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GLP-1 receptor agonists reduce body mass index and total daily insulin dose in youth with type 1 diabetes: a retrospective cohort study

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Abstract

Objectives: Youth with type 1 diabetes (T1D) and obesity face challenges in achieving optimal glycemic control and experience higher risk for long-term complications. While glucagon-like peptide-1 receptor agonists (GLP-1RA) have shown weight and glycemic benefits in adults with type 1 diabetes, data in pediatric populations are scarce. We report here changes in glycemia, weight, and insulin doses in youth with T1D and obesity prescribed GLP-1RA.

Methods: We conducted a single-center retrospective observational study of adolescents and young adults (ages 10–20) with T1D and obesity prescribed GLP-1RA (liraglutide, exenatide, dulaglutide, semaglutide, or tirzepatide) between 2019 and 2024. Data collected included HbA_{1c}, body weight, BMI, total daily insulin dose (TDD), and continuous glucose monitoring (CGM) metrics. Linear mixed effects models assessed changes over time, adjusting for age and gender.

Results: Among 24 patients (75 % female, 67 % public insurance, 88 % CGM users, 67 % insulin pump users), 12 months of GLP-1RA treatment led to significant reductions in weight (−9.49 kg, p<0.0001), BMI (−3.69 kg/m^2, p<0.0001), and BMI Z-score (−0.30, p=0.04). CGM time-in-range increased by +7.96 % (p=0.08), and time above range (180–250 mg/dL) decreased by −3.04 % (p=0.06). TDD among pump users declined by −21.42 % (p=0.002). After approximately 16 months, HbA_{1c} decreased by −0.81 % (p=0.04). Side effects were mainly gastrointestinal and transient.

Conclusions: This first longitudinal report of GLP-1RA use in youth with T1D and obesity shows clinically meaningful improvements in weight, glycemia, and insulin requirements, supporting the potential role of GLP-1RA as adjunct therapy. Larger prospective studies are needed to guide clinical practice.

Keywords: GLP1; type 1 diabetes; pediatric diabetes; obesity and type 1 diabetes

Introduction

Despite advancements in diabetes technology and development of new insulin analogs, 80 % of children with type 1 diabetes (T1D) do not reach a hemoglobin A1c (HbA_{1c}) target of less than 7 %, as recommended by the American Diabetes Association (ADA), increasing their risk for diabetes-related complications [1, 2]. As the prevalence of overweight and obesity in children with type 1 diabetes has increased globally [3–5], their risk for early coronary artery disease, stroke, and other severe cardiovascular events has also increased. Obesity also causes systemic inflammation, increasing the risk for metabolic syndrome, which can compound the long-term cardiovascular risk [5]. In addition, the Diabetes Control and Complications Trial and the Type 1 Diabetes Exchange Clinic Registry both demonstrate that people with overweight or obesity have higher HbA_{1c} despite utilizing higher daily insulin doses, suggesting they have developed insulin resistance despite intensive management [4, 6].

As insulin resistance becomes more common in people with type 1 diabetes and overweight or obesity, medications approved for management of type 2 diabetes have been considered as adjunct therapies. In adults with type 1 diabetes, metformin has been shown to reduce fasting plasma glucose levels and total daily insulin dose but did not improve HbA_{1c} or BMI [7]. In adolescents with type 1 diabetes, metformin similarly reduced total daily insulin dose and mitigated weight gain, but had no sustained effect on HbA_{1c}, body weight or BMI [8, 9]. Because of its minimal effect on weight and notable gastrointestinal side effects,

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metformin is not commonly used in people with type 1 diabetes.

