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RESEARCH LETTER

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Glucagon-like peptide-1 receptor agonist prescribing patterns in adolescents with type 2 diabetes

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1 | INTRODUCTION

Type 2 diabetes (T2D) in youth is a more aggressive disease that is associated with earlier co-morbidities compared with T2D in adulthood.[1] Treatment guidelines for paediatric T2D first recommend lifestyle management and metformin, which rarely achieve meaningful body mass index (BMI) reduction.[2,3] Because of limited options for treatment, medications approved for adult T2D have been used in an 'off-label' fashion in adolescents. One such medication class is glucagon-like peptide-1 receptor agonists (GLP-1RAs), which stimulate postprandial insulin secretion, reduce glucagon secretion, delay gastric emptying, and decrease appetite, leading to improvements in glycaemic control and weight reduction.[4] The United States Food and Drug Administration (FDA) has approved two GLP-1RAs, liraglutide 1.8 mg/d and exenatide extended-release (ER), for T2D in youth aged 10 years or older.[2] However, little is known about GLP-1RA prescribing patterns in youth. The objective of this retrospective chart review was to explore GLP-1RA prescribing practices for adolescents with T2D.

2 | METHODS

The electronic health record (EHR) of a large medical centre was queried for all patients, aged 10-20 years, billed for T2D from January 2018 to August 2020 with a diagnosis of T2D after 2015. Patients were included if they had been diagnosed with T2D by a HbA1c measurement of 6.5% or higher and did not have diabetes autoantibodies. Each participant's EHR was reviewed from date of diagnosis to August 2021 to ensure that all patients had T2D, and all data at least 1 year postdiagnosis were included. This study was approved by the institution's Institutional Review Board.

2.1 | Measures

2.1.1 | Demographic information

Sex, race, and ethnicity were obtained at T2D diagnosis. Age was obtained at diagnosis and initial GLP1-RA prescription.

2.1.2 | Anthropometrics and glycaemic control

BMI and HbA1c at diagnosis and initial GLP-1RA prescription were recorded. BMI percentage of the 95th percentile was calculated to characterize the severity of obesity.

TABLE 1 Characteristics at diagnosis and glucagon-like peptide-1 receptor agonist (GLP-1RA) prescriptions within the first year of diagnosis[a]

	Overall (n = 100)	No GLP-1RA prescription (n = 72)	GLP-1RA prescription (n = 28)	Estimated contrast between prescribing groups[b] (95% CI)
Age (y)	14.0 (2.1)	14.0 (2.1)	14.2 (2.1)	0.22 (−0.71, 1.15)
BMI (kg/m^2)	37.0 (7.8)	36.6 (7.2)	38.0 (9.0)	1.41 (−2.03, 4.84)
BMI percentage of the 95th percentile	136 (29.9)	134 (29.8)	140 (30.3)	5.72 (−7.52, 18.96)
HbA1c (%)	8.6 (2.5)	8.4 (2.4)	9.3 (2.7)	0.88 (−0.22, 1.97)
Male sex (%)	43 (43.0)	28 (38.9)	15 (53.6)	1.81 (0.75, 4.38)
Race/ethnicity (%)				
African-American/Black	32 (32.0)	25 (34.7)	7 (25.0)	Reference
White, non-Hispanic	20 (20.0)	14 (19.4)	6 (21.4)	1.53 (0.43, 5.46)
White, Hispanic	17 (17.0)	12 (16.7)	5 (17.9)	1.49 (0.39, 5.67)
Asian	12 (12.0)	10 (13.9)	2 (7.1)	0.71 (0.13, 4.05)
Multiple	5 (5.0)	2 (2.8)	3 (10.7)	5.36 (0.74, 38.64)
Native American	3 (3.0)	2 (2.8)	1 (3.6)	1.79 (0.14, 22.70)
Missing	11 (11.0)	7 (9.7)	4 (14.3)	

Abbreviation: BMI, body mass index.
[a]Continuous variables are described as value (SD). Categorical variables are described as n (%).
[b]Estimates are mean differences or odds ratios.

2.1.3 | Medications

Date and the type of the first GLP-1RA prescribed were obtained. Concomitant anti-obesity medications (topiramate, stimulants, naltrexone, or bupropion) and anti-diabetes (metformin, dipeptidyl peptidase-IV inhibitors, sodium-glucose co-transporter-2 inhibitors, sulphonylureas, or insulin) medications, and long-acting insulin dose (units/kg/d) at the time of the GLP-1RA prescription, were obtained.

