

CASE REPORT

Safe use of a once-a-week glucagon-like peptide-1 receptor agonist in a 16-year-old girl with type 2 diabetes when approved therapy options fail

Louisa van den Boom¹  | Theresa Stuecher² | Julia K. Mader^{1,3} 

¹Division of Pediatrics, DRK Hospital Kirchen, Kirchen, Germany

²Division of Pediatrics, DRK-Kinderklinik Siegen gGmbH, Siegen, Germany

³Medical University of Graz, Endocrinology and Diabetology, Graz, Austria

Correspondence

Louisa van den Boom, Division of Pediatrics, DRK Hospital Kirchen, Bahnhofstraße 24, 57548 Kirchen, Germany.
Email: l.vdbo@t-online.de

Abstract

This case report demonstrates that using a non-approved long-acting GLP-1-RA (dulaglutide) in adolescents with T2D is possible and feasible under special circumstances when approved therapeutic options for the pediatric population fail to achieve adequate glycemic control.

KEYWORDS

adolescents, dulaglutide, type 2 diabetes

1 | INTRODUCTION

Nowadays, type 2 diabetes (T2D) rarely occurs in European children or adolescents. While multiple drugs are approved and successfully used to achieve good glycemic control in adult T2D care, prescribing metformin or insulin constitutes the main therapeutic approach to pediatric T2D care. In recent years, liraglutide, a once-daily GLP-1-RA, was approved for children >10 years of age while once-a-week diabetes medications are not yet approved for children and adolescents with T2D. Here, we present the case of a 16-year-old girl with T2D treated with dulaglutide in off-label use. Dulaglutide is used to treat T2D in adults. It is a glucagon-like peptide that stimulates pancreatic islet cells to produce more insulin when injected once weekly. We decided to initiate dulaglutide in an adolescent due to psychiatric comorbidities: dulaglutide overdosing is almost impossible, it carries no risk of hypoglycemia, it is easy to apply, and is injected only once a week.

Although type 2 diabetes (T2D) is still rare among children and adolescents in Europe, the numbers are increasing, and T2D is therefore recently becoming an emerging public health concern. The onset of T2D occurs most often during the second decade of life in youths, with a median age of onset of 13.5 years. This coincides with the peak of physiologic pubertal insulin resistance and accordingly, the median age of onset is 1 year later in boys than girls. Before puberty, the youth-onset T2D is rare.¹ At 2.42 per 100,000, the prevalence of T2D in children and adolescents in Germany is still low.² Nevertheless, managing T2D in childhood and adolescence presents an enormous challenge in everyday life. The primary goals here include achieving and maintaining good glycemic control, avoiding weight gain, and even striving for weight loss. According to the international pediatric diabetes guidelines, oral metformin can safely be used in the youth population (age >10 years) in combination with lifestyle changes.¹ However, if treatment goals cannot be achieved

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with metformin, such as when blood sugar levels are exceedingly high, or in case of metabolic abnormalities, it is recommended to start insulin therapy with HbA1c target of <7% (<53 mmol/mol),¹ despite the possible side effects of hypoglycemia and weight gain.

Generally, antihyperglycemic agents other than metformin are not yet approved for children with T2D. However, in 2019 liraglutide, a once-daily glucagon-like peptide-1 receptor agonist (GLP-1-RA) was approved by the European Medicines Agency (EMA) for treatment of adolescents with T2D aged 10–17 years.³ In contrast, many non-insulin-based treatment options for adults with T2D are readily available, hence T2D therapy in adults can be individualized according to the patients' specific needs, comorbidities, clinical presentation, and possible side effects.⁴

