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Effects of once-weekly dulaglutide on juvenile type 2 diabetes mellitus and obesity in Korea: a pilot study

Ji Young Seo[1,*], Cha Gon Lee[1,*], Hoonsung Choi[2], Hong Kyu Lee[3], So Young Lee[4], Hyo-Jeong Kim[4], Kyong Yeun Jung[4], Jin Taek Kim[4]

[1]Department of Pediatrics, Nowon Eulji University Hospital, Eulji University School of Medicine, Seoul, Korea
[2]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Nowon Eulji University Hospital, Eulji University School of Medicine, Seoul, Korea

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Address for correspondence:
Jin Taek Kim
Division of Endocrinology and Metabolism, Department of Internal Medicine, Nowon Eulji University Hospital, Eulji University School of Medicine, 68 Hangeulbiseok-ro, Nowon-gu, Seoul 01830, Korea
Email: jtkimmd@eulji.ac.kr
https://orcid.org/0000-0001-7389-4867
*These authors contributed equally to this study as co-first authors.

Purpose: We sought to investigate the effects and side effects of once-weekly dulaglutide treatment for type 2 diabetes mellitus (T2DM) in patients <18 years of age in Korea.

Methods: : From the Eulji University Hospital database, we identified all patients <18 years of age diagnosed with T2DM and treated with dulaglutide from January 1, 2017, to July 31, 2022.

Results: We identified 5 patients <18 years of age treated with dulaglutide for T2DM management. Their mean (standard deviation [SD]) age was 16.6 (0.5) years. Four (80%) patients were female. The mean (SD) body mass index was 29.4 (5.1) kg/m^2, and the mean (SD) age at diagnosis was 15.2 (1.6) years. Four patients had been treated previously with metformin alone or in combination with insulin. Four patients were treated with 1.5 mg of dulaglutide and one was treated with 0.75 mg of dulaglutide. The mean (SD) hemoglobin A1c concentrations at baseline, 3 months after treatment, and 1 year after treatment, respectively, were 10.0% (2.2%), 6.5% (1.5%), and 6.7% (1.4%), with significant differences. In addition, at baseline, 3 months after treatment, and 1 year after treatment, the mean (SD) body weight values were 79.7 (13.3) kg, 80.2 (14.0) kg, and 81.1 (15.3) kg, with no significant difference.

Conclusion: Use of once-weekly dulaglutide for juvenile T2DM ensures very good glycemic control, with few side effects and good adherence, indicating its potential as a promising therapeutic agent in this age group. Nationwide studies are warranted to confirm our results.

Keywords: Adolescent, Dulaglutide, Obesity, Type 2 diabetes mellitus

Highlights

- The study shows the effects and side effects of once-weekly dulaglutide treatment for type 2 diabetes mellitus (T2DM) in patients under 18 years of age in Korea.
- We identified 5 patients treated with dulaglutide and found that the treatment led to significant improvements in glycemic control with minimal side effects.
- The patients' hemoglobin A1c concentrations showed notable changes over the study period over 1 year but the body weight change was not significant.
- This suggests that once-weekly dulaglutide could be a promising therapeutic option for juvenile T2DM.

Introduction

With the global epidemic of adult type 2 diabetes mellitus (T2DM), the number of children and adolescents with T2DM is also increasing dramatically.[1,2] Lifestyle change, measured as an increase in obesity rates due to excessive calorie intake and reduced physical activity, is

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the most important cause. In patients with juvenile diabetes, family history and genetic background are also important underlying factors. Diabetes is an important public health and social problem in the pediatric population, as, in this group, poor glycemic control is very common, and the occurrence rate of diabetic complications associated with longer lifetime disease exposure is very high.[3] Metformin and insulin are the traditional drugs approved for juvenile T2DM.[4] However, pharmacological therapies lead to suboptimal outcomes in many of these patients. Although insulin treatment is often required, in our daily practice, poor adherence to insulin has been observed commonly and has been associated with side effects, including hypoglycemia, weight gain, and the inconvenience of frequent injections.[5] Psychological problems, such as depression, anxiety, and low self-esteem, have also been observed frequently.[6,7] This group is usually under a high level of stress associated with academic and social achievements. Lifestyle modifications (i.e., diet and exercise therapy) are often not performed well.[8] Intervention studies using very-low-calorie diets are also limited in this age group. As a result, adolescent diabetic patients have often been neglected and exist in a treatment blindspot.