2.2 | Statistical methods

Descriptive statistics were calculated as mean (SD) or count (percentage) for continuous and categorical characteristics, respectively. Mean differences between groups (continuous variables) and odds ratios (categorical variables) were estimated through simple linear, logistic, and multinomial logistic regression models. Patients who were prescribed a GLP-1RA within 1 year of T2D diagnosis were compared with those who were not. Patients prescribed a GLP-1RA within 1 year of T2D diagnosis had their characteristics at the time of prescription compared with those of patients prescribed a GLP1-RA at any time after 1 year of T2D diagnosis. All analyses were conducted using R v. 4.04 (R Core Team, 2019). Statistical significance was defined as *P* less than .05. No adjustments were made for multiple comparisons.

3 | RESULTS

Characteristics at the time of diagnosis from 100 patients found to meet the eligibility criteria are outlined in Table 1.

3.1 | Overall prescribing patterns

The most frequently prescribed GLP-1RA was liraglutide (n = 32; 59.3% of prescriptions); 46.9% (n = 15) prescriptions were written prior to FDA approval of liraglutide for youth with T2D. Semaglutide subcutaneous was prescribed for 13 patients (24.1%), followed by exenatide ER (n = 4; 7.4%), exenatide twice-daily (n = 2; 3.7%), deglutide (n = 2; 3.7%), and semaglutide oral (n = 1; 1.8%). The majority of GLP-1RA prescriptions (n = 35; 64.8%) were prescribed 'off-label'; either for patients prescribed liraglutide or exenatide ER prior to approval or another GLP-1RA prescribed for patients younger than 18 years. Among all patients prescribed GLP-1RAs, 66.7% (n = 36) were also prescribed long-acting insulin with a mean dose of 0.42 ± 0.32 units/kg/d. Sixteen patients (29.6%) prescribed GLP-1RAs were prescribed metformin without insulin, and 64.4% (n = 29) were prescribed both metformin and insulin.

3.2 | First year of T2D diagnosis

At the time of diagnosis, patients had a mean age of 14.0 ± 2.1 years and a mean BMI of 37.0 ± 7.8 kg/m^2 (Table 1). Twenty-eight patients (28.0%) were prescribed a GLP-1RA within 1 year of diagnosis. There were no significant differences in any of the measured characteristics between patients who were prescribed a GLP-1RA and those who were not within 1 year of diagnosis.

3.3 | All GLP-1RA prescriptions

In total, 54 patients (54.0%) were prescribed a GLP-1RA from January 2015 to August 2021 (Table 2). The mean age of patients at the time

TABLE 2 Characteristics at the time of glucagon-like peptide-1 receptor agonist (GLP-1RA) prescription[a]

	Overall (n = 54)	After the first year of T2D diagnosis (n = 26)	Within the first year of T2D diagnosis (n = 28)	Estimated contrast between prescribing groups[b] (95% CI)
Age (y)	14.8 (1.9)	15.2 (1.9)	14.5 (1.9)	−0.69 (−1.73, 0.35)
BMI (kg/m^2)	37.9 (7.7)	37.5 (6.3)	38.3 (8.8)	0.79 (−3.43, 5.01)
BMI percentage of the 95th percentile	137 (26.9)	134 (24.4)	140 (29.3)	5.68 (−9.11, 20.47)
HbA1c (%)	9.4 (2.8)	10.4 (2.8)	8.5 (2.4)	−1.83 (−3.28, −0.39)*
Male sex (%)	26 (48.1)	11 (42.3)	15 (53.6)	1.57 (0.54, 4.61)
Race/ethnicity (%)				
African American/Black	17 (31.5)	10 (38.5)	7 (25.0)	Reference
White, non-Hispanic	10 (18.5)	4 (15.4)	6 (21.4)	2.14 (0.44, 10.53)
White, Hispanic	9 (16.7)	4 (15.4)	5 (17.9)	1.79 (0.35, 9.13)
Asian	6 (11.1)	4 (15.4)	2 (7.1)	0.71 (0.10, 5.04)
Multiple	4 (7.4)	1 (3.8)	3 (10.7)	4.29 (0.37, 50.21)
Native American	3 (3.0)	2 (2.8)	1 (3.6)	1.79 (0.14, 22.70)
Missing	6 (11.1)	2 (7.7)	4 (14.3)	
Concomitant insulin (%)	36 (66.7)	21 (80.8)	15 (53.6)	0.27 (0.08, 094)*
Long-acting insulin dose (units/kg/d)	0.42 (0.32)	0.5 (0.38)	0.32 (0.15)	−0.18 (−0.39, 0.03)
Concomitant weight-loss medications (%)				
Stimulants	9 (16.7)	5 (19.2)	4 (14.3)	0.73 (0.17, 3.09)
Topiramate	8 (14.8)	3 (11.5)	5 (17.9)	1.67 (0.36, 7.80)
Bupropion	5 (9.3)	3 (11.5)	2 (7.1)	0.59 (0.09, 3.85)
Naltrexone	2 (3.7)	0 (0.0)	2 (7.1)	N/A
Concomitant diabetes medications (%)				
Metformin	45 (83.3)	22 (84.6)	23 (82.1)	0.84 (0.20, 3.53)
DPP-IV inhibitors	4 (7.4)	1 (3.8)	3 (10.7)	3.00 (0.29, 30.84)
SGLT-2 inhibitors	10 (18.5)	2 (7.7)	8 (28.6)	4.80 (0.91, 25.23)
Sulphonylureas	3 (5.6)	1 (3.8)	2 (7.1)	1.92 (0.16, 22.56)

