Baseline low-density lipoprotein cholesterol predicts the hemoglobin A1c-lowering effect of dapagliflozin in Japanese patients with type 2 diabetes mellitus

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Abstract

Aims Our purpose was to clarify the predictive clinical characteristics of add-on therapy using dapagliflozin in patients with type 2 diabetes mellitus.

Methods This single-center, open-label, pilot study was conducted in 50 patients with type 2 diabetes mellitus. They were treated with 50 mg dapagliflozin, once daily. A total of 46 patients were successfully followed over 12 weeks of treatment with dapagliflozin. They were assessed for several clinical parameters before the start of the study and at 12 weeks. Multiple linear regression analysis was used to search for independent predictors of reduction of hemoglobin A1c (HbA1c) levels after 12 weeks of dapagliflozin add-on treatment (Δ HbA1c).

Results Dapagliflozin administration for 12 weeks resulted in significant reductions in baseline body mass index, systolic blood pressure, fasting plasma glucose, HbA1c, alanine aminotransferase, and uric acid. We were also able to show that HbA1c levels and low-density lipoprotein cholesterol (LDL-C) significantly correlated with Δ HbA1c. Furthermore, multiple linear regression analysis showed that baseline HbA1c and LDL-C significantly correlated with Δ HbA1c.

Conclusion Our prospective 12-week study showed that baseline HbA1c and LDL-C significantly contribute to the HbA1c-lowering effect of dapagliflozin.

Trial registration UMIN Clinical Trials Registry (UMIN000014922).

Keywords Type 2 diabetes mellitus · Dapagliflozin · Sodium-glucose cotransporter 2 inhibitor · Predictive clinical characteristics

Introduction

There is a continuing unmet need for novel glucose-lowering therapies that provide durable glycemic control while avoiding hypoglycemia, weight gain, and fluid retention, which are recognized problems with a number of existing glucose-lowering drugs [1–3]. Dapagliflozin is a new orally active sodium-glucose cotransporter 2 (SGLT2) inhibitor under development by Bristol-Myers Squibb and AstraZeneca. Dapagliflozin's mechanism of action is different from and complementary to the mechanism of currently available antidiabetic medications, resulting in direct and insulin-dependent elimination of glucose by the kidneys. The resulting glycosuria is associated with plasma glucose reductions and caloric loss, leading to weight reduction, and mild osmotic diuresis, leading to blood pressure reduction [4, 5]. Furthermore, because SGLT2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target effects [6]. As such, dapagliflozin offers an important additional strategy for improving glycemic control in patients with type 2 diabetes mellitus.

In order to use dapagliflozin as an add-on therapy for patients with type 2 diabetes mellitus, it is important to know the predictive clinical characteristics for its therapeutic efficacy. Therefore, we performed multiple linear regression analyses, with the index of reduction in

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the hemoglobin A1c (HbA1c) level as the dependent variable, to search for independent predictors of the reduction in the HbA1c level after 12 weeks of dapagliflozin treatment in Japanese patients with type 2 diabetes mellitus.

Materials and methods

Subjects

This single-center, open-label, pilot study was conducted in 50 patients with type 2 diabetes mellitus whose HbA1c was higher than 6.0 % at Iwasaki Naika Clinic. Patients were enrolled between August 2014 and January 2015. The specific patient eligibility criteria for inclusion were as follows: male and female patients with type 2 diabetes mellitus; age ≥ 20 years; treated with hypoglycemic agents that had not been changed for at least 6 months. Patients were excluded if they had type 1 diabetes; had nephropathy (serum creatinine: >1.1 mg/dl); were pregnant or breastfeeding; intended to become pregnant or were female and of childbearing age and not using adequate contraceptive methods; had known/suspected allergy to trial medication(s), excipients, or related products; and had any contraindications to dapagliflozin-therapy.

The 50 patients with type 2 diabetes mellitus were treated with 50 mg dapagliflozin once daily. They were assessed for several clinical parameters, including body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), HbA1c levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine, and uric acid before the start of the study and at 12 weeks. The primary outcome of the study was changes in HbA1c at 12 weeks after the start of the study (Δ HbA1c).

