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REVIEW

A Review of Interventional Trials in Youth-Onset Type 2 Diabetes: Challenges and Opportunities

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ABSTRACT

Introduction: In recent decades, the dramatic rise of obesity among youth in the US has been accompanied by a rise in the prevalence of type 2 diabetes (T2D) in this population. This alarming trend underscores the importance of conducting trials to evaluate new therapies in children with T2D.

Methods: A targeted review of peer-reviewed literature and trials registered on www.clinicaltrials.gov was conducted in January 2021 to identify pharmaceutical interventional studies in youth with T2D. Information regarding enrollment data, study design elements, subjects' baseline characteristics, and key treatment outcomes was documented.

Results: Among the 16 clinical studies included in this review, only five appeared to meet projected enrollment targets in < 4 years. Although three other studies met recruitment targets, two took approximately 5 years to complete and the third took nearly 10 years.

Conclusions: Despite legislation requiring evaluation of pharmaceutical treatments in pediatric populations, surprisingly few interventional studies have been conducted in children with T2D. This review highlights that recruitment challenges may be impeding the conduct and completion of interventional studies. Consequently, few pharmaceutical treatments have been proven to be effective and approved for children with T2D. Metformin and liraglutide remain the only non-insulin treatments formally approved in the US for use in this population. More clinical research is needed to support regulatory decision-making as well as treatment decisions for children with T2D in clinical settings. Sponsors and investigators will need to implement strategies for improving trial enrollment as well as work with regulatory agencies to develop novel study designs that may require fewer patients.

Keywords: Adolescent; Clinical trial; Pediatric; Type 2 diabetes; Youth

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Key Summary Points

Why carry out this study?

There has been a dramatic rise of obesity among youth in the US, accompanied by a rise in the prevalence of youth-onset type 2 diabetes (T2D).

Unlike adults with T2D, treatment options are limited in youth with T2D, underscoring the need to conduct clinical trials evaluating new therapies in children and adolescents with T2D.

The purpose of the current literature review was to gather updated information on completed interventional phase 3 and 4 studies in youth with T2D and to identify factors that may be limiting research in this area.

What was learned from the study?

Relatively few pediatric trials evaluating products for T2D have been completed in the past 20 years, with recruitment challenges likely impeding the conduct and completion of these studies.

Strategies for improving trial enrollment and potentially leveraging data from outside the traditional trial context could help address the lack of efficacy data in this population.

INTRODUCTION

In recent decades, the increasing prevalence of obesity among youth in the US has been accompanied by a corresponding rise in the prevalence of youth-onset type 2 diabetes (T2D) [1, 2]. The SEARCH for Diabetes in Youth study, a population-based epidemiology and surveillance registry, found an increase of approximately 30% in T2D from 2001 to 2009, with minority youth particularly affected [1, 3]. Though still considered a rare disease among youth, the rising trends point to the growing need for high-quality trials evaluating T2D therapies in children to inform regulatory and clinical decision-making.

The number of pediatric trials has increased over the past 20 years partly due to the passage of US legislation that requires and incentivizes evaluation of medical products in children [4, 5]. These include the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003. While BPCA incentivizes sponsors to voluntarily conduct pediatric research in therapeutic areas beyond the approved adult indication, PREA provides legislative authority to the FDA to require studies in children whenever the use of a new treatment approved in adults is relevant to a pediatric population. Despite these legislative efforts, relatively few trials focusing on treatment for T2D in children have been successfully completed. Consequently, only three (i.e., metformin, insulin, and liraglutide) of the many treatments approved for the treatment of T2D in adults are currently approved for use in children.

The purpose of the current literature review was to gather updated information on completed interventional phase 3 and 4 studies in youth with T2D and to identify factors that may be limiting research in this area.

METHODS

Literature Review

A targeted literature search was performed to identify peer-reviewed publications of interventional phase 3 or 4 clinical trials involving the use of one or more pharmaceutical agents for the treatment of T2D in children and adolescents. The search was conducted using Medline and Embase and was restricted to articles written in English and published in 2000 or later. The search was also limited to trials enrolled fully or in part in the US. Key search terms included: (1) diabetes, mellitus, type 2, non-insulin dependent; (2) child, adolescent, pediatric; (3) clinical trial. Adult-only trials, phase 1 and 2 trials, trials with no US patients, case reports, animal trials, and subgroup analyses were excluded. The literature search was conducted on 19 January 2021.

Resulting abstracts identified through the search were reviewed for relevancy. Abstracts were selected for full-text review if they met the pre-determined inclusion criteria. Abstracted information from the peer-reviewed papers included: basic trial information (i.e., sponsor, objective, duration, inclusion/exclusion criteria, etc.), study sample information, key efficacy and safety results, and any information identified regarding recruitment challenges or difficulties.

This review is based on previously conducted studies. No new studies of human or animal subjects were performed by any of the authors for the purpose of conducting this review.

Review of Completed Trials

A search of www.clinicaltrials.gov was conducted to identify any trials that may have been completed but not published. Clinical trials were required to meet the same criteria as noted above. A "completed" study, as defined on the www.clinicaltrials.gov website, is a study that has ended 'normally' and whose participants are no longer being examined or treated. After searching for studies listed with a "completed" status, a second search was conducted to identify any studies that had completed enrollment and posted primary data results but were not yet categorized as "completed." These studies were listed as "active—not recruiting" rather than "completed" because of their ongoing data collection efforts to inform secondary endpoints (e.g., open-label extensions). The clinical trials search was performed on 23 January 2021. Data were abstracted and categorized utilizing the same variables abstracted for the scientific publications noted above.

When information on www.clinicaltrials.gov or in publications was limited, additional internet searches were conducted to identify regulatory review documents or other publicly available sources of information that could provide additional details.

RESULTS

Summary of Completed Pediatric T2D Studies

A total of 16 completed interventional studies (phase 3 and 4) among children and adolescents with T2D were identified and included in this review (Fig. 1, Table 1). Thirteen of these studies were funded by a pharmaceutical company; three were funded by a mix of government and academic institutions.

The 16 studies spanned > 2 decades with the earliest study (A) [6] launching in 1998 and the latest completed study having concluded in April 2020 (N) [7] (Table 2). Two studies (O and P) [8, 9] completed data collection in April and May (respectively) 2020 to inform their primary endpoints, but are still ongoing to inform their secondary endpoints. Study duration or enrollment period for the studies varied, ranging from 1–2 years (five trials) to 3–5 years (eight trials) to 6–11 years (four trials). Note study K [10] was a pooled analysis of two clinical trials (NCT01760447 and NCT01472367); the enrollment period for NCT01760447 lasted 5 years and over 6 years for NCT01472367. Ten trials included metformin in at least one treatment arm. Other study drugs (either alone or in combination) included: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, bile acid sequestrants, amylin analogs, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and insulin.

