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Authors

Seetharaman, Sujatha
Cengiz, Eda

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The Promise of Adjunct Medications in Improving Type 1 Diabetes Outcomes: GLP-1 Receptor Agonists (GLP-1 RAs)

Sujatha Seetharaman, MD, MPH[1], Eda Cengiz, MD[1]

[1]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of San Francisco, CA

Corresponding author:
Sujatha Seetharaman, MD, MPH
Division of Pediatric Endocrinology & Diabetes
University of California San Francisco
Box 0110 | 550-16th Street | San Francisco, CA 94143
Email: sujathasri.seetharaman@ucsf.edu
Phone: (508) 808-1743

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Abstract

Type 1 diabetes mellitus (T1D) necessities lifelong insulin therapy due to the autoimmune destruction of insulin producing pancreatic beta cells. Despite advancements in diabetes technology and insulin formulations, maintaining optimal glucose control remains challenging in these patients. Obesity, accompanied by insulin resistance is common not only in type 2 diabetes (T2D) but also in many patients with T1D. Glucagon-like peptide -1 receptor agonists (GLP- 1 RAs), approved for T2D and obesity, are now being explored for off-label use in patients with T1D. This review examines their efficacy, safety, and potential benefits in T1D management. We reviewed articles published up to May 2024 from databases like PubMed and Scopus, mainly focusing on human studies of GLP -1 RAs in T1D, as well as cardiorenal and metabolic outcomes in patients with T2D and obesity. Semaglutide and other GLP- 1 RAs showed significant improvements in glycemic control, hemoglobin A1c levels, reduced insulin doses and notable weight loss. Studies in patients with obesity and T2D showed significant improvements in lipid profile and offered cardiorenal protection. Common side effects include gastrointestinal issues, and while some studies reported hyperglycemia and ketosis, others did not. Despite these challenges, GLP-1 RAs offer significant therapeutic benefits, making them a promising adjunct to insulin therapy for improving clinical outcomes in T1D management.

Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease marked by the destruction of insulin-producing pancreatic beta cells, necessitating lifelong dependence on exogenous insulin. This condition presents substantial public health and clinical challenges, with diagnosis rates increasing annually (1-5). Effective management requires precise insulin therapy to prevent ketoacidosis and maintain normal metabolic function, alongside frequent blood glucose monitoring to optimize glycemic control and prevent complications.

Since the discovery of insulin over a century ago, significant strides in treatment have transformed care for countless individuals living with T1D. Despite advancements in insulin formulations, delivery systems, continuous glucose monitoring (CGM), maintaining optimal glucose control remains challenging (6). Data from the T1D registry indicated that only a minority of individuals with T1D achieve the American Diabetes Association (ADA) hemoglobin A1c (HbA1c) goal, with particularly high HbA1c levels observed in adolescents and youth (7). Furthermore, recent studies highlight significant long-term complications including brain changes (8) and reductions in life expectancy for individuals with T1D, underscoring the urgent need for improved management strategies (9, 10).

T1D is a significant burden for children and families, being one of the most common chronic childhood diseases (11). Despite advancements, there has not been a significant breakthrough in treating T1D. It is critical to develop interventions that can halt or slow disease progression and preserve residual beta-cell function, while addressing abnormal physiology and factors causing beta cell stress. Recently, new tools, such as glucagon-like peptide -1 receptor agonists (GLP-1 RAs), effective nutrient-stimulated hormone-based anti-obesity pharmacotherapeutics, have emerged and are FDA approved for the treatment of type 2 diabetes (T2D) and obesity (12).

Recent research has explored use of GLP-1 RAs as an adjunctive pharmacotherapy for individuals with T1D (13, 14). Obesity, accompanied by insulin resistance is prevalent not only in T2D but also in many patients with T1D. (15-19). Although GLP-1 RAs are not FDA- approved for T1D, several providers have been prescribing these medications off-label, especially for adults. This narrative review examines the emerging role of GLP-1 RAs in the management of T1D among both adults and adolescents, focusing on their efficacy, safety, and potential benefits.