Furthermore, a long-acting once-a-week GLP-1-RA (dulaglutide) was approved for the treatment of adults with T2D in 2014. Dulaglutide can be used as monotherapy or an add-on to other antihyperglycemic agents (including oral antihyperglycemic drugs and/or insulin) and is effective and generally well-tolerated in adults with inadequately controlled T2D, including high-risk patients (e.g., obese and elderly patients, patients with stage 3 or 4 chronic kidney disease and/or cardiovascular disease).⁵ Due to its long-acting properties, dulaglutide is injected only once a week and it mimics incretin effects by increasing the glucose-dependent insulin secretion of the beta cells in the pancreas. The GLP-1-RAs slow gastric emptying, inhibits unwanted post-prandial glucagon secretion, increase satiety and reduce food intake. By these mechanisms of action, the GLP-1-RAs not only lower blood glucose (BG) levels but also have a positive impact on body weight.^{6,7}

We present the case of a 16-year-old girl with T2D who was treated with dulaglutide after a regimen of metformin and multiple daily injections (MDI) of basal and bolus insulin failed to achieve the recommended glycemic target (HbA1c <7% (53 mmol/mol)).

2 | CASE REPORT

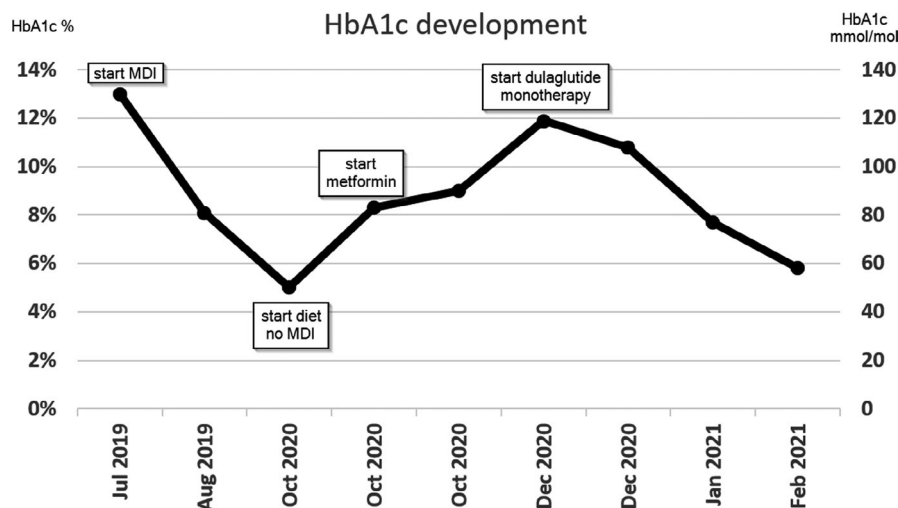
A girl presented with high BG levels in July 2019 when she was 14 years old. Her HbA1c at that time was 13% (119 mmol/mol). The girl's body weight was 72 kg, her body height was 157 cm, and her BMI was 29.2 kg/m² (99th percentile). No ketones or type 1 diabetes-specific autoantibodies were present. Before, the girl was incorrectly diagnosed with type 1 diabetes (T1D) and was prescribed MDI therapy. A few weeks later, she was admitted to the emergency room with severe hypoglycemia (BG 1.4 mmol/L (25 mg/dl)). Following a brief inpatient stay,

during which she was retrained in diabetes management the girl was discharged to continue MDI therapy at home. Only 4 weeks later, she was readmitted following another severe hypoglycemic event, and her parents reported that no insulin was injected at the time. The c-peptide and the insulin lab results came back normal. Consequently, the diagnosis was revised as T2D, and the insulin therapy was discontinued, while a dietary regimen was established instead. During the subsequent weeks, the HbA1c dropped to 5% (31 mmol/mol).