Each study with a peer-reviewed publication (n = 6) is included in all data tables. One study (B) [11] had minimal information posted on www.clinicaltrials.gov and had no publication. However, details of this trial were found in regulatory review documents available online [12, 13], so this study was also included in all tables. Six studies (K, L, M, N, O, and P) [7–10, 14, 15] with no associated publications had sufficient information posted on www.clinicaltrials.gov to be included in all tables. Three studies (E, F, G) [16–18] had sufficient enrollment and study design information posted on the trial registry site to be included in

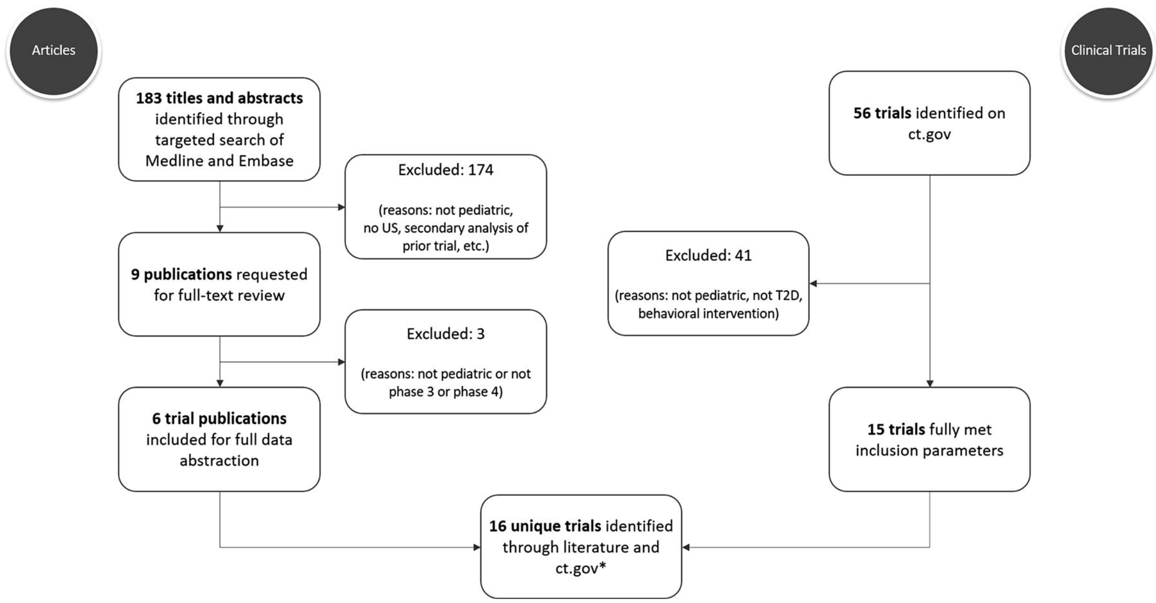

Fig. 1 Combined results from literature and www.ct.gov searches. *Five trial publications had a listing on ct.gov while one publication was not listed on ct.gov. Ten trials on ct.gov did not have an associated publication

Tables 2 and 3 but were excluded from Table 4 due to lack of available information on study results.

Enrollment and Enrollment Challenges

Most of the 16 studies appeared to have difficulty recruiting patients. Enrollment for eight studies (A, B, C, E, H, J, O, and P) [6, 8, 9, 11, 18–24] was conducted within a relatively short period of approximately 1–3 years; however, only five of these eight shorter studies (A, C, E, J, and O) [6, 9, 18, 19, 21–23] met their projected enrollment numbers. Significant recruitment challenges were reported in the publications associated with studies A and H [6, 20, 24]. Although study A [6] surpassed projected enrollment by ten subjects, the authors described recruitment difficulties related to the study inclusion criteria. In this study, 481 subjects were screened and only 82 were randomized. This high screen failure rate may be in part related to the fact that investigators were screening subjects who had not yet been diagnosed with T2D. The authors also noted that many potential study subjects failed screening based on the required fasting plasma glucose (FPG) levels. For the second of these eight shorter studies (B) [11], projected enrollment information for the trial could not be found but 167 subjects were randomized in the study. For the third shorter study (C) [19, 22], investigators met projected enrollment within approximately 18 months, and recruitment challenges were not mentioned in the publication. Study E [18] achieved its projected enrollment target within 2 years, although the target was only 16 subjects for this government-funded, single-center phase 4 trial. Study J (RISE) [21, 23] investigators were successful in meeting projected enrollment goals within a slightly longer period of time (3 years). Study H [20, 24] ceased enrollment due to unreasonably slow recruitment after 17 months, which resulted in a total of 42 subjects despite an enrollment goal of 358 subjects. The authors did not speculate or provide reasons for the trial's slow recruitment [24]. Study O [9] slightly exceeded its enrollment target after 3 years of recruitment, but the projected enrollment was relatively modest at only 54 subjects. Study P [8] began recruitment in August 2014; however, recruitment efforts were suspended for approximately a year and a half for unknown reasons. Following re-

Table 1 Completed pediatric T2D trials ($N = 16$)

Brief citation and/or trial number	Abbreviated title	Study sponsor(s)	Completion date[a]	Study drug(s)
A. Jones et al. 2002	Effect of Metformin in Pediatric Patients with T2D	BMS	1999	Metformin
B. NCT00035542	Safety and Efficacy of Glucovance Compared to Metformin and Glyburide in Children and Adolescents with T2D	BMS	2003	Glucovance® (glyburide/ metformin HCl) Metformin HCl Glyburide
C. Gottschalk et al. 2007/NCT00353691	Glimepiride Versus Metformin as Monotherapy in Pediatric Patients with T2D	Sanofi	2004	Glimepiride Metformin
D. TODAY study group 2012/NCT00081328	Treatment Options for T2D in Adolescents and Youth	TODAY Study Group and NIDDK	2011	Metformin Metformin + rosiglitazone Metformin + lifestyle program
E. NCT00950677[b]	Effect of Byetta and Symlin on Post-meal Meal Blood Sugar Levels in Children with T2D	Baylor, NIH, and NIDDK	2011	Byetta® (exenatide) Symlin® (pramlintide acetate)
F. NCT01204775[b]	Efficacy, Safety, Tolerability, and Pharmacokinetics of Saxagliptin as Monotherapy in Pediatric Patients with T2D	AstraZeneca	2016	Saxagliptin Metformin Placebo
G. NCT01434186[b]	Efficacy and Safety of Saxagliptin (BMS-477118) in Combination with Metformin IR or Metformin XR in Pediatric Patients with T2D who have Inadequate Glycemic Control on Metformin Alone	AstraZeneca	2016	Metformin + saxagliptin Metformin + placebo
H. Wheeler et al. 2018/NCT02131272	Efficacy and Safety of Insulin Detemir Versus Insulin NPH in Combination with Metformin and Diet/Exercise in Children and Adolescents with T2D (iDEAt2)	Novo Nordisk	2016	Insulin NPH + diet/ exercise Insulin detemir + diet/ exercise
I. Tamborlane et al. 2019/NCT01541215	Efficacy and Safety of Liraglutide in Combination with Metformin Compared to Metformin Alone in Children and Adolescents with T2D	Novo Nordisk	2017	Liraglutide + metformin Placebo + metformin
J. RISE Consortium 2018/NCT01779375	Impact of Insulin and Metformin Versus Metformin Alone on b-Cell Function in Youth with Impaired Glucose Tolerance or Recently Diagnosed T2D	RISE Study Group and NIDDK	2017	Metformin Basal insulin glargine followed by metformin

