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Liraglutide for Pediatric Patients With Type 2 Diabetes

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Rapid Review

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Abbreviations

BMI	body mass index
CI	confidence interval
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
A1C	hemoglobin A1C
SD	standard deviation
T2D	type 2 diabetes

Key Messages

- While metformin is the treatment of choice for most children and adolescents with type 2 diabetes, along with lifestyle interventions such as diet and exercise, approximately half of youth with type 2 diabetes fail to maintain glycemic control when treated with metformin, either alone or in conjunction with lifestyle interventions.
- Basal insulin can be used in children and adolescents with type 2 diabetes who do not have an adequate response to metformin monotherapy; however, basal insulin therapy has been associated with weight gain and hypoglycemia.
- There is very limited evidence of moderate to moderately high-quality to support the effectiveness of liraglutide (Victoza) in attaining glycemic control when added to treatment with metformin, with or without basal insulin, in children and adolescents with type 2 diabetes.
- Adverse events, such as hypoglycemia and gastrointestinal issues, are reportedly higher in patients receiving liraglutide (Victoza) than in those receiving placebo.
- There is a lack of long-term safety data evaluating the use of liraglutide (Victoza) in children and adolescents with type 2 diabetes.

Context and Policy Issues

The incidence of type 2 diabetes (T2D) in children and adolescents is increasing worldwide, with a reported incidence in Canada estimated at 1.54 per 100,000 per year.¹ T2D onset in youth can result in earlier and more serious long-term complications than T2D in adulthood, including macrovascular complications such as myocardial infarction, cerebral stroke, and other conditions such as amputation and end-stage renal disease.²

Along with lifestyle interventions, such as diet and exercise, metformin is the treatment of choice for most children and adolescents with T2D.³ However, approximately half of youth with T2D fail to maintain glycemic control when treated with metformin alone or in conjunction with lifestyle interventions.⁴ Basal insulin can be used in youth who do not have an adequate response to metformin monotherapy; however, insulin therapy has been associated with weight gain and hypoglycemia.^{4,5}

In cases where metformin monotherapy fails to maintain glycemic control, glucagon-like peptide-1 (GLP-1) agonists can be added to ongoing treatment. Liraglutide (Victoza) is a GLP-1 agonist indicated in adults, adolescents, and children aged 10 years and older with T2D, as an adjunct to metformin with or without basal insulin, when diet and exercise plus the maximal tolerated dose of metformin do not achieve adequate glycemic control.⁶ There are no alternative metformin adjuncts to liraglutide for glucose control in children and adolescents currently approved in Canada.⁷ Liraglutide is also available under the brand name Saxenda, but this is a higher dose indicated for weight management in adults and certain youth aged 12 to younger than 18.⁸ Saxenda is not indicated for glycemic control and hence is out of scope for this review.

CADTH previously reviewed Liraglutide in 2011 for adults, where it received a do not list recommendation, and in 2016, a manufacturer resubmission for a reimbursement review was withdrawn.^{9,10} Since then, data on pediatric populations has become available, and Health Canada has studied and approved liraglutide for pediatric use.

The objective of this review is to evaluate the clinical effectiveness of liraglutide (Victoza) for pediatric patients with T2D, alone or in combination with metformin, with or without basal insulin, as compared with standard of care (i.e., basal insulin, metformin, diet and exercise, alone or in combination) or placebo with or without standard of care.

Research Question

What is the clinical effectiveness of liraglutide for pediatric patients with type 2 diabetes?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were liraglutide, type 2 diabetes, and children/pediatrics. Conference abstracts were excluded. The search was completed on June 12, 2023 and limited to English-language documents published since January 1, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), they were duplicate publications or were published before 2013. Systematic reviews/meta-analyses without separate presentations of liraglutide outcomes were excluded, as were systematic reviews that included partial results from just 1 liraglutide study (the individual study, Tamborlane et al.,³ was included in this report). Liraglutide (Saxenda) studies were excluded, as were studies that evaluated liraglutide against other GLP-1 agents. Case reports, in vitro and animal studies, and narrative reviews were also excluded.

Table 1: Selection Criteria

Criteria	Description
Population	Pediatric patients with type 2 diabetes
Intervention	Liraglutide up to 1.8 mg per day, alone or in combination with metformin, with or without basal insulin
Comparator	Standard of care (i.e., insulin, metformin, diet and exercise, alone or in combination) or placebo with or without standard of care
Outcomes	Clinical benefits (e.g., glycemic control, health-related quality of life, changes in insulin requirements, change in weight, treatment duration) and harms (e.g., hypoglycemic events, adverse events, pancreatitis)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Downs and Black checklist¹¹ for measuring study quality as a guide. Summary scores were not calculated for the included studies; rather, each publication's strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 129 citations were identified in the literature search. Following the screening of titles and abstracts, 123 citations were excluded and 6 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 5 publications were excluded for various reasons, and 2 publications met the inclusion criteria and were included in this report. These comprised 2 randomized controlled trials (RCTs).^{3,4} [Appendix 1](#) presents the PRISMA¹² flow chart of the study selection.

Additional references of potential interest are provided in [Appendix 5](#).

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in [Appendix 2](#).