In February 2020, the girl was again admitted to the emergency room due to a severe hypoglycemic event with seizure. While giving her medical history, she confessed to have injected many units of insulin, she had found in the fridge at home. She denied suicidal intent but could also provide no other reason for her behavior. Consequently, the event was classified as self-induced hypoglycemia. The clinical workup was repeated: c-peptide and insulin were again in the normal range, diabetes autoantibodies were negative, so the diagnosis of T2D was confirmed. Hence, metformin therapy was initiated and the recommendation to stop insulin therapy was repeated due to the second severe hypoglycemic event. A psychiatry referral was refused by both the girl and her parents. However, the recommended glycemic targets could not be met with metformin monotherapy resulting in an increase of HbA1c to 9% (75 mmol/mol) 8 months later and a further increase to 11.9% (107 mmol/mol) another 2 months later. At that time, the girl's body weight was 78 kg, her body height was 163 cm and her BMI was 29.4 kg/m² (99th percentile). To avoid a recurrence of insulin overdosing, this treatment option was not reconsidered.

At present, only one antihyperglycemic agent (liraglutide, at once daily GLP-1-RA) used in the treatment of adult T2D is also approved in patients under the age of 18. However, since liraglutide requires titration and one pen holds multiple doses, deliberate overdosing was feared. The off-label use of dulaglutide, which is currently approved only in patients >18 years of age, was therefore considered instead. The patient and her parents were presented with this treatment option and gave their written consent after the off-label use, the complete treatment plan, and the common side effects. We started with 0.75 mg once weekly administrations, initially under supervision in the diabetes outpatient clinic and then at home under parents' supervision. After 3 weeks, the HbA1c dropped to 10.8% (95 mmol/mol) and the BG was in the 3.9–8.3 mmol/L (70–150 mg/dl) range. The girl suffered from constipation, so we initiated a stool emollient therapy which proved to be effective. One month later, the HbA1c dropped further to 7.7% (61 mmol/mol), while her body weight remained unchanged (body weight 78.7 kg, body height 163.5 cm, and BMI 29.44 kg/m² (99th percentile)) and no side effects

FIGURE 1 HbA1c development over the time



were recorded. Another month later, the HbA1c was 5.8% (40 mmol/mol), with the BG in the 4.4–6.1 mmol/L (80–110 mg/dl) range. The girl reported feeling well and experiencing no side effects and the whole family was very satisfied with the dulaglutide therapy. So, continuation with dulaglutide treatment was recommended and subsequent follow-ups will be scheduled every 3 months.

3 | DISCUSSION

The girl was diagnosed with diabetes mellitus (initially misdiagnosed as T1D which is the most common type of diabetes in the pediatric population) at the age of 14, subsequently, insulin therapy was started according to established pediatric treatment guidelines.⁸ At the time of initial diagnosis, her BMI was 29.2 kg/m² which is above the 99th percentile. Furthermore, there was a positive family history of T2D and obesity, with her maternal grandmother having T2D, and both of her parents being overweight. Consequently, MDI therapy was prescribed due to high HbA1c and exceedingly high blood glucose levels, even though a weight reduction would be exceedingly difficult to achieve while being on insulin. In addition to the MDI therapy, a healthy diet plan in combination with moderate physical activity was also developed for the girl and her entire family. However, due to three severe hypoglycemic episodes (including factitious hypoglycemia) during the 7 months on the MDI regimen (from July 2019 to February 2020), we reevaluated the initial diagnosis and considered possible therapy options other than insulin. Moreover, since c-peptide and insulin levels were always in the normal range the initial diagnosis was changed to T2D and lifestyle changes were suggested to achieve the treatment target. However, by October 2020, the HbA1c increased to 8.3% (67 mmol/mol), requiring a more effective treatment than lifestyle changes alone,

with insulin being off the table due to an episode of factitious hypoglycemia. Furthermore, although the family rejected a psychiatric co-treatment, we recognized a depressive component in the girl's emotional behavior and could determine a combination of three (chronic) comorbidities at this point: T2D, obesity, and a depressive disorder. The goal here was to find the best therapy option with respect to all three comorbidities.

