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【 ORIGINAL ARTICLE 】

Efficacy of Low-dose Dapagliflozin in Young People with Type 1 Diabetes

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Abstract:

Objective Young people with type 1 diabetes are likely to gain body weight and not achieve optimal glycemic control with only high doses of insulin. This study examined the efficacy of the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin as an adjunct-to-insulin therapy in young Japanese subjects with type 1 diabetes who had been diagnosed before 15 years old, were overweight, and had inadequate control despite receiving intensive insulin therapy.

Methods Twenty-two patients with type 1 diabetes (12 boys and 10 girls 16.0-33.9 years old) were involved in the study. All patients had a body mass index (BMI) >25 kg/m^2, glycated hemoglobin (HbA1c) level >7.0%, and daily insulin dose >0.5 units/kg. They were treated with a low dose of dapagliflozin (5.0 mg/day) as an adjunctive therapy to insulin. Fourteen patients were treated with multiple daily injections of insulin, while eight used an insulin pump.

Results The body weights and BMIs were significantly reduced during the 12-month study period (change of -4.4 kg and -1.7 kg/m^2, p<0.001, respectively). Their insulin dose was significantly decreased (-0.17 units/kg, *P* <0.001), and glycemic control was significantly improved (fasting plasma glucose: -18.7 mg/dL, HbA1c: -0.62%, p<0.001) during the study period. There was one episode of diabetic ketoacidosis, with no other problematic adverse events, including severe hypoglycemia, observed.

Conclusion The use of low-dose dapagliflozin as an adjunct therapy may be beneficial in overweight young people with poorly controlled type 1 diabetes.

Key words: dapagliflozin, glycemic control, sodium-glucose cotransporter 2 inhibitor, type 1 diabetes

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Introduction

Type 1 diabetes is caused by autoimmunity against pancreatic β-cells and is characterized by a lean phenotype and the absence of adipose tissue accumulation, leading to insulin resistance. However, patients with type 1 diabetes are often considered overweight, partly because of the rising prevalence of obesity in the general population and possibly due to intensive insulin therapy (1-4).

Intensive insulin therapy mimics physiological insulin secretion, thereby creating a hyperinsulinemic environment. This can contribute to weight gain and increased insulin resistance. Some young people require high doses of insulin to achieve optimal glycemic control owing to an approximately 30% increase in insulin resistance during puberty due to growth-hormone surges (5, 6) as well as irregular lifestyles and a low adherence to diabetes management in this age group (7). It was reported that 20-40% of children and adolescents with type 1 diabetes are overweight or obese (8). In addition, the majority with type 1 diabetes do not attain adequate glycemic control despite intensive therapy with high-dose insulin. Therefore, there is an unmet need for adjunct therapies to improve glycemic control without increasing the risk of hypoglycemia and body weight gain.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven effective as an adjunct-to-insulin therapy in type 1 diabetes. SGLT2 inhibitors improve glycemic control, including decreasing glycosylated hemoglobin (HbA1c) and

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glucose variability, maintaining optimal glycemic range, and preventing hypoglycemia (9). In addition, SGLT2 inhibitors can reduce body weight and decrease daily insulin doses (10). SGLT2 inhibitors function by decreasing glucose reabsorption in the proximal renal tubules, thereby increasing glucose excretion in the urine, a process that is independent of endogenous insulin secretion (10, 11). SGLT2 inhibitors are thus particularly attractive adjunct therapies to insulin, particularly in overweight patients with type 1 diabetes.

In Japan, two types of SGLT2 inhibitors, dapagliflozin and ipragliflozin, have been approved for use. The efficacy and safety of dapagliflozin in type 1 diabetes were initially evaluated in the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT) clinical trial, which comprised two studies: DEPICT 1 (24-week short term plus 28-week extension) (12, 13) and DEPICT 2 (24 weeks) (14). An important adverse event that was noted was the higher incidence of diabetic ketoacidosis (DKA) in the dapagliflozin groups than in the placebo groups for both DEPICT trials. The majority of these DKA cases resulted from insulin pump failure or a missed insulin dose; one case resulted from excessive alcohol intake. All events were resolved with standard care.

There have been several studies demonstrating the efficacy of SGLT2 inhibitors in adults with type 1 diabetes, but few have been conducted in young people with type 1 diabetes. It is important to evaluate the efficacy of this inhibitor class in young people because they are susceptible to glycemic dysregulation and body weight gain with intensive insulin therapy alone. This aggravation of glycemic control contributes to the occurrence or progression of microvascular and macrovascular complications. Therefore, we evaluated the efficacy of the SGLT2 inhibitor dapagliflozin as an adjunct-to-insulin therapy in young Japanese subjects diagnosed with type 1 diabetes before 15 years old who were overweight and had inadequate glycemic control despite intensive insulin therapy.

Materials and Methods

Study population

We enrolled young Japanese subjects with type 1 diabetes who were diagnosed before 15 years old and were <35 years old at the time of the study. They agreed to receive dapagliflozin (5 mg daily) as an adjunct therapy to insulin.