Table 1 continued

Brief citation and/or trial number	Abbreviated title	Study sponsor(s)	Completion date[a]	Study drug(s)
K. NCT01760447[c]	A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Participants with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin) (MK-0431A-170/MK-0431A-289)	Merck	2019	Sitagliptin + metformin FDC Sitagliptin + metformin XR FDC Metformin XR Insulin (if participant entered study already on background insulin)
L. NCT01485614	Study to Assess Safety and Efficacy of Sitagliptin as Initial Oral Therapy for Treatment of Type 2 Diabetes Mellitus in Pediatric Participants (MK-0431–083)	Merck	2019	Sitagliptin Metformin Insulin (if participant entered study already on background insulin)
M. NCT01258075	Colesevelam for Children with Type 2 Diabetes (WELKid DM)	Daiichi Sankyo, Inc	2019	Colesevelam HCl in oral suspension
N. NCT00658021	Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes	AstraZeneca	2019	Exenatide
O. NCT02725593	Study to Evaluate Safety and Efficacy of Dapagliflozin in Patients with Type 2 Diabetes Mellitus Aged 10–24 Years	AstraZeneca	2020	Dapagliflozin
P. NCT01554618	Safety and Efficacy Study of Exenatide Once Weekly in Adolescents with Type 2 diabetes	AstraZeneca	2020	Exenatide

BMS Bristol Myers Squibb, *FDC* fixed-dose combination, *IR* immediate release, *NIDDK* National Institute of Diabetes and Digestive and Kidney Diseases, *NIH* National Institutes of Health, *NPH* neutral protamine Hagedorn, *T2D* type 2 diabetes, *XR* extended release

[a] Final data collection data to inform primary outcome

[b] No publication, limited information on www.clinicaltrials.gov and/or no results posted yet; study excluded from Table 4

[c] NCT01760447 is a pooled data analysis of the NCT01760447 and NCT01472367 trials. The study sponsor made the decision to merge the trials to facilitate data analysis

initiation of recruitment in early 2016, the trial was still unable to meet its projected enrollment of 100 subjects.

Six studies (D, I, K, L, M, and N) [7, 10, 14, 15, 25–28] appear to have encountered significant recruitment difficulties, with each taking approximately ≥ 5 years to complete and many not meeting enrollment goals. Projected enrollment numbers were not met for studies D, I, K, L, or N [7, 10, 15, 25–28]. Despite pooling data from two trials, study K [10] still failed to meet the projected enrollment numbers for either of the original studies. Study M [14] met projected enrollment numbers; however, given its lengthy duration (beginning in late 2010 and concluding its recruitment in 2019), it likely experienced enrollment challenges as well.

Table 2 Pediatric T2D trials: enrollment ($N = 16$)

Brief citation or trial name/number	Projected enrollment	Screened/ randomized (final sample size)/ completed	No. of sites	Study duration or enrollment duration
A. Jones et al. 2002	72	481/82/22[b]	44	September 1998–November 1999 (NR if this represents study duration or enrollment duration)
B. NCT00035542	NR	NR/167/125	NR	First subject enrolled August 2001; last subject completed double-blind April 2003
C. Gottschalk et al. 2007/NCT00353691[a]	200	536/285/210	96	Enrollment: October 2002–May 2004
D. TODAY study group 2012/NCT00081328	750	1211/699/NR	16	Enrollment: July 2004–February 2009
E. NCT00950677	16	NR/NR/NR	1	Study started in July 2009. First participant enrollment date unknown. Final data collection to inform primary outcome was in May 2011
F. NCT01204775	204	26/8/NR	16	Enrollment: August 2011–February 2016
G. NCT01434186	224	32/6/NR	16	Enrollment: July 2013–February 2016
H. Wheeler et al. 2018/NCT02131272	358	71/42/39	82	Study began recruiting in June 2014. Trial was terminated early because of slow recruitment rate. Final data collection to inform primary outcome was in June 2016 [52]
I. Tamborlane et al. 2019/NCT01541215	172	307/135/109	185	Enrollment: November 2012–May 2017
J. RISE Consortium 2018/NCT01779375	90	236/91/86	4	Enrollment: July 2013–April 2016
K. NCT01760447	240	NR/NR/220	NR	Two trials pooled: NCT01472367 enrollment: December 2011–August 2018 NCT01760447 enrollment: February 2013–February 2018
L. NCT01485614	360	NR/200/184	NR	Enrollment: February 2012–August 2018
M. NCT01258075	200	NR/236/171	NR	Study began in December 2010. Initiation of recruitment unknown. Recruitment ended in April 2019
N. NCT00658021	195	NR/122/81	NR	Enrollment: May 2008–April 2019
O. NCT02725593	54	NR/72/61	42	Enrollment: June 2016–April 2019

Table 2 continued

Brief citation or trial name/number	Projected enrollment	Screened/randomized (final sample size)/completed	No. of sites	Study duration or enrollment duration
P. NCT01554618	100	NR/82/73	29	Enrollment: August 2014 (suspended until February 2016) to March 2019

EMA European Medicines Agency, *EU CTR* European Union Clinical Trials Register, *FDA* Food and Drug Association, *HbA1c* glycated hemoglobin, *NPH* neutral protamine Hagedorn, *NR* not reported

[a] Discrepancy between publication and www.clinicaltrials.gov: Final sample listed on www.clinicaltrials.gov was $n = 100$; however, Gottschalk et al. (2007) noted that 210 completed the study [19]. Estimated enrollment end date based on when the last subject completed the study (November 2004) and assuming they completed the full 24-week treatment duration. Information on sites is based on a study summary document posted online by the sponsor [22]

[b] Low completion number is attributed to the fact that any subject who required rescue medication during the trial was removed from the study

Finally, two studies (F and G) [16, 17], both examining the safety and efficacy of saxagliptin and conducted by the same study sponsor, appear to have failed because of recruitment challenges. Their final sample sizes were recorded as $N = 8$ and $N = 6$, respectively, while projected enrollment for each of these studies was greater than 200 subjects. Based on publicly available regulatory review documents, it appears that the sponsor discontinued enrollment for these trials based on a recommendation from their independent Data Monitoring Committee (DMC) [29]. The DMC noted that the continued slow accrual of subjects was preventing the studies from achieving their objectives. It appears that the sponsor proposed replacing these two terminated studies with a different study (NCT03199053), which is still actively recruiting subjects according to www.clinicaltrials.gov and thus not included in this review.