Recently, once-daily liraglutide and once-weekly exenatide injections were approved for adolescent T2DM patients.[9,10] When using the glucagon-like peptide (GLP)-1 agonist, the risk of hypoglycemia is very low, and it also has appetite-control, weight-loss, and glucose-control effects. Furthermore, the once-weekly dulaglutide injection, approved in 2014 and widely used for adult diabetes, showed good blood glucose-control efficacy, reduced cardiovascular events, and limited renal complications in adult T2DM patients.[11,12] The dulaglutide formulation is delivered via a once-weekly disposable pen, which does not require needle manipulation and is simple to use, facilitating better compliance than to insulin injections.

Recently, a clinical study on dulaglutide for juvenile T2DM was published.[13] In the study, at 26 weeks, the 0.75-mg and 1.5-mg administration groups showed average hemoglobin A1c (HbA1c)-lowering effects of 0.6% and 0.9%, respectively, and the rate of achieving an HbA1c concentration of <7% was 51%. The effectiveness was greater than that of the control group who received lifestyle modification alone or with metformin (14%). In addition, there were very few side effects. Notably, the study included a large number of Caucasians and Hispanics but very few Asians.

In this study, we aimed to describe, for the first time, the effects and side effects of dulaglutide in the 12- to 18-year-old juvenile T2DM age group.

Materials and methods

In this retrospective analysis, we used data from the Eulji University Hospital database. We identified all T2DM patients <18 years of age treated with dulaglutide from January 1, 2017, to June 31, 2022. Clinical characteristics, such as the age at the diagnosis of T2DM, sex, body mass index (BMI), blood pressure, and family history of diabetes, were obtained by reviewing patient medical records. Laboratory data, including plasma glucose, HbA1c, and fasting C-peptide levels, were also obtained. The presence of islet auto-antibodies (auto-Abs) (antiglutamic acid decarboxylase antibody [anti-GAD Ab], Islet antigen 2 antibodies [IA-2 Abs], and insulin auto-Abs) was determined from the data in the medical records. Levels of GAD Ab were measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA), those of insulin autoAb was measured by a different radioimmunoassay (BioSource, Nivelles, Belgium), and those of IA-2 Abs were measured by enzyme immunoassay assays using radiolabeled recombinant ICA512 as an antigen.

1. Statistical analysis

All continuous variables with normal distributions are expressed as mean±standard deviation (SD) values. To examine the changes in body weight and HbA1c concentration, the values at baseline, 3 months, and 12 months were compared. A Friedman test was conducted for the nonparametric analysis using repeated measured data. $P<0.05$ was taken to indicate statistical significance. All statistical analyses were performed using STATA 16.1 (StataCorp LLC, College Station, TX, USA).

2. Ethical statement

This study was approved by the Institutional Review Board (IRB) of Eulji University Hospital, Seoul, Korea (IRB No. 22-7-26). Informed consent was obtained from all individual participants included in the study.