The inclusion criteria were as follows: 1) age between 15 and 35 years old; 2) duration of diabetes more than 1 year; 3) body mass index (BMI) more than 25 kg/m^2 (15); 4) HbA1c level over 7.0%; 5) daily insulin requirement more than 0.5 units/kg; 6) serum C-peptide level less than 0.5 ng/mL; and 7) existence of β-cell associated autoantibodies at the time of the diagnosis.

The subjects were treated with either multiple daily injections of insulin (MDI) using rapid-acting analogs and long-acting insulin analogs or continuous subcutaneous insulin infusion (CSII) using rapid-acting insulin analogs. No subjects used sensor-augmented insulin pump. The bolus insulin doses were determined by a carbohydrate-counting method, and the basal insulin doses were adjusted to attain self-monitored fasting plasma glucose (FPG) levels of 90-140 mg/dL. Twelve patients performed self-monitoring of blood glucose (SMBG), and the mean time of SMBG was 3.7±1.1 (2-6)/day, while 10 patients used intermittently scanned continuous glucose monitoring (isCGM) for their glucose management. The subjects regularly visited the outpatient clinic, and their FPG, HbA1c, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels were assessed at least once every two months. For glucose management, the subjects self-monitored their blood glucose or used sensor-based flash glucose monitoring (FreeStyle Libre; Abbott Diabetes Care, Witney, UK).

Study design

This study was a single-center, retrospective observational study and was conducted between May 2019 and April 2020. After obtaining informed consent from the patients and parents (for those <20 years old), dapagliflozin (5 mg daily) was added to insulin as an adjunct therapy. We compared changes in the body weight, BMI, and total daily insulin dose between baseline and 3, 6, and 12 months after the administration of dapagliflozin. We also compared changes in the FPG, HbA1c, fasting total cholesterol, and fasting LDL cholesterol levels during the study period, and the occurrence of severe hypoglycemia (SH) and DKA was also assessed. In the 10 patients using isCGM, changes in the frequency of time spent in the target glucose range (TIR; 70-180 mg/dL) and time spent below the target glucose range (TBR; <70 mg/dL) were assessed during the study period. Furthermore, we concurrently compared all measured glycemic indicators between the 3-, 6-, and 12-month periods. In addition, we compared laboratory data, including the hemoglobin (Hb) value and liver and renal functions [serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine and uric acid, urinary microalbumin/creatine ratio, and estimated glomerular filtration rate (eGFR)], between baseline and the 12-month study period to evaluate adverse events associated with the use of dapagliflozin.

Severe hypoglycemia was defined as plasma glucose (PG) levels <40 mg/dL with impaired consciousness or seizures necessitating assistance from other persons (16). DKA was defined as PG levels >200 mg/dL with venous pH <7.3, serum bicarbonate <5 mmol/L, and ketonemia with blood β-hydroxybutyrate levels >3 mmol/L or with moderate or severe ketonuria (17).

The PG concentration was measured using a glucose oxidase method. HbA1c was determined using high-performance liquid chromatography (reference range: 4.6-6.1%). Total cholesterol was measured using an enzymatic method (reference range: 120-220 mg/dL), and LDL choles-

Table 1. Patients' Characteristics at the Diagnosis.

Sex: male/female	12/10
Age (years)	25.5±5.1 (16.0-33.9)
Diabetic duration (years)	13.3±4.1 (7.0-20.3)
Body weight (kg)	73.2±6.9 (58.0-82.1)
BMI (kg/m^2)	28.4±2.4 (25.0-32.1)
C-peptide (ng/mL)	0.2±0.2 (<0.2-0.4)
Insulin treatment: MDI/CSII	14/8
Total insulin dose (unit/kg/day)	0.9±0.2 (0.6-1.3)
Ratio of basal inulin/ bolus insulin	0.4±0.2 (0.3-0.6)

BMI: body mass index. MDI: multiple daily injections of insulin, CSII: continuous subcutaneous insulin infusion

terol was measured using a direct method (reference range: 60-163 mg/dL).

Statistical analyses

The results are expressed as the means±standard deviation (SD). Two-sided 95% confidence intervals (CIs) for the mean change from baseline within the groups and for the difference in mean change between the groups were calculated. For the analyses, paired *t*-tests and Welch's *t*-test were used to detect differences within and between groups, respectively. The correlation between groups was evaluated using Spearman's rank correlation coefficient. p<0.05 was considered to indicate statistical significance.

All statistical analyses were performed with the Statistical Package for Social Science (SPSS) version 25.0 (IBM, Armonk, USA). Regarding the power calculation to detect a difference in HbA1c of 0.5% between the values at baseline and study end, using an α error of 0.05 and statistical power of 80%, a sample size of 17 patients was needed. Consequently, 22 patients were included in the analyses.

Study approval

This study was approved by the Human Ethics Review Committee of Nihon University Hospital (approval no. 20200901) and was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.

