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Use of GLP-1 Receptor Agonists for the Management of Type 1 Diabetes: A Pediatric Perspective

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Keywords
Type 1 diabetes · GLP-1 receptor agonists · Hyperglycemia · Obesity

Abstract
Background: Despite all the technological advances in treatment of patients with type 1 diabetes (T1D), glucose control remains suboptimal in most patients. In addition, a relatively high percentage of patients with T1D, including children, have obesity. Therefore, new interventions are required that focus their effects on weight loss, in order to help with associated insulin resistance and improve glycemic control. ***Summary:*** GLP-1 receptor agonists (GLP-1 RAs) have proven to be effective and safe in adults with T1D, showing improvement in glycemic control, body weight and cardiorenal protection. GLP-1 RAs are also approved for children with obesity (above the age of 12 years) or type 2 diabetes (above the age of 10 years). However, currently these medications are not approved for use in children with T1D. Only a few published studies have evaluated their efficacy and safety for this indication. ***Key Message:*** This review presents the rationale and experience of add-on GLP-1 RA therapy to pediatric and adolescent patients with T1D, otherwise treated, from RCTs and real-world data. Results of studies of GLP-1 RA in children with T1D are still pending, while large multicenter randomized controlled trials (RCTs) in this population are lacking.

Introduction

Type 1 diabetes (T1D) is the most common type of diabetes in children and estimates suggest that around 100,000 children develop the disease annually [1]. The primary goal in the management of T1D is to maintain blood glucose levels as close to normal as possible, with the aims of preventing and/or delaying microvascular and macrovascular complications [2]. T1D has also been shown to be linked to cardiovascular outcomes more than any other disease [3, 4], while the all-cause mortality risk is around threefold higher for individual with T1D than for the general population [5].

The persistent development of innovations, including modern technologies such as insulin pumps, continuous glucose monitors, and hybrid closed-loop (HCL) systems offer the potential to optimize glycemic control, improve quality of life, and reduce the burden of T1D [6]. However, despite all the advances in treatment of patients with T1D, glucose control remains suboptimal in most patients with T1D [7–9].

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Numerous studies have documented an increase in obesity among both adults and youth with T1D, reflecting the global obesity epidemic [10–12]. In addition, epidemiological data establish the connection between T1D and subsequent development of obesity [13–16]. Current data show that patients with T1D have a shorter life expectancy in comparison with the general population (by approximately 13 years). Cardiovascular disease is the leading cause of death, with a mortality rate 3–18 times higher than expected amongst patients with T1D in their countries of residence [17]. Therefore, new interventions are required to improve the prognosis for the increasing number of people diagnosed with T1D. This review presents the rationale of additional treatment with glucagon like peptide-1 receptor agonists (GLP-1 RA) for patients with T1D, including pediatric patients, and the experience of using GLP-1 RA in patients with T1D from studies and real-world data.

GLP-1 Receptor Agonists

Incretin hormones are a group of gastrointestinal (GI) hormones that are released after food intake and stimulate a decrease in blood glucose levels. The two primary incretin hormones are glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) that constitute >90% of all incretin function.

GLP-1 is produced in the intestinal epithelial endocrine L-cells and is primarily involved in glucose regulation. It enhances insulin secretion from the pancreas after an oral glucose load in a glucose-dependent manner, inhibits glucagon release, delays stomach emptying, and promotes feelings of satiety due to direct actions on the hypothalamus [18]. Other functions of GLP-1 include increased glucose uptake in muscle [19], decreased glucose production in the liver [20], and neuroprotection [21]. GLP-1 is inactivated by dipeptidyl peptidase-4 (DPP4) and has a very short plasma half-life.

GIP is produced in the enteroendocrine K-cells, which are present in high density in the duodenum and upper jejunum but throughout the small intestine. Like GLP-1, it enhances insulin secretion in response to food intake.

These hormones play a crucial role in glucose homeostasis and are the basis for certain therapeutic approaches in diabetes and obesity management. To overcome the challenges posed by the rapid degradation of GLP-1, researchers have developed GLP-1 RA that mimic the actions of GLP-1 but are engineered to resist DPP4 degradation [22]. As a result, GLP-1 RA have a prolonged half-life, with improved pharmacokinetic properties, making them suitable therapeutic agents for managing diabetes, obesity, and related metabolic disorders. Their extended duration of action allows for sustained activation of GLP-1 receptors and offers promising benefits in terms of glycemic control and other physiological effects.

The different GLP-1 RA approved for use by the FDA and other regulatory bodies as the EMA (European medicine agency) differ by their duration of action. Exenatide (Byetta), the first FDA approved GLP-1 RA has a short half-life and is administered twice daily. Other GLP-1 RA with longer duration of action include: liraglutide (Victoza, Saxenda) and lixisenatide (Adlyxin) administrated once daily; exenatide (Bydureon BCise), dulaglutide (Trulicity), semaglutide (Ozempic, Wegovy, Rybelsus), albiglutide (Tanzeum, Eperzan), and tirzepatide (a dual GIP/GLP-1 receptor co-agonist) administrated once weekly [23].

Rationale behind Treatment with GLP-1 RA in T1D

In type 2 diabetes (T2D), the incretin effect can become blunted or even absent with low levels of GLP-1. However, the utilization of pharmacological levels of GLP-1 can revive insulin excretion. Indeed, during the last decade several pharmacotherapeutic choices were introduced, including GLP-1 RA in patients with T2D, focusing on reducing long-term microvascular and macrovascular complications, beyond improvement of glycemic control and weight loss [24–27].

A large percentage of patients with T1D do not achieve glycemic targets, despite the technological advances in treatment [7–9]; a relatively significant number of patients with T1D, including pediatric patients, are overweight or obese [13–16] with an increased risk of metabolic syndrome compared to healthy controls [28].

Insulin resistance (IR) is increasingly recognized as a prominent feature of T1D [29]. IR is linked to alterations in lipoprotein profiles, obesity, and worse diabetes control and subsequently the development of microvascular and macrovascular complications [30]. New interventions are required focusing their effects on weight loss to help with associated IR and improve glycemic control.