Over the last 20 years, glucagon-like peptide-1 receptor agonists (GLP-1RA) have gained attention as an off-label adjunct therapy for people with type 1 diabetes and obesity [10–12]. Meta-analyses of randomized controlled trials of adults with these conditions demonstrated that liraglutide reduced HbA_{1c}, weight, blood pressure, prandial insulin, basal insulin dose, and total daily insulin dose with minimal gastrointestinal side effects [10, 13]. Patients given higher liraglutide doses experienced greater weight loss and patients with residual C-peptide levels had lower HbA_{1c} after treatment [13]. Recent retrospective observational studies also show that semaglutide and tirzepatide reduce HbA_{1c}, body weight, and BMI, while improving continuous glucose monitor (CGM) metrics [12, 14]. A case series of 10 adults with type 1 diabetes further showed that semaglutide and carbohydrate restriction eliminated insulin usage in seven patients within 6 months of diagnosis [15]. Taken together, these studies suggest that GLP-1RA should be evaluated for its glycemic and weight benefits in people with type 1 diabetes and obesity.

Despite some evidence supporting use of GLP-1RA in adults with type 1 diabetes, there is a paucity of data on their efficacy and safety in the pediatric population. Such studies are needed to inform pediatric endocrinologists on best practice management for children with type 1 diabetes and obesity. This retrospective study represents the first investigation, to our knowledge, that evaluated the efficacy of GLP-1RA on glycemia, BMI, and total daily insulin dose in adolescents and young adults (ages 10 to 20) with type 1 diabetes and obesity.

Materials and methods

In this retrospective cohort study, data was extracted from the electronic medical record (EMR) from a single pediatric center in compliance with regulations set forth by the Children's Hospital Los Angeles Institutional Review Board. STROBE reporting guidelines for cohort studies were followed [16]. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was granted a waiver of informed consent and patients were not consented for inclusion in this analysis. Patients were included if they met the following criteria: diagnosis of type 1 diabetes; visit date between January 1, 2019, to August 20, 2024; and a prescription for liraglutide, exenatide, dulaglutide, semaglutide, or tirzepatide. This study period was chosen based on the availability of GLP-1RA for pediatric use. Patients were excluded if they never received or started administering GLP-1RA. The choice of GLP-1RA initiation is conducted through a shared decision-making process between the endocrinologist and the patient/caregiver for indications including obesity, insulin resistance, and high total daily insulin dose. A patient's baseline visit was defined as the visit when GLP-1RA was prescribed. Clinical outcome data were recorded from subsequent visits that occurred every 4 months on average (±2 months) following the initial visit, including each visit where a GLP-1RA dosage was changed; all visit data were binned in 4-month-wide intervals, reflecting the average frequency of patient visits. GLP-1RA treatment adherence was self-reported by patients (*full*: no missed doses; *partial*: missing some doses; *none*: not taking doses). Anthropomorphic data was collected from all in-person visits but was not available from telehealth encounters. CGM readings for 28 days were used to report time-in-range, time-above-range, and time-below-range. When HbA_{1c} was not available (e.g. telehealth encounters), the 90-day Glucose Management Indicator (GMI) was used if available to estimate HbA_{1c}. Basal insulin dose for subjects on multiple daily insulin injections (MDI) was recorded from clinician documentation in the EMR. Total daily insulin dose for 28 days was recorded only for subjects on insulin pump therapy. Insulin delivery mode was determined based on clinical note documentation. Caregiver-preferred languages, race, and ethnicity were extracted from the EMR.

Demographic and clinical characteristics were summarized using descriptive statistics (mean±standard deviation; or counts and percentages). Changes in clinical outcomes over time, including weight (kg); BMI (kg/m^2) and standardized BMI Z-score; HbA_{1c}; total daily insulin dose; blood glucose time-in-range (70–180 mg/dL), time-below-range (<70–54 mg/dL, and <54 mg/dL), and time-above-range (>180–250 mg/dL, and >250 mg/dL) were examined using linear mixed effects (LME) models adjusting for gender and age at each visit, and fit via restricted maximum likelihood estimation with a degrees of freedom correction for small samples [17]. All analyses were conducted using Stata/SE 14.2 (College Station, TX). p-Values less than<0.05 were considered statistically significant.

Results

Study patients and adherence

Out of 2,492 patients with type 1 diabetes and an appointment between January 1, 2019, and August 20, 2024, 28

Table 1: Baseline characteristics.