Results

Clinical background data

Twenty-two young people (12 boys and 10 girls) with type 1 diabetes were included in the study. All patients continued the 12-month study without dropping out. Patients' characteristics at the diagnosis are shown in Table 1. Fourteen patients were treated with MDI, and 8 were treated with CSII, with a mean daily total insulin dose of 0.9±0.2 (0.6-1.3) units/kg and a mean ratio of basal insulin/total insulin of 0.4±0.2 (0.3-0.6). No patient had progressive microvascular or macrovascular complications, autoimmune thyroiditis, or other autoimmune disease. Three patients had experienced severe hypoglycemia prior to the study.

Regarding laboratory data, the mean levels of FPG and HbA1c were 140.8±9.1 (126-162) mg/dL and 8.2% ±0.6% (7.3-9.5%), respectively. The mean fasting levels of serum total cholesterol and LDL cholesterol were 248.5±33.2 (189-298) mg/dL and 146.5±25.6 (110-203) mg/dL, respectively.

Changes in the body weight and BMI at 3, 6, and 12 months after dapagliflozin administration

From baseline, body weight was significantly reduced at 3, 6, and 12 months after administration of dapagliflozin. The mean changes (95% CI) at 3, 6, and 12 months were -2.4 kg (-1.4, -3.4, p<0.001), -2.9 kg (-1.4, -4.4, p<0.001), and -4.4 kg (-2.6, -6.3, p<0.001), respectively (Fig. 1). The BMI was also significantly reduced during the same period. The mean changes (95% CI) at 3, 6, and 12 months were -0.9 kg/m^2 (-0.5, -1.3, p<0.001), -1.1 kg/m^2 (-0.5, -1.6, p=0.001), and -1.7 kg/m^2 (-1.0, -2.4, p<0.001), respectively (Fig. 2).

Changes in total daily insulin doses at 3, 6, and 12 months after dapagliflozin administration

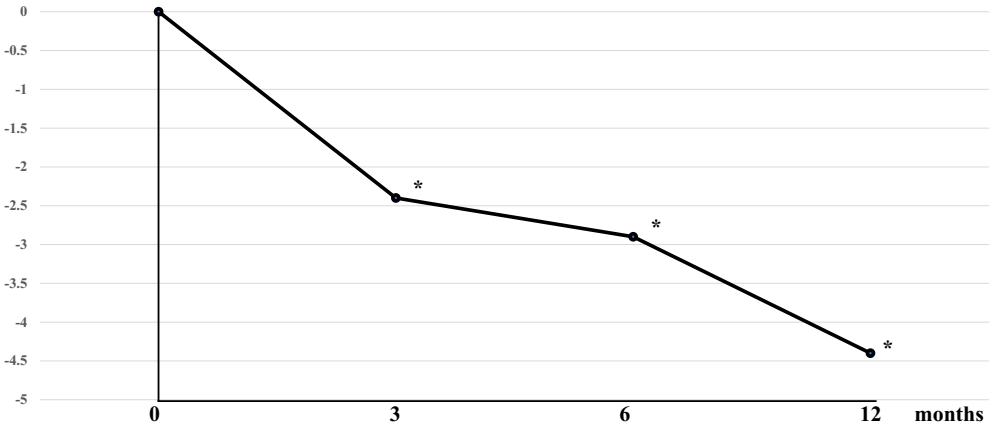
From baseline, the total daily insulin dose was significantly reduced at 3, 6, and 12 months after administration of dapagliflozin. The mean changes (95% CI) at 3, 6, and 12 months were -0.14 units/kg (-0.08, -0.20, p<0.001), -0.13 units/kg (-0.07, -0.20, p=0.001), and -0.17 units/kg (-0.10, -0.25, p<0.001), respectively (Fig. 3). The mean basal insulin/total insulin ratio at baseline, 3-, 6-, and 12-month period was 0.4±0.2 (0.3, 0.6), 0.4±0.3 (0.3, 0.6), 0.4±0.3 (0.3, 0.6) and 0.4±0.2 (0.3, 0.5), respectively, showing no significant changes during the study period.

Changes in FPG and HbA1c levels at 3, 6, and 12 months after dapagliflozin administration

From baseline, there was a significant reduction in FPG levels by dapagliflozin at 3, 6, and 12 months. The mean changes (95% CI) at 3, 6, and 12 months were -9.6 mg/dL (-3.5, -15.6, p=0.003), -12.8 mg/dL (-7.3, -18.3, p<0.001), and -18.7 mg/dL (-11.1, -26.4, p<0.001), respectively (Fig. 4). HbA1c levels were also reduced by dapagliflozin during the same period. The mean changes (95% CI) at 3, 6, and 12 months were -0.38% (-0.18, -0.57, p=0.001), -0.45% (-0.26, -0.64, p<0.001), and -0.62% (-0.36, -0.87, p<0.001), respectively (Fig. 5). Two of the 22 patients showed an HbA 1c level of <7.0 by 12 months.