Study Characteristics and Key Results

The number of enrolling sites varied widely ranging from a single center for 1 of the phase 4 studies (E) [18] to as many as 185 sites (I) [26, 27] (Table 2). Inclusion and exclusion criteria varied across studies; however, there were some similarities (Table 3). Ten studies targeted the age group of 10–17 years, while three studies targeted a slightly younger range (8–16 [A], 9–16 [B], and 8–17 [C]) [6, 11, 19, 22] and three recruited an older group (12–21 years [E], 10–19 years [J], and 10–24 years [O]) [9, 18, 21, 23]. The three studies with younger age ranges were older studies, conducted before regulatory expectations for interventional studies in youth-onset T2D were established, and two of the three studies with older age ranges were academic studies, which would not be subject to these regulatory expectations. The required HbA1c for study enrollment varied slightly across trials and even varied within some trials depending on a subject's treatment history. The most common required HbA1c range was $\geq 7.0\%$ and $\leq 10.5\%$. Most studies stipulated a body mass index (BMI) of $\geq 85\%$ (adjusted for age and gender) and/or a weight of ≥ 30 kg. Exclusion criteria also varied across studies; however, some common exclusion criteria included diabetic ketoacidosis, previous use of antidiabetic agents other than metformin, use of corticosteroids, use of weight loss agents, and diabetes of monogenic or secondary etiology.

It is important to note that the largest studies included in this review (D and J) [21, 23, 25, 28], which were both academic- and government-sponsored trials, were not designed to assess effect of treatment on change from baseline in HbA1c or other parameters. Study D (TODAY) [25, 28] was designed to assess time to treatment

Table 3 Pediatric T2D trials: study design characteristics and key results ($N = 16$)

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
A. Jones et al. 2002	Randomized double-blind placebo-controlled trial (Phase 3)	16 weeks	Multinational	Age 8–16 years FPG levels 126–240 mg/dl HbA1c > 7.0% Stimulated C-peptide ≥ 1.5 ng/ml BMI > 50th percentile No recent DKA No current insulin therapies Absence of pancreatic autoantibodies	The metformin group had significantly lower A1c and FPG at the final visit versus placebo ($p < 0.001$). Metformin found to be safe and effective in pediatric patients with T2D	Abdominal pain Diarrhea Nausea/vomiting
B. NCT00035542	Randomized, double-blind study (Phase 3)	26 weeks	Multinational[b]	Age 9–16 years Weight > 50th percentile Failed diet/exercise ± oral antidiabetic therapy	Metformin alone, glyburide alone, and metformin/glyburide together were all associated with reduced A1c	NR
C. Gottschalk et al. 2007/NCT00353691	Randomized, single-blind, active comparator, parallel group (Phase 3)	24 weeks	Multinational[c]	Age 8–17 years HbA1c > 7.1 and < 12.0% Stimulated C-peptide levels ≥ 1.5 ng/ml) Failed diet/exercise ± oral antihyperglycemic therapy No recent DKA No current/recent insulin therapy Absence of pancreatic autoantibodies	Glimepiride and metformin associated with similar and significant reduction in A1c ($p \leq 0.001$ for both), but there was a significant difference in weight change (weight loss with metformin [$p = 0.003$] and gain with glimepiride [$p = 0.005$])	Hyperglycemia (glimepiride: 2.8%; metformin: 0.7%) Upper abdominal pain (glimepiride: 1.4%; metformin: 0.7%) Abdominal pain (1.4% in both groups)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
D. TODAY study group 2012/NCT00081328	Randomized, parallel assignment, quadruple blind, treatment study (Phase 3)	2 years[d]	US only	Age 10–17 years HbA1c ≥ 6% if asymptomatic; ≥ 8% if receiving medication[a] Fasting C-peptide > 0.6 ng/ml BMI ≥ 85th percentile No prior DKA No current/recent use of oral antidiabetic agents other than metformin No current/recent use of inhaled or oral glucocorticoids Absence of pancreatic autoantibodies [a]Note these criteria were to enter run-in phase; HbA1c was required to be < 8% at end of run-in to be randomized	Metformin plus rosiglitazone was superior to metformin alone ($p = 0.006$) with regard to the primary outcome, which was a composite endpoint including A1c level as one component	Infection requiring medical attention (metformin alone: 64.2%; metformin + rosliglitazone: 51.5%; metformin + lifestyle: 64.5%) Gastrointestinal symptoms (metformin alone: 55.6%; metformin + rosiglitazone: 42.9%; metformin + lifestyle: 58.1%) Hyperglycemia symptoms (metformin alone: 49.6%; metformin + rosiglitazone: 42.1%; metformin + lifestyle: 44.0%)
E. NCT00950677	Randomized, single-group assignment, single-masked, treatment study (Phase 4)	Single dose	US only	Age 12–21 years HbA1c < 8.5% On stable dose of oral antidiabetic agent ± insulin or well controlled on diet BMI ≥ 40 kg/m² Weight ≥ 60 kg Absence of pancreatic autoantibodies	NR	NR

