showed that in participants who had onset of type 2 diabetes in youth, the risk of complications increased over time and affected the majority of participants once they reached young adulthood. These data indicate that diabetes-related complications appear early, thus reiterating the need and importance of better treatments for this population [32].

Since 2019, other therapies have been approved for the treatment of youth-onset T2D, including liraglutide, exenatide, and dapagliflozin. Liraglutide and exenatide, injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs), were approved for use in young people (≥ 10 years old) with T2D by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2021. These drugs mainly act by stimulating glucose-dependent insulin release from the pancreatic beta-cells. A daily injection of liraglutide, when added to metformin with or without basal insulin, was superior to placebo in reducing A1c at 26 weeks (estimated treatment difference, − 1.06%; $P < 0.001$) and 52 weeks (estimated treatment difference, − 1.30%) in patients aged 10–17 years [33]. Similarly, a study evaluating once-weekly injection of exenatide in patients aged 10–18 years with T2D receiving metformin and/or sulfonylurea and/or insulin also demonstrated superiority over placebo in reducing A1c at 24 weeks (mean treatment difference, 0.85%; $P = 0.012$) [34]. Both GLP-1 RAs (liraglutide and exenatide) caused gastrointestinal side effects, similar to observations in adult studies [35]. Furthermore, treatment adherence is a concern in younger people with diabetes [36], and while data are lacking specifically on GLP-1 RAs in this population, a study investigating adherence to GLP-1 RA in adults in the US, demonstrated that more than 50% of patients were non-adherent and 70.1% discontinued therapy within 24 months [37].

Dapagliflozin, a sodium-glucose transporter-2 (SGLT2) inhibitor [38], was the first oral glucose-lowering medication since metformin to be approved by the EMA in 2021 for children (≥ 10 years old) and young adults with T2D (NCT02725593). The efficacy and safety of dapagliflozin 10 mg as add-on therapy was assessed in young people (aged 10–24 years) receiving metformin with or without insulin [39]. In protocol-compliant patients after 24 weeks, dapagliflozin was superior to the control group in reducing A1c (mean treatment difference, − 1.13%; $P = 0.012$). Safety was consistent with previous studies in adult populations, and there was a low risk of severe hypoglycemia and no adverse events of diabetic ketoacidosis [39]. In adults with T2D, large outcome studies have shown that dapagliflozin reduces the risk of worsening heart failure, kidney disease, and mortality in patients with heart failure or chronic kidney disease, regardless of the presence or absence of T2D [40–42]. Given the adverse cardio- [17–19] and microvascular[5] profile of many young people with T2D, and the evidence that long-term complications increase over time [15, 16], these non-glycemic benefits of dapagliflozin may

become increasingly important in the management of youth-onset T2D.

There are a number of other drugs that have been investigated in young people with T2D, but with limited success, including sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Glimepiride, a sulfonylurea that increases insulin secretion and peripheral glucose uptake, was assessed in 263 obese young patients (aged 8–17 years) with T2D, achieving similar A1c levels and lipid profiles versus metformin, but with greater levels of weight gain and hypoglycemia [43]. Thiazolidinediones increase insulin sensitivity and decrease hepatic gluconeogenesis, achieving durable glycemic control in adults. In the TODAY study, the addition of rosiglitazone to metformin was superior to metformin alone when assessing glycemic failure rates in patients aged 10–17 years (39 vs. 52%, respectively; $P = 0.006$) [30]. Nevertheless, in the context of safety concerns around use of these agents in adults [44], thiazolidinediones have not been approved for youth-onset T2D. Another class of compounds, DPP-4 inhibitors, block the enzyme that inactivates incretin, increasing insulin secretion while reducing glucagon secretion. Recently published data from three studies have demonstrated that sitagliptin 100 mg daily in youth with T2D showed no significant improvement in glycemic control when added to metformin with or without insulin, or when used as initial oral therapy [45, 46]. Similarly, alogliptin 2 mg once daily (as monotherapy or add-on therapy to metformin and/or insulin) demonstrated no significant difference versus control [47].