We therefore immediately considered the GLP-1-RA liraglutide which is approved for adolescents with T2D and is especially beneficial for patients with obesity as it not only improves glycemic control but can also lead to a significant BMI reduction. Due to its gastrointestinal side effects profile, the treatment may not be suitable for all patients.⁹ GLP-1-RAs lower glycemia by inducing the glucose-dependent insulin secretion in the islet cells of the pancreas. One advantage over other insulin secretagogues such as sulfonylureas is their hypoglycemic potential.^{6,7} Both, its positive metabolic effects and the low hypoglycemic potential were relevant to our patient. However, since liraglutide comes in a multi-dose prefilled pen and since it also requires titration in the first weeks following therapy initiation, we feared the patient may experience another episode of factitious hypoglycemia.¹⁰ Alternatively, dulaglutide that combines the positive effects of GLP-1-RAs with once-weekly injection and a lower risk of deliberate overdosing was chosen.¹¹ Dulaglutide monotherapy was started at a dose of 0.75 mg per week. After 2 months of therapy, HbA1c dropped from 11.9% (107 mmol/mol) to 5.8% (40 mmol/mol), glucose levels were in the normal range of 4.4–7.2 mmol/L (80–130 mg/dl) and no relevant side effects occurred (Figure 1).

Factitious hypoglycemia typically occurs in adolescents with T1D who use insulin to induce hypoglycemia, but no cases of factitious hypoglycemia in adolescents with T2D were found in the literature so far.¹² A high percentage of adults with factitious hypoglycemia suffer

from psychological disorders (e.g., depression and suicidality). Other common features in adolescents with T1D with factitious hypoglycemia are being in puberty, having poor diabetes control, limited self-management skills, low self-esteem, and living in difficult family constellations or psychosocial environments.^{13–15} In our case, there is the suspicion that the 16-year-old girl was suffering from comorbid psychiatric conditions or that psychosocial challenges were present. Her mother is a single parent, she had experienced domestic violence several times while the girl was present. Now, the mother is separated from the girl's father and has a new partner with whom the girl and the mother live together. The mother is working as a nurse. The family has no migration background. As we offered a psychological intervention, the family refused that option and denied the need of a family or individual psychotherapy. This aspect will be addressed, and psychotherapeutic treatment options will be discussed during all subsequent outpatient clinic visits. The girl's emotional well-being and the girl's mental health changed significantly after rediagnosis and change of her treatment. While being on MDI, she struggled with the everyday burden of her diabetes management (insulin injections, carb counting blood glucose monitoring) and felt strongly burdened by this chronic illness, especially dealing with friends and peers. The reclassification to T2D and change of therapy showed some relief in this regard. The girl no longer felt so restricted in her daily life. The diagnosis of T2D and obesity did not mean any additional stigma for her personally. Dealing with these two diseases was part of everyday life for her because her grandmother and parents were affected.

Factitious hypoglycemia is a life-threatening behavior, as it can cause brain damage and in the worst-case death of the affected patient. These patients use blood sugar lowering medications deliberately to cause hypoglycemia or severe symptoms for the purpose of seeking hospital admission or other primary gains e.g., getting parental attention. To avoid multiple hospitalizations, prevent unnecessary blood testing, and provide psychiatric referral, the recognition of this psychiatric disorder is crucial. Typical findings include low blood glucose, no or suppressed c-peptide levels, and an inappropriate high serum insulin concentration. So, there is an urgent need to diagnose and treat this condition at an early stage.

This case report shows that using a long-acting GLP-1-RA (dulaglutide) in adolescents with T2D is possible and feasible when approved therapeutic options for the pediatric population do not lead to adequate glycemic control in special situations. Additionally, our case emphasizes a lack of knowledge and therapeutic options on factitious hypoglycemia in adolescents with T2D, obesity, and psychiatric comorbidities.