Two RCTs were identified that met the inclusion criteria.^{3,4} One systematic review which included liraglutide along with several other glucose-lowering agents, was excluded because it reported partial results of 1 of the RCTs³ that met our inclusion criteria.⁵ One meta-analysis¹³ and 1 network meta-analysis¹⁴ were excluded because they made additional comparisons of glucose-lowering medications beyond those of interest in the current report.

Study Design

There were 2 RCTs identified that evaluated liraglutide compared with placebo, 1 published in 2014⁴ and 1 published in 2019.³ Both were randomized, parallel-group, placebo-controlled trials, with 1 of the RCTs³ having a 26-week double-blind period followed by a 26-week open-label extension period. The other RCT had a 5-week follow-up.⁴

Country of Origin

One RCT with a US-based lead author was conducted across 84 sites in 25 countries, with the majority of participants coming from the US, Mexico, Russia, and Israel.³ The other RCT also had a US-based lead author, and was conducted across 16 sites in 4 countries (the US, UK, Slovenia, and Belgium).⁴

Patient Population

The RCT by Tamborlane et al³ included youth with T2D between 10 and 17 years of age (at randomization), with a hemoglobin A1C (A1C) of 7% to 11% if treated with diet and exercise only or A1C of 6.5% to 11% if treated with metformin with or without basal insulin, with a BMI greater than the 85th percentile (age- and sex-matched population as reference). Eligible patients entered an 11-to-12-week pretrial run-in period during which metformin was increased to the maximum tolerated dose between 1,000 mg and 2,000 mg per day, for at least 8 weeks for all participants. Of the 134 study participants (liraglutide: n = 66, placebo: n = 68) the mean age was 14.6 years (standard deviation [SD] 1.7), with a mean BMI z score of 2.9 (SD 1.3). As per the study details, mean weight was 91.5 kg (SD 26.8), and 83 were classified as female (61.9%). Within the RCT, it was noted that 3 of the participants were American Indian or Alaska Native (2.2%), 39 (29.1%) were Hispanic or Latino, 18 were Asian (13.4%), 16 were Black (11.9%), 87 were white (64.9%), and 10 (7.5%) were classified as other. The mean duration of T2D was 1.9 years (SD 1.5). The mean A1C was 7.8% (SD 1.3), and the mean fasting plasma glucose (FPG) was 8.4 mmol/L (SD 2.5). The mean systolic and diastolic blood pressure (mmHg) was 116.8 (SD 11.8) and 72.2 (SD 8.1), respectively. Mean metformin use at baseline was 1,894 mg/day (SD 339), and insulin was used at baseline by 25 (18.7%) participants. No significant differences between intervention and control groups were reported at baseline.

The RCT by Klein et al⁴ included participants with T2D who were 10 to 17 years of age, with a BMI of more than the 85th percentile for age and gender, treated with diet and exercise alone or in combination with a stable dose of metformin for at least 4 weeks before screening. At baseline, metformin was being used by 11 participants in the liraglutide arm and by 5 participants in the placebo arm. The mean age of the 21 included study participants (liraglutide: n = 14, placebo: n = 7) was 14.8 (SD 2.2) years, with 3 participants under 12 years of age. The majority of participants were white, female, and postpubertal. The mean baseline body weight was 113.2 kg (SD 35.6, range 57 to 214), body mass index (BMI) was 40 kg/m² (range 29.2 to 71.6 kg/m²), and the mean BMI z scores were 3.41 for liraglutide and 3.38 in the placebo group at baseline. The mean duration of T2D was 1.7 years (SD 1.4). The mean A1C level was 8.1% (SD 1.2%), and 76% of participants had been previously treated with metformin and continued the regimen unchanged during the trial. Demographic and baseline characteristics were generally similar between groups except for baseline mean A1C, which was slightly higher (8.3%) in the liraglutide group compared with the placebo group (7.8%). In terms of

ethnicity/race, 3 participants (14.3%) were Hispanic or Latino, 16 were described as not being Hispanic or Latino, 14 (67%) were described as white, and 7 (33.3%) were described as Black or African American. Patients treated with basal insulin at baseline were excluded from participation in the study.

Interventions and Comparators

The RCT by Tamborlane et al³ evaluated metformin combination therapy with subcutaneous liraglutide (≤ 1.8 mg per day) compared to metformin with placebo (in a visually identical prefilled pen injector with the same procedure as the liraglutide group).³ The liraglutide was administered subcutaneously at 0.6 mg/day, escalated in approximately 0.6 mg/week increments over 2 to 3 weeks, followed by a maintenance period to a maximum of 1.8 mg/day. Dose adjustment was made based on side effects and the efficacy of low doses. Most patients did not receive the maximum dose of liraglutide or placebo because the FPG level was less than 6.1 mmol/L (110 mg/dL). At the end of week 3, a total of 55.6% of the patients in the liraglutide group and 72.7% in the placebo group reached the 1.8-mg dose equivalent. Throughout the remainder of the trial, doses in both groups remained relatively stable. After 26 weeks, there was a further 26-week open-label extension period with participants in the liraglutide group continuing assignment and participants in the placebo group remaining on metformin/insulin only. Diet and exercise counselling was provided at several visits.