Results

We identified 5 T2DM patients <18 years of age who were treated with 0.75 or 1.5 mg of dulaglutide administered once weekly. The clinical characteristics are shown in Table 1. The mean (SD) age of patients was 16.6 (0.5) years, 4 patients (80%) were female, and the mean (SD) BMI was 29.4 (5.1) kg/m^2. Additionally, the mean (SD) age at diagnosis was 15.2 (1.6) years. Four patients had been treated previously with metformin alone or in combination with insulin. Four patients were treated with 1.5 mg of dulaglutide and one was treated with 0.75 mg of dulaglutide. In addition, 1.5 mg of dulaglutide was used according to a dose-escalation schedule (i.e., for 2 weeks after treatment with 0.75 mg of dulaglutide). The previous metformin treatment was maintained. The mean (SD) HbA1c concentrations at baseline, 3 months after treatment, and 1 year after treatment, respectively, were 10.0% (2.2%), 6.5% (1.5%), and 6.7% (1.4%) (Fig. 1). These results were statistically different ($P=0.019$). Meanwhile, the mean (SD) body weight values at baseline, 3 months after treatment, and 1 year after treatment, respectively, were 79.7 (13.3) kg, 80.2 (14.0) kg, and 81.1 (15.3) kg (Fig. 1). These results were not statistically different ($P=0.819$).

1. Patient 1

Patient 1 was a 16-year-old male diagnosed with T2DM at 14 years of age. His weight was 96.7 kg, his height was 174.8 cm, and his BMI was 31.6 kg/m^2. He was diagnosed with fatty liver disease by abdominal sonography. His grandfather and his father's younger brother both had been diagnosed with T2DM. At diagnosis, his anti-GAD Ab, insulin Ab, and islet cell Ag results were all triple negative, and his fasting C-peptide level was 1.6 ng/mL. He was treated using 50 units of insulin and 1,700 mg of metformin; however, he showed poor insulin compliance, and his A1c level had remained very high for 2 years. His blood pressure was 130/80 mmHg. Prior to commencing the dulaglutide treatment, his A1c level was 11.7%, which decreased to 5.9% after 3 months of treatment with 1.5 mg of dulaglutide, and it was 6.7% at 1 year after beginning treatment. He felt that his appetite was controlled after treatment. His body weight was 96.7 kg before starting dulaglutide, 100.3 kg at 3 months after beginning treatment, and 104.3 kg at 1 year after beginning treatment. Other than poor appetite, he did not report any side effects. He showed a >90% rate of compliance with the injections.

2. Patient 2

Patient 2 was a 17-year-old female individual diagnosed with T2DM at 17 years of age. Her weight was 75 kg, her height was 167.2 cm, and her BMI was 26.8 kg/m^2. She was taking an antihypertensive medication, and her blood pressure was 130/80 mmHg. None of her family members had T2DM. At diagnosis, her anti-GAD Ab result was negative, and her fasting C-peptide level was 1.8 ng/mL. She had been treated previously with 24 units of insulin and 500 mg of metformin. Prior to commencing with the dulaglutide treatment, her A1c level was 12.5%, which decreased to 5.5% after 3 months of treatment with 1.5 mg of dulaglutide, and it was 6.2% at 1 year after beginning treatment. Her body weight was 75 kg before starting dulaglutide, 79 kg at 3 months after beginning treatment, and 82 kg at 1 year after beginning treatment. She reported a decreased appetite and no other side effects.

3. Patient 3

Patient 3 was a 17-year-old female individual diagnosed with T2DM at 14 years of age. Her height was 170.2 cm, her weight was 62.8 kg, and her BMI was 21.7 kg/m^2. Also, her blood pressure was 130/80 mmHg. Her mother and mother's family members had T2DM. At diagnosis, her anti-GAD Ab result was negative, and her fasting C-peptide level was 1.3 ng/mL. She was treated using 1,000 mg of metformin; however, her A1c level had remained high for 2 years. Prior to commencing dulaglutide treatment, her A1c level was 9.2%, which decreased to 6.1% after 2 months of treatment with 1.5 mg of dulaglutide, and it was 5.7% at 1 year after beginning treatment. Her body weight was 62.8 kg before starting dulaglutide, 62.5 kg at 3 months after beginning, and 64 kg at 1 year after beginning treatment. She felt that her appetite was controlled and continued with treatment.