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
F. NCT01204775	Randomized, parallel assignment, quadruple-masked, treatment study (Phase 3)	52 weeks Placebos administered for the first 16 weeks	Multinational	Age 10–17 years and 32 weeks HbA1c $\geq$ 7.0% and $\leq$ 10.5% BMI > 85th percentile Body weight $\geq$ 30 kg FPG $\leq$ 255 mg/dl No monogenic or secondary diabetes No recent DKA No recent use of systemic corticosteroids No current/recent use of oral antidiabetic medication or insulin No recent use of weight loss medication or programs Absence of pancreatic autoantibodies	Among the final sample (N = 8), saxagliptin resulted in average of 0.7% reduction in HbA1c, while placebo group showed 0.6% increase	Oropharyngeal pain (placebo: 25.0%; saxagliptin: 50.0%) Upper respiratory tract infection (25.0% in both groups) Headache (25.0% in both groups)
G. NCT01434186	Randomized, parallel assignment, double blind, treatment study (Phase 3)	52 weeks	Multinational	Age 10–17 years and 30 weeks HbA1c $\geq$ 7.0% and $\leq$ 10.5% Body weight $\geq$ 30 kg On stable dose of metformin for $\geq$ 2 months FPG $\leq$ 255 mg/dl No recent DKA No current/recent use of antidiabetic medication other than metformin	Among the final sample (N = 6), from week 0 to week 16, saxagliptin resulted in average of 1.0% reduction in HbA1c, while placebo group showed 0.9% increase	Headache (saxagliptin: 50.0%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
H. Wheeler et al. 2018/NCT02131272	Randomized, open-label, two-armed, parallel group (Phase 3)	26 weeks	Multinational	Age 10–17 years HbA1c $\geq$ 7.0% and $\leq$ 10.5% despite metformin at MTD for $\geq$ 3 months Other OADs and basal insulin allowed; bolus insulin allowed only as rescue No monogenic or secondary diabetes No recent use of antidiabetic therapy other than metformin $\pm$ other OADs $\pm$ basal insulin No recent use of weight loss medication	Mean HbA1c value decreased by 0.61% points in the insulin detemir group and 0.84% points in the NPH insulin group at 26 weeks, $p = 0.3075$	Gastroenteritis (insulin detemir: 10.0%) Headache (insulin detemir: 15.0%; insulin NPH: 4.6%) Oropharyngeal pain (insulin detemir: 5.0%; insulin NPH: 13.6%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
I. Tamborlane et al. 2019/NCT01541215	Randomized, parallel-group, placebo-controlled trial with a 26-week double-blind period followed by a 26-week open-label extension period (Phase 3)	52 weeks	Multinational	Age 10–17 years HbA1c $\geq$ 7.0% and $\leq$ 11% if diet and exercise treated $\geq$ 6.5% and $\leq$ 11% if treated with metformin BMI > 85% percentile Treated for at least 90 days with diet and exercise alone, or diet and exercise in combination with metformin monotherapy Metformin dose stable for at least 30 days prior to screening No monogenic or secondary diabetes No current/recent use of antidiabetic medication other than metformin No recurrent severe hypoglycemia or hypoglycemic unawareness (per investigator)	Liraglutide provided additional glycemic control when added to metformin with or without basal insulin in pediatric patients with T2D (significant difference between liraglutide and placebo in A1c change from baseline to week 26; ETD: -1.058, $p < 0.001$)	Nausea (liraglutide: 28.8%; placebo: 13.2%) Vomiting (liraglutide: 25.8%; placebo: 8.8%) Diarrhea (liraglutide: 22.7%; placebo: 16.2%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
J. RISE Consortium 2018/NCT01779375	Randomized, parallel open-label clinical trial (Phase 3)	52 weeks	US only	Age 10–19 years HbA1c $\leq$ 8.0% if treatment naïve, $\leq$ 7.5% if on metformin for $<$ 3 months and $\leq$ 7.0% if on metformin for 3–6 months FPG $\geq$ 90 mg/dl, plus 2-h glucose $\geq$ 140.4 mg/dl on 75 g OGTT BMI $\geq$ 85th percentile (and $<$ 50 kg/m^2) If metformin treatment, $<$ 6 months in duration prior to screening No prior insulin use No recent use of weight loss medication or weight loss $\geq$ 5% of body weight within 3 months	Results varied by time point. Although between-group differences were observed at 3 months, neither metformin alone nor insulin glargine followed by metformin resulted in a significant decrease in HbA1c at one year of treatment ($p > 0.05$)	GI discomfort (metformin: 34.0%; insulin glargine: 38.6%) Polyuria or polydipsia (metformin: 23.4%; insulin glargine: 25.0%) Low blood sugar (insulin glargine: 13.6%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
K. NCT01760447	Randomized, parallel assignment, triple-masked, treatment study (Phase 3)	54 weeks	Multinational[b]	Age 10–17 years HbA1c $\geq$ 6.5% and $\leq$ 10.0% on metformin monotherapy for $\geq$ 12 weeks OR $\geq$ 7.0% and $\leq$ 10% on metformin and insulin for $\geq$ 12 weeks No monogenic or secondary diabetes No prior use of DPP-4 inhibitor or GLP-1 RA No symptomatic hyperglycemia or ketonuria requiring treatment augmentation	Change from baseline in A1c to week 20 for sitagliptin/metformin and sitagliptin/metformin XR pooled group: − 0.58% Change from baseline in A1c to week 20 for metformin and metformin XR pooled group: − 0.09% ETD: − 0.49%, $p = 0.018$	Hypoglycemia (sitagliptin/metformin and sitagliptin/metformin XR pooled group: 17.8%; metformin and metformin XR pooled group: 14.2%) Headache (sitagliptin/metformin and sitagliptin/metformin XR pooled group: 4.7%; metformin and metformin XR pooled group: 15.9%) Upper respiratory tract infection (sitagliptin/metformin and sitagliptin/metformin XR pooled group: 13.1%; metformin and metformin XR pooled group: 8.0%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
L. NCT01485614	Randomized, parallel assignment, double-masked, treatment study (Phase 3)	56 weeks	Multinational[b]	Age 10–17 years HbA1c $\geq$ 6.5% and $\leq$ 10.0% OR $\geq$ 7.0% and $\leq$ 10% if on insulin Has not received treatment with AHA for $\geq$ 12 weeks prior to screening visit/visit 1, or is on stable dose of insulin (without any other AHA) for at least 12 weeks prior to screening visit/visit 1 No history of type 1 diabetes No previous use or DPP-4 inhibitor or GLP-1 RA	At week 20, mean change in HbA1c was − 0.01% in sitagliptin group and 0.18% in placebo group. Between group difference − 0.19%, $p = 0.45$	Upper respiratory tract infection (sitagliptin: 12.6%; placebo/metformin: 13.3%; metformin: 11.1%; placebo/sitagliptin: 20.0%) Nasopharyngitis (sitagliptin: 15.8%; placebo/metformin: 6.7%) Diarrhea (sitagliptin: 8.4%; placebo/metformin: 12.2%; metformin: 22.2%)
M. NCT01258075	Interventional, randomized, parallel assignment, double-masked treatment study (Phase 4)	Up to 12 months	US only	Age 10–17 years HbA1c $\geq$ 7.0% and $\leq$ 10% Fasting C-peptide > 0.6 ng/ml Treatment-naïve at screening OR on metformin monotherapy No FPG > 270 mg/dl No history of type 1 diabetes	Month 6 change in HbA1c: Welchol 3.75 g: 0.09% Welchol 0.625 g: 0.21% ETD: − 0.13, $p = 0.5494$ No decrease from baseline with either dose	Upper respiratory tract infection (Welchol 3.75 g: 17.0%; Welchol 0.625 g: 9.5%) Vomiting (Welchol 3.75 g: 14.2%; Welchol 0.625 g: 11.6%) Diarrhea (Welchol 3.75 g: 9.2%; Welchol 0.625 g: 10.5%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
N. NCT00658021	Interventional, randomized, parallel assignment, double-masked, treatment study (Phase 3)	Up to 28 weeks	Multinational	Age 10–17 years HbA1c $\geq$ 7.0% and $\leq$ 10.5% Treated with metformin, a sulfonyl urea, or both for at least 3 months, or are naïve to anti-diabetic agents and treated with diet and exercise alone No previous exposure to exenatide	Mean A1c increased by 0.11 (0.215) in exenatide participants and by 0.38 (0.293) in placebo participants. ETD: − 0.28%, p = 0.444	Headache (exenatide 5 mcg: 22.0%; exenatide 10 mcg: 24.3%; placebo: 26.2%) Nausea (exenatide 5 mcg: 9.8%; exenatide 10 mcg: 29.7%; placebo: 16.7%)
O. NCT02725593	Interventional, randomized, parallel assignment, double-masked, treatment study (Phase 3)	Up to 28 weeks	Multinational	Age 10–24 years HbA1c $\geq$ 6.5% and $\leq$ 11% Currently on diet and exercise and stable dose of metformin, insulin, or both for at least 8 weeks FPG $\leq$ 255 mg/dl at screening visit No previous use of SGLT2 inhibitors	HbA1c Week 24 ETD: − 0.75%, p = 0.101 (dapa − 0.25% vs. placebo + 0.50%)	Headache (dapaliflozin: 12.8%; placebo: 12.1%) Vitamin D deficiency (dapagliflozin: 12.8%; placebo: 6.1%) Nasopharyngitis (dapagliflozin: 12.8%; placebo: 6.1%)