The study protocol conformed to the principles of the Declaration of Helsinki, and the study was approved by an institutional review committee at Iwasaki Naika Clinic. Written informed consent was obtained from all the patients. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000014922).

Statistical analysis

Data are expressed as mean $\pm$ standard deviation, unless indicated otherwise. Differences between two variables were examined for statistical significance using two-tailed Student's paired or unpaired *t* tests where appropriate.

Baseline HbA1c level minus HbA1c level at 12 weeks after the start of add-on dapagliflozin is expressed as Δ HbA1c. Baseline BMI level minus BMI level at 12 weeks after the start of add-on dapagliflozin is expressed as Δ BMI. Because the relationships between continuous variables (i.e., age, duration of diabetes, BMI, SBP, DBP, FPG, HbA1c, AST, ALT, GGT, LDL-C, HDL-C, TG, creatinine, uric acid, and Δ HbA1c) were nonlinear, correlations between sets of two independent continuous variables were determined using Spearman's rank correlation coefficient. Multiple stepwise regression analysis was used to determine independent predictors of Δ HbA1c and Δ BMI. All variables considered a clinically meaningful parameter for a given patient's background were employed as independent variables in multivariate analysis (i.e., sex, age, duration of diabetes, BMI, HbA1c, and LDL-C). The *F* value for the inclusion of the variables was set at 4.0. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed with StatView version 5.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient demographics and baseline characteristics

A total of 50 patients were enrolled in the present study, and 46 were successfully followed over the 12-week treatment with dapagliflozin. Four patients were excluded from analysis: one with cystitis, one with a feeling of exhaustion, and two who dropped out (Fig. 1). The baseline demographics and clinical characteristics of the study subjects are shown in Table 1. The mean age was

Fig. 1 Patient attrition

Table 1 Baseline demographics and characteristics of the patients

Variables	
<i>N</i>	46
Sex (male/female)	15/31
Age (years)	62.5 ± 10.8
Duration of diabetes (years)	14.3 ± 8.08
BMI (kg/m ²)	26.0 ± 4.85
SBP (mmHg)	131 ± 12.0
DBP (mmHg)	71.3 ± 10.9
FPG (mg/dl)	139 ± 18.1
HbA1c (%)	7.72 ± 0.925
AST (IU/l)	23.8 ± 13.2
ALT (IU/l)	31.7 ± 21.1
GGT (IU/l)	49.6 ± 34.8
LDL-C (mg/dl)	89.9 ± 20.9
HDL-C (mg/dL)	59.7 ± 18.5
TG (mg/dl)	124 ± 55.1
Creatinine (mg/dl)	0.667 ± 0.156
Uric acid (mg/dl)	4.94 ± 1.39
Antidiabetic medications (<i>n</i>)	
Sulfonylurea	36
Metformin	27
Thiazolidinedione	6
DPP-4 inhibitor	43
Insulin injection	10
GLP-1 analog injection	2
Hypolipidemic agents (<i>n</i>)	
Statins	35
Fibrates	5
Antihypertensive agents (<i>n</i>)	
ARBs/ACEIs	29
CCBs	23
β-blockers	0
Diuretics	4

Data are mean ± SD

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *ARBs* angiotensin II receptor blockers, *ACEIs* angiotensin-converting enzyme inhibitors, *CCBs* calcium channel blockers

62.5 ± 10.8 years, mean HbA1c was 7.71 ± 0.925 %, mean BMI was 26.4 ± 4.85 kg/m², and mean disease duration was 14.8 ± 8.08 years. Table 1 also shows the number of participants who received antidiabetic agent(s) orally prior to the study: sulfonylurea, 38; metformin, 30; thiazolidinedione, 7; dipeptidyl peptidase-4

(DPP-4) inhibitor, 47; insulin injection, 11; glucagon-like peptide-1 (GLP-1) analogue injection, 2.