Methods

We reviewed articles published up to May 2024 using databases such as PubMed, Scopus, and ClinicalTrials.gov, with keywords including "Type 1 Diabetes," "GLP-1

receptor agonists," "liraglutide," "Semaglutide," "Tirzepatide," "Exenatide," and "Dulaglutide." Pertinent articles' references were also manually searched for relevant papers. We included papers involving human subjects and focused on the use of GLP-1RAs in T1D. Excluded were animal studies and non-peer reviewed articles.

The Potential of GLP-1 RAs in adolescents with T1D

GLP-1 RAs exhibit several mechanisms of action beneficial for managing diabetes. These include enhancing insulin secretion in response to hyperglycemia, suppressing glucagon secretion during hyperglycemia and euglycemia, slowing gastric emptying to stabilize post-meal glucose levels, and promoting weight loss through direct action on the brain (12, 20). Currently FDA approved GLP-1 RAs among adults and adolescents are summarized in Table 1.

Tirzepatide (TZT) is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and a GLP-1 RA and is approved for treatment of obesity in adults (21). There is an ongoing clinical trial (NCT06075667) trial investigating effect of TZT on adolescent obesity. Providers are also using TZT ‘off-label” to treat adolescents with T2D and/or obesity.

Given their effectiveness in reducing of HbA1c and promoting weight loss without risk of hypoglycemia, GLP-1 RAs are recommended as adjunct medications for audits and youth with T2D (22). They can be combined with basal insulin, and newer agents like semaglutide offer enhanced efficacy in lowering blood glucose and body weight (20). However, there are currently no established guidelines for using GLP-1RAs in T1D due to lack of robust studies, with limited research primarily focused on adults.

Table 1. Currently approved GLP-1 RAs in adults and adolescents

Medication	**Year of FDA approval**	**US FDA Indication**	**Mechanism of action**	**Side effects**	**Contraindications**
Tirzepatide Initiated at 2.5 mg weekly; titrated to target dose, max dose 15 mg weekly, subcutaneously (23)	Adults: Mounjaro for T2D (2022) Zepbound (2023) for obesity	T2D and/or Obesity in adults	Glucose-dependent insulin secretion, slows gastric emptying, suppresses glucagon,	GI side effects (nausea, vomiting, diarrhea, constipation, decreased appetite), hypoglycemia when used	Personal history of pancreatitis History of Multiple Endocrine Neoplasia (MEN) type 2 Family history of

Semaglutide 2.4 mg weekly (24) (Wegovy), subcutaneously	Adults: Ozempic, 2017 Wegovy, 2021 Adolescents: Wegovy, 2022	Adult obesity, T2D Obesity* in adolescents ≥12 years	directly acts on the brain to decrease appetite,	with insulin, renal impairment or kidney failure, hypersensitivity, acute gallbladder disease	medullary thyroid cancer Pregnancy
Oral Semaglutide 7,14 mg daily (25) (Rybelsus)	Adults: Rybelsus, 2019	T2D in adults			
Liraglutide (Victoza- 1.8 mg daily) (26, 27) (Saxenda 3 mg daily) (28, 29), subcutaneously	Adults: Victoza, 2010 Saxenda,2014 Adolescents: 2019 (Victoza) 2020 (Saxenda)	T2D in children ≥10 years Obesity in adolescents ≥12 years			
Dulaglutide 0.75 mg or 1.5 mg weekly **(30, 31),** subcutaneously	Adults: Trulicity, 2014 Adolescents: Trulicity, 2022	T2D in adults T2D in children ≥10			
Exenatide (32, 33), twice daily or weekly, subcutaneously	Adults: Byetta, 2005 twice daily Adolescents: Bydureon once weekly 2021	T2D in adults and children ≥10 years			

*BMI at or above the 95th percentile for their age and sex.