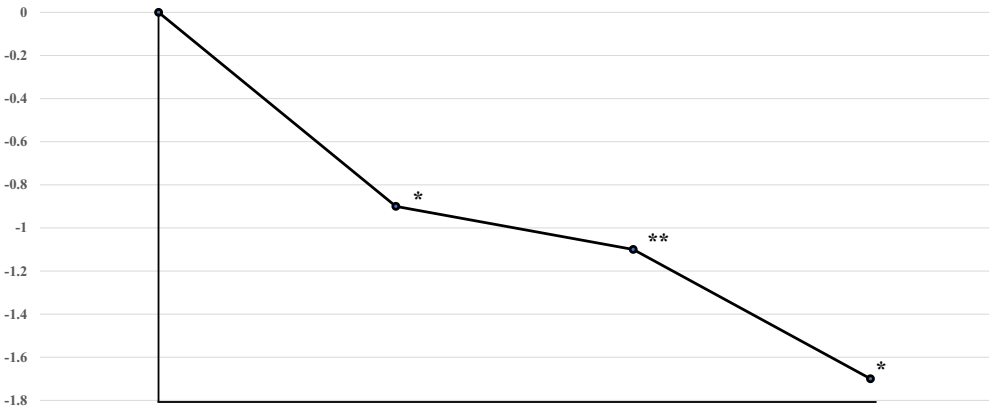
Changes in TIR and TBR in 10 patients using isCGM at 3, 6, and 12 months after dapagliflozin administration

The mean frequencies of TIR and TBR at baseline were 42.6±11.3% (23.0-77.0%) and 10.0±5.4% (5.0-14.0%), respectively. From baseline, there was a significant increase in TIR by dapagliflozin at 3, 6, and 12 months. The mean changes (95% CI) at 3, 6, and 12 months were 3.4 (0.5, 6.3, p=0.026), 5.9 (4.4, 7.4, p<0.001), and 10.3 (7.0, 10.3, p<



	0	3	6	12 months
BW (SD): kg	73.2 (6.9)	70.9 (5.9)	70.3 (5.9)	68.8 (6.3)
Change in BW (SD): kg		-2.4 (2.2)	-2.9 (3.3)	-4.4 (4.2)

Figure 1. **Changes in body weight at 3, 6, and 12 months after dapagliflozin administration. * vs. baseline, p<0.001. The solid lines show the changes in the mean of the population.**



	0	3	6	12 months
BMI (SD): mg/dL	28.4 (2.4)	27.5 (2.3)	27.3 (2.4)	26.7 (2.6)
Change in BMI (SD): kg/m^2		-0.9 (0.8)	-1.1 (1.2)	-1.7 (1.6)

Figure 2. **Changes in the BMI at 3, 6, and 12 months after dapagliflozin administration. BMI: body mass index. * vs. baseline, p<0.001, ** vs. baseline, p=0.001. The solid lines show the changes in the mean of the population.**

0.001), respectively (Table 2-A). In contrast, there was no significant change in TBR due to dapagliflozin at any time-point (Table 2-B).

Changes in serum total cholesterol and LDL cholesterol levels at 3, 6, and 12 months after dapagliflozin administration

From baseline, there was no significant reduction in serum total cholesterol levels with dapagliflozin at 3, 6, or 12 months. The mean changes (95% CI) at 3, 6, and 12 months were -1.3 mg/dL (1.6, -4.1, p=0.361), -2.4 mg/dL (0.4, -5.2, p=0.706), and -2.4 mg/dL (0.4, -5.3, p=0.710), respectively. The serum levels of LDL cholesterol were also not significantly reduced with dapagliflozin during the same period. The mean changes (95% CI) at 3, 6, and 12 months were -1.8 mg/dL (0.4, -12.0, p=0.096), -2.7 mg/dL (5.5, -5.3, p=0.057), and -2.6 mg/dL (5.6, -5.4, p=0.061), respectively.

Correlation between the reduction in body weight and changes in FPG, HbA1c, and total insulin doses after dapagliflozin administration

In the sub-analysis, we examined the correlation between the reduction in body weight and changes in FPG, HbA1c, and total insulin doses at 12 months after dapagliflozin administration. There was no significant correlation between the reduction in body weight and decrease in FPG, HbA1c, or total insulin dose (r=-0.375, p=0.086 for FPG, r=-0.326, p=0.138 for HbA1c, r=0.049, p=0.836 for total insulin dose, respectively).