Clinical characteristics of 46 patients who received dapagliflozin at baseline and after 12 weeks of treatment

Dapagliflozin administration for 12 weeks resulted in significant reductions in BMI (26.0 ± 4.85 to 25.9 ± 4.99 kg/m², $P < 0.0001$), SBP (131 ± 12.0 to 124 ± 12.6 mmHg, $P < 0.0001$), FPG (139 ± 18.1 to 123 ± 16.9 mg/dL, $P < 0.0001$), HbA1c (7.72 ± 0.925 to 7.22 ± 0.730 %, $P < 0.0001$), ALT (31.7 ± 21.1 to 27.9 ± 16.1 IU/l, $P = 0.0447$), and uric acid (4.94 ± 1.39 to 4.55 ± 1.36 mg/dl, $P = 0.0101$) (Table 2).

Correlation between baseline characteristics and change in HbA1c levels and BMI levels

We examined the correlation between the baseline characteristics and the change in HbA1c levels (ΔHbA1c) and found that baseline HbA1c levels and LDL-C significantly correlated with ΔHbA1c (Table 3). The distribution plots among ΔHbA1c and baseline HbA1c as well as baseline LDL-C are shown in Fig. 2. We also examined the correlation between the baseline characteristics and the change in BMI levels (ΔBMI) and found that baseline SBP, DBP, and HDL-C significantly correlated with ΔBMI (Table 3).

Table 2 Clinical characteristics of 46 patients who received dapagliflozin at baseline and after 12 weeks of treatment

Characteristic	Before treatment	After 12 weeks	<i>P</i> value
BMI (kg/m ²)	26.0 ± 4.85	25.9 ± 4.99	<0.0001
SBP (mmHg)	131 ± 12.0	124 ± 12.6	<0.0001
DBP (mmHg)	71.3 ± 10.9	70.5 ± 11.1	0.5383
FPG (mg/dl)	139 ± 18.1	123 ± 16.9	<0.0001
HbA1c (%)	7.72 ± 0.925	7.22 ± 0.730	<0.0001
AST (IU/l)	23.8 ± 13.2	22.4 ± 9.26	0.3315
ALT (IU/l)	31.7 ± 21.1	27.9 ± 16.1	0.0447
GGT (IU/l)	49.6 ± 34.8	44.8 ± 40.6	0.0967
LDL-C (mg/dl)	89.9 ± 20.9	91.0 ± 21.4	0.6848
HDL-C (mg/dl)	59.7 ± 18.5	60.8 ± 18.9	0.4554
TG (mg/dl)	124 ± 55.1	125 ± 58.3	0.9411
Creatinine (mg/dl)	0.667 ± 0.156	0.691 ± 0.164	0.1541
Uric acid (mg/dl)	4.94 ± 1.39	4.55 ± 1.36	0.0101

Data are means ± SD

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ-glutamyltransferase, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides

Multivariate linear regression analysis of baseline characteristics to assess the contribution to change in HbA1c levels

To assess the contribution to change in HbA1c levels, we performed multivariate linear regression analysis of the baseline clinical characteristics. In the analysis, HbA1c levels and LDL-C significantly correlated with the change in HbA1c levels (Δ HbA1c), suggesting that these characteristics may be predictive factors for the efficacy of dapagliflozin add-on therapy (Table 4). To assess the contribution to change in BMI levels, we also performed multivariate linear regression analysis of baseline clinical characteristics; however, there were no significant

correlations with change in BMI levels (Δ BMI) (data not shown).

Discussion

In this single-center, open-label, pilot study, we investigated the efficacy of dapagliflozin treatment in 50 Japanese outpatients with type 2 diabetes mellitus; 46 patients were successfully followed over a 12-week treatment period. We demonstrated that dapagliflozin administration for 12 weeks resulted in significant reductions in BMI, SBP, FPG, HbA1c, ALT, and uric acid (Table 2). Kaku et al. also reported that in Japanese patients with type 2 diabetes mellitus, dapagliflozin administration for 12 weeks resulted in significant reductions in FPG and HbA1c [7]. Kashiwagi et al. reported that ipragliflozin as an add-on to a sulfonylurea or pioglitazone significantly improved glycemic control in Japanese type 2 diabetes patients [8, 9]. We were also able to show that HbA1c levels and LDL-C significantly correlated with Δ HbA1c (Table 3). Furthermore, multiple linear regression analysis showed that baseline HbA1c and LDL-C significantly correlated with Δ HbA1c. Therefore, we demonstrated that baseline HbA1c and LDL-C contributed to the HbA1c-lowering effect of dapagliflozin in Japanese patients with type 2 diabetes mellitus (Table 4), confirming the previously reported association between the baseline HbA1c and the HbA1c-lowering effect of dapagliflozin [10].