Moreover, novel therapies are required for prevention and management of T1D. Beyond ensuring accurate titration of exogenous insulin, there is a need to act early to prevent or delay the destruction of functional beta-cell mass by immunomodulatory intervention or other disease-modifying means. Second, stimulating or reprogramming the remaining beta-cell mass to secrete insulin in a balanced way is required to avoid major blood glucose excursions with the lowest possible exogenous insulin dose. Recent evidence from rodent models indicates a role for GLP-1 RA in protecting beta cells from

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Table 1. Randomized control trials and retrospective trials of GLP-1 receptor agonists therapy in adult patients with T1D

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
RCT	1,393	18–75 years	T1D (inclusion criteria: T1D ≥12 months, insulin therapy with MDI/CSII ≥6 months, BMI ≥20 kg/m^2, age 18–75 years	Liraglutide 0.6 mg, 1.2 mg, 1.8 mg/day (dose increase every 2 weeks until final 1.8 mg) + insulin therapy	52 weeks	**Glycemic control** – HbA1c level reduced 0.34–0.54% (3.7–5.9 mmol/mol) from mean baseline of 8.2% (66 mmol/mol) Estimated treatment differences 1.8 mg liraglutide 20.20% [95% CI 20.32; 20.07]; 1.2 mg liraglutide 20.15% [95% CI: 20.27; 20.03]; 0.6 mg liraglutide 20.09% [95% CI: 20.21; 0.03]) **Insulin dose reduction** estimated treatment ratios: 1.8 mg liraglutide 0.92 [95% CI: 0.88; 0.96]; 1.2 mg liraglutide 0.95 [95% CI: 0.91; 0.99]; 0.6 mg liraglutide 1.00 [95% CI: 0.96; 1.04]) **Weight loss** - 4.0, 2.7, and 1.3 kg for liraglutide 1.8, 1.2, and 0.6 mg, respectively	**Hypoglycemia** - increased in all liraglutide groups; estimated rate ratios: 1.8 mg liraglutide 1.31 [95% CI: 1.07; 1.59]; 1.2 mg liraglutide 1.27 [95% CI" 1.03; 1.55] 0.6 mg liraglutide 1.17 [95% CI: 0.97; 1.43] **Hyperglycemia with ketosis** – increased significantly for liraglutide 1.8 mg (event rate ratio 2.22 [95% CI: 1.13; 4.34] **GI**, most commonly nausea – dose dependent **Pancreatitis** – 1 case	Mathieu et al. [33] (2016)
RCT	832	≥18 years	T1D and inadequate glycemic control (inclusion criteria: diabetes duration ≥1 year, age ≥18 years, BMI ≥20 kg/m^2, treatment with MDI/	Liraglutide 0.6 mg, 1.2 mg, 1.8 mg/day (dose increase every 2 weeks until final 1.8 mg) + insulin treatment	26 weeks	**Glycemic control** – seen for all liraglutide doses: estimated HbA1C treatment difference: 1.8 mg, −0.35%/–3.8 mmol/mol [95% CI: −0.50; −0.20]; 1.2 mg, −0.23%/	**Hypoglycemia** - increased in all liraglutide groups; estimated rate ratios 1.31 [95% CI: 1.03; 1.68]	Ahren et al. [34] (2016)

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Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
			CSII ≥6 months, HbA1c 7.0–10.0% (53.0–85.8 mmol/mol) with stable insulin dose			–2.5 mmol/mol [95% CI: –0.38; –0.08]; 0.6 mg, –0.24%/–2.6 mmol/mol [95% CI: –0.39; –0.10] **Insulin dose reduction** - reported with all liraglutide doses: estimated treatment ratio: 1.8 mg, 0.90 [95% CI: 0.86; 0.93]; 1.2 mg, 0.93 [95% CI: 0.90; 0.96]; 0.6 mg, 0.95 [95% CI: 0.92; 0.99] **Weight loss** –5.1, –4, –2.5 for liraglutide 1.8, 1.2, 0.6 mg respectively **Quality of life** – treatment related impact measures-diabetes [TRIM-D] questionnaire scores increased in all liraglutide groups	**DKA** – 1 event with liraglutide 1.2 mg **GI**, most commonly nausea – dose dependent; elevated lipase and amylase levels in all liraglutide treatment groups (values remained within normal range)	
RCT	15	18–40 years	T1D (inclusion criteria: diabetes duration ≥1 year, insulin pump therapy	Liraglutide 1.2 mg/ day + insulin via a closed loop system	2 days	**Glycemic measures** – lower BG values in the treatment group versus placebo - 144.6±36.31 versus. 159.7±50.88 mg/ dL; lower AUC post-meal glucose level **Insulin doses** – lower in treatment group (2.5±0.3 vs. 2.1±0.3 units/h)	**GI** - Nausea, emesis, **Headache**	Ilkowitz et al. [35] (2016)

Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
RCT	44	18–70 years	T1D + overweight/ obese + non-optimal glycemic control (inclusion criteria: diabetes duration≥1 year, CSII, HbA1c >7.5% (58 mmol/mol), BMI >25 kg/m^2	Liraglutide 1.8 mg/ day + insulin via CSII (0.6 mg, 1.2 mg. 1.8 mg dose increase every week until final 1.8 mg)	26 weeks	**Glycemic control** – HbA1c level decreased from 8.2% (66 mmol/mol) to 7.7% (61 mmol/mol); 0.7% (7 mmol/mol) difference between treatment group and placebo TIR 57% versus 45% between treatment group and placebo **Weight loss** – –6.38 kg between tx group and placebo **Patient reported outcome measures** – increased treatment satisfaction score in treatment group via DTSQ questionnaire	**GI** – nausea, diarrhea, vomiting No DKA or symptomatic hypoglycemia events	Dejgaard et al. [36] (2020)
RCT	40	18–70 years	Poorly controlled T1D (Inclusion criteria: age 18–70 years, BMI 18–28 kg/m^2, HbA1c≥8% (64 mmol/ mol), stimulated plasma C-peptide <60 pmol/L), Caucasian descent, diabetes diagnosed between ages of 5–40, no use of other medication affecting glucose metabolism)	Liraglutide 1.2 mg/day + insulin tx	12 weeks	**Glycemic control** - change in HbA1c from baseline not statistically significant between tx and placebo group **Insulin dose** – bolus dose decreased by –4±IU in tx group, no change in placebo **Body weight** – –3.13 and +1.12 kg with liraglutide and placebo, respectively	**GI**, all transient	Frandsen et al. [37] (2015)

Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
RCT	108	>18 years	T1D (inclusion criteria: diabetes duration ≥1 year, age ≥18 years, BMI≥22 kg/m^2; HbA1c 7.5–10% (59–88 mmol/mol)	Exenatide 10 μg 3 times daily + insulin treatment	26 weeks	**Glycemic control** - Change in HbA1c from baseline not statistically significant between treatment and placebo group **Insulin dose** - exenatide reduced total insulin requirements by 9 units/ day (95% CI: 5.9–12.1)	**GI** No DKA or symptomatic hypoglycemia events	Johansen et al. [38] (2020)
RCT	84	18–75 years	T1D (inclusion criteria: diabetes duration ≥1 year, age ≥18 years, BMI≥25 kg/m^2; HbA1c ≤10%(88 mmol/mol)	Liraglutide 1.8 mg/ day + insulin treatment	26 weeks	**Glycemic control** – HbA1c reduced by 0.34±0.14 (3.6±1.5 mmol/ mol) compared to placebo at 12 weeks; no significant difference between groups at 26 weeks; TIR increased 7±2% (from 42±3% to 49±2%) and hyperglycemia decreased by 8±3% (from 52±4 to 44±4%) **Insulin dose** – total insulin dose decreased by 5±2 units/d in tx group versus placebo group **Body weight** – –4.0±0.5 kg versus placebo, achieved by 12 weeks of treatment and maintained until study end Lower fasting FFAs, glycerol, leptin levels Changes in expression of lipid oxidation- and metabolism-related genes in adipose tissue	No DKA or symptomatic hypoglycemia events	Ghanim et al. [39] (2020)

Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
RCT – secondary outcome analysis of Lira-pump trial	44	18–70 years	T1D + overweight/ obese + non-optimal glycemic control (inclusion criteria: diabetes duration≥1 year, CSII, HbA1c >7.5% (58 mmol/mol), BMI >25 kg/m^2	Liraglutide 1.8 mg/ day + insulin via CSII (0.6 mg, 1.2 mg. 1.8 mg dose increase every week until final 1.8 mg)	26 weeks	**Total fat mass decreased** in tx group –4.6 kg [95% CI: –5.7,–3.5] **Lean body mass decreased** in treatment group –2.5 [95% CI: –3.2, –1.7] **Energy intake derived from added sugars decreased** by 27% in treatment group versus 14% increase in placebo group	**GI** – nausea, diarrhea, vomiting No DKA or symptomatic hypoglycemia events	Schmidt et al. [40] (2022)
RCT	27	>18 years	T1D	Liraglutide 1.2 mg/ day + insulin tx	6 months	Urine – decreased excretion of type IV collagen, cystatin C, increased excretion of uromodulin Plasma - decreased levels of osteopontin, NGAL and cystatin C in tx group		Vikulova et al. [41] (2018)
RCT	307	18–45 years	T1D and residual β-cell function (inclusion criteria: diagnosis of T1D within 20 weeks before screening, peak C-peptide≥ 0.2 nmol/L (MMTT), GAD Ab + either islet antigen-2 or zinc transporter-8, or both)	Liraglutide 1.8 mg/ day + anti-IL-21, liraglutide only, anti-IL-21 only, placebo + insulin treatment	54 weeks of tx (+ another 26 weeks follow-up)	**C-peptide secretion** – initial increase in MMTT-derived stimulated C-peptide secretion observed with combination therapy (anti-IL-21 and liraglutide) and with liraglutide alone; however, by end of tx/end of post treatment analysis – secretion decreased in all groups **Insulin dose** – total daily insulin dose decreased from baseline to week 54 by 12% in anti-IL-21 + liraglutide group Changes in immune cell subsets across groups - transient and mild	**GI** **Severe hypoglycemia** - 3 participants – 1 on liraglutide +anti IL-21, 2 on anti IL-21 only) No DKA events	von Herrath et al. [42] (2021)

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Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
Interventional	11	>18 years	T1D (inclusion criteria: T1D, >18 years old, sensor augmented pump use)	Semaglutide 0.5 mg/week	6 months	**Glycemic control** – no significant change in TIR over study period **Body weight** – –8.8 kg (10.6%) at 6 months; proportion of patients with BMI >30 kg/m^2 reduced from 6/11 to 0/11 **Insulin dose** – bolus insulin decreased by 0.04 U/kg/day **Carbohydrate intake** – reduction of 28 g/day	**GI** – nausea, transient	Grassi et al. [43] (2024)
Retrospective	54	>18 years	T1D (Inclusion criteria: T1D, age>18, use of long-acting GLP-1 medication for ≥6 months	long-acting GLP-1 (semaglutide, dulaglutide, exenatide extended-release, albiglutide)	at least 6 months of data (mean GLP-1 treatment duration was 23.85±15.46 months)	**Glycemic control** – HbA1c values decreased by –0.71%; TIR increased by a mean difference of 12%, 14-day BG average decreased by a mean difference of –19 mg/dL **Insulin dose** – non significant decrease **Body weight** – decreased by mean difference of 3.16 kg	N/A	Mohandas et al. [44] (2023)
Retrospective	104 (65 – GLP-1 RA only, 28 - SGLT2i only, 11 both either concurrently or sequentially)	>18 years	T1D	GLP-1 receptor analogues or SGLT2 inhibitors	≥90 days	**Glycemic control** – HbA1c values decreased by –0.4% in GLP-1 group **Insulin dose** – baseline 61.8 units [53.3–71.7] versus 12 months 49.9 [42.4–58.8] units in GLP-1 group **Body weight** – decreased by mean difference of 5 kg in GLP-1 group	**GI** – nausea, vomiting, diarrhea, constipation, abdominal pain, GI acid reflux Severe hypoglycemia – 1 episode DKA – 3 episodes in GLP-1 group (pump failure/infection)	Edwards et al. [45] (2023)