Rationale for Use of GLP-1 RAs as Adjunct Therapies in adults and adolescents with T1D

A. <u>GLP-1 RAs as a tool to manage glycemic and weight outcomes in T1D</u>

GLP-1 RAs offer multiple mechanisms to manage glycemic control and weight in individuals with T1D. These mechanisms include delaying gastric emptying, reducing postprandial glucagon secretion, and decreasing carbohydrate intake. Additionally, GLP-1 RAs promote weight reduction and decrease insulin dosing. Research indicates that T1D is characterized not only by insufficient insulin but also by an inappropriate glucagon response, contributing to postprandial hyperglycemia and impaired glucagon response to low blood sugar (34). This dysregulation is commonly attributed to the absence of insulin secretion, which normally suppresses glucagon release (34). Without this insulin-mediated inhibition, alpha cells may increase glucagon secretion following meals (34, 35). Studies show that individuals with T1D can suppress glucagon secretion after intravenous glucose administration, suggesting that inappropriate glucagon responses are likely triggered by oral glucose intake through gut signaling or direct gut glucagon secretion rather than alpha cell dysfunction or lack of insulin's paracrine inhibition (36-38).

Research studies in youth with recent-onset T1D show similar patterns. For example, research by Sherr et al., demonstrated that youth with recent-onset T1D exhibit significantly elevated glucagon levels compared to non-diabetic controls during mixed meal tolerance tests, suggesting that suppressing these responses could enhance glycemic control (39). Brown RJ et al., investigated the evolution of glucagon levels in children with newly diagnosed T1D, finding that post-prandial hyperglycemia intensified alongside declining C-peptide levels over a year. This highlights the therapeutic implications of glucagon dysregulation and its connection to diminishing beta cell function (40). Fredheim et al., studied a large cohort of 129 Danish children (mean age 10 years) with T1D over 60 months, finding that postprandial glucagon levels increased 160% from diagnosis and correlated with higher glucose levels and lower C-peptide levels (41). This suggests disrupted alpha cell secretion regulation and beta cell dysfunction (41). These findings underscore the complex role of glucagon dysregulation in T1D pathophysiology highlighting the need for targeted therapies. By addressing both insulin and glucagon dysregulation, GLP-1RAs offer a multifaceted approach to improving glycemic control and overall management of T1D.

Below, we summarize recent studies and meta-analyses evaluating the use of GLP-1RAs in improving glycemic control in adults with T1D.

<u>Liraglutide:</u>

Liraglutide has been extensively studied as an adjunct to insulin therapy in patients with T1D.

In the Adjunct One Treat-To-Target Randomized Trial (42), adding liraglutide to insulin therapy in 1398 adults T1D over 52 weeks resulted in reduced HbA1c levels (0.34%–0.54% from an initial 8.2%), lower insulin doses, and significant weight loss. However, liraglutide was associated with higher rates of symptomatic hypoglycemia, particularly at the 1.8 mg dose, and increased instances of hyperglycemia with ketosis (42). Similarly, in the Adjunct Two randomized trial over 26-weeks (43) among 835 patients with T1D, adding liraglutide to capped insulin doses significantly reduced HbA1c levels and body weight compared to placebo.

Nonetheless, higher rates of symptomatic hypoglycemia were observed with the 1.2 mg dose and increased hyperglycemia with ketosis with the 1.8 mg dose (43). These results highlight the benefits of liraglutide in T1D while emphasizing the need for careful monitoring and management of associated risks. Since then, a multitude of studies have drawn comparable conclusions.

In a randomized study by Kuhadia et al, involving 72 patients (placebo = 18, liraglutide = 54) with T1D, the addition of 1.2 mg and 1.8 mg liraglutide to insulin over a 12-week period in patients with T1D who were overweight or had obesity resulted in modest reductions in average blood glucose, HbA1c, small reductions in insulin doses, significant weight loss, decreased postprandial plasma glucose concentration and frequent gastrointestinal side effects (44).

Sherr et al., explored the effects of liraglutide on postprandial hyperglycemia during closed loop insulin delivery. The study found that liraglutide reduced glucose excursions and insulin needs while promoting weight loss, suggesting that liraglutide could improve glycemic control in individuals using closed loop delivery systems (45).