The RCT by Klein et al⁴ randomized eligible participants in a 2:1 ratio to once-daily subcutaneous injections of either liraglutide or placebo, either as monotherapy ($n = 5$), or in combination with metformin ($n = 16$). Liraglutide treatment was initiated with 0.3 mg daily during the first week and increased weekly to 0.6 mg, 0.9 mg, 1.2 mg, and 1.8 mg, for a total of 5 weeks of treatment. Drug dose was not increased if FPG (average of measurements on 3 consecutive days) was less than 6.1 mmol/L, and participants whose dose was not escalated to the next higher 1 continued on the highest dose attained for the remainder of the trial. Nine of the 14 participants receiving liraglutide reached the highest dose (1.8 mg), and doses were not escalated for 4 participants who did not meet the FPG-based dose escalation criterion. These 4 participants received either liraglutide 0.3 mg ($n = 1$) or 0.6 mg ($n = 3$) for the remainder of the trial. The liraglutide dose was not escalated in 1 other participant because of early withdrawal. All participants in the placebo group were escalated to the 1.8 mg dose equivalent.

Outcomes

Indicators of Glycemic Control

A1C Levels

The A1C levels, as well as the estimated mean treatment difference between liraglutide and placebo groups, was reported for both RCTs.^{3,4} The Tamborlane et al³ RCT also reported the number of participants who attained A1C levels of less than 7%.

FPG Levels

The estimated mean treatment difference between the liraglutide and placebo groups for FPG levels was reported in both RCTs.

Rescue Insulin Requirement

One RCT reported the need for insulin administration to maintain acceptable glycemic control.³

BMI Z Score and/or Weight Gain or Loss

Mean body weight was reported for both RCTs,^{3,4} and BMI z scores were reported for 1 RCT.³

Adverse Events, Including Hypoglycemic Episodes

For both RCTs, adverse events, including serious adverse events, were assessed throughout the trial, and hypoglycemic episodes were classified according to the Novo Nordisk and American Diabetes Association definitions.

Safety and Tolerability Parameters

Both RCTs evaluated safety and tolerability parameters.^{3,4} Tamborlane et al³ evaluated fasting lipid levels, systolic and diastolic, blood pressure, lipase, amylase, and calcitonin levels, at baseline and during the trial with standard laboratory tests. Klein et al⁴ conducted laboratory tests, including biochemistry, hematology, urinalysis, calcitonin, amylase, lipase, fasting lipids, vital signs, physical examination, electrocardiogram, funduscopy, and antilraglutide antibodies), along with a range of biomarkers and hormones.

Summary of Critical Appraisal

One of the included RCTs³ was of moderately high quality when appraised using the domains detailed in the Downs and Black checklist.¹¹ The other RCT by Klein et al⁴ was of moderate quality. In the domain of *Reporting*, both RCTs were well reported, including a clearly stated objective and outcomes; the characteristics of the included participants were clearly described, as was the distribution of potential confounders, and the treatment and placebo were described (Klein et al⁴ did not describe the placebo in detail but did mention dose escalation of the placebo). The main findings are clearly described, and the investigators have presented SDs and confidence intervals where required. Adverse events were comprehensively measured and reported, characteristics of patients lost to follow-up were reported where it occurred, and actual P values were reported.

In the domain of *External Validity*, neither RCTs described the source population for the included participants, nor described whether the subjects who were prepared to participate were representative of the entire population from which they were recruited, nor did they describe whether the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive. However, the RCTs were both multicentre from multiple countries, suggesting considerable variation in populations and processes, which would, therefore, likely capture a more real-world variability in treatment, increasing the generalizability of the findings. A detailed list of exclusion criteria was presented in the Tamborlane et al³ RCT, potentially limiting generalizability of findings to the general T2D population, and the Klein et al⁴ group excluded potential participants that were using basal insulin at baseline. The Klein et al⁴ authors also included 5 participants not using metformin at baseline. Due to external validity issues for both RCTs, there may be some concerns regarding the generalizability of findings.

Both RCTs performed well in the Internal Validity (Bias) domain. Study participants were blinded to the intervention, outcome assessors were blinded (assumed as the 2 RCTs are described as double-blind), there were no unplanned subgroup analyses, and follow-up was described as being at the same time point for all participants in both RCTs. Statistical tests used to evaluate outcomes were appropriate in both RCTs, and the outcome measures used are clearly described and considered valid. One RCT⁴ reported a suspected (but not confirmed) case of noncompliance, while the other RCT³ reported equal noncompliance in both treatment arms (n = 4 in each group).

In the domain of Internal Validity (Confounding), neither of the included RCTs provided information concerning the source of patients included in the study, but they did appear to be recruited over the same period of time. In both RCTs, study participants were randomized to treatment groups, but concealment allocation was not described. There appeared to be adequate adjustment for confounding in both RCTs, and loss to follow-up was addressed.

In the *Power* domain, only Tamborlane et al.³ provided a power calculation, suggesting that the RCT had sufficient power to detect a clinically important effect not due to chance alone. A power calculation was not performed in the Klein et al.⁴ RCT, which had a relatively small study population, N = 21, allowing for the possibility that any observed clinical effect may have been due to chance.

Both RCTs were at least partially funded by the manufacturer of liraglutide. Also, due to recruitment challenges, both RCTs made amendments to the protocols after the study started.

Overall, there were just 2 RCTs evaluating liraglutide in the pediatric and adolescent population, and the quality of the 2 RCTs was assessed to be of moderate⁴ to moderately high³ quality, with external validity concerns potentially affecting the generalizability to the general population of children and adolescents with T2D.