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Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
						Lipid profile – reduction in total cholesterol (baseline 183.0 mg/dL [173.5–192.5 mg/dL] vs. 12 months 156.6 mg/dL [135.1–178.0 mg/dL]) and LDL (baseline 103.9 mg/dL [95.7–112.0 mg/dL] versus. 12 months 77.0 mg/dL [58.2–95.8 mg/dL] in GLP-1 group **Renal outcomes** – no statistically significant change in eGFR or urine albumin/creatinine ratio compared to baseline		
Retrospective	50	>18 years	T1D + overweight/ obese (inclusion criteria: T1D, age 18–80 years, CGM	Semaglutide 0.63 mg (±0.46)/ week at 3 months, increased up to 0.92 mg (±0.28)/ week at 12 months	1 year	**Glycemic control** – HbA1c improved by −0.60±0.11%, TIR improved by 6.2±1.8% **Body weight** – decreased by 3.8±2.3 kg; BMI decreased by −4.2±2.4%	N/A	Garg et al. [46] (2024)
Retrospective	26	>18 years	T1D	Tirzepatide 2.5 mg/week at initiation, titrated as necessary – up to 15 mg/week	8 months	**Glycemic control** – HbA1c decreased by 0.45% at 3 months, sustained over 8 months; TIR increased by 12.6% at 3 months, sustained over 8 months **Insulin dose** – reduced by 21.6 IU/day (95% CI: 34.8, −8.4) 3 months, sustained at 6 and 8 months **Body weight** – −3.4% at 3 months and −10.5% at 6 months with no further reduction at 8 months; BMI decreased−3.35% at 3 months and −10.5% at 6 months	Severe hypoglycemia event (n = 1) Severe constipation (n = 1) led to discontinuation of medication in 2 patients Peroneal nerve palsy (n = 1) No DKA	Akturk et al. [47] (2024)

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Table 1 (continued)

Type of study –RCT/ retrospective	Patients, *N*	Age of patients	Indication of treatment	Type of treatment	Trial length	Outcomes (only statistically significant outcomes included in the table, $p \leq 0.05$)	Side effects	Ref No.
Retrospective	62	>18 years	T1D + overweight/ obese (inclusion criteria: T1D, BMI >27 kg/m^2, tirzepatide at least 3 months)	Tirzepetide/week	1 year	**Glycemic control** – HbA1c decreased in the treated group as early as 3 months, sustained at 1-year follow-up (–0.67%) **Body weight** – average 18.5% weight loss over 1 year	No severe hypoglycemia events No DKA	Garg et al. [48] (2024)
Retrospective	11	>18 years	T1D (inclusion criteria: T1D, detectable C-peptide, positive GAD-65 Abs)	Liraglutide: 0.6, 1.2, 1.8 mg/day (dose increase over 3 weeks); dulaglutide (2 patients) – 0.75, 1.5 mg/weekly the other with 1.5 mg weekly for 12 weeks	14 weeks	**Glycemic control** - HbA1c decreased from 10.74±0.96% (95±10.5 mmol/mol) to 7.4±0.58% (58±6.3 mmol/mol) **Insulin dose** – reduced by 64% from 33±6 to 11±5 units/day **Body weight** – decreased from 71±2.0 to 69±2 kg; BMI decreased from 23±1 to 22±1 kg/m **C-peptide concentrations** - increased from 0.43±0.09 ng/mL (0.14±0.02 nmol/L) to 1.42±0.42 ng/mL (0.47±0.13 nmol/L)	**GI** – nausea No severe hypoglycemia, no DKA	Kuhadiya et al. [49] (2019)

RCT, randomized controlled trial; T1D, type 1 diabetes; MDI, multiple daily injections; CSII, continuous subcutaneous insulin infusion.

apoptosis as well as promoting beta-cell replication and mass [31, 32]. Third, reducing the risk of long-term complications is increasingly important.

Studies of GLP-1 RA in Adults with T1D

Table 1 presents the summary of randomized controlled trials (RCTs) and retrospective trials of GLP-1 RA therapy in adults with T1D. Table 2 presents the summary of meta-analysis of studies including GLP-1 RA therapy in adults with T1D.

Impact on Diabetes Control

Two of the first RCTs using GLP-1 RA in T1D were the ADJUNCT ONE and ADJUNCT TWO trials [33, 34]. Both studies evaluated the yield of liraglutide as add-on therapy amongst adults with T1D, showing improvement in HBA1C, total insulin doses, and body weight; however, the rate of symptomatic hypoglycemia was increased (in all dosages of liraglutide) as was the rate of hyperglycemia and ketosis (Table 1). A subgroup analysis [53] of the ADJUNCT ONE and TWO trials [33, 34] showed that the degree of weight loss did not differ significantly between patients with BMI greater than and less than 27 mg/kg^2, and between patients with baseline HbA1c values greater than and less than 8.5%.

A proof-of-concept study assessed the effect of adjuvant liraglutide on HCL insulin delivery in adults with T1D [35]. This study showed better glycemic control both overall and postprandially for the liraglutide arm, without increased incidence of hypoglycemic events. The Lirapump trial investigated the efficacy of adding liraglutide to insulin pump treatment in overweight or obese adults with T1D [36]. Changes were shown in HbA1C reduction, improved time in range (TIR), and decreased total daily insulin dose. Notably, a similar trial with liraglutide as add-on therapy in normal weight adults with T1D did not show an impact on HbA1C level or glycemic excursions, but rather only on a reduction in body weight and insulin requirements. Of note, there was no correlation between starting BMI and the change in body weight [37]. The MAG1C trial evaluated the effect of short acting exenatide as add-on therapy during meals for adults with T1D [38], not showing any improvement in HbA1C level or postprandial glucose excursions between the study groups. The authors speculated that specific subgroups among T1D patients (e.g., obese persons, those with severe postprandial hyperglycemia) might benefit from such therapy, but further studies are needed.