TREATMENTS IN DEVELOPMENT FOR YOUTH WITH T2D

Among the multiple therapeutic agents available for adults with T2D, some treatments have shown promising results in treating youth-onset T2D. Aside from the already approved liraglutide and extended-release exenatide, there have been several GLP-1 RAs that have demonstrated efficacy and safety in younger patients (< 18 years old) with T2D. Since 2016, four clinical trials of GLP-1 RAs and two clinical trials of SGLT2 inhibitors or DPP-4 inhibitors for use in youth-onset T2D have been listed on ClinicalTrials.gov (Table 1). Two of these are now complete. In a Phase 3 study, dulaglutide, at a once-weekly injectable dose of 0.75 or 1.5 mg, significantly lowered A1c (0.6 and 0.9% reduction, respectively) in young patients treated with or without metformin or insulin ($P < 0.001$ for both comparisons vs. control) [48]. The safety profile was consistent with that previously observed in adult studies, with a higher incidence of gastrointestinal adverse events with dulaglutide treatment. In a Phase 1 trial, the injectable GLP-1 RA lixisenatide was associated with improved glycemic control and a trend in body weight reduction in youth with T2D receiving metformin or insulin, compared with the control group. The safety profile of repeated lixisenatide doses of up to 20 μg per day in children and adolescents with T2D was consistent with its known profile in adults [49].

At present, various Phase 3 randomized multicenter studies are evaluating other drugs, already approved for use in adults with T2D, in youth (10–17/18 years old) with T2D currently receiving metformin, insulin, or both (Table 1). The PIONEER TEENS trial is assessing the efficacy and safety of semaglutide, the first oral GLP-1 RA approved by the FDA in 2019 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D [50]. Children and adolescents with T2D are also being recruited into a trial (SURPASS-PEDS) that will evaluate tirzepatide, a once-weekly injectable gastric inhibitory polypeptide (GIP)-1 RA with similar activity to GLP-1 RA, that the FDA and EMA approved in 2022 for use in adults with T2D [51]. There has been much effort to explore the activity of SGLT-2 inhibitors (canagliflozin [52], ertugliflozin [53], dapagliflozin [54], empagliflozin [55]) in youth T2D due to their glycemic and cardio-renal benefits already established in adult populations. The oral route of administration of SGLT2 inhibitors favors patient compliance, overcoming adherence issues typical for other routes such as injection, particularly in a population of children and adolescents. Studies assessing the effect of dapagliflozin and empagliflozin in

Table 1 Clinical trials in youth-onset T2D

NCT Number	Acronym	Arms and Interventions	MoA	Phase	Primary outcome	Enrollment (*n*)	Start Date	Primary Completion Date	Completion Date	Locations
NCT02963766 [48]	AWARD-PEDS	Dulaglutide/placebo 0.75 mg (s/c) Dulaglutide 0.75 mg (s/c) Dulaglutide 1.5 mg (s/c)	GLP-1 RA	3	Change from baseline in Hemoglobin A1c at Week 26	154	29-Dec-16	12-Jun-21	12-Jan-22	BR, FR, DE, HU, IN, MX, PR, SA, TR, UK, US
NCT02803918 [49]		Lixisenatide 3 ascending doses (s/c) Placebo (s/c)	GLP-1 RA	1	N with AEs; N with TEAEs; N with anti-lixisenatide antibodies up to Week 10	23	17-May-17	27-Jan-20	27-Jan-20	ES, MU, MX, TR, US, ZA
NCT05260021 [51]	SURPAS-PEDS	Tirzepatide Dose 1 (s/c) Tirzepatide Dose 2 (s/c) Placebo/switch to Tirzepatide Dose 1 (s/c)	GLP-1 RA	3	Change from baseline in Hemoglobin A1c at Week 30	90	13-Apr-22	30-Nov-27	31-Dec-27	AU, BR, FR, IL, IN, IT, MX, UK, US
NCT04596631 [50]	PIONEER TEENS	Semaglutide maximum tolerate dose (p.o.) Placebo (p.o.)	GLP-1 RA	3	Change from baseline in Hemoglobin A1c at Week 26	132	2-Nov-20	17-Feb-25	17-Feb-25	AU, AT, BE, CZ, GR, IL, IN, LB, MX, MA, MK, MY, NL, NZ, PR, PT, RO, RU, TW, UA, UK, US
NCT04029480 [53]		Ertugliflozin 5 mg (p.o.) Ertugliflozin 5 mg/15 mg (p.o.) Placebo (p.o.)	SGLT2 inhibitor	3	Change from baseline in Hemoglobin A1c at Week 24	150	8-Oct-19	10-Jul-25	10-Jul-25	AE, BE, CA, CO, CR, DO, FR, GT, HU, IL, IT, MU, MX, MY, PH, PL, RU, SA, TR, UA, UK, US