Table 3 continued

Brief citation or trial name/number	Study design	Duration of treatment (for each patient)	US-only or multinational	Key inclusion/Exclusion criteria	Key efficacy results	Key safety results (most commonly reported AEs)[a]
P. NCT01554618	Interventional, randomized, parallel assignment, quadruple-masked, treatment study (Phase 3)	Up to 52 weeks	Multinational	Age 10–17 years HbA1c $\geq$ 6.5% and $\leq$ 11.0% for patients not taking insulin HbA1c $\geq$ 6.5% and $\leq$ 12.0% for patients taking insulin Treated with diet and exercise alone or in combination with stable dose of antidiabetic agent or insulin for $\geq$ 2 months FPG < 280 mg/dl at screening No previous use of exenatide	HbA1c Week 24 ETD: − 0.85%, p = 0.012 (exenatide QW − 0.36% vs. placebo, + 0.09%)	Headache (exenatide: 6.8%; placebo: 8.7%) Nasopharyngitis (exenatide: 6.8%; placebo: 8.7%) Upper respiratory tract infection (exenatide: 10.2%)

AE adverse event, *AHA* antihyperglycemic agent, *BMI* body mass index, *DKA* diabetic ketoacidosis, *DPP-4* dipeptidyl peptidase IV, *ETD* estimated treatment difference, *FPG* fasting plasma glucose, *GAD* glutamic acid decarboxylase, *GLP-1* glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *ICA* islet cell autoantibody, *MTD* maximum tolerated dose, *OAD* oral antidiabetic drug, *OGTT* oral glucose tolerance test, *RA* receptor agonist, *SGLT2* sodium-glucose co-transporter 2, *T2D* type 2 diabetes

[a] Percentage of participants reporting each AE presented when available

[b] Multinational status was determined based on review of European Union Clinical Trials Register (not www.clinicaltrials.gov)

[c] Information on countries/sites was based on a study summary document posted online by the sponsor [22]

[d] Participants were followed for an average of 3.86 years but lifestyle program was approximately 2 years in duration

Table 4 Pediatric T2D trials: patient baseline demographic and clinical characteristics ($N = 13$)

Brief citation or trial name/number	Age—mean (SD)	Race/ethnicity	% Female	Mean baseline weight (kg)	Mean baseline BMI (kg/m^2)	Mean baseline HbA1c (SD)
A. Jones et al. 2002	*Metformin/placebo:* 13.9 ± 1.8/ 13.6 ± 1.8	*Metformin/placebo:* White: 40.5%/32.5% Black: 26.2%/32.5% Asian/Pacific Islander: 7.1%/ 2.5% Hispanic/Latino: 21.4%/ 22.5% Other: 4.8%/10.0%	*Metformin/placebo*: 71.4%/67.5%	*Metformin/placebo:* 92.8 ± 31.8/90.3 ± 38.1	*Metformin/placebo*: 34.2 ± 10.6/ 33.9 ± 12.7	*Metformin/placebo:* 8.3 ± 1.3%/ 9.0 ± 1.4%
B. NCT00035542	13.7 ± 1.9	White: 62% Black: 21% Asian/Pacific Islander: 4% Hispanic/Latino: 13% Other: 0.6%	65%	79.3 ± 28.4	NR	7.83 ± 1.65%
C. Gottschalk et al. 2007/NCT00353691	13.8 ± 2.3	*Glimepiride/metformin:* White: 12.9%/16.0% African American: 22.8%/ 21.4% Asian/Pacific Islander: 17.4%/14.5% Hispanic/Latino: 39.4%/ 39.7% Other: 7.6%/8.4%	*Glimepiride/ metformin*: 66.7%/ 66.4%	*Glimepiride/metformin*: 82.60 ± 25.60/ 83.83 ± 27.47	*Glimepiride/ metformin:* 31.6 ± 8.5/ 31.6 ± 8.2	*Glimepiride/ metformin:* 8.5 ± 1.6%/ 8.5 ± 1.6%

Table 4 continued

Brief citation or trial name/number	Age—mean (SD)	Race/ethnicity	% Female	Mean baseline weight (kg)	Mean baseline BMI (kg/m^2)	Mean baseline HbA1c (SD)
D. TODAY study group 2012/NCT00081328	14.0 (2.0)	White non-Hispanic: 20.3% Black non-Hispanic: 32.5% Hispanic/Latino: 39.7% American Indian: 5.9% Asian: 1.6%	64.7%	NR	34.9 ± 7.6	5.9%[a]
H. Wheeler et al. 2018/NCT02131272[b]	15.0 (2.1)	Hispanic/Latino: 35.7% White: 45.2% Black: 2.4% Asian: 42.9% American Indian or Alaska Native: 2.4% Other: 7.1%	64.3%	*Insulin detemir/NPH insulin*: 75.9 ± 16.6/73.2 ± 23.4	*Insulin detemir/ NPH insulin:* 28.7 ± 4.8/ 27.7 ± 6.6	8.84% (0.96)
I. Tamborlane et al. 2019/NCT01541215[b]	14.6 ± 1.7	Hispanic/Latino: 29.1% White: 64.9% Black: 11.9% Asian: 13.4% American Indian or Alaska Native: 2.2% Other or unknown: 7.5%	61.9%	91.5 ± 26.8	33.9 ± 9.2	7.78 ± 1.34%
J. RISE Consortium 2018/NCT01779375	14.4 (2.1)	White: 27.5% Black: 25.3% Hispanic/Latino: 37.4% Other: 9.9%	71.4%	*Glargine followed by metformin/metformin alone:* 102.0 ± 25.7/97.7 ± 23.3	36.7 ± 6.4	5.7 ± 0.6