4. Patient 4

Patient 4 was a 16-year-old female individual diagnosed with T2DM at 14 years of age. Her height was 149 cm, her weight was 75 kg, and her BMI was 33.8 kg/m^2. Also, her blood pressure was 120/80 mmHg. She had been diagnosed previously with fatty liver disease using abdominal sonography. Her mother had T2DM. At diagnosis, her anti-GAD Ab, insulin Ab, and islet cell Ag results were all triple negative, and her fasting C-peptide level was 2.5 ng/mL. She was treated using 1000 mg of metformin; however, her A1c level had remained high for 2 years. Prior to commencing dulaglutide treatment, her A1c level was 9.6%,

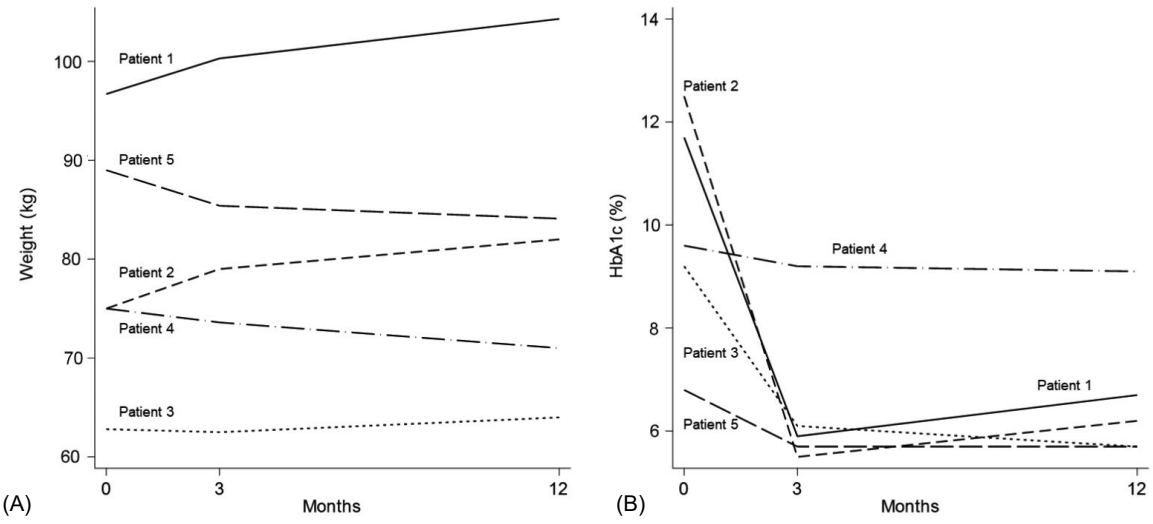

Fig. 1. Changes in the body weight (A) and hemoglobin A1c concentration (B) of each patient during the 12-month period.

which decreased to 9.2% at 3 months after beginning treatment with 1.5 mg of dulaglutide, and it was 9.1% at 1 year after beginning treatment. Her body weight was 75 kg before starting dulaglutide, 73.6 kg at 3 months after beginning treatment, and 71 kg at 1 year after beginning treatment. Although she showed no side effects, her A1c level remained higher than 7%, and additional insulin injection treatment commenced.

5. Patient 5

Patient 5 was a 17-year-old female individual who was diagnosed with T2DM at 17 years of age. Her height was 163.9 cm, her weight was 89 kg, and her BMI was 33.1 kg/m^2. She was diagnosed previously with hypertension and was treated with medication, and her blood pressure was 130/70 mmHg. There was no family history of diabetes. At diagnosis, her anti-GAD Ab result was negative, and her fasting C-peptide level was 10.3 ng/mL. She was drug-naive. Prior to commencing dulaglutide treatment, her A1c level was 6.8%, which decreased to 5.7% at 3 months after beginning treatment with 0.75 mg of dulaglutide, and it was 5.7% at 1 year after treatment. Since the initial hyperglycemia was mild and an appetite-suppressing effect was evident, the 0.75-mg dose of dulaglutide was maintained without increase. Her body weight was 89 kg before starting dulaglutide, 85.4 kg at 3 months after beginning treatment, and 84.1 kg at 1 year after beginning treatment. She felt that her appetite was controlled and showed no side effects.