Additional details regarding the strengths and limitations of included publications are provided in [Appendix 3](#).

Summary of Findings

[Appendix 4](#) presents the main study findings.

A1C and FPG

Two RCTs were identified that evaluated the effectiveness of liraglutide as compared with placebo in children and adolescents with T2D, with 1 RCT reporting follow-up at 5 weeks (N = 19),⁴ and the other RCT³ (N = 135) reporting follow-up at 26 weeks, and then again at 52 weeks (open-label for the second half of study). Both authors reported on indicators of glycemic control, such as A1C and FPG. Both RCTs reported statistically significant reductions in A1C levels in the liraglutide group compared to the group receiving placebo, with A1C levels either remaining stable or increasing in the placebo group. One RCT reported that participants attained statistically significant A1C levels of less than 7% compared to the placebo group.³ For FPG, 1 RCT reported a statistically insignificant improvement from baseline in the liraglutide group compared to the

placebo group.⁴ The second RCT reported statistically significant reductions in FPG levels in the liraglutide group and increases in FPG levels in the placebo group.³ One RCT reported that a greater number of participants in the liraglutide group were able to finish the study without the use of rescue insulin to ensure acceptable glycemic control as compared with the placebo group at both 26 weeks (86.4% versus 66.7%) and 52 (71.2% vs. 50.7%) weeks (statistical significance not reported).³

BMI Z Score and Weight

The included RCTs^{3,4} reported minor reductions in mean body weight in both the liraglutide and placebo groups. The weight loss was maintained in the liraglutide group only (at week 52) as compared with the placebo group in 1 RCT (statistical significance not reported), and the same RCT reported an insignificant reduction in BMI z scores at 26 weeks, which subsequently increased at week 52.³

Adverse Events

Adverse events were reportedly higher in the liraglutide group in both of the included RCTs,^{3,4} with Tamborlane et al³ reporting a relative risk for all adverse events of 1.05. The majority of adverse events reported in both RCTs were gastrointestinal, including nausea, vomiting, and diarrhea. They were mild in severity and resolved quickly. One RCT⁴ did not report any serious adverse events during the trial, while the Tamborlane et al.³ RCT reported an RR of 2.32 in the liraglutide group for serious adverse events (9 serious events reported in the liraglutide group versus 4 in the placebo group). The serious adverse events in the liraglutide participants were described as follows: neck abscess, viral infection, hyperglycemia, abdominal pain, diarrhea, vertigo, scoliosis, A1C increase.

Hypoglycemic events were reportedly higher in the liraglutide arm than in the placebo arm for both of the included RCTs using either the Novo Nordisk classification or the American Diabetes Association classification (note Tamborlane et al³ did not report separate values for the Novo Nordisk classifications). The RR of a hypoglycemic event (both documented symptomatic and asymptomatic) in the liraglutide group was 1.82 in 1 RCT which reported an RR.³

Safety and Tolerability Parameters (Laboratory Tests to Evaluate Thyroid and Pancreatic Function)

Both RCTs reported no statistically significant changes in safety parameters. While amylase and calcitonin remained within the normal range for the study populations in both RCTs, and the majority of patients did not have elevated lipase levels, there were higher lipase levels reported in both RCTs for the liraglutide group as compared with the placebo group. The authors of the Klein et al⁴ RCT reported that the clinical significance of the elevated lipase levels observed in some participants was unknown. No significant changes were reported in either RCT for other safety and tolerability parameters and tests, such as very-low-density lipoprotein cholesterol levels, triglyceride levels, and systolic and diastolic blood pressure.

Limitations

There is a limited amount of evidence evaluating liraglutide in children and adolescents. There are 2 RCTs^{3,4} evaluating liraglutide for glycemic control in the pediatric population, and the study participant numbers for both RCTs are relatively small, particularly in the Klein et al⁴ RCT that had 14 participants in the liraglutide arm. The small study populations also contribute to the observed wider confidence intervals, leading to less confidence in the observed treatment effects. However, the available research is limited because there is a relatively low prevalence of pediatric T2D patients, which impedes recruitment into clinical trials.^{4,5} The Klein et al⁴ RCT had a 5-week follow-up period, which brings into question the usefulness of measuring A1C levels, given that A1C reflects average plasma glucose over the previous 8 to 12 weeks.^{14,15}

There is limited data generalizable to Canadian populations. There were 3 patients from 1 Canadian centre included in 1 RCT.³ Most patients included in both RCTs were described as white and female, which means that the data may also not be generalizable to non-white populations and males.

Another limitation is the lack of safety data in children, particularly in the long term since children would be taking medication for a long time. Klein et al.⁴ had a 5-week follow-up, and the Tamborlane et al.³ RCT had a 52-week follow-up. The authors of both RCTs reported that not all study participants had received the highest dose of liraglutide (1.8 mg), limiting data collection regarding the safety profile of liraglutide. Approximately half the patients in 1 RCT did not receive the highest dose.³ In the other RCT, 9 of 14 participants received the highest dose.⁴ Karavanaki et al.² have indicated uncertainties regarding the potential long-term effects of liraglutide on brain and body growth, given a lack of long-term studies in children and adolescents. There are also concerns about the potential for pancreatitis and even pancreatic cancer associated with liraglutide.^{4,16}

The Klein et al⁴ study did not include participants who were receiving basal insulin at baseline, while the Tamborlane et al³ study included a total of 25 (out of 134) participants who were receiving insulin at baseline. Klein et al⁴ also included 5 participants who were not receiving metformin therapy at baseline. Hence there is limited evidence for the effectiveness and safety of liraglutide in patients receiving therapy that includes basal insulin and for liraglutide monotherapy (i.e., without metformin).