Exenatide

In a study by Herold et al., 79 participants were randomized to receive exenatide ER or placebo for 24 weeks. At week 12, exenatide ER significantly reduced HbA1c levels, particularly in those with detectable C-peptide, and promoted significant weight loss compared to placebo. However, these benefits were not sustained at 24 weeks, indicating limited long-term efficacy. Adverse effects were more common with exenatide ER, but hypoglycemia rates did not increase (46).

Metanalyses Comparing Efficacy of GLP-1 RAs (Liraglutide, Albiglutide, Exenatide) in T1D

A meta-analysis by Park et al., reviewed 24 studies involving 3377 patients (mean age 39.3 years, 54.8% male, mean diabetes duration 1.8 years, mean A1c 7.9%, mean BMI 26.4 kg/m2) to evaluate the efficacy of GLP-1 RAs (Liraglutide, Albiglutide, Exenatide) as adjunctive therapy for T1D. Liraglutide demonstrated significant efficacy in reducing A1c effect sizes (-0.09%/mg), weight (-2.2 kg/mg), and total daily insulin (TDI) (-4.32 IU/mg) (47). However, higher doses of liraglutide were associated with increased odds of nausea and ketosis. While newly diagnosed or C-peptide positive patients experienced greater A1c reductions with liraglutide, weight loss and insulin reduction benefits were similar (47). Exenatide showed comparable efficacy, but with higher study bias and limited safety data. Overall, liraglutide appeared beneficial for weight management and insulin dose reduction in T1D, with caution warranted for associated adverse effects like nausea and ketosis (47).

Another metanalysis by Tan et al., reviewed 11 randomized controlled trials involving 2,856 adults with T1D (48). The analysis found that GLP-1 RAs (Liraglutide, Albiglutide, Exenatide) led to reductions in HbA1c levels by −0.21% (95% CI, −0.33 to −0.10), weight by −4.04 kg (−4.8 to −3.27), systolic pressure by −2.57 mmHg

(−4.11 to −1.03), and diastolic blood pressure by −1.02 mmHg (−1.99 to −0.06). In addition, there was a decrease in prandial insulin dose (weighted mean difference of −4.23 IU; 95% CI, −5.26 to −3.20), basal insulin dose (−2.40 IU; −3.93 to −0.87), and total insulin dose (−5.73 IU; −10.61 to −0.86) (48). Importantly, these benefits were not associated with a risk of severe hypoglycemia, diabetic ketoacidosis, or severe adverse events but were associated with higher rates of gastrointestinal adverse events (48). Overall, GLP-1 RAs showed moderate beneficial effects on metabolic outcomes in adults with T1D.

Semaglutide

A retrospective study evaluated semaglutide in 50 patients with overweight or obesity with T1D (92% non-Hispanic white, mean age 42 ± 11 years, duration of diabetes 27 ± 12 years), over a year (49). Compared to a matched control group not on weight loss medications, semaglutide significantly reduced BMI (7.9% ± 2.6%), body weight (15.9 lbs. ± 5.4 lbs.), and improved glycemic control measures including HbA1c and CGM glucose standard deviation and coefficient of variation (CV), with an increase in TIR (49).

A letter to the *NEJM* by Dandona et al., reported studying 10 patients (ages 21-39 years, mean A1c 11.7±2.1%, mean fasting C-peptide level was 0.65±0.33 ng per milliliter) who were initiated semaglutide, soon after T1D, alongside dietary changes. Within six months, all patients were able to eliminate prandial insulin, and seven discontinued basal insulin (50). After 12 months, their HbA1c levels significantly dropped to 5.7±0.4%, fasting C-peptide levels increased to a mean of 1.05±0.40 ng/mL, TIR according to CGM was 89±3% (50). The letter also reported a 64% reduction in total insulin dose and minor weight loss , with no episodes of severe hypoglycemia, diabetic ketoacidosis or other serious side effects after dose stabilization (50).