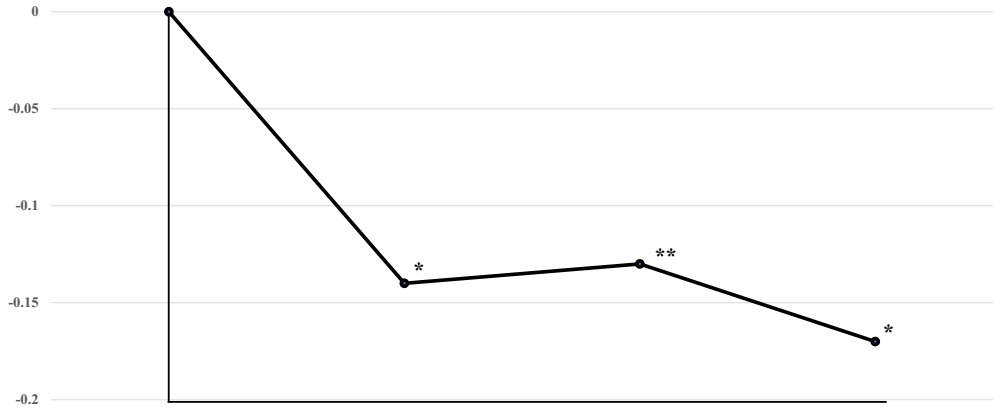


Figure 3. **Changes in total daily insulin doses at 3, 6, and 12 months after dapagliflozin administration. ID: insulin dose. * vs. baseline, p<0.001, ** vs. baseline, p=0.001. The solid lines show the changes in the mean of the population.**

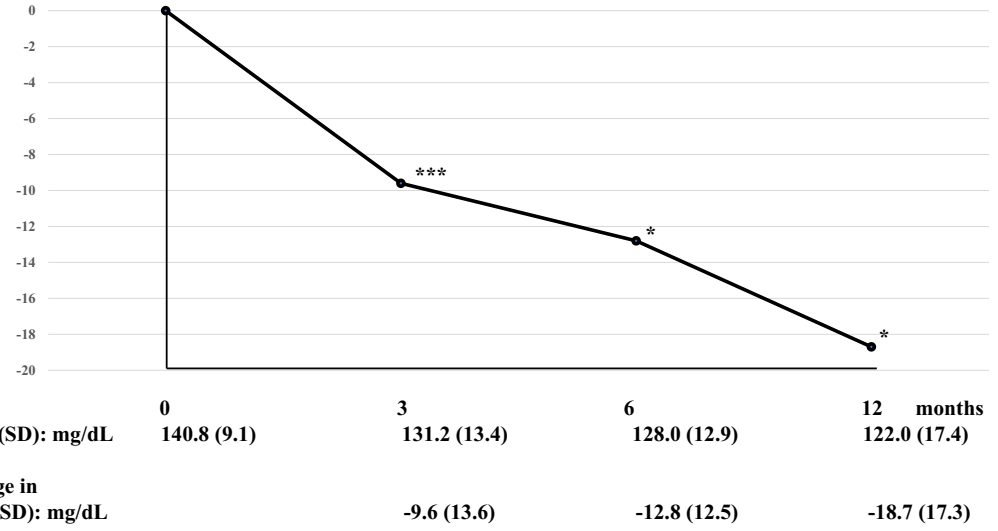


Figure 4. **Changes in FPG levels at 3, 6, and 12 months after dapagliflozin administration. FPG: fasting plasma glucose. * vs. baseline, p<0.001, *** vs. baseline, p=0.003. The solid lines show the changes in the mean of the population.**

Occurrence of SH and DKA

No patients experienced SH during the study period, but one girl (16 years old) developed DKA after using dapagliflozin for 2 months. Her body weight was 57.0 kg, with a BMI of 25.8 kg/m^2, and her HbA1c level was 9.3%. She received a daily insulin dose of 0.93 units/kg using MDI. She was experiencing psychological problems, received guidance from a psychotherapist, and was prescribed a minor tranquilizer. She voluntarily skipped injections of her long-acting insulin for 2 days because of improved SMBG values and appetite loss. She developed DKA with mildly elevated plasma glucose and β-hydroxybutyrate levels of 380 mg/dL and 6.8 mmoL/L, respectively, as measured at home by self-monitoring. After recovering from the DKA, she was reinstructed not to discontinue insulin injections and not to reduce insulin doses without physician approval. She understood the instructions and restarted the dapagliflozin adjunctive therapy. She did not experience DKA afterwards and completed the study as scheduled. Except for this patient, no patient showed a positive result for urine ketone body during the study period.

Adverse events associated with use of dapagliflozin

We compared the liver and renal functions between baseline and the 12-month study timepoint to evaluate adverse events associated with the use of dapagliflozin. Hemoglobin values, serum creatinine and uric acid levels, urinary micro-