Conclusions and Implications for Decision- or Policy-Making

While metformin is the treatment of choice for most children and adolescents with T2D, along with lifestyle interventions such as diet and exercise, approximately half of youth with T2D fail to maintain glycemic control when treated with metformin, either alone or in conjunction with lifestyle interventions.^{3,4} Basal insulin can be used in children and youth who do not respond adequately to metformin monotherapy; however, insulin therapy has been associated with weight gain and hypoglycemia. In cases where metformin monotherapy fails to maintain glycemic control, glucagon-like peptide-1 (GLP-1) agonists can be added. Liraglutide (Victoza) is a GLP-1 agonist indicated in adolescents and children aged 10 years and older with T2D as an adjunct to metformin with or without basal insulin when diet and exercise plus a maximally tolerated dose of metformin do not achieve adequate glycemic control. There are no metformin adjunct alternatives to liraglutide for glucose control in children and adolescents currently approved in Canada.⁷

There is limited evidence to evaluate the effectiveness of liraglutide alone or when added to treatment with metformin, with or without basal insulin, in children and adolescents. There were 2 RCTs published that evaluated the effectiveness of liraglutide in children and adolescents, 1 of moderate quality with a relatively short follow-up of 5 weeks and a limited number of participants (n = 14 in the liraglutide group),⁴ and 1 of moderately high quality with follow-up at 26 and at 52 weeks (n = 66 patients in the liraglutide arm).³ Both RCTs reported statistically significant improvements in indicators of glycemic control. In the liraglutide group, both RCTs reported statistically significant improvements in A1C, and 1 RCT³ reported that significantly more patients in the liraglutide arm were able to attain A1C levels of less than 7%. One RCT³ reported significant improvements in FPG levels, while the other RCT⁴ showed an insignificant trend toward improvement of FPG levels. Neither RCT showed significant improvements in weight loss, and the RCT that reported BMI z scores also reported no significant improvements. However, liraglutide (Victoza) is not indicated for weight loss. One RCT reported that a greater percentage of participants were able to complete the trial without using insulin to attain optimal glycemic control in the liraglutide group (71.2%) than in the placebo group (50.7%).³

Adverse events were higher in the liraglutide group in both of the included RCTs.^{3,4} The majority of adverse events reported in both RCTs were gastrointestinal, including nausea, vomiting, and diarrhea. They were considered mild in severity and resolved quickly. More serious adverse events were reported in the liraglutide group in 1 RCT,³ and no serious events were reported in the other RCT.⁴ The percentage of patients who had hypoglycemic episodes and the incidence of hypoglycemia were higher with liraglutide than with placebo in both RCTs. It is widely accepted that GLP-1 receptor agonists do not cause hypoglycemia,¹⁷ and Tamborlane et al.¹⁸ felt that the observed hypoglycemic events could only be partially explained by the use of insulin during the trial.

There have been postmarketing reports of pancreatitis during T2D treatment with liraglutide, and it is not known whether patients with a history of pancreatitis are at higher risk for developing pancreatitis with liraglutide treatment.^{4,6} The Tamborlane et al.³ RCT excluded children with a history of pancreatitis; it is unknown if the Klein et al. RCT⁴ excluded children with a history of pancreatitis. It is worth noting that lipase levels were reportedly higher with liraglutide than with placebo at follow-up for both RCTs, though most participants did not have elevated lipase levels, and no events meeting the diagnostic criteria for pancreatitis occurred. The clinical significance of the elevated lipase levels is unknown.⁴ There appears to be no evidence for or against the use of liraglutide in children with a history of pancreatitis, and the product monograph cautions that patients given liraglutide be observed carefully for signs and symptoms of pancreatitis. Overall, there is a lack of long-term safety data for using liraglutide in children, and children could be more at risk as they grow and use liraglutide over a long period.¹⁶ In the largest RCT to date with the longest follow-up duration of 1 year, only approximately half of the study participants received the maximum dose of liraglutide, limiting data collection relating to the safety profile of liraglutide.³

The available research may not be generalizable to the Canadian population due to a paucity of data in Canadians and limited data for males and non-white individuals. Of the 2 included RCTs, 1⁴ excluded participants receiving basal insulin at baseline, limiting the amount of evidence available to evaluate the effectiveness and safety profile of liraglutide in children and adolescents currently receiving insulin therapy.