Discussion

In this study, we showed that the use of a once-weekly dulaglutide treatment in juvenile T2DM in Koreans <18 years of age provided very good glycemic control and efficacy in the majority of patients. In addition, it led to few side effects and good compliance, which suggests its potential as a promising therapeutic agent in this age group. In 4 of the 5 enrolled patients, near-remission of glycemic dysregulation was maintained for 1 year. The maximum dose of 1.5 mg was used as the initial hyperglycemia was severe in the 4 patients, who did not experience any unacceptable side effects. With the use of a dose-escalation schedule, 1.5 mg of dulaglutide led to few gastrointestinal side effects. In 2 of the patients, the possibility

Table 1. Baseline clinical characteristics and treatment response

Characteristic	Patient (n=5)				
	1	2	3	4	5
Age (yr)	16	17	17	16	17
T2DM diagnosis (yr)	14	17	14	14	17
Sex	Male	Female	Female	Female	Female
BMI (kg/m^2)	31.6	26.8	21.7	33.8	33.1
BW (kg)	96.7	75	62.8	75	89
Height (cm)	174.8	167.2	170.2	149	163.9
BP (mmHg)	130/80	130/80	130/80	120/80	130/70
T2DM FH	Yes	No	Yes	Yes	No
Comorbid conditions	Fatty liver	HTN	None	Fatty liver	HTN
Islet autoAb					
GAD Ab	Neg	Neg	Neg	Neg	Neg
IA-2 Abs	Neg	N/A	N/A	Neg	N/A
Insulin autoAb	Neg	N/A	N/A	Neg	N/A
Fasting C-peptide (ng/mL)	1.6	1.8	1.3	2.5	10.3
HOMA-IR	6.4	N/A	N/A	2.9	11.2
Fasting G/I ratio (mg/10-4 U)	21.2	N/A	N/A	31.4	2.1
Previous treatment	Insulin/Metformin	Insulin/Metformin	Metformin	Metformin	None
Dulaglutide dosage (mg)	1.5	1.5	1.5	1.5	0.75
A1c (%)					
Initial	11.7	12.5	9.2	9.6	6.8
3 Months	5.9	5.5	6.1	9.2	5.7
12 Months	6.7	6.2	5.7	9.1	5.7
BW (kg)					
Initial	96.7	75	62.8	75	89
3 Months	100.3	79	62.5	73.6	85.4
12 Months	104.3	82	64	71	84.1
Side effects	None	None	None	None	None

T2DM, type 2 diabetes mellitus; BMI, body mass index; BW, body weight; BP, blood pressure; FH, family history; GAD Ab, glutamic acid decarboxylase antibody; IA-2 Abs, Islet antigen 2 antibodies; HTN, hypertension; autoAb, autoantibody; Neg, negative; N/A, not applicable; HOMA-IR, homeostatic model assessment for insulin resistance; Fasting G/I ratio, fasting glucose to insulin ratio.

of replacing the previous insulin treatment arose, while in the other 2 patients, insulin treatment could be delayed. In 1 patient, however, the glucose-lowering efficacy of 0.5% was less than expected. This patient was obese and had a family history of T2DM. Despite her normal fasting C-peptide level, beta-cell failure may have been the cause of her high glucose levels and suboptimal treatment response.

Our patients were in early stages of diabetes and did not have microvascular complications. However, in 4 of the 5 patients, obesity-related complications, such as fatty liver disease and hypertension, were observed despite their young age. Four of the 5 patients in this study were obese T2DM patients, and a genetic predisposition to diabetes was identified in 3 of these patients. All 3 patients with available homeostatic model assessment for insulin resistance data showed increased insulin resistance.

An appetite-control effect and a decrease in food intake were reported by all patients, but there was a significant difference in weight change.