A case report by Raven et al., described a 36-year-old female (body mass index 29.3 kg/m^2) with a 27-year history of T1D and undetectable c-peptide, who used semaglutide (0.25 mg weekly increased to 0.5 mg weekly) “off-label”. Over six months, she experienced a 16 kg weight loss and a 36% reduction in insulin dose, with improved HbA1c and reduced glycemic variability, without an increase in hypoglycemia (3).

These studies suggest the potential benefits of semaglutide in T1D, indicating the need for larger prospective clinical trials. Currently three trials are underway investigating semaglutide in this population (NCT03899402; NCT05819138; NCT05822609).

GLP-1 RAs versus sodium-glucose cotransporter-2 inhibitors (SGLT2is)

A study by Edwards et al., reviewed the real-world use of GLP-1 RAs and SGLT2is as adjunct therapies to insulin in adults with T1D. After more than 90 days of therapy, GLP-1RAs users showed significant reductions in weight, HbA1c and total daily insulin over one year (51). SGLT2is users also saw significant reductions in HbA1c

and basal insulin but had a higher incidence of diabetic ketoacidosis. Both therapies had comparable rates of discontinuation due to adverse effects (51).

These studies highlight the potential benefits and risks associated with GLP-1 RAs in t1D management, emphasizing the need for careful patient monitoring and larger studies to establish optimal treatment protocols.

A. Cardioprotective effects of GLP-1 RAs

Semaglutide

Semaglutide has shown significant cardiovascular benefits in patients with and without T2D. Both the STEP-1 trial (52) and the STEP TEENS trial (53) in adolescents showed that semaglutide 2.4 mg (Wegovy) group was associated with reductions in body weight and improvement with respect to cardiometabolic risk factors such as waist circumference and levels of glycated hemoglobin and lipid profile compared with placebo.

The SELECT trial, a large-scale multicenter randomized trial with 17,604 participants, showed that semaglutide 2.4 mg significantly reduced major adverse cardiovascular events (MACE) including heart attack, stroke, or cardiovascular death in adults 45 years and older (who had preexisting cardiovascular disease and obesity but without diabetes, over nearly 40 months of follow-up, compared to placebo (54).

The ENDIS study involving 89 participants examined empagliflozin and semaglutide on endothelial function and arterial stiffness in T1D without cardiovascular disease (4). Both drugs significantly improved endothelial function, as measured by brachial artery flow-mediated dilation, compared to controls after 12 weeks (4). Semaglutide also reduced peripheral resistance, indicating improved arterial stiffness, suggesting potentially superior effects on arterial health.

Tirzepatide

A study by Jasterboff et al., assessed the efficacy of once weekly Tirzepatide (5 mg, 10 mg or 15 mg) to placebo in adults with obesity in a phase 2 trial (N= 2539) (21). All doses of Tirzepatide resulted in a significant weight reduction compared to placebo and improved cardiometabolic measures. Common adverse events included mild gastrointestinal issues (21).

A study by Taktaz et al., assessed the potential cardioprotective effects of tirzepatide (TZT) through a meta-analysis of major clinical trials. TZT significantly reduced the risk of MACE (5). In cellular experiments using human AC16 cardiac cells exposed to high glucose levels, TZT treatment mitigated the expression of markers associated with cardiac fibrosis, hypertrophy, and cell death, indicating protective benefits against diabetes-related cardiac damage (5). Bioinformatics analysis further validated these results by revealing TZT’s interactions with pathways involved in apoptosis, fibrosis, and contractility in cardiac cells. These

findings suggest TZT may provide therapeutic benefits in managing diabetes-related cardiac complications.

These studies highlight the significant cardioprotective effects of GLP-1 RAs like semaglutide and tirzepatide, emphasizing their potential in improving cardiovascular outcomes in patients with diabetes and those at high cardiovascular risk.

B. Renoprotective effects of GLP-1 RAs

Chronic kidney disease (CKD) is a common complication in patients with both T2D and T1D. The FLOW trial (NCT03819153) (55-57), a phase 3b study, included 3534 participants with an average age of 66.6 years, average diabetes duration of 17.4 years, and a mean eGFR of 47.0 ml/min/1.73 m^2. Of these 68.2% were at very high risk for CKD progression. Participants were randomized to receive either once weekly semaglutide 1 mg or placebo alongside standard care. Novo Nordisk halted the trial early due to positive interim efficacy results, with final outcomes expected in 2024.