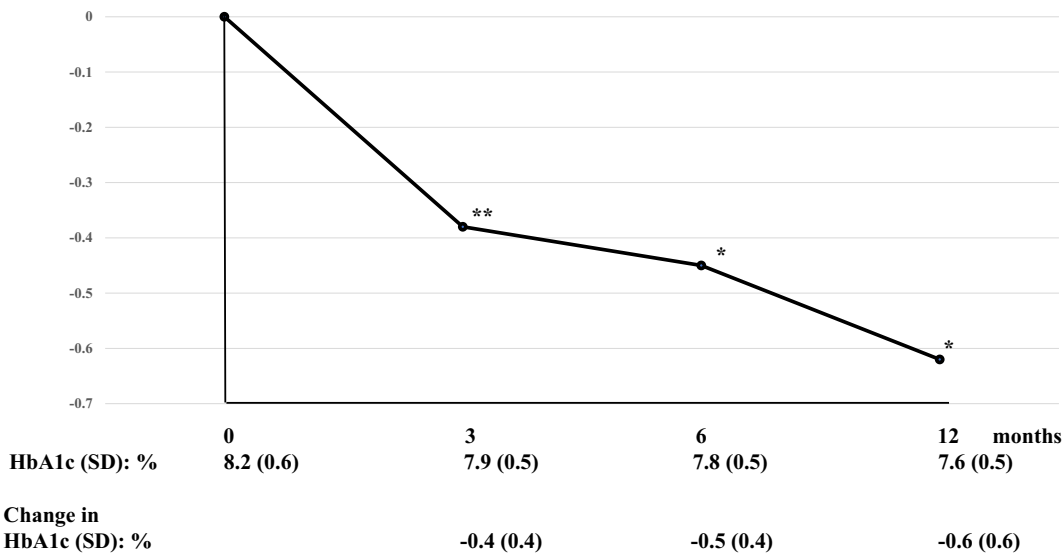


Figure 5. Changes in HbA1c levels at 3, 6, and 12 months after dapagliflozin administration. HbA1c: glycosylated hemoglobin. * vs. baseline, p<0.001, ** vs. baseline, p=0.001. The solid lines show the changes in the mean of the population.

Table 2-A. Changes in the TIR in 10 Patients Using IsCGM at 3, 6, and 12 Months after Dapagliflozin Administration.

	Mean TIR (95% CI)	Mean changes (95% CI)	p value
Basal line	42.6 (40.0, 45.2)	-	-
3 months	46.0 (42.0, 50.0)	3.4 (0.5, 6.3)	0.026
6 months	48.5 (46.2, 50.8)	5.9 (4.4, 7.4)	<0.001
12 months	52.9 (48.8, 57.0)	10.3 (7.0, 13.6)	<0.001

TIR: time in range, isCGM: intermittently scanned continuous glucose monitoring

Table 2-B. Changes in the TBR in 10 Patients Using IsCGM at 3, 6, and 12 Months after Dapagliflozin Administration.

	Mean TBR (95% CI)	Mean changes (95% CI)	p value
Basal line	10.0 (8.0, 12.0)	-	-
3 months	9.6 (7.8, 11.4)	-0.4 (-1.2, 0.4)	0.269
6 months	9.5 (7.3, 11.7)	-0.5 (-1.4, 0.4)	0.244
12 months	9.6 (7.3, 11.9)	-0.4 (-1.1, 0.3)	0.223

TBR: time below range, isCGM: intermittently scanned continuous glucose monitoring

Table 3. Adverse Events Associated with Use of Dapagliflozin.

	Baseline	24-month period	p value
Hb (g/dL)	13.3±0.7	13.2±0.7	0.1105
AST (U/L)	29.3±9.6	26.2±5.9	0.0298
ALT (U/L)	32.0±7.3	23.8±5.3	0.0001
Creatinine (mg/dL)	0.6±0.8	0.6±0.7	0.4803
Uric acid (mg/dL)	4.1±0.8	4.0±0.7	0.1765
eGFR (mL/min/1.73 m^2)	96.1±11.6	94.6±11.6	0.1093
Urine albumin (mg/g·creatinine)	9.9±3.7	8.4±2.9	0.1559
Urine ketone body	Negative in all patients	Negative in all patients	-

Hb: hemoglobin, eGFR: estimated glomerular filtration rate

albumin/creatinine ratio, and the eGFR did not markedly differ during the study period, but there was a significant decrease in the AST and ALT levels at 12 months (from 29.3±9.6 U/mL to 26.2±5.9 U/L in AST, p=0.0298, from 32.0±7.3 U/L to 23.8±5.3 U/L in ALT, p=0.0001), which may have been a beneficial effect of the reduction in body weight after dapagliflozin administration (Table 3). With regard to clinical adverse events of dapagliflozin, 15 of the 22 patients experienced polyuria, but none developed clinical dehydration. One girl suffered from a genital mycotic infection, and another developed a urinary tract infection, but these infections were mild. No participants discontinued dapagliflozin due to adverse events, and all completed the study.

Discussion

Young people with type 1 diabetes have difficulties achieving optimal glycemic control because of growth hormone-induced insulin resistance as well as their irregular lifestyles and dietary habits. Intensive insulin therapy, such as MDI and CSII, has been shown to be the only means for effectively improving glycemic control in young people with type 1 diabetes. However, fear of hypoglycemia and body weight gain are often barriers to achieving optimal insulin therapy (18). Therefore, adjunct therapies to achieve adequate glycemic control without the risks of hypoglycemia or body weight gain are required. Most adjunct therapies are not helpful in type 1 diabetes. However, one adjunct therapy to achieve satisfactory outcomes may involve SGLT2 inhibitors.