Abbreviations: BMI, body mass index; DPP-IV, dipeptidyl peptidase-IV; SGLT-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.
[a]Continuous variables are described as value (SD). Categorical variables are described as n (%).
[b]Estimates are mean differences or odds ratios.
*$P < .05$.

of the initial prescription was 14.8 ± 1.9 years with a mean BMI of 37.9 ± 7.7 kg/m^2. The mean HbA1c at the time of prescription was lower in patients who were prescribed within 1 year of diagnosis versus patients who were prescribed after 1 year since their diagnosis (8.5% ± 2.4% vs. 10.3% ± 2.8%; $P = .014$). Patients prescribed a GLP-1RA within 1 year of diagnosis were less probable to be prescribed concomitant insulin therapy than patients who were prescribed a GLP-1RA after 1 year since their diagnosis (53.6% vs. 80.8%; $P = .039$). Age, sex, race, ethnicity, BMI, and BMI percentile at the time of T2D diagnosis, or prescriptions of other antiobesity or antidiabetes medications, did not differ between groups.

4 | DISCUSSION

This retrospective chart review described GLP-1RA prescribing patterns for adolescents with T2D and predominantly severe obesity (BMI > 1.2 × 95th percentile). Interestingly, patients who were prescribed a GLP-1RA within 1 year of T2D diagnosis were more probable to be in better glycaemic control and less probable to also be prescribed insulin than those who were prescribed a GLP-1RA after 1 year since their diagnosis. Factors other than HbA1c or age, such as co-morbidities or medication adherence, may have influenced GLP-1RA prescribing in this sample population. This differs from findings in adults in which predictors of any therapy 1 year after T2D diagnosis include younger age and poor baseline glycaemic control.[5]

The majority of patients were prescribed a GLP-1RA in an 'off-label' fashion. 'Off-label' medications, such as GLP-1RAs prescribed for youth with T2D and obesity, are often prescribed when the standard-of-care has failed or there are no other FDA-approved medications.[6] Prior to the FDA approval of liraglutide and exenatide ER, metformin and insulin were the only FDA-approved treatment options for youth with T2D. However, metformin therapy has a high failure rate (requiring insulin therapy or having a persistently elevated

HbA1c) and poor medication adherence in youth.[3,7,8] Insulin therapy, although needed to control hyperglycaemia, is not ideal for patients with both T2D and obesity because insulin can lead to increased hunger, weight gain, and worsening insulin resistance.[9] In adults, GLP-1RAs have been found to reduce weight, improve glycaemic control, and decrease insulin dosage.[10-18] Therefore, GLP-1RAs were an attractive 'off-label' adjunct therapy in youth with T2D and obesity to reduce body weight and HbA1c prior to the FDA approval of liraglutide and exenatide ER.[19-21] As more GLP-1RAs become FDA approved, an area of additional research should be to evaluate how prescribing patterns change over time with increasing access to these medications.

4.1 | Limitations

This study describes cross-sectional data at the time of diagnosis and GLP-1RA prescription, and did not include data on co-morbidities, clinic attendance, or medication adherence that may affect prescriber decision-making. Only the first GLP-1RA prescribed was recorded, which does not capture if insurance approval was obtained or if the patient actually received this medication.

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AUTHOR CONTRIBUTIONS

MOB, JMW, KDR, and ASK designed the study. MOB collected the data. MOB, JMW, KDR, ASK, and SA analyzed the data and prepared the manuscript.

CONFLICT OF INTEREST

ASK serves as an unpaid consultant for Novo Nordisk, Vivus, Eli Lilly, and Boehringer Ingelheim, as well as receives donated drug/placebo from Vivus for a National Institutes of Health-funded clinical trial. SA receives grant support from and serves as a consultant for AZ DMC, Novo, and Lilly. MOK, JMW, and KDR have no conflicts of interest to disclose.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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