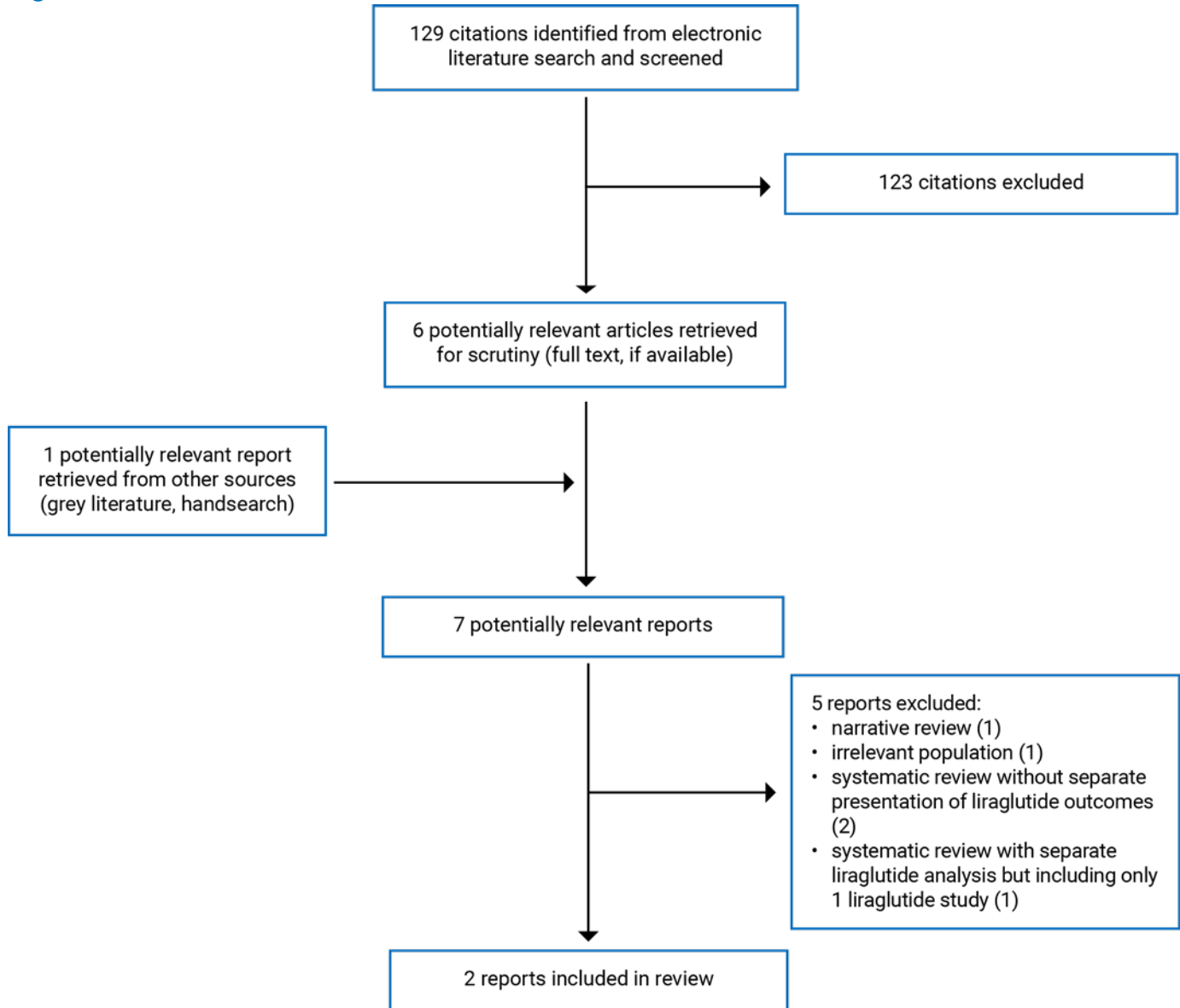
Finally, 1 of the included RCTs included 5 participants who were not receiving metformin at baseline, which may have affected the trial results and limited the generalizability in patients receiving metformin.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Tamborlane et al. (2019) ³ Multicentre (US lead author) Funding source: Novo Nordisk; UK Medical Research Council; National Institutes of Health Research (NIHR); Translational Research Collaboration for Rare Diseases; NIHR Wellcome Clinical Research Facility	Double-blind RCT for 26 weeks, followed by a 26-week open-label extension	Mean Age: 14.6 years (SD 1.7) Mean BMI z score: 2.9 (SD 1.3) Mean weight: 91.5 kg (SD 26.8) Gender: 83 (61.9%) were classified as female Ethnicity/Race American Indian or Alaska Native: 3 (2.2%) Hispanic or Latino: 39 (29.1%) Asian: 18 (13.4%) Black: 16 (11.9%) White: 87 (64.9%) Other: 10 (7.5%) Mean duration of T2D: 1.9 years (SD 1.5). Mean A1C: 7.8% (SD 1.3) Mean FPG: 8.4 mmol/L (SD 2.5). Mean systolic and diastolic blood pressure (mmHg): 116.8 (SD 11.8) and 72.2 (SD 8.1) respectively Mean metformin use at baseline: 1,894 mg/day (SD 339) Basal insulin use at baseline: n = 25 (18.7%)	Intervention: liraglutide (n = 66) Comparator: ^a placebo (n = 68) Dose escalation: Administration of liraglutide was initiated at a dose of 0.6 mg per day, and increased in increments of 0.6 mg per week to a max of 1.8 mgs, based on side effects and efficacy. Doses were not increased if FPG levels were < 6.1 mmol/L.	Outcomes A1C ETD Attainment of A1C levels of < 7%FPG Requirement for insulin rescue Weight BMI z scores Adverse events Safety and tolerability parameters (lipase, amylase and calcitonin, etc.) Follow-up 26 weeks (RCT) 52 weeks (open label)
Klein et al. (2014) ⁴ Multicentre (US lead author) Funding source: Novo Nordisk	Double-blind RCT	Mean age: 14.8 years (SD 2.2) Gender: 67% female Ethnicity/Race Hispanic or Latino: 3 (14.3%) White 14 (67%) Black or African American: 7 (33.3%)	Intervention: Liraglutide (n = 14) Comparator: Placebo (n = 7) Dose Escalation: Liraglutide treatment was initiated with 0.3 mg daily during	Outcomes Adverse events Safety and tolerability parameters A1C ETD FPG Weight