Kim et al. [50] published a meta-analysis assessing the effects of various add-on therapies to insulin amongst people with T1D, including liraglutide and exenatide (Table 2). The studies with liraglutide and exenatide treatment showed a significant reduction in HbA1C levels. Neither liraglutide nor exenatide led to a change in total daily insulin dose, while exenatide but not liraglutide showed a significant decrease in body weight.

Mohandas et al. [44] published the results of a study based on real-life retrospective data of adults with T1D using GLP-1 RA (Table 1), reporting a decrease in HbA1C by an average of 0.7% as compared to data pretherapy as well as a significant increase in TIR (12.15% on average) with a decrease in hyperglycemia (11.9% on average). The study also showed a decrease in the incidence of diabetic ketoacidosis (DKA) events. Another retrospective real-world study examining the efficacy and safety of GLP-1 RA (as well as SGLT2) among adults with T1D using GLP-1 RA assessed changes in HbA1C, body weight, and total daily insulin dose [45]. People using GLP-1 RA showed a significant reduction in HbA1C and total daily insulin dose. Significant reduction was also seen in total cholesterol and LDL, with no significant change in triglyceride values. The difference in the change in weight between the 2 groups (GLP-1 RA and SGLT2) after 12 months was statistically significant, favoring GLP-1 RA for weight loss, including those with high versus low weight at baseline.

In a small pilot retrospective study Garg et al. [46] showed that semaglutide was effective and safe in lowering BMI significantly after 1 year of treatment in patients with T1D, while improving glycemic metrics including HbA1c, TIR, and glycemic variability, with no difference in insulin dose. A current systemic review and meta-analysis published by Park et al. [51] assessed the efficacy and adverse outcomes of GLP-1 RA as adjunct therapy for T1D, based on a total of 24 prospective RCTs (Table 2). Outcomes showed a significant decrease in HbA1c and total daily insulin dose in people using liraglutide as well as exenatide.

A proof-of-concept observational study by Akturk et al. [47] evaluated the effects of tirzepatide on glycemic control and BMI among adults with T1D. Participants showed a significant reduction in HbA1c and increased TIR of 12.6% at 3 months, sustained at 8 months, without an increased rate of hypoglycemia or DKA events during follow-up. There was a significant association between weight loss and HbA1C reduction. Garg et al. [48] published a retrospective single-center real-world study in adults with T1D who used tirzepatide for at least 3 months with 1-year follow-up. Their results showed a significant decrease in HbA1C starting at 3 months, sustained over the 1-year follow-up period as well as an increase in TIR. Larger studies are required to assess the

yield and safety of GLP-1 RA as add-on therapy to insulin in patients with T1D, including pediatric patients and those using closed loop systems.

Impact on Obesity and Weight Control

Ghanim et al. [39] conducted an RCT to investigate the effects of liraglutide as add-on therapy to insulin in obese persons with T1D. The use of liraglutide for 6 months significantly decreased body weight, with weight loss mostly attributed to loss of fat mass. People treated with liraglutide also showed a decrease in fasting free fatty acids, glycerol, and leptin levels. HbA1C also decreased significantly in the liraglutide group, not at the expense of hypoglycemia, as did systolic blood pressure. Schmidt et al. [40] published a secondary endpoint analysis of the Lira-pump trial with regard to body composition and weight loss in overweight persons with T1D, using insulin pump therapy. They showed a significant decrease in total fat and lean body mass with no change in participants' physical activity status. The study also showed a reduction in energy, particularly energy derived from added sugars amongst the liraglutide group.

A small interventional study conducted by Grassi et al. [43] evaluated treatment with low dose semaglutide in adults with T1D who had been treated with sensor augmented pump therapy. Participants showed significant weight loss, with a relative reduction of ~10% as well as a decrease in BMI of less than 30.

Akturk et al. [47] reported the effects of tirzepatide on BMI amongst adults with T1D and showed a significant weight reduction of ~10% over 8 months. In the real-world study by Garg et al. [48], adults with T1D who used tirzepatide for at least 3 months, during a 1-year follow-up period showed a significant decrease in weight compared to controls. Large and long-term RCTs are required to evaluate safety and efficacy of these medications in patients with T1D including pediatric patients, similar to studies conducted in T2D.

Impact on Cardiovascular and Renal Protection

T1D has been shown to be linked to cardiovascular outcomes more than any other disease [3]. Graves et al. [54] reported that people with T1D between 0 and 10 years of age have a nearly 30 times increased risk of coronary heart disease compared with matched controls. They also have a greater than 7 times risk of cardiovascular death. After over 40 years of T1D, approximately 33% of adults will develop albuminuria and approximately 25% will have an eGFR <60 mL/min per 1.73 m^2. The overall lifetime risk of end-stage kidney disease is 10–30% in people with T1D [55]. Kristofi et al. [56] showed that adult patients with T1D have a 1.4 to 3 times higher risk of chronic kidney disease compared to adult patients with T2D, after adjusting for age. However, among teenagers and young adults who had been diagnosed with diabetes during childhood or adolescence, the prevalence of comorbidities, including kidney disease, was higher in those with T2D compared to those with T1D, though it was still frequent in both groups [57].

In patients with T2D, medications such as GLP-1 RA, SGLT2 inhibitors, and mineralocorticoid receptor antagonists have proven to be both cardio and renal protective [58]. A meta-analysis of six trials of GLP-1 RA in people with T2D showed an approximate reduction of 21% in the risk of new-onset macroalbuminuria, eGFR decline, and progression to end-stage kidney disease or death attributable to kidney causes compared to controls [59]. Tirzepatide was shown to improve cardiovascular risk factors in people with T2D and cardiovascular risk factors, as well as those with obesity but without T2D [60–62].