Table 4 continued

Brief citation or trial name/number	Age—mean (SD)	Race/ethnicity	% Female	Mean baseline weight (kg)	Mean baseline BMI (kg/m^2)	Mean baseline HbA1c (SD)
K. NCT01760447	14.4 ± 1.9	American Indian or Alaskan Native: 5.9% Asian: 29.1% Native Hawaiian or Other Pacific Islander: 0.9% Black or African American: 4.5% White: 43.6% More than one race: 15.9%	65.9%	NR	NR	8.0 ± 1.1
L. NCT01485614	14.0 (2.0)	American Indian or Alaska Native: 7.5% Asian: 15.1% Black or African American: 5.5% White: 52.3% More than one race: 19.6%	60.8%	NR	NR	7.50 ± 1.04
M. NCT01258075	14.2 (2.06)	American Indian or Alaska Native: 0.4% Asian: 3.0% Native Hawaiian or Other Pacific Islander: 0.4% Black: 36.9% White: 49.6% More than one race: 8.5% Unknown or not reported: 1.3%	76.7%	NR	NR	NR

Table 4 continued

Brief citation or trial name/number	Age—mean (SD)	Race/ethnicity	% Female	Mean baseline weight (kg)	Mean baseline BMI (kg/m^2)	Mean baseline HbA1c (SD)
N. NCT00658021	14.0 (1.91)	White: 20.5% Black: 23.8% Asian: 8.2% American Indian or Alaska Native: 0.8% Hispanic: 46.7%	67.2%	NR	NR	NR
O. NCT02725593	16.1 (3.4)	White: 61.1% Black: 25.0% Asian: 1.4% Native Hawaiian or other Pacific Islander: 1.4% American Indian or Alaska Native: 6.9% Other: 4.2% Hispanic/Latino: 33.3%	59.7%	NR	NR	NR

Table 4 continued

Brief citation or trial name/number	Age—mean (SD)	Race/ethnicity	% Female	Mean baseline weight (kg)	Mean baseline BMI (kg/m^2)	Mean baseline HbA1c (SD)
P. NCT01554618	15.1 (1.84)	White: 42.7% Black: 30.5% Asian: 3.7% American Indian or Alaska Native: 6.1% Other: 17.1% Hispanic/Latino: 40.2%	58.5%	NR	NR	NR

When available, data for total sample were provided. Some studies provided data only by treatment arm; in these cases, the treatment arms are listed in the relevant cells

BMI body mass index, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *NPH* neutral protamine Hagedorn, *OAD* oral antidiabetic drug, *SD* standard deviation, *T2D* type 2 diabetes, *NR* not reported

[a] As reported by Copeland et al. (2011) [51] (a publication that preceded TODAY study group 2012 paper)

[b] US-only sample was not described in publication or on ct.gov; thus entire study sample is presented in this table (including ex-US subjects). Where not available in the publication, baseline information on the total sample was supplemented based on an online regulatory review document [52]

failure in youth with T2D already under glycemic control treated with metformin, while study J (RISE) [21, 23] compared the effect of insulin followed by metformin with metformin alone in preserving or improving beta-cell function in youth with either impaired glucose tolerance (IGT) or recently diagnosed T2D.

Study E [18] has no posted results on the trial registry site; however, for the 15 trials with available results, there was a wide range of final sample sizes ($N = 6$ to $N = 699$) and outcome measures (Table 3). In studies F [17], G [16], and H [20, 24], no efficacy conclusions could be drawn because of their small sample sizes. For 9 of the 13 remaining studies, significant differences between treatment and placebo were found for at least one of the three efficacy measures; however, it is notable that four studies failed to meet their primary endpoints (L, M, N, and O) [7, 9, 14, 15]. Study L [15] (sitagliptin monotherapy), study O [9] (dapaglifloxin), study M [14] (colesevelam), and study N [7] (exenatide twice daily) failed to demonstrate a statistically significant reduction in HbA1c compared with placebo. Study P [8], which assessed the safety and efficacy of exenatide as a once weekly treatment, did meet its primary HbA1c endpoint; however, regulatory decisions regarding approval for its use in children are currently unknown. Finally, although statistically significant results were reported on www.clinicaltrials.gov for study K [10] (sitagliptin + metformin), collectively the results from this study and study L [15] (sitagliptin monotherapy) did not ultimately support pediatric approval in the US. Labelling for sitagliptin was updated in 2020 to note that efficacy in pediatrics was not established.

Safety information, reported for most trials, is shown in Table 3. While difficult to attribute to specific medications given the use of permitted background therapies such as metformin, the most commonly reported adverse events (AEs) across trials were gastrointestinal symptoms/pain, headache, and upper respiratory tract infection. In general, medication safety and tolerability findings in subjects with youth-onset T2D were consistent with those observed in adults.

Patient Baseline Characteristics

Mean age of study subjects ranged from about 13.7 to 16.1 years (Table 4). Excluding four studies (H, I, K, and L) [10, 15, 20, 24, 26, 27], Black subjects represented approximately 25% to 35% of the sample. In studies H [20, 24], I [26, 27], K [10], and L [15], a lower proportion of Black subjects were enrolled and represented only between 2.4% and 11.9% of the sample. Except for study C [19, 22] where White subjects represented < 20% of the sample, White patients represented anywhere from 20% to 65% of the sample in the other 12 studies included in Table 4. Hispanic and Latino subjects typically represented about 30% to 40% of the sample, although study B [11] had only 13% Hispanic/Latino representation and study N [7] had nearly 47% Hispanic/Latino representation. In line with the epidemiology of youth-onset T2D, there was a consistent female majority with about 60% to 70% of the sample being female across the 13 studies included in Table 4.

Mean baseline weight ranged from about 73 to 102 kg and BMI ranged from approximately 28 to nearly 37 kg/m^2 depending on the study. Mean baseline HbA1c ranged from 5.7% (J) [21, 23] to approximately 9.0% (A and H) [6, 20, 24]. Only 40% of randomized patients in study J (RISE) [21, 23] had T2D; the rest had IGT, which is likely why this study had the lowest mean baseline HbA1c (5.7%).

DISCUSSION

In spite of legislation designed to increase the number of pharmaceutical treatments evaluated in pediatric populations and good faith efforts by sponsors to conduct trials of new treatments, relatively few interventional phase 3 studies have been successfully enrolled and completed in children with T2D. Only 16 trials met criteria for inclusion in this review, and these studies varied widely in trial duration, number of enrolling sites, and sample size. For ten of these studies, available information was quite limited because results had not been published at the time of this review.