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		<p>Mean baseline body weight: 113.2 kg (SD 35.6, range 57 to 214)</p> <p>Mean BMI: 40 kg/m², (range from 29.2 to 71.6 kg/m²)</p> <p>Mean BMI z scores for liraglutide group: 3.41; placebo: 3.38.</p> <p>Mean duration of T2D: 1.7 years (SD 1.4, range 0.12 to 5.45 years)</p> <p>Mean hemoglobin A1C level: 8.1% (SD 1.2%)</p> <p>Previously treated with metformin: 76%</p> <p>Basal insulin use at baseline: 0</p>	<p>the first week and increased weekly to 0.6 mg, 0.9 mg, 1.2 mg, and 1.8 mg unless FPG levels were < 6.1 mmol/L.</p>	<p>Follow-up 5 weeks</p>

A1C = hemoglobin A1C; BMI = body mass index; ETD = estimated treatment difference; FPG = fasting plasma glucose; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; T2D = type 2 diabetes.

*Placebo in visually identical pen injector.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist)¹¹

Strengths	Limitations
Tamborlane et al. (2019)³	
<p>The authors clearly stated the objectives, main outcomes, patient characteristics, distribution of potential confounders, and interventions (treatment and placebo).</p> <p>The main findings were clearly described, with SD, CI and P values provided.</p> <p>Adverse events were comprehensively measured and reported, and characteristics of patients lost to follow-up were reported.</p> <p>Study participants were blinded to intervention. There were no unplanned subgroup analyses, and follow-up was described as being at 26 and 52 weeks for all participants.</p> <p>Statistical tests used to evaluate outcomes seemed to be appropriate and the outcome measures utilized are widely used and considered valid (not described in the RCT).</p> <p>Participants were recruited over the same time period and were randomized to treatment groups. There appeared to be adequate adjustment for confounding, and loss to follow-up was described. Nonadherence was the same in both treatment arms.</p> <p>A power calculation was performed, suggesting that the RCT had sufficient power to detect a clinically important effect not due to chance alone.</p>	<p>It is unclear whether the patients recruited, patients prepared to participate, or the staff, places, and facilities where patients were treated, were representative of the source population.</p> <p>Concealment allocation was not reported.</p> <p>It is not known if outcome assessors were blinded.</p> <p>Partial funding from liraglutide manufacturer</p> <p>Protocol amendment due to recruitment challenges and resulting long recruitment period.</p>
Klein (2014)⁴	
<p>The authors clearly stated the objectives, main outcomes, patient characteristics, distribution of potential confounders, and interventions (treatment but not placebo).</p> <p>The main findings were clearly described, with SD, CI and p values provided.</p> <p>Adverse events were comprehensively measured and reported, and characteristics of patients lost to follow-up were reported.</p> <p>Study participants were blinded to intervention. There were no unplanned subgroup analyses, and follow-up was described as being at 26 and 52 weeks for all participants.</p> <p>Statistical tests used to evaluate outcomes seemed to be appropriate and the outcome measures utilized are widely used and considered valid (not described in the RCT). There was equal nonadherence in both treatment arms.</p> <p>Participants were recruited over the same time-period and</p>	<p>It is unclear whether the patients recruited, patients prepared to participate, or the staff, places, and facilities where patients were treated, were representative of the source population.</p> <p>Concealment allocation was not reported.</p> <p>It is not known if outcome assessors were blinded.</p> <p>The placebo was not described.</p> <p>Relatively small sample size</p> <p>No power calculation was performed.</p> <p>Relatively short follow-up period which may not have captured changes in hemoglobin A1C levels in response to treatment (hemoglobin A1C reflects average plasma glucose over the previous 8 to 12 weeks)</p> <p>Protocol amendment due recruitment challenges due to small pool of participants</p>

Strengths	Limitations
were randomized to treatment groups. There appeared to be adequate adjustment for confounding, and withdrawal from the study was the same in both arms.	