Mean (SD) or n (%)	
n	24
Age, years	16.43 (2.51)
Gender=female, %	18 (75)
Diabetes duration, years	7.15 (3.24)
Duration of GLP-1RA use, years	0
Insurance, %	
Private	8 (33)
Public	16 (67)
Race/Ethnicity, %	
Asian	1 (4)
Black or African American	3 (13)
Hispanic or Latinx	10 (42)
More than 1 race	1 (4)
Native Hawaiian and other Pacific Islander	1 (4)
Non-conforming data	2 (8)
Other	2 (8)
White	5 (21)
Language, %	
English	20 (83)
Spanish	4 (17)
CGM use, %	21 (88)
Pump use, any modality, %	16 (67)
Pump use, AID, %	14 (58)

patients met eligibility criteria at the time of medical record review, and 24 were included in analyses. One patient was excluded because of negative islet antibodies and subsequent clinical suspicion for type 2 diabetes. Three patients were excluded because they never received or started using the prescribed GLP-1RA. As shown in Table 1, the study population was mostly female (18, 75 %), identified as Latinx (10, 42 %), used public insurance (16, 67 %), and spoke English (20, 83 %). Eighty-eight percent of patients used CGM (n=21), 67 % used insulin pumps (n=16), and 58 % using automated insulin delivery systems (AID, n=14). Three patients on MDI started CGM during the analysis period, and no one switched from MDI to insulin pump therapy.

Clinical outcomes

Weight and BMI

On average, patients lost −9.49 kg after approximately 12 months of treatment (at Visit 3; 95 % CI: −4.48, −14.50; p<0.0001; see Figure 1A). This change was reflected in both raw BMI (−3.69 kg/m2; 95 % CI: −1.92, −5.45; p<0.0001) and BMI Z-score (−0.30; 95 % CI: −0.01, −0.60; p=0.04; see Figure 1B), and was maintained through 16 months of follow-up (see Table 2, Visit 4).

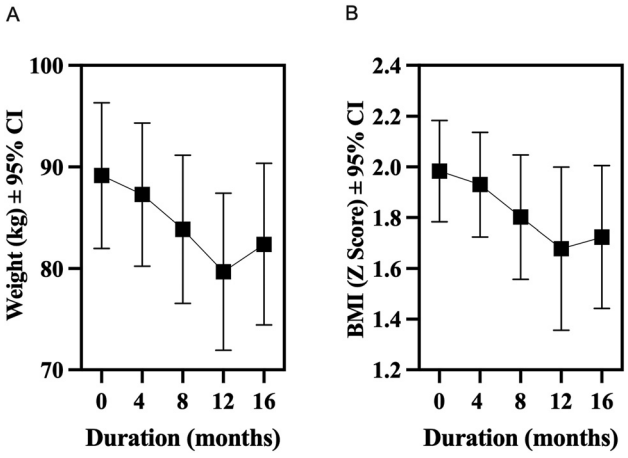

Figure 1: Adjusted mean changes in (A) weight and (B) BMI Z-score. Error bars represent 95 % confidence interval.

HbA_{1c}

Patients demonstrated significant reductions in HbA_{1c} over the follow-up period, beginning as early as four months after starting treatment (Visit 1, −0.59; 95 % CI: −0.14, −1.03; p=0.01; see Figure 2A). Sixteen months after starting treatment (Visit 4), patients continued to show large reductions in HbA_{1c} (−0.81 %; 95 % CI: −0.04, −1.58; p=0.04), although these changes were not observed consistently over follow-up (see Table 2).

Total daily insulin dose (TDD)

Among insulin pump users (n=15), the total daily insulin dose dropped significantly by the first follow-up visit (Visit 1, −15.52 units; 95 % CI: −6.18, −24.86; p=0.002), and this reduction was maintained after one year (Visit 3, -21.42 units, p=0.002; see Figure 2B). We observed similar reductions when TDD was adjusted for body weight (Visit 1, -0.15 units/kg; 95 % CI: −0.04, −0.25, p=0.008; Visit 3, -0.17 units/kg; 95 % CI: 0.01, −0.34, p=0.06; see Table 2), and also when TDD was standardized based on the percentage of a patient's baseline dose (Visit 1, −15.11 %; 95 % CI: −6.53, −23.69; p=0.001; Visit 3, −21.95 %; 95 % CI: −11.66, −32.24; p<0.0001).