The relative lack of trial data to inform regulatory decisions coupled with the failure of a number of recently completed trials to demonstrate efficacy has led to a paucity of approved medications for children and limited the information available to clinicians caring for these patients. In contrast to the numerous therapies available to adults with T2D, metformin and liraglutide remain the only non-insulin treatments formally approved in the US for use in children with T2D. While most insulins are not specifically indicated for treatment of children with T2D, they are used for this purpose and are recommended in treatment guidelines for patients who present with ketosis or for whom metformin does not provide adequate glycemic control [30]. The approval of liraglutide in June 2019 was the first approval of a medication for treatment of T2D in children since 2000 when metformin was approved. Most of the studies with recently posted results on www.clinicaltrials.gov (other than study P [8], which assessed exenatide once weekly) failed to meet their primary HbA1c endpoint and, in the case of sitagliptin, did not support approval for a pediatric T2D indication. This reiterates the challenges of managing T2D in youth, given its more aggressive course as compared to T2D in adults, and suggests that metformin and liraglutide may, for now, remain the only approved non-insulin options for treating these patients.

The majority of studies included in this review appeared to encounter challenges when recruiting patients. Only five studies (A, C, E, J, and O) [6, 9, 18, 19, 21–23] achieved projected enrollment targets in < 4 years, while seven trials (F, G, H, K, L, N, and P) [7, 8, 10, 15–17, 20, 24] failed to meet their initial recruitment targets altogether. There was no clear relationship between trial success or recruitment speed and number of sites involved. For example, study I [26, 27] had 109 participants complete the trial after 5 years using 185 sites. However, study C [19, 22] had 210 participants complete after only 2 years using 96 sites, and study J [21, 23] had 86 participants complete after 3 years using four sites. This suggests that when conducting clinical trials in pediatric T2D, careful consideration must be given to the location and type of sites selected. For example, sites in areas that serve communities of color may be able to increase diversity in trials. Moreover, sites that have long-standing and trusted relationships with families (e.g., general practices) may recruit more successfully than sites that do not (e.g., designated research sites that do not regularly see patients or manage their care). There are several factors that may interfere with recruiting pediatric T2D samples. In general, regardless of the medical condition, pediatric samples tend to be more difficult to recruit and retain than adult samples [31, 32]. For diabetes in particular, the low prevalence of T2D in children (i.e., 0.46 per 1000 children aged 10–19 years in the US [1]) further limits the number of potential subjects for trials. Demographic characteristics associated with T2D may also play a role. T2D is particularly prevalent in non-white communities with socioeconomic challenges and poor access to healthcare [33–35]. These demographic groups are generally considered difficult to enroll in clinical trials [36]. To address this challenge, investigators or sponsors can select clinical sites that specialize in treatment of pediatric T2D and serve communities with higher proportions of demographic groups that may be difficult to recruit elsewhere.

Restrictive study eligibility requirements may also interfere with recruitment of children with T2D. For example, pediatric T2D trials often exclude children with either very high or near-normal HbA1c levels, which limits the potential pool of trial participants [37]. In addition, many potential patients may be excluded because of obesity-related comorbidities that are common in this population (e.g., hypertension, hyperlipidemia, obstructive sleep apnea) [38–40]. These restrictive eligibility requirements may be the reason for the high rate of screen failures in trials included in the current review. In most of the trials that eventually met enrollment targets (e.g., C, D, I, and J) [19, 21–23, 25–28], only 40% to 60% of potential subjects assessed for eligibility were randomized. Adult T2D trials generally report similarly high rates of screen failures [41–44]. However, because T2D is more common in adults than in children, there is a larger pool of adult patients, and it may be more feasible to meet recruitment targets despite high screen failure rates. To maximize the pool of potential patients and minimize screen failures, researchers designing clinical trials may want to consider less restrictive eligibility criteria and allow for more comorbidities, a wider HbA1c range, and increased variety of pre-trial medication treatments.

One approach for locating and retaining pediatric patients for trials may be to engage members of children's social and medical support network. These individuals can act as advisors reviewing protocols, procedures, and consent forms during the study design process. For example, parents and pediatricians may be able to identify potential recruitment or retention problems that can be addressed prior to finalizing study materials. Unlike with type 1 diabetes, there is little organized advocacy activity specific to pediatric T2D. Advocacy groups that do exist seem to be mostly local rather than national in scale. As awareness of pediatric T2D grows, patient advocacy groups may emerge and play a facilitative role in trial recruitment for this population.

Finally, it may not always be necessary to design and conduct a traditional fully randomized controlled clinical trial to evaluate treatments in this population. It may be possible to use alternative study approaches and designs to assess treatment outcomes while limiting the number of patients needed for trials [45, 46]. For example, the use of master protocols and other collaborative approaches, while requiring extensive cooperation and engagement from investigators, regulatory agencies, and pharmaceutical companies, could potentially facilitate more efficient completion of trials or focus efforts on the most promising drugs to be tested [45, 46]. Augmenting the placebo arm of a clinical trial with historical controls from prior trials or from well-curated and matched real-world cohorts also holds the potential to decrease the overall size of trials and limit exposure to placebo in those trials while potentially increasing power to detect efficacy signals [47, 48]. In addition, should we find, as we come to better understand youth-onset T2D, that the response to therapies is sufficiently similar to that in adults, sponsors may be able to extrapolate from adult data based on pharmacokinetic and pharmacologic data from adolescents with T2D [49]. Future use of such innovative approaches will require careful consultation and coordination between industry sponsors and regulators.

Findings of this literature review should be interpreted in the context of several limitations. First, the level of detail in this review was limited by the information provided in the original sources. Second, even among the published studies, the sample characteristics, endpoints, and study designs varied. This heterogeneity makes it difficult to identify trends and draw conclusions across studies. Third, there were several instances where information on www.clinicaltrials.gov diverged from the published articles, leading to some uncertainty in the findings.

CONCLUSION

Overall, this review highlights limitations and challenges in research on treatment for T2D in pediatric populations. Compared to the body of clinical research in adult patients with T2D, few studies have been conducted in children. Furthermore, many pediatric T2D studies have failed to meet sample size targets, likely because of recruitment challenges. Several recently completed trials, including those that assessed the safety and efficacy of DPP-4 inhibitors and SGLT2 inhibitors, failed to meet their primary HbA1c endpoints. Consequently, few pharmaceutical treatments have been proven to be effective and approved for use in this population. With over 30 new T2D medications currently in the phase 2 development pipeline across sponsors, the number of phase 3 trials in pediatric patients with T2D is only expected to grow in the near future [50]. To address these challenges, sponsors and investigators will need to implement strategies for improving clinical trial enrollment and potentially leverage data from outside the traditional trial context.

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