Among the 46 patients who completed the study, 35 (76 %) received statin prior to the study. Therefore, we performed multiple linear regression analysis that included LDL-C and statin therapy prior to the study. LDL-C was significantly associated with Δ HbA1c, including statin therapy (data not shown).

Dapagliflozin had varied effects on plasma lipids. Changes in LDL-C (−0.5 to +9.5 %), HDL-C (+2.1 to +9.3 %), and TG (−0.9 to −10.6 %) were noted in clinical trials [11]. In a pooled analysis of 13 clinical trials, patients treated with 10 mg of dapagliflozin had increased LDL-C

Table 3 Correlation of the Δ HbA1c and Δ BMI with other associated baseline variables

	Δ HbA1c		Δ BMI	
	<i>r</i> value	<i>P</i> value	<i>r</i> value	<i>P</i> value
Age	−0.033	0.8267	0.246	0.0999
Duration of diabetes	−0.066	0.6648	0.277	0.0624
BMI	−0.152	0.3164	−0.232	0.1206
SBP	0.234	0.1173	−0.323	0.0279
DBP	0.057	0.7050	−0.307	0.0374
FPG	0.118	0.4376	0.073	0.6339
HbA1c	0.628	<0.0001	−0.046	0.7615
AST	0.139	0.3602	−0.011	0.9429
ALT	0.191	0.2059	−0.116	0.4448
GGT	−0.038	0.8028	−0.135	0.3742
LDL-C	0.427	0.0028	0.129	0.3932
HDL-C	−0.211	0.1591	0.336	0.0219
TG	−0.023	0.8779	−0.133	0.3801
Creatinine	−0.125	0.4111	0.021	0.8927
Uric acid	0.042	0.7845	−0.105	0.4875

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* γ -glutamyltransferase, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides

Fig. 2 Distribution plots of **a** Δ HbA1c (%) versus baseline HbA1c and **b** baseline LDL cholesterol

Table 4 Multiple regression analysis of the relationship between Δ HbA1c and other associated variables

Risk factors	Regression coefficient	Standard error	Standardized regression coefficient	P
Age (years)	0.001	1.102	0.009	0.9476
Gender	0.205	0.167	0.138	0.2274
Duration of diabetes	−0.021	0.011	−0.246	0.0594
BMI	−0.012	0.018	−0.081	0.5161
HbA1c	0.460	0.087	0.606	<0.0001
LDL-C	0.011	0.004	0.317	0.0079

The dependent variable is the Δ HbA1c. The independent variables are age, gender, duration of diabetes, BMI, HbA1c, and LDL-C. R^2 for the entire model = 0.561

BMI body mass index, *LDL-C* low-density lipoprotein cholesterol

(2.9 versus −1.0 %) at 24 weeks compared with patients treated with placebo [12]. In our study, LDL-C was also increased after 12 weeks of treatment with dapagliflozin, but not significantly.

It was reported that conditions with increased glucagon levels decreased plasma LDL-C by inducing the number of hepatic LDL receptors [13] and that dapagliflozin increased the postprandial plasma glucagon concentration [14, 15]. As LDL-C is associated with a component of glucagon, baseline LDL-C might be related to the HbA1c-lowering effect of dapagliflozin.

The major limitation of this study is the limited number of subjects studied. All the subjects received add-on therapy of various kinds. Drug-naïve patients should be included in our study. In addition, the study duration may be a limitation, because the extent of glycemic response may not have been fully elucidated over this time frame. Furthermore, other markers that could have affected the HbA1c reduction due to dapagliflozin were not measured in this study, such as waist circumference as a marker of central obesity, markers for the assessment of β -cell function in homeostatic models, and basal active GLP-1. Therefore, more subjects and more detailed clinical parameters are needed in the future to avoid overestimation of the data obtained.

In conclusion, this prospective 12-week study showed that baseline HbA1c and LDL-C significantly contribute to the HbA1c-lowering effect of dapagliflozin. More long-term analysis of a larger patient population is warranted to confirm these findings.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study.

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