CI = confidence interval; SD = standard deviation; RCT = randomized controlled trial.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 4: Summary of Findings by Outcome – Glycemic Control Parameters, BMI Z Score, and Weight Change

Outcome	Tamborlane et al. (2019) ³ RCT		Klein et al. (2014) ⁴ RCT
	26-week follow-up	52-week follow-up (open label between 26 and 52 weeks)	5-week follow-up
Glycemic control parameters			
A1C (mean ETD mmol/mol)	-1.06 (95% CI, -1.65 to -0.46; P < 0.001)	-1.30 (95% CI, -1.89 to -0.70) ^a	-0.90 (95% CI, -1.36 to -0.45; P = 0.0007)
Attainment of A1C levels of < 7%	Liraglutide: 63.7% Placebo: 36.5% OR 5.35 (95% CI, 2.10 to 13.61, P < 0.001)	NR	NR
FPG (mean ETD mmol/mol)	-1.88 (95% CI, -3.09 to -0.66; 0.66; P = 0.002)	-1.81 (95% CI, -3.17 to -0.44) ^a	-1.44 (95% CI, -3.61 to 0.73; P = 0.1797)
BMI z score (mean ETD)	-0.05 (95% CI, -0.15 to 0.06; P = 0.39)	-0.18 (95% CI, -0.33 to -0.03) ^a	NR
Mean body weight ^a	Liraglutide: -2.3 kg Placebo: -0.99 kg	Liraglutide: -1.91 kg Placebo: 0.87 kg	Liraglutide: -0.5 kg Placebo: -0.5 kg
Insulin rescue requirement (% completed without need for insulin rescue)	Liraglutide: 86.4% Placebo: 66.7%	Liraglutide: 71.2% Placebo: 50.7%	NR

CI = confidence interval; ETD = estimated treatment difference; NR = not reported; OR = odds ratio.

Note: ETD is mean change from baseline in the liraglutide group compared to placebo in percentage points.

^aSignificance not reported.

Table 5: Summary of Findings by Outcome – Adverse Events, Safety and Tolerability Parameters

Outcome	Tamborlane et al ³		Klein et al ⁴	
	Liraglutide (N = 66)	Placebo (n = 68)	Liraglutide (n = 14)	Placebo (n = 7)
Adverse events				
Total adverse events	n = 56 (84.8%) 426 events Event rate: 7.144 RR: 1.05 (0.90, 1.22)	n = 55 (80.9%) 321 events Event rate: 5.425	n = 10 (71.4%) 38 events	n = 3 (42.9%) 18 events

Outcome	Tamborlane et al ³		Klein et al ⁴	
	Liraglutide (N = 66)	Placebo (n = 68)	Liraglutide (n = 14)	Placebo (n = 7)
Serious adverse events	n = 9 (13.6%) experienced 10 events Event rate: 0.168 RR: 2.32 (0.75, 7.16)	n = 4 (5.9%) experienced 5 events Event rate: 0.085	0	0
Hypoglycemia ^a	n = 30 (45.5%) 160 events RR: 1.82 (1.11 to 2.97)	n = 17 (25%) 63 events	n = 5 (35.7%) 11 events	n = 1 (14.3%) 1 event
Gastrointestinal events^b				
Diarrhea	N = 15 (22.7%) 22 events 1.40 (0.70 to 2.83)	n = 11 (16.2%) 13 events	N = 6 (42.9%) 7 events	n = 1 (14.3%) 1 event
Nausea	n = 19 (28.8%) 25 events RR: 2.18 (1.06 to 4.46)	n = 9 (13.2%) 12 events	n = 3 (21.4%) 4 events	n = 1 (14.3%) 1 event
Vomiting	17 (25.8%) 46 events RR: 2.92 (1.23 to 6.95)	6 (8.8%) 8 events	2 (14.3%) 2 events	2 (28.6%) 3 events
Safety and tolerability parameters^c				
Lipase levels	Treatment ratio in liraglutide vs placebo group: 1.20 (95% CI, 1.08 to 1.32)	Treatment ratio in liraglutide vs placebo group: 1.11 (95% CI, 1.01 to 1.23)	Liraglutide^d Screening: 25.5 +/- 7.1 U/L Follow-up: 37.5 +/- 18.4U/L	Placebo^d Screening: 27.1 +/- 12.0 Follow-up: 33.2 +/- 18.5 U/L

CI = confidence interval; RR = relative risk.

^aUsing American Diabetes Association definition.

^bTop 3 most frequently reported events.

^cAmylase, calcitonin levels, blood pressure and more are not reported here because they were in low to normal range for all participants with no significant differences between groups.

^dNormal lipase levels range from: < / = 13 years, < / = 37 U/L; > 13 to 18 years, < / = 46 U/L).

Appendix 5: References of Potential Interest

Systematic Reviews

- Diabetes (type 1 and 2) in children and young people: diagnosis and management. [D] Evidence review for glucose-lowering agents for managing blood glucose levels in children and young people with type 2 diabetes. (*NICE guideline NG18*). London (GB): National Institute for Health and Care Excellence (NICE); 2023: <https://www.nice.org.uk/guidance/ng18/evidence/d-glucoselowering-agents-for-managing-blood-glucose-levels-in-children-and-young-people-with-type-2-diabetes-pdf-13060839133>
- Carydias E, Tasho A, Kani C, Bacopoulou F, Stefanaki C, Markantonis SL. Systematic Review and Meta-Analysis of the Efficacy and Safety of Metformin and GLP-1 Analogues in Children and Adolescents with Diabetes Mellitus Type 2. *Children*. 2022 Oct 18;9(10):18. [PubMed](#)
- Wu S, He Y, Wu Y, et al. Comparative efficacy and safety of glucose-lowering drugs in children and adolescents with type 2 diabetes: A systematic review and network meta-analysis. *Front Endocrinol (Lausanne)*. 2022;13:897776. [PubMed](#)

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