SGLT2 inhibitors reduce reabsorption of glucose and increase its urinary excretion according to plasma glucose levels (19). The risk of occurrence of hypoglycemia is low, as they naturally stop working when the filtered glucose load falls under 80 g daily and do not interfere with metabolic counterregulation (20). A previous animal-model study demonstrated that SGLT2 is expressed on pancreatic α-cells, and SGLT2 inhibitors increase glucagon secretion and hepatic gluconeogenesis (21). SGLT2 inhibitors are available as adjunct therapies for type 1 diabetes in several countries, including European countries, USA, Korea, Thailand, and Japan. In the present study, we used the SGLT2 inhibitor dapagliflozin, which has been approved for adjunctive use with insulin in Japan. A recent randomized, placebo-controlled study with dapagliflozin added to intensive insulin therapy in patients with inadequately controlled type 1 diabetes demonstrated effective reduction in HbA1c to -0.4% at 6 months and -0.3% at 12 months and increased time-in-range (70-180 mg/dL) without increasing the time below range (<70 mg/dL) (12-14). Treatment was well tolerated with similar frequencies of hypoglycemia to those observed for a TBR of less than 10% The overall adverse events profile was consistent with that observed in type 2 diabetes (12-14). It was also reported that the total daily insulin dose was reduced by -11.0% with moderate weight loss (-3.2% at 6 months and -3.5% at 12 months) (22). Recent studies have also shown more time spent in the optimal glucose range with the adjunct use of dapagliflozin without significant changes in the insulin dose (23, 24).

In the present study, we found significant improvements in glycemic control with decreased FPG and HbA1c levels and increased TIR using dapagliflozin as adjunct therapy for 12 months in Japanese young people with type 1 diabetes. Reductions in body weight and insulin requirement were also significant. These results corroborate those reported in previous Caucasian studies and show a beneficial effect of adjunct therapy of dapagliflozin in young people with type 1 diabetes, (13, 14, 17, 22); however, there was no change in TBR despite an increase in TIR. Several reports demonstrated an improved TIR without an increasing TBR (14, 24), and our results agree with those reported in previous studies. Furthermore, SGLT2 inhibitors can reportedly improve glycemic control and decrease daily insulin doses concomitant with a reduction in the body weight (9, 10, 12-14), but we did not note any correlation between the reduction in body weight and changes in any glycemic indicators.

Garg et al. reported that prandial and meal-associated insulin levels were largely reduced in clinical trials with SGLT 2 inhibitors (25), whereas some studies showed that a proportional dose reduction was similarly seen for both basal and bolus insulin (12, 14), namely, the basal insulin doses were primarily reduced basal insulin doses (26). In the present study, the basal insulin/total insulin ratio did not markedly differ before and after administration of dapagliflozin, so we considered that both the bolus and basal insulin doses decreased to the same extent. In obese and uncontrolled patients, both insulin doses may be reduced with dapagliflozin, as it can reduce both meal-associated hyperglycemia and FPG (12, 14, 25).

We did not evaluate the change in frequency of hypoglycemia in detail, but the TBR decreased and problematic hypoglycemic events did not occur during the study period. Young people are unlikely to maintain optimal glycemic levels despite intensive insulin therapy, and they tend to be overweight due to high-dose insulin. Even the low dose of dapagliflozin (5 mg) used in the present study was effective in improving glycemic control with a reduction in body weight and decrease in the insulin dose in overweight patients with uncontrolled type 1 diabetes. Therefore, the adjunctive use of dapagliflozin can be a beneficial option in young people with type 1 diabetes when insulin alone does not provide adequate glycemic control and promotes body weight increases concomitant with increased insulin doses.

Several studies of SGLT2 inhibitors with large sample sizes have shown that SGLT2 inhibitors increase LDL cholesterol levels (27-29). Increased LDL cholesterol might increase atherogenic risk in patients treated with SGLT-2 inhibitors. Conversely, the majority of studies have demonstrated that SGLT-2 inhibitors reduce triglycerides (TGs) and elevate high-density lipoprotein cholesterol levels, which decrease atherogenic risk (29-31). TG-lowering drugs, such as

fibrates and omega-3 fatty acids, are likely to increase LDL cholesterol, probably because they reduce lipid transfer between TG-rich lipoproteins, TGs, and LDL cholesterol (32). These findings were observed in adults with type 2 diabetes; however, we did not note any significant changes in the serum levels of total cholesterol or LDL cholesterol in the present study. Furthermore, high-density lipoprotein cholesterol levels were not evaluated in the present study.