In T1D where cardiovascular and renal disease is just as relevant, prevention and treatment of these complications is currently done by maintaining optimal glycemic control, treatment with ACE inhibitors as necessary, and management of risk factors such as hypertension and hyperlipidemia [63]. Since GLP-1 receptors are present on kidney glomerular and tubular cells and lead to a reduction of oxidative stress and inflammation, these medications can prove beneficial in terms of renal protection in T1D as well. Kodera et al. [64] showed a reduction of inflammatory markers such as tumor growth factor-β1 and intercellular adhesion molecule-1 in a rat model of T1D treated with exendin-4.

A small study assessed the effects of liraglutide on early markers of kidney damage in adults with T1D [41] over a 6-month period. Markers of kidney damage such as albuminuria, GFR, and urinary kidney biomarkers such as nephrin, podocyne, uromodulin, neutrophilic gelatinase-associated lipoxalin (NGAL), molecule renal damage of type 1 (KIM-1), collagen type IV, cystatin C, and plasma levels of NGAL, KIM-1, cystatin C, and osteopontin were evaluated. A significant decrease in urinary excretion of type IV collagen and cystatin C as well as decreased plasma levels of osteopontin, NGAL, and cystatin C was seen, indicating a possible renal-protective effect of GLP-1 RA treatment in this population. The real-world study of patients with T1D [65] reported that GLP-1 RA treatment had no impact on changes in eGFR or microalbumin/creatinine ratio after 12 months compared to baseline values. Further studies are required to evaluate the effect of GLP-1 RA on cardiovascular and renal outcomes amongst people with T1D, both in the pediatric and young adult population.

Table 2. Meta-analysis of studies including GLP-1 receptor agonists therapy in adult patients with T1D

Number of studies of GLP-1 analogue therapy	Overall number of patients	Indication for treatment	Patient age (average)	Treatment drug	Outcomes/Conclusions	Side effects	Ref. no.
6	886 (intervention 442, control 444)	T1D	39.5 years	Liraglutide 1.2 mg (4 studies), exenatide 10 μg (2 studies)	Glycemic control - No significant change in HbA1c compared to insulin alone Insulin dose – no significant change in daily insulin doses Body weight – decrease shown with exenatide −5.1 kg (95% CI: −8.4, −2)	No severe hypoglycemia event, no DKA	Kim et al. [50] (2020)
24	3,377	T1D	39.3 years (22.5–50.4)	Liraglutide (16 studies)	Glycemic control – estimated HbA1c decrease from GLP-1 agonists compared with placebo: liraglutide 1.8 mg −0.28% (95% CI, −0.38 to −0.19) liraglutide 1.2 mg −0.21% (−0.30 to −0.12), liraglutide 0.6–0.9 −0.17% (−0.26 to −0.07) exenatide −0.17% (−0.28 to 0.02)	GI – nausea, vomiting, diarrhea	Park et al. [51] (2023)
				Exenatide (6 studies)	Insulin dose – compared with placebo - liraglutide 1.8 mg −7.51 IU/day (95% CI, −9.52 to −5.49), liraglutide 1.2 mg −5.28 IU/day (−8.53 to −2.04), 1iraglutide 0.6–0.9 mg −1.58 IU/day (−3.40 to +0.24), exenatide −9.76 IU (−15.59 to −3.92)	No severe hypoglyemia events, no DKA	
				Albiglutide (1 study) Lixisenatide (1 study)	Body weight – compared with placebo - liraglutide 1.8 mg to −4.89 kg (95% CI, −5.33 to −4.45), liraglutide 1.2 −3.77 kg (−4.24 to −−4.89 kg (95% CI, −5.3–0.9 mg −2.27 kg (−2.75 to −1.79), exenatide −4.06 kg (−5.33 to −2.79)		
8	427	T1D	36 years	Liraglutide (1 study), Exenatide (1 study), dipeptidyl peptidase	Incretin-based therapies did not preserve B-cell function in patients with T1D	N/A	Wu et al. [52] (2021)

CGM, continuous glucose monitor.

Impact as an Immune Modulator

The use of GLP-1 RA that directly target beta cells may enhance their function whilst protecting them from immune-mediated inflammatory stress. Recent evidence from rodent models indicates a role for GLP-1 RA in protecting beta cells from apoptosis and in promoting beta-cell replication and mass [27, 31, 32, 65, 66]. As such, although remained to be confirmed, it is conceivable that GLP-1 RA may offer a way to prevent the "unmasking" of beta cell to immune effector cells, e.g., by downregulating expression of MHC class I proteins. Intriguingly, nonclinical evidence shows that liraglutide also limits immune cell infiltration into pseudo-islets (von Herrath M, unpublished results). In addition, studies in NOD mice have shown that GLP-1 RA administered in combination with various immunomodulatory agents, including anti-CD3 compounds [67], were more efficient in inducing diabetes remission than when given as monotherapy [68].

Continuous transfusion of GLP-1 in NOD mice significantly increased beta-cell mass, while replication and transfusion in prediabetic NOD mice significantly reduced the apoptotic rate of beta cells [69]. Furthermore, anti-inflammatory effects of GLP-1 RA are well-documented, with liraglutide being associated with reduced systemic levels of C-reactive protein and pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [70–73]. Whilst these findings have mainly been observed in animal models or in patients with T2D, their relevance to (clinical) T1D is conceivable but, so far, largely unexplored. Due to unclear benefits of GLP-1 RA and other incretins in people with T1D, Wu et al. [52] published a systemic review and meta-analysis evaluating these effects on beta-cell function in T1D. The analysis included eight RCTs of people with T1D treated by either GLP-1 RA or DPP4 inhibitors compared to placebo. There was a trend for an increase in 2-h postprandial C-peptide levels in people with newly diagnosed T1D. The C-peptide area under the curve decreased less in people with T1D receiving incretin-based therapies. Another retrospective study showed a 3.5 increase in C-peptide concentration after GLP-1 RA treatment in people with T1D [49]. Herrath et al. [42] published their results of a phase 2 trial treating adults with recent onset of T1D with a combination of anti-IL-21 antibody and liraglutide for preservation of beta-cell function. The treated group had significantly higher mixed-meal tolerance test (MMTT)-stimulated C-peptide secretion, reflecting preservation of endogenous insulin secretion. Fasting baseline C-peptide secretion was almost completely maintained among the treated group, with an almost 30% reduction in the need for exogenous insulin. These findings show another relevant and beneficial aspect of treatment with GLP-1 RA in T1D. Larger RCTs are needed to evaluate the yield and safety of this group of drugs in earlier stages of T1D as well and in younger age groups.