Blood glucose range

Similar to changes in HbA_{1c} and TDD, effects of treatment on blood glucose time-in-range were significant by the first

Table 2: Glycemic, weight, and insulin metrics.

Adjusted mean (SD)	Baseline	Visit 3 (12 months)			Visit 4 (16 months)		
	(n=24)	(n=9)	Difference from baseline	p-Value	(n=7)	Difference from baseline	p-Value
HbA_{1c}, %	8.29 (1.46)	8.01 (2.02)	−0.28	0.39	7.48 (0.89)	−0.81	0.04
Weight, kg	89.17 (16.14)	79.68 (13.70)	−9.49	<0.0001	82.39 (8.56)	−6.77	0.02
BMI, kg/m^2	33.98 (5.27)	30.29 (5.62)	−3.69	<0.0001	31.49 (5.25)	−2.49	0.01
BMI, Z-score	1.98 (0.41)	1.68 (0.80)	−0.30	0.04	1.72 (0.68)	−0.26	0.04
Total daily insulin dose, n=15							
Units	101.44 (31.65)	80.02 (26.40)	−21.42	0.002	87.61 (33.92)	−13.83	0.06
Units/kg	1.16 (0.41)	1.00 (0.42)	−0.17	0.06	1.15 (0.50)	−0.01	0.90
Target glucose range (%)							
In range, 70–180 mg/dL	50.38 (17.81)	58.34 (22.68)	7.96	0.08	57.99 (13.60)	7.61	0.12
>180–250 mg/dL	26.13 (7.15)	23.08 (5.28)	−3.04	0.06	23.91 (7.69)	−2.22	0.20
>250 mg/dL	22.41 (14.36)	17.61 (19.37)	−4.80	0.23	15.68 (7.09)	−6.73	0.11
<70-54 mg/dL	0.79 (0.67)	0.76 (0.84)	−0.03	0.94	1.74 (2.86)	0.94	0.08
<54 mg/dL	0.22 (0.24)	0.26 (0.43)	0.04	0.86	0.42 (0.73)	0.20	0.30

Data obtained from 28-day report. Means and p-values obtained from mixed model analyses adjusted for age and sex. SDs calculated from unadjusted data.

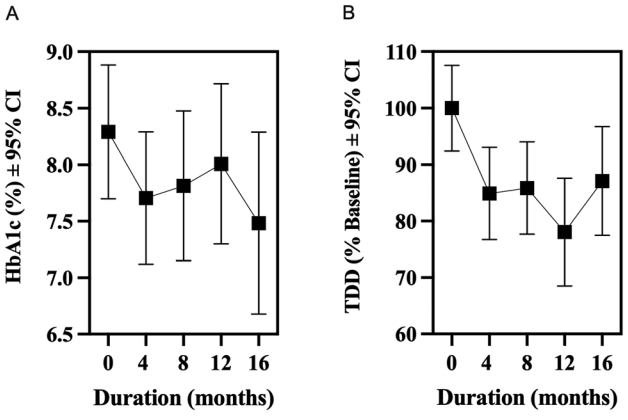

Figure 2: Adjusted mean changes in (A) HbA_{1c} and (B) total daily insulin dose for insulin pump users. Error bars represent 95 % confidence interval.

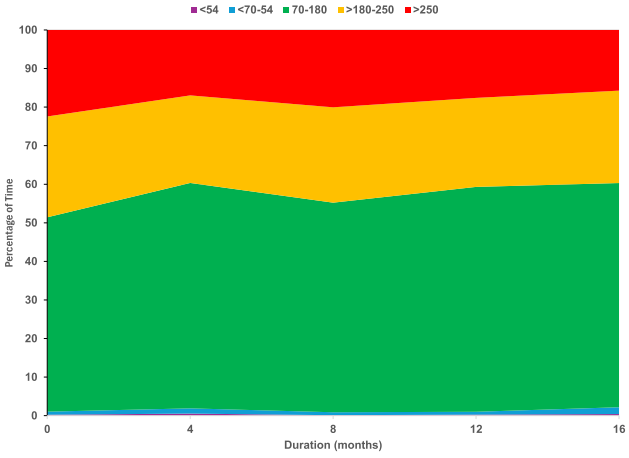

Figure 3: Adjusted mean changes in blood glucose range from continuous glucose monitor readings.