These findings are just that semaglutide may offer significant renoprotective benefits in managing CKD in patients with diabetes.

Table 2. Overview of Trial Characteristics and Main Findings.

Study	Condition	Duration	N	Mean age	Duration of Diabetes	BMI	Results
A. Studies evaluating glycemic control							
Liraglutide							
Mathieu et al., 2016 (42)	T1D	52 weeks, Mean HbA1c 8.2%, Participants randomized to receive once-daily injections of liraglutide (1.8, 1.2, or 0.6 mg) or placebo added to insulin.	1389	43.7 years, 47.7% male	24.1 years	29.5 kg/m2	Liraglutide added to insulin therapy reduced HbA1c levels (-0.34-0.54%), total insulin dose, and body weight. Rate of symptomatic hypoglycemia increased in all liraglutide

							groups.
Ahren et al., 2016 (43)	T1D	Liraglutide, 26 weeks RCT Mean Hb A1c 8.1%	831	43.2 years, 46% male	21.1 years	28.9 kg/m 2	Liraglutide reduced HbA1c, body weight, daily insulin use, increased Rates of symptomatic hypoglycemia and hyperglycemia with ketosis compared to placebo.
Kuhadia et al., 2016 (44)	T1D	12-week RCT; participants on Liraglutide plus insulin randomized to receive either dapagliflozin 10 mg or placebo. Mean Hb A1c 7.6%.	30	44.8 years, 44.4 % male	24.1 years	28.8 kg/m 2	Addition of dapagliflozin to insulin and liraglutide group resulted in reduction in Hb A1c, caused weight loss, while increasing ketosis.
Dejgaard et al., 2016 (58)	T1D	26-week RCT; participants randomized to receive liraglutide 1.8 mg or placebo. Mean Hb A1c 8.7%.	100	48 years, 65% male	22.5 years	30.1 kg/m 2	No significant difference in HbA1c between liraglutide and placebo groups; decreased hypoglycemic episodes, insulin doses, body weight and

							increased heart rate in the liraglutide group
Exenatide							
Herold et al., 2020 (46)	T1D	24-week RCT Mean Hb A1c 7.6%; participants randomized to receive exenatide 2 mg weekly versus placebo	79	36.1 years, 31.6% male	19.6 years	29.4 kg/m 2	HbA1c levels were significantly reduced in the exenatide group after 12 weeks but no difference between the groups at 6 months. Weight loss seen in exenatide group, but no difference in hypoglycemia between the groups.
Johansen et al., 2020 (59)	T1D	26-week RCT, participants randomized to receive exenatide 10 µg or placebo three times daily. Mean HbA1c 8.2%	108	50.3 years, 72.4% male	21.1 years	28.3 kg/m 2	No significant reduction in HbA1c between the 2 group. Increased self-reported GI issues noted in the exenatide group.
Semaglutide							
Garg et al., 2024,	T1D	Retrospective study; participants	50	42 ± 11 years, 30%	27 ± 12 years	33.5 ± 5.8 kg/m	At 1 year, semaglutide group

(49)		on semaglutide for at least 3 months were followed for 1 year and compared with a control group; Mean HbA1c 7.6 ± 1.2 in semaglutide group		male		2	had significant weight loss, improved glycemic metrics (HbA1c, CGM TIR, and glycemic variability), no change in insulin dose between the 2 groups.
Case report: Raven et al., 2022, (3)	T1D	Semaglutide given at a dose of 0.25 mg weekly and increased to 0.5 mg weekly.	1	36-year-old female	27 years	29.3 kg/m^2	At 6 months, patient had weight loss of 16 kg, insulin dose decreased by 36%, HbA1c improved, glycemic variability reduced, no increase in hypoglycemia.
Letter to the Editor NEJM: Dandona et al., 2023, (50)	T1D	Retrospective analysis: Semaglutide started within 3 months after T1D diagnosis, followed for 1 year. Mean Hb A1c 11.7±2.1% at diagnosis	10		Between 21-39 years		Prandial insulin was eliminated in all the patients within 3 months, and basal insulin was eliminated in 7 patients within 6 months. These