CONFLICT OF INTEREST

LvdB is a member of the Medtronic and Abbott Diabetes Care advisory boards and has received speaker honoraria from Astra Zeneca, Medtronic, and Johnson & Johnson. JKM is a shareholder of deciding Clinical Software Ltd., a member of the Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor A/S, Roche Diabetes Care, and Sanofi-Aventis advisory boards and has received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, Novo Nordisk A/S, Roche Diabetes Care, Servier, and Takeda. TS declares no conflict of interest.

AUTHOR CONTRIBUTION

LvdB and JM collected and interpreted the data and drafted the manuscript. TS contributed to discussions. All authors critically revised and approved the final version of the manuscript.

ETHICAL APPROVAL

Verbal and written consent were obtained from the patient and her parents. Written informed consent was obtained from the patient and her parents for publication of this case series.

CONSENT

The patient and her parents provided written informed consent to publish her medical information.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Louisa van den Boom  <https://orcid.org/0000-0003-4823-2620>

Julia K. Mader  <https://orcid.org/0000-0001-7854-4233>

REFERENCES

1. Zeitler P, Arslanian S, Fu J, et al. ISPAD clinical practice consensus guidelines 2018: type 2 diabetes mellitus in youth. *Pediatr Diabetes*. 2018;19(Suppl 27):28-46. <https://doi.org/10.1111/pedi.12719>
2. Neu A, Feldhahn L, Ehehalt S, et al. No change in type 2 diabetes prevalence in children and adolescents over 10 years: update of a population-based survey in South Germany. *Pediatr Diabetes*. 2018;19(4):637-639. <https://doi.org/10.1111/pedi.12622>
3. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med*. 2019;381(7):637-646. <https://doi.org/10.1056/NEJMoa1903822>
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55(6):1577-1596.

5. Scott LJ. Dulaglutide: a review in type 2 diabetes. *Drugs*. 2020;80(2):197-208. <https://doi.org/10.1007/s40265-020-01260-9>
6. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8(12):728-742. <https://doi.org/10.1038/nrendo.2012.140>
7. Gribble FM, Reimann F. Metabolic messengers: glucagon-like peptide 1. *Nat Metab*. 2021;3(2):142-148. <https://doi.org/10.1038/s42255-020-00327-x>
8. Danne T, Bangstad HJ, Deeb L, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Insulin treatment in children and adolescents with diabetes. *Pediatric Diabetes*. 2014;15(S20):115-134. <https://doi.org/10.1111/pedi.12184> Erratum in: *Pediatr Diabetes*. 2015;16(6):463-464.
9. Kelly AS, Auerbach P, Barrientos-Perez M, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med*. 2020;382(22):2117-2128. <https://doi.org/10.1056/NEJMoa1916038>
10. Page LC, Freemark M. Role of GLP-1 receptor agonists in pediatric obesity: benefits, risks, and approaches to patient selection. *Curr Obes Rep*. 2020;9(4):391-401. <https://doi.org/10.1007/s13679-020-00409-7>
11. Sharma D, Verma S, Vaidya S, Kalia K, Tiwari V. Recent updates on GLP-1 agonists: current advancements & challenges. *Biomed Pharmacother*. 2018;108:952-962. <https://doi.org/10.1016/j.biopha.2018.08.088>
12. Bauman V, Sturkey AC, Sherafat-Kazemzadeh R, et al. Factitious hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2018;19(4):823-831. <https://doi.org/10.1111/pedi.12650>
13. Hood KK, Huestis S, Maher A, et al. Depressive symptoms in children and adolescents with type 1 diabetes. Association with diabetes-specific characteristics. *Diabetes Care*. 2006;29:1389.
14. Buchberger B, Huppertz H, Krabbe L, et al. Symptoms of depression and anxiety in youth with type 1 diabetes: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016;70:70-84.
15. Jain V, Satapathy AK, Yadav J. Surreptitious insulin overdosing in adolescents with type 1 diabetes. *Indian Pediatr*. 2015;52:701-703.

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