follow-up visit. Patients' average time in normal range increased from 50.38 % at baseline to 58.61 % at four months (+8.24 %; 95 % CI: 2.12, 14.36; p=0.009). This trend continued through the follow-up period (see Figure 3 and Table 2). Time above range decreased, with significant reductions in the time spent between 180 and 250 mg/dL observed at the first follow-up visit (Visit 1, −3.35 %; 95 % CI: −1.18, −5.52; p=0.003), and similar reductions were maintained throughout the follow-up period. Patients showed less consistent reductions for the highest range values (>250 mg/dL; e.g., Visit 1, −5.41 %; 95 % CI: 0.0007, −10.82; p=0.05). Patients using GLP-1RA treatment did not experience significant amounts of time-below-range (<70 mg/dL) except at the first follow-up Visit, when lows were recorded by CGM approximately 1 % of the time (Visit 1, +0.96 %; 95 % CI: 0.12, 1.86; p=0.03).

GLP-1RA dosage and safety

The final dosages of GLP-1RA prescribed are listed in Supplementary Table 1. Most patients were prescribed weekly semaglutide (n=21, 88 %), 2 patients were on dulaglutide (8 %), and 1 patient was on liraglutide (4 %). Semaglutide 1.0 mg was the most prescribed dosage (50 %), followed by 2.4 mg (17 %).

Adherence to GLP-1RA and barriers to administration are reported in Supplementary Table 2. At each visit, 60–100 % of the patients endorsed taking all doses of GLP-1RA. All patients endorsed at least partial adherence at all visits. A single patient reported difficulty obtaining GLP-1RA during the study period. Side effects were commonly reported in the

first follow-up visit (n=10, 42 %) and were predominantly gastrointestinal (nausea, diarrhea, constipation). By Visit 2, side effects were only reported by a single individual. One patient experienced diabetic ketoacidosis during the study period due to insulin omission when not wearing CGM.

Discussion

To our knowledge, this is the first retrospective cohort study to demonstrate that GLP-1RA usage reduced body weight and BMI and improved glycemic outcomes in adolescents and young adults with type 1 diabetes. For participants who wore CGM, the amount of time patients spent in normal range increased by nearly 10 % over follow-up, while time above range decreased over the same time period. Hypoglycemia was rare, occurring less than 1 % of the time (primarily around the first follow-up visit). In insulin pump users, total daily insulin dose decreased over time. GLP-1RA was generally well-tolerated and administered consistently. Most patients were prescribed weekly semaglutide, and they reported mild, transient gastrointestinal side effects, comparable to prior reports of GLP-1RA use [18, 19].

While there are increasing number of studies on GLP-1RA usage in adults with type 1 diabetes, similar data in the adolescent population is limited. Seetharaman and Cengiz recently reported on a case series of eight adolescents and young adults with type 1 diabetes prescribed semaglutide or tirzepatide as adjunct therapy [20], which included only three adolescents (ages 13 and 14) with variable weight loss and GLP-1RA use of 2–5 months. Our report here differs from the prior report by having a larger cohort (17 out of 25 patients were under the age of 18) and longer duration of GLP-1RA (mean duration of one year). With the larger sample size and duration, we were able to demonstrate the longitudinal glycemic and weight benefits of GLP-1RA in adolescents and young adults with type 1 diabetes.

Despite semaglutide's indication for obesity management, insurance routinely denies coverage for adolescents with type 1 diabetes. Based on our data, we strongly believe that a prospective clinical trial would provide sufficient evidence for regulatory agencies to approve the usage of GLP-1RA in youth with type 1 diabetes. The early initiation of GLP-1RA in youth with obesity and type 1 diabetes has the potential to reduce their long-term risk for major adverse cardiovascular events and chronic kidney disease [21, 22]. Future studies should evaluate if early GLP-1RA usage in young people with type 1 diabetes reduces the development of cardiovascular disease and diabetic nephropathy in the long term.