							doses were maintained until the end of the 12-month follow-up period. The mean HbA1c reduced to 5.9±0.3% at 6 months and to 5.7±0.4% at 12 months. Mild hypoglycemia occurred during the semaglutide dose increase. After stabilization, no DKA, hypoglycemic episodes or other serious side effects.
Metanalysis							
Park et al., 2023 (47)	T1D	24 studies using 4 different GLP-1 analogues (liraglutide,exenatide, albiglutide, Lixisenatide), for 12 weeks	3377	39.3 years, 54.8% male	15.8 years	26.4 kg/m2	Liraglutide reduced A1c (-0.09%/mg), weight (-2.2 kg/mg), and TDI (-4.32 IU/mg), with higher doses causing more nausea (OR

							6.5), and ketosis (OR 1.8), but no significant increase in hypoglycemia risk.
Tan et al., 2023 (48)	T1D	11 RCTs included. Mean Hb A1c 8.1% (SD 1.0%)	2856	43.4 (SD 13.6) years, 52% female	22.6 years	29.2 (SD 5.3) kg/m^2	Among individuals with obesity, GLP-1 RA and insulin combination resulted in improvement of metabolic profile, HbA1c reduction (−0.43%), weight loss (−6.28 kg) , a lower insulin dose, and lower blood pressure No increase in the incidence of severe hypoglycemia, diabetic ketoacidosis, or severe adverse events.
B. Studies evaluating weight and cardiovascular outcomes							
Semaglutide							
Weghuber et al., 2023 (53)	Obesity, adolescents	68 -week RCT. Participants randomized to receive Semaglutide 2.4 mg	201	15.4±1.6 years, 62% female	NA	37.0 ±6.4	Mean change in BMI at week 68 was -16.1% with semaglutid

		weekly versus placebo.					e and 0.6% with placebo. 73% participants in semaglutide group had weight loss of 5% or more compared to 18% in placebo group.
Wilding et al., 2021 (52)	Obesity, adults	68-week RCT; Participants randomized to receive Semaglutide 2.4 mg weekly versus placebo.	1961	46 years, 73.1 % female	NA	37 kg/m2	Mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo
Lincoff et al., 2023 (54)	Obesity, pre-existing CVD* in adults, no diabetes	104-week RCT; Participants randomized to receive Semaglutide 2.4 mg weekly versus placebo.	17,604	61.6±8.9 years, 72.3% male	NA	33.3 ±5.0	semaglutide was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
Navodn	T1D, no	12 week	89	48 years;	21	28	Improveme

ik et al., 2023 (4)	CVD	RCT; Participants randomized to receive empagliflozin or semaglutide with a control group			years	kg/m2	nt in FMD (brachial artery flow-mediated dilation) was significant in both intervention groups compared to controls. Arterial stiffness improvements were seen only in the semaglutide group, with a decline in peripheral resistance by 5.1%.
Tirzepatide (TZT)							
Jastreboff et al., 2022 (23)	Obesity, adults	72-week RCT, phase 3, participants assigned in a 1:1:1:1:1 ratio to receive TZT, 5,10,15 mg or placebo for 72 weeks, including a 20-week dose escalation period.	2539	44.9 years, 67.5% female	NA	38 kg/m2	Mean percentage change in weight was -15% with 5 mg, -19.5% with 10 mg and -20.9 % with 15 mg dose of TZT and -3.1% with placebo.
Taktaz et al., 2024 (5)	Adults with or without diabetes. Enrolled participants from	Metanalysis, assigned to TZT vs. placebo. Investigated effects oof TZT on	7778	NA	NA	NA	Reduction in MACE compared to placebo (Hazard ratio was 0.59). In