An important adverse event in the use of SGLT2 inhibitors is the occurrence of DKA. Several reports have indicated a high incidence of DKA when using dapagliflozin and other SGLT2 inhibitors in large clinical trials (9, 12-14, 33). Both DEPICT trials using dapagliflozin reported a higher incidence of DKA in patients administered dapagliflozin than in those administered placebo: 2.2-3.4% in the 10 mg dapagliflozin group, 2.6-4.0% in the 5 mg dapagliflozin group, and 0-1.9% in the placebo group (12-14). Thus, the incidence of DKA appears to be dose-dependent. The majority of cases resulted from failure of CSII or missed insulin doses, and one case was caused by excessive alcohol intake. Some recent studies have also shown a significant increase in the risk of DKA (34-36). Some study patients with DKA had only slightly elevated glucose levels, referred to as euglycemic DKA. SGLT2 inhibitors may fail to suppress lipolysis and ketogenesis even if plasma glucose levels are not elevated (37, 38). Decreased renal clearance of ketone bodies is another mechanism underlying the aggravation of ketoacidosis. In this condition, the recognition, diagnosis, and treatment of DKA may be substantially delayed. Advanced Technologies & Treatments for Diabetes (ATTD) proposed an international consensus concerning the risk management of DKA, including appropriate points for the diagnosis, risk factors, and treatment in patients with type 1 diabetes treated with SGLT2 inhibitors (39). According to this international consensus, reduced carbohydrate/calorie intake, cessation of insulin or its inappropriate reduction, and female sex are risk factors for DKA related to SGLT2 inhibitor use, which are consistent with the characteristics of our DKA case. Our patient was also experiencing mental health issues, associated with a reduced adherence to diabetic management and non-compliance to basal-insulin injections. Lower doses of SGLT2 inhibitors are known to be related to lower risks of DKA (13, 14); however, in our case, DKA was observed despite treatment with the lowest dose of dapagliflozin (5 mg). The international consensus by ATTD did not include a young age as a potential risk factor for DKA (39); however, young people might be prone to developing DKA because they tend to have an irregular lifestyle and to fail their diabetes management. It is necessary to educate patients about the risk factors, monitoring, and management of DKA before initiation of dapagliflozin therapy. It is particularly important to inform patients with type 1 diabetes that insulin supplementation and carbohydrate intake are essential for adjunctive treatment with SGLT2 inhibitors (39). With regard to other adverse events, 15 of the 22 patients experienced polyuria, but none developed clinical dehydration, and only 1 girl suffered from a genital mycotic infection, while another developed a urinary tract infection. The frequency of genital and urinary tract infection was lower than previously reported (9, 12-14), and there has been no report describing an increase in infections in young people with type 1 diabetes. Huang et al. (40) reported that the use of dapagliflozin in patients with type 1 diabetes increased the risk of total adverse events compared with placebo but did not increase the risks of infection, DKA, or discontinuation due to adverse events in the meta-analysis of randomized controlled trials.

Several strengths associated with the present study warrant mention. First, the study subjects included young people with type 1 diabetes and BMIs greater than 25 who were expected to show substantial insulin resistance compared with leaner subjects and senior ones. Furthermore, their conditions were inadequately controlled even with intensive insulin therapy. Patients who are overweight with inadequate disease control despite receiving optimal insulin therapy are recommended as candidates for the use of adjunct SGLT2 inhibitors (41, 42). Second, we used the lowest reported dose of dapagliflozin, which is known to minimize adverse events, including DKA. Even this low dose of dapagliflozin proved effective in improving glycemic control and decreasing insulin requirements with reduced body weight management and minimum adverse events.

However, several limitations associated with the present study also warrant mention. First, this study was a single-center, retrospective, and observational study. The number of subjects was small. In addition, there was no control groups. Therefore, this study might be insufficient to conclude the efficacy of the SGLT2 inhibitor in young people with type 1 diabetes, and it will be necessary to corroborate the results with a larger number of subjects in a prospective multicenter study with control arms. Second, the study period was only one year, and adverse events could not be sufficiently assessed in such a short period. To address the issue of the long-term effects and safety, a longer observation period will be necessary in future studies. Third, we did not evaluate the frequency of mild-to-moderate hypoglycemia because we did not analyze detailed SMBG data and sensor-based flash glucose monitoring. Severe hypoglycemia was only evaluated according to recognized clinical symptoms and glucose levels <40 mg/dL. It is favorable to monitor mild-to-moderate hypoglycemia using continuous glucose monitoring with an alarm system. Fourth, we did not study the efficacy or safety of another SGLT2 inhibitor, ipragliflozin, which has been approved for use in type 1 diabetes in Japan. Miyauchi et al. (43) reported a case with atypical DKA and protracted hyperglycosuria after treatment with ipragliflozin. It will be necessary to examine the efficacy and safety, particularly regarding the occurrence of euglycemic DKA, of ipragliflozin among young Japanese subjects with type 1 diabetes. Finally, we did not encounter any patients with psychological problems or poor adherence to diabetic management. However, some young people with type 1 dia-

betes are unlikely to conduct regular injections of insulin and SMBG (7). These events might influence the efficacy of the treatment.

In conclusion, adjunct therapy with a low dose of the SGLT2 inhibitor dapagliflozin in Japanese young people with type 1 diabetes who were overweight with poorly controlled disease improved glycemic control and decreased insulin requirements, accompanied by a reduced body weight with the absence of problematic adverse events. Young people with type 1 diabetes are likely to gain body weight and not achieve optimal glycemic control, even with intensive therapy of high-dose insulin. Therefore, the use of low-dose dapagliflozin may be effective and safe as an adjunctive therapy in young people with type 1 diabetes.

Author's disclosure of potential Conflicts of Interest (COI).
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