Table 1 continued

NCT Number	Acronym	Arms and Interventions	MoA	Phase	Primary outcome	Enrollment (*n*)	Start Date	Primary Completion Date	Completion Date	Locations
NCT03170518 [52]		Canagliflozin 100 mg (p.o.) Canagliflozin 300 mg (p.o.) Placebo (p.o.)	SGLT2 inhibitor	3	Change from baseline in Hemoglobin A1c at Week 26	171	21-Jul-17	1-Oct-23	1-Oct-23	BR, CN, GR, IN, MX, MY, PH, PL, RU, US
NCT03429543 [55]	(DINAMO)^{TM}	Linagliptin 5 mg (p.o.) Empagliflozin 10 mg/25 mg (p.o.) Placebo/switch to active treatments (p.o.)	SGLT2 inhibitor/ DPP-4 inhibitor	3	Change from baseline in Hemoglobin A1c at Week 26	175	20-Mar-18	5-May-23	26-May-23	AR, BR, CA, CN, CO, DE, IL, KR, MX, PR, RU, TH, UK, US
NCT03199053 [54]	T2NOW	Dapagliflozin 5 mg (p.o.) Dapagliflozin 5 mg/ 10 mg (p.o.) Saxagliptin 2.5 mg (p.o.) Saxagliptin 2.5 mg/ 5 mg(p.o.) Placebo/switch to active treatments (p.o.)	SGLT2 inhibitor/ DPP-4 inhibitor	3	Change from baseline in Hemoglobin A1c at Week 26	256	11-Oct-17	2-Feb-23	4-Jan-24	AR, AU, BR, CA, CL, CO, FI IL, IN, IT, KR, MX, MY, NZ, PH, PL, RU, TH, TR, TW, UA, UK, US

AEs adverse events, *AE* United Arab Emirates, *AR* Argentina, *AT* Austria, *AU* Australia, *BE* Belgium, *BG* Bulgaria, *BR* Brazil, *CA* Canada, *CL* Chile, *CN* China, *CO* Colombia, *CR* Costa Rica, *CZ* Czechia, *DE* Germany, *DO* Dominican Republic, *DPP-4* dipeptidyl peptidase-4, *ES* Spain, *FI* Finland, *FR* France, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *GR* Greece, *GT* Guatemala, *HU* Hungary, *IL* Israel, *IN* India, *IT* Italy, *KR* Republic of Korea, *LB* Lebanon, *MA* Mauritius, *MoA* mode of action, *MK* North Macedonia, *MX* Mexico, *MY* Malaysia, *N* number of patients, *NL* Netherlands, *NZ* New Zealand, *PH* Philippines, *PL* Poland, *p.o.* per os, *PR* Puerto Rico, *PT* Portugal, *RO* Romania, *RU* Russian Federation, *SA* Saudi Arabia, *s/c* subcutaneous, *SGLT2* sodium-glucose co-transporter-2, *TEAEs* treatment-emergent adverse events, *TH* Thailand, *TR* Turkey, *TW* Taiwan, *UA* Ukraine, *UK* United Kingdom, *US* United States, *ZA* South Africa

youth also assessed the effect of the DPP-4 inhibitors saxagliptin (T2NOW) [54] and linagliptin (DINAMO) [55], respectively, in this patient population. The DINAMO study investigated the effect of empagliflozin and linagliptin in youth with T2D. Results demonstrated that use of empagliflozin led to clinically relevant reductions in A1c, whereas linagliptin did not have this effect. Compared to placebo, the adjusted mean change from baseline in A1c at Week 26 in the empagliflozin group was − 0.84% (95% CI − 1.50 to − 0.19; $P = 0.012$); the corresponding change in the linagliptin group versus placebo was –0.34% (− 0.99 to 0.30; $P = 0{\cdot}29$) [56]. Similarly, the T2NOW study assessed the effect of dapagliflozin and saxagliptin in youth with T2D; the results from this study are yet to be released.

However, it must be kept in mind that while these therapies have shown promising results in the short term, their long-term benefits are still unknown and future trials will be needed to estimate this.

CONCLUSION

Youth-onset T2D mainly affects an under served population. The lack of adequate treatments represents an important unmet need for optimal management of youth with T2D. Considering the projected fourfold increase in youth-onset T2D by 2050, the treatment of this disorder in the young population is challenging. With the corresponding increase in cardio-renal morbidity and mortality at younger ages, there is an urgent need for effective drugs to be approved for children and adolescents with T2D. Given the fast progression and aggressiveness of T2D complications in younger patients, disease-modifying therapies (e.g., SGLT2 inhibitors and GLP-1 RAs) are needed, alongside treatments regulating blood glucose levels. Emphasis should also be on customizing the treatment protocol specifically for this patient population, including but not limited to faster access to new therapies and support to access medication and promote treatment adherence.

In addition to medical treatment, it must be noted that the overall management of youth-onset T2D depends on overcoming various obstacles, including social, environmental and financial ones, and hence intervention may have to be multimodal in nature. However, it is necessary to ensure that long-term benefits of these therapies are clearly demonstrated in youth with T2D, with future trails aiming to overcome the current challenges associated with clinical studies in this patient population.

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Declarations

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