Studies in Pediatric Patients

GLP-1 RA in T2D and Obesity

GLP-1 RAs have been proven both safe and efficient in children and adolescents with T2D and obesity [74]. Liraglutide was approved in 2019 by the FDA for the treatment of children with T2D [75]. A pivotal study by Tamborlane et al. [76] showed that children with T2D ages 10–17 years receiving 1.8 mg liraglutide on top of metformin for 26 weeks had significantly lower HbA1C and fasting plasma glucose at the end of the trial period. In 2021, the FDA approved the once weekly exenatide (Bydureon BCise) for treatment of children aged 10 years and above with T2D.

In 2020, liraglutide was FDA approved for the treatment of children older than 12 years with obesity. The RCT published by Kelly et al. [77] showed that liraglutide 3 mg along with lifestyle modification led to a significantly greater decrease in BMI and body weight compared to the placebo group. In 2022, the FDA approved semaglutide as an adjunct to lifestyle modifications in children aged 12 years and older with obesity. The interventional STEPTEENS trial [78] showed that semaglutide 2.4 mg was superior to placebo in BMI reduction. The GLP-1 RA exenatide also showed a significant reduction in BMI in adolescents with severe obesity, but this medication is currently not FDA approved for this indication, due to significant side effects [79, 80].

GLP-1 RA in Pediatric and Adolescence T1D

Despite these proven benefits of GLP-1 RA among children and adolescents, currently these medications are not approved for use in children with T1D. Several clinical trials have been conducted to address the limited data on the efficacy and safety of GLP-1 RA treatment in pediatric patients with T1D. However, only a few small studies have published their results. Raman et al. [81] evaluated the role of adjunctive exenatide therapy in 8 adolescents with T1D. They found that combing exenatide treatment with insulin reduced postprandial hyperglycemia and glucose excursions, despite a reduction in insulin dose. Another clinical trial, completed at the Command Hospital in India, investigated the effects of exenatide and the DPP4 inhibitor sitagliptin in patients ≥12 years old with newly diagnosed T1D (within 3 months from diagnosis and presenting with DKA at onset). The data showed that the addition of

exenatide or sitagliptin shortly after diagnosis of T1D reduced insulin requirements and prevented weight gain, although there was no significant difference in the preservation of endogenous insulin secretion [82]. A finish phase 2 study aimed to determine whether treatment with liraglutide improved insulin secretion (as assessed via serum C-peptide area under the curve during a 2-h MMTT) and whether is tolerable and safe amongst persons with early T1D aged 10–30 years [83]. Another phase 2 study assessed whether treatment with liraglutide improved endogenous insulin secretion and postponed progression to overt T1D, and whether it is tolerable and safe amongst persons aged 10–30 years with multiple islet autoantibodies and dysglycemia [84]. Results from both studies are pending.

An ongoing study in Vanderbilt University, USA aimed to determine how GLP-1 RA affect people with stage 2 T1D (this stage includes individuals who have developed two or more diabetes-related autoantibodies and are experiencing abnormal blood sugar levels due to the progressive loss of beta cells, without clinical symptoms) undergoing treatment with the anti-CD3 monoclonal antibody teplizumab. The study is recruiting patients aged 12–50 years old [85]. Another ongoing trial conducted at the University of Buffalo, USA is researching the effect of liraglutide on mean weekly blood sugars, postprandial glucose, glucagon levels, and insulin doses in adolescents, aged 15–21 years, with at least 1 year of T1D, treated with insulin pump and continuous glucose monitor [86].

A group at the David Sanchez Garcia Mexican Institute of Social Security completed a trial in patients aged 15–60 years with at least 1 year of T1D investigating the effects of 6 months of liraglutide additional to insulin treatment on subclinical atherosclerosis, evaluated by changes in lipid profile and carotid Doppler US [87]. The study results are pending. Hopefully, results from the above trials as well as other future RCTs, specifically designed for children and adolescents with T1D, will enable expanding the treatment options beyond insulin, allowing for improved glycemic control, BMI, and cardiovascular health.

Side Effects of GLP-1 RA

Gastrointestinal

GI side effects, such as nausea, vomiting, constipation, and diarrhea, are commonly associated with GLP-1 RA, though these effects are generally transient. These adverse effects are thought to arise from the delayed gastric emptying induced by GLP-1 RA. Also, since GLP-1 receptors are expressed in the central nervous system, particularly in the area postrema and nucleus tractus solitarius regions, it is noteworthy that this hindbrain site also mediates the adverse effects such as nausea and emesis [88]. Nausea accounts for approximately 6–10% of treatment discontinuation, while diarrhea is reported in 10–20% of patients receiving GLP-1 RA therapy. Implementing a gradual titration of the medication can significantly mitigate GI side effects [89].

Zhang et al. [90] conducted a systematic review and meta-analysis examining GI adverse reactions leading to the discontinuation of treatment with GLP-1 RA. The study included 64 randomized controlled trials encompassing over 16,000 patients, primarily those with T2D. The review also included one trial among patients with T1D patients, some among patients with obesity, females with polycystic ovary syndrome, and one trial involving adolescents over 14 years of age. The meta-analysis found that liraglutide and semaglutide had a higher risk of intolerable GI adverse effects, while dulaglutide had the lowest risk. Additionally, for semaglutide, the occurrence of adverse effects was positively correlated with the dose. When treating patients with impaired renal function, GI side effects should be taken into consideration, as they may cause dehydration, potentially leading to a deterioration of renal function.