Weight gain was observed in 3 of the 5 treated patients who had very high blood glucose levels at baseline, and their weight gain may have occurred due to improvement in the catabolic status from initial hyperglycemia. In the other 2 patients, the weight reduction was substantial, ranging from 4–5 kg of loss during a period of 1 year. Overall, the weight effect was neutral before and after dulaglutide treatment. In previously published clinical studies of juvenile T2DM using GLP-1 agonists, the GLP-1 agonist group did not exhibit a significant BMI-reduction effect compared to the placebo group. In the placebo group, the weight may have decreased due to rapidly worsening hyperglycemia, and, in the GLP-1 agonist group, the blood glucose reductions and release from the catabolic state may have caused weight gain. In adult T2DM studies, the counteracting effects of initial severe hyperglycemia on weight-loss from dulaglutide treatment have been reported.[14,15]

It is known that there are significant differences in the pathophysiology and natural course of T2DM between adolescents and adults. The rate of onset of the disease and the interaction between insulin resistance and impaired insulin secretory function may be different in early-onset T2DM.[16,17] Usually in adults, it takes several years for hyperglycemia to appear and progress; however, in children, the course progresses very rapidly. The TODAY (treatment options for type 2 diabetes in adolescents and youth) study showed that beta-cell function decreased by 20%–35% annually in pediatric T2DM, which was faster than the annual decline of 3%–5% recorded in adults.[16,18] Therefore, additional research is needed to determine whether the effectivity of dulaglutide seen in Korean juvenile diabetes occurs through an improvement in insulin resistance, an improvement in insulin secretory function, or both. GLP-1 agonist therapy acts on GLP-1 receptors in the pancreas, resulting in blood glucose–dependent insulin secretion and glucagon suppression. In addition, it acts on receptors in the central nervous system to suppress appetite and also acts in the intestine to slow gastric emptying and decrease postprandial blood glucose.[19,20]

Previously, T2DM had only been reported in 1%–2% of children, with type 1 diabetes mellitus accounting for the vast majority (>97%) of cases in children. However, recent reports from some areas in the United States have suggested as many as 8%–45% of newly diagnosed diabetes cases in children are T2DM cases.[21] Recently, it has become increasingly difficult to distinguish between the 2 subtypes of diabetes—namely, type 1 diabetes mellitus and T2DM—and double or hybrid diabetes, in which the 2 subtypes of diabetes coexist in a single patient, has been proposed as a new disease category.[22,23]

There are several limitations in this study. First, this study was a small retrospective study with short-term follow-up, and it is necessary to confirm the effect of dulaglutide on diabetic complications and additional side effects through long-term follow-up. Second, the test for the maturity-onset diabetes of youth (MODY) gene was not conducted in our patients; thus, MODY patients may have been included in this study. Third, it is difficult to analyze the exact mechanism of the glycemic effect of dulaglutide in these patients because the insulin secretion and resistance index were not regularly assessed during the treatment period.

In this study, there were a few patients in whom the switch from insulin to dulaglutide was successful. Since it is an important issue in children who use insulin, additional prospective clinical studies are required to confirm the results of this study. Moreover, it is also necessary to investigate whether the combination of insulin and dulaglutide therapy can be effective in hybrid types of pediatric diabetes, such as pediatric double diabetes.

In conclusion, once-weekly dulaglutide treatment was effective with few side effects in Korean juvenile T2DM. Nationwide studies are urgently needed to confirm the findings of this study.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Data availability: The data that support the findings of this study can be provided by the corresponding author upon reasonable request.

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ORCID

Ji Young Seo: 0000-0003-3471-7803
Cha Gon Lee: 0000-0001-7294-229X
Hoonsung Choi: 0000-0002-7202-7777

Hong Kyu Lee: 0000-0002-4926-0984
So Young Lee: 0000-0002-8904-3781
Hyo-Jeong Kim: 0000-0002-2180-891X
Kyong Yeun Jung: 0000-0003-4029-6312
Jin Taek Kim: 0000-0001-7389-4867

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