We observed a trend toward mild hypoglycemia at the first follow-up visit. Although GLP-1RA has a low risk of hypoglycemia, this risk is increased with concomitant administration of sulfonylureas and insulin [23]. Hypoglycemia risk was variable from studies of adults with type 1 diabetes. The ADJUNCT ONE study of adults with overweight or obesity and type 1 diabetes treated with liraglutide showed an increase in symptomatic hypoglycemia in a dose dependent fashion, whereas more recent studies using semaglutide and tirzepatide did not detect an increase in CGM time below range [12, 14, 24]. To mitigate this safety concern, we recommend that young people with type 1 diabetes remain in close contact with their diabetes team after initiating GLP-1RA to consider adjustments of insulin doses.

This report presents several strengths. First, this is the initial longitudinal retrospective cohort study to evaluate the efficacy of GLP-1RA in adolescents and young adults with type 1 diabetes, whereas previous studies were limited to adult populations or case series. Second, most patients were prescribed very-high potency GLP-1RA [25], which may offer more realistic insights into the weight loss and anti-hyperglycemic effects of these medications within the study population. Lastly, continuous glucose monitoring (CGM) was utilized by 88 % of the patients, enabling a comprehensive analysis of changes in time-in-range throughout the study period.

There are several limitations to this report. There is likely a prescribing bias related to gender and prescriber preference. Seventy-five percent of the study cohort was female, whereas only 44 % of our clinic type 1 diabetes cohort was female. This skewed gender distribution has also been reported in other adolescent studies examining GLP-1RA prescription patterns, which may reflect the societal pressure on women for weight management [26, 27]. As GLP-1RA usage is not common in the pediatric type 1 diabetes population, only a subset of clinicians more comfortable with GLP-1RA prescribed these agents, limiting the patient cohort size and generalizability to this population. The observational design of the study did not allow for evaluation of the effects of GLP-1RA at set timepoints when given to a random subset of patients. The sample size was sufficient to answer study questions but relatively small, although LME models were adjusted to account for small sample size. More data were available for earlier follow-up visits, impacting our ability to reliably estimate outcomes at visits that occur later in the follow-up period. Anthropomorphic data were also missing for virtual visits, although LME

models are ideal when data are missing at random. Since medication adherence was extracted from clinical documentation, this information is also subject to bias based on patient self-report and completeness of documentation. Due to missing HbA_{1c} data with virtual visits, 90-day GMI was used as a proxy for approximately 9.2 % of data (7 out of 76 HbA_{1c} values). We mitigated the variability between GMI and HbA_{1c} by using the 90-day time frame, which more closely approximates the time span estimate of HbA_{1c}. The lack of a control cohort is another limitation of the study. However, the modest sample size of the GLP1 cohort is not powered to adjust for age, BMI, and diabetes technology use against a heterogeneous T1D cohort. Finally, as this study excluded patients who never started GLP1-RA, the proportion of patients who could not access these medications is unknown.

Conclusions

GLP-1RA is a potentially revolutionary treatment for youth with type 1 diabetes and obesity. The current study suggests that patients could see prompt, short-term benefits of greater glycemic control and weight reduction. Future studies should randomize a larger cohort of participants to verify short-term effects of GLP-1RA and evaluate long-term effects of treatment on cardiovascular and renal health.

Research ethics: The Children's Hospital Los Angeles Institutional Review Board approved the study (CHLA-24-00026) on February 12, 2024. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).
Informed consent: This study has been granted a waiver of informed consent/assent/permission.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. F.G. participated in data acquisition and drafted the manuscript. M.W.R. analyzed the data. J.F.G. critically reviewed the manuscript. J.K.R. contributed to the study design and critically reviewed the manuscript. L.C.C. conceived the study design and contributed to the writing of the manuscript. Dr. Lily C. Chao is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: L.C.C. is a site investigator for Novo Nordisk and Eli Lilly. All other authors state no conflict of interest.
Research funding: None declared.
Data availability: The data that support the findings of this study are available from the corresponding author, L.C.C., upon reasonable request.

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