	the SURPASS -4 study, the SURPASS Clinical Trials Program SURMOUNT-1 trials	human cardiac AC16 cell lines, that were exposed to TZT under normal and high glucose conditions for 7 days					AC16 cardiac cells, T reduced fibrosis, hypertrophy and cell death markers, lowering heart failure risk
C. Studies evaluating renal outcomes							
Semaglutide							
Mann et al., 2024 (55, 57)	T2D and CKD**	RCT, 28 countries An 8-week regimen, 0.25 mg/week for 4 weeks, increased to 0.5 mg for 4 weeks, maintained 1.0 mg/week	3534	66.6 years, Male 69.7%	17.4 years	32 kg/m2	Trial ended early since it met primary endpoint. Delayed CKD progression, reduced renal and CV mortality, Improved eGFR, fever MACEs, lower mortality

*CVD: Cardiovascular disease

**Chronic kidney disease

Safety of GLP-1 medications

GLP-1 agonists mimic the action of the native peptide produced endogenously in the GI tract. The most commonly reported side effects include gastrointestinal issues such as nausea, vomiting and diarrhea, which are typically dose dependent. Therefore, gradual dose titration is recommended to minimize these effects. Some studies have shown that use of GLP-1 RAs can be associated with hypoglycemia (43), particularly when used in combination with insulin and other glucose lowering agents. Additionally, some studies report increased occurrence of diabetic ketosis, particularly in studies involving, necessitating close monitoring (42, 47). Rapid improvements in glycemic control have also been associated with worsening of diabetic retinopathy, as observed in a study involving Semaglutide (60). Due to their effect on gastric emptying, individuals with gastroparesis or inflammatory bowel disorders are not good candidates for GLP-1 RAs. Some case reports (61) and studies have noted an increased risk of depression and suicidal ideation, particularly

with Semaglutide and Liraglutide, although other studies have reported a lower risk of these issues among people with T2D and obesity (62). The US FDA has been evaluating these reports and, while they have not found conclusive evidence, they cannot rule out a small risk. Therefore, it is important to screen patients for depression before and during treatment with GLP-1 RAs.

Conclusions

The mounting evidence strongly supports the use of GLP-1 RAs as adjunct therapies to insulin in adolescents with T1D. Studies on semaglutide have demonstrated substantial benefits, including improved glycemic control, weight reduction and enhanced cardiovascular and renal health. The STEP TEENS trial showed significant reductions in body weight and cardio metabolic risk factors in adolescents with obesity. The SELECT Trial confirmed semaglutide's efficacy in reducing major adverse cardiovascular events in adults. The ENDIS Study further highlighted its positive effects on endothelial function and arterial stiffness in T1D patients without cardiovascular disease. Additionally, the FLOW trial indicated semaglutide's potential renoprotective benefits in managing chronic kidney disease in diabetes patients.

Furthermore, GLP-1 RAs help mitigate postprandial hyperglycemia by delaying gastric emptying and reducing glucagon secretion after meals. They also address weight gain, a common issue associated with long term insulin use in T1D, by promoting weight loss. These multifaceted benefits highlight the therapeutic potential of GLP-1 RAs in providing comprehensive management of T1D.

Common gastrointestinal issues such as nausea, vomiting, and diarrhea can be minimized with gradual dose titration. Some studies have reported hypoglycemia and ketosis with Liraglutide and therefore close monitoring is required. Additionally, there is a potential risk of depression and suicidal ideation, necessitating screening before and during treatment. Careful monitoring can mitigate these risks, making GLP-1 RAs a valuable adjunct therapy.

In conclusion, these findings underscore the therapeutic advantages of GLP-1 RAs, such as semaglutide and tirzepatide, in addressing diabetes-related complications. Given the compelling evidence and the ongoing clinical trials, incorporating GLP- 1 RAs as adjuncts to insulin therapy in adults and adolescents with T1D could provide significant clinical benefits. As research in both adolescents and adults continues to progress, the use of GLP-1 RAs should be considered an essential addition to T1D management strategies, offering a promising avenue for improving patient outcomes.

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