Recent data support potential therapeutic advantages of combination therapies targeting GIP and GLP-1 systems together, with the finding that GIP receptor agonism may have antiemetic properties [88]. As nausea and vomiting are the most common side effects of GLP-1 pharmacotherapies, the ability for GIP agonism to reduce GLP-1–induced nausea and vomiting but retain weight loss and glycemic control may offer a new era in the treatment of obesity and diabetes with the dual GIP/GLP-1 receptor co-agonist.

Retrospective studies generally did not find an association between exenatide use and pancreatitis [91, 92], with only a few exceptions [93]. In the registration trials for liraglutide, which included approximately 4,500 patients, 7 cases of pancreatitis were reported. However, a meta-analysis by Monami et al. [94] did not show an overall increased risk of pancreatitis with liraglutide. In 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) stated that, based on current data, there is no increased risk of pancreatitis with GLP-1 RAs [95]. Nonetheless, caution should be exercised in patients with a history of pancreatitis.

Thyroid

Studies in rodents have shown increased rates of thyroid tumors with the use of GLP-1 RA [96]. GLP-1 RAs have been shown to stimulate C-cell hyperplasia and neoplasia in rats and mice. However, these proliferative effects on C-cells

have not been observed in nonhuman primates or humans, suggesting that the response may be rodent-specific. While GLP-1 receptors are present on normal rodent C-cells, they are either absent or exist in low numbers on C-cells in nonhuman primates and humans [97].

While the relevance to humans is considered low, it cannot be entirely excluded. Clinical trials have yielded inconclusive results regarding the increased risk [98]. However, a nationwide population based French study [99], which included approximately 50,000 adults with T2D treated with GLP-1 RA, indicated an increased risk of developing thyroid cancer. The risk was higher in patients treated for over 3 years, with a hazard ratio of 1.36 for 1–3 years of use and 1.58 for over 3 years of use. Another study based on the nationwide registries in Sweden, Denmark, and Norway investigated the association between GLP-1 RA and the increased risk of thyroid cancer [100]. This study compared patients treated with GLP-1 RA to those treated with DPP4 inhibitors over an average follow-up period of 3.9 years. The cohort included over 400,000 patients (about 33% treated with GLP-1 RA and 66% with DPP4 inhibitors). The results showed no significant increased risk of thyroid cancer associated with GLP-1 RA use during the follow-up period. There is a definite need for careful patient selection, especially among pediatric patients, and close monitoring of all patients treated with GLP-1 RA for this potential risk.

Retinopathy

Previous studies have indicated a link between rapid glucose levels reductions and the worsening of retinopathy in adults with T1D [101]. In the SUSTAIN 6 trial [102], which evaluated the effects of semaglutide in patients with T2D, the treatment group experienced a higher incidence of retinopathy-related complications such as vitreous hemorrhage, blindness or need for intravitreal agent or photocoagulation.

The PIONEER 6 trial, which excluded patients with proliferative diabetic retinopathy, still reported a 0.8% increase in retinopathy among the oral semaglutide group [103]. Wang et al. [104] conducted a meta-analysis of 23 trials involving over 22,000 patients with T2D to evaluate the association between semaglutide and retinopathy risk. While the overall findings did not indicate an increased risk with semaglutide use, a subgroup analysis revealed a higher risk of retinopathy for patients over 60 years old and those with more than 10 years of T2D. The precise cause of retinopathy worsening – whether due to improved glycemic control or a direct effect of semaglutide – remains unclear.

To address this, a dedicated ophthalmic trial (FOCUS), with a 5-year follow-up period, is currently underway to assess the long-term effects of semaglutide on retinopathy, with results expected in 2026. Until then, it is recommended that patients undergo screening for diabetic retinopathy before starting treatment with GLP-1 RA [105]. Patients with known diabetic retinopathy treated with semaglutide and insulin should be monitored closely including periodic eye examinations.

Loss of Fat Mass and Lean Body Mass

Liraglutide usage results in significant changes in body composition, notably decreasing both total fat and lean body mass [39, 40]. A systematic review and meta-analysis examining the effects of GLP-1 RA on adipose distribution revealed reductions in total, visceral, subcutaneous, epicardial, and liver adipose tissue [106]. This reduction in adipose tissue contributes to improvement in obesity-related metabolic disorders. However, the impact on lean body mass requires further investigation, particularly concerning pediatric patients who might use GLP-1 RA for extended periods.

Pregnancy/Teratogenic Side Effects

GLP-1 RA are used off-label for the treatment of polycystic ovary syndrome, showing benefits in improving menstrual cycles, ovulation, insulin sensitivity, and promoting weight loss [107, 108]. However, no controlled studies have been conducted in animals or humans to assess the teratogenicity of GLP-1 RA during pregnancy. Given that GLP-1 RA can indirectly improve fertility, it is crucial to offer contraception counseling to young women before starting this treatment.

As GLP-1 RA treatment gains popularity among pediatric patients, it is essential to conduct long-term studies to assess potential adverse side effects in this population. Additionally, proper follow-up for children and adolescents prescribed these drugs is crucial.

Conclusions

Children with T1D are prone to cardiovascular and renal complications as well as a 3-18-fold higher risk for all-cause mortality. Despite technology improvement with HCL insulin delivery systems, achieving and maintaining glycemic control remains difficult, with many children and adolescents not reaching recommended goals for HbA1c and TIR. Obesity is also prevalent in children with T1D, making reaching glycemic control even more complicated.

New interventions, such as GLP-1 RA, have proven effective and safe in adults with T1D, showing improvement

in glycemic control, body weight as well as cardiorenal protection. Studies have shown that GLP-1 RAs are also efficient and safe in children with T2D and obesity. Results of studies of GLP-1 RA in children with T1D are still pending, while large multicenter RCTs in this population are lacking. Hopefully, following further research, this group of medications will reduce complications, enable improved glycemic control, and increase quality of life also among children with T1D.

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Conflict of Interest Statement

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