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ORIGINAL RESEARCH

Predictors for the Treatment Effect of Sodium Glucose Co-transporter 2 Inhibitors in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Predictors for the effect of sodium glucose co-transporter 2 (SGLT2) inhibitors at lowering hemoglobin A1c (HbA1c) levels in type 2 diabetes mellitus patients remain unclear. We therefore aimed to elucidate these predictors in type 2 diabetes patients after 3 months of SGLT2 treatment.

Methods: A total of 302 consecutive type 2 diabetes patients who had been treated with SGLT2 inhibitors as monotherapy or add-on therapy to existing antidiabetic treatments were enrolled retrospectively. After excluding 27 patients whose HbA1c levels could not be evaluated 3 months after treatment, the glucose-lowering effects of SGLT2 inhibitors were assessed in 275 patients by measuring HbA1c levels before and 3 months after treatment. The predictors for changes in HbA1c levels after 3 months of treatment were evaluated.

Results: SGLT2 inhibitor treatment for 3 months decreased HbA1c levels from $7.8 \pm 1.2\%$ to $7.4 \pm 1.0\%$ ($p < 0.0001$). A multiple regression analysis showed that the independent determinants for SGLT2 inhibitor treatment effect included decreased HbA1c levels after 1 month of treatment, high baseline HbA1c levels, and a high estimated glomerular filtration rate (eGFR).

Conclusion: We show that type 2 diabetes patients who received the greatest glucose-lowering effect with SGLT2 inhibitor treatment were those with preserved renal function (high

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baseline eGFR) and high baseline HbA1c levels. Moreover, SGLT2 inhibitor treatment efficacy could be predicted by the patients' initial response to treatment.

Keywords: Estimated glomerular filtration rate; Glucose-lowering; HbA1c; Predictors; Type 2 diabetes mellitus

INTRODUCTION

Selective sodium glucose co-transporter 2 (SGLT2) inhibitors improve glucose metabolism by inhibiting SGLT2, which is expressed in the proximal tubule of the kidney. Thus, SGLT2 inhibitors enhance the renal excretion of glucose and decrease blood glucose levels in patients with type 2 diabetes [1].

The EMPA-REG OUTCOME trial has shown a significant reduction in cardiovascular-related and all-cause mortality in patients with type 2 diabetes, who are at high risk for cardiovascular events, when the SGLT2 inhibitor empagliflozin was added to their standard care [2]. The pleiotropic effects of SGLT2 inhibitors, including lower blood pressure, body weight, visceral fat content, uric acid, albuminuria, increased high-density lipoprotein (HDL) cholesterol, and improved endothelial function might be involved in the improvement of cardiovascular outcomes [3, 4].

There are some patients whose HbA1c levels do not respond to SGLT2 inhibitors therapy, or whose HbA1c levels rebound after an initial decrease in response to SGLT2 inhibitors. If we can predict patients who show a significant response to treatment with SGLT2 inhibitors, it would be of great clinical value; however, few studies have distinguished the patients who show the greatest glucose-lowering effect upon treatment with SGLT2 inhibitors.

In this study, we aimed to elucidate the predictors for changes in HbA1c levels after 3 months of treatment in a clinical setting.

METHODS

Study Population

SGLT2 inhibitors (ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, or empagliflozin) were administered to 302 consecutive type 2 diabetic patients as monotherapy or as an add-on therapy to existing antidiabetic treatments at the Department of Cardiovascular Medicine and Department of Endocrinology and Metabolism at the Tokushima University Hospital, Japan, and the Department of Internal Medicine at the Shikoku Central Hospital, Japan, from July 2014 to August 2016.

A total of 27 patients were excluded from the analysis as we could not evaluate their HbA1c levels 3 months after treatment due to several reasons, including discontinuation of treatment or minor adverse effects of the SGLT2 treatment (Fig. 1). No patients experienced severe side effects such as hypoglycemic episodes or diabetic ketoacidosis resulting in a hospital visit or hospitalization during the 3-month SGLT2 inhibitor treatment period.

We enrolled 275 type 2 diabetes patients and evaluated the glucose-lowering effects of SGLT2 inhibitors (Fig. 1).

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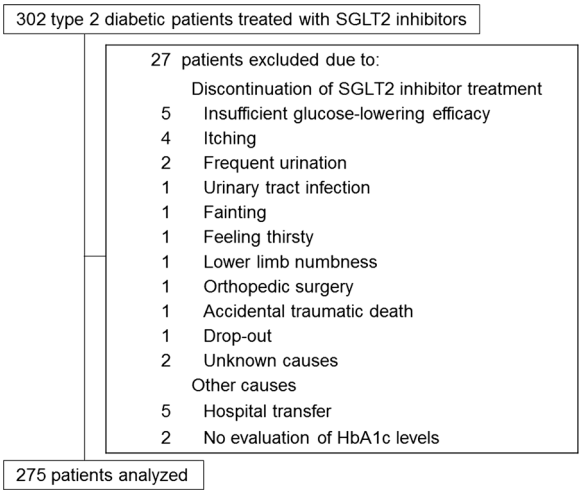

Fig. 1 Flow chart of the study

Measures

The glucose-lowering effects of the SGLT2 inhibitors (HbA1c at 3 months—baseline HbA1c) were retrospectively assessed in 275 patients by measuring HbA1c levels (National Glycohemoglobin Standardization Program reference values) before and 3 months after treatment. The proportion of patients who achieved glycemic control of the HbA1c target of < 7%, recommended by the guideline to reduce complications of diabetes, was also calculated [5]. In addition to HbA1c levels, we assessed the patients' serum lipid profiles [including low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglyceride levels]; renal function, including serum creatinine levels and estimated glomerular filtration rates (eGFR); hematocrit; body weight; and blood pressure. Predictors for changes in HbA1c levels after 3 months of treatment were evaluated by single and multiple regression analysis.

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, as revised in 2013. The study protocol was approved by the Ethics Committee of Tokushima University Hospital (No. 2432) and Shikoku Central Hospital (No. 25).

Statistical Analysis

We calculated the averages for continuous variables. Values are expressed as means ± standard deviations and percentages for continuous and categorical parameters, respectively. Seasonal changes in HbA1c levels were evaluated by analysis of variance (ANOVA), and changes in HbA1c levels with/without concomitant antidiabetic drug treatment were evaluated using the unpaired *t* test and multiple regression analysis. HbA1c levels, blood glucose levels, and other clinical parameters before and 3 months after treatment with SGLT2 inhibitors were compared using the paired *t* test. The degrees of association among independent variables for HbA1c levels after 3 months of treatment were assessed by multiple regression analysis. All statistical analyses were performed using the JMP software (v.11; SAS Institute, Cary, NC, USA). Statistical significance was defined as $p < 0.05$.

RESULTS

Clinical Characteristics of the Study Participants

The characteristics of the patients enrolled in this study are shown in Table 1. They had moderate diabetes with a mean HbA1c level of 7.8 ± 1.2% and were obese with a mean body mass index (BMI) of 31 ± 7 kg/cm^2. Their mean eGFR was 83 ± 26 mL/min/1.73 m^2.

Effects of SGLT2 Inhibitor Treatment on HbA1c Levels

Three months of treatment with SGLT2 inhibitors led to a significant decrease in HbA1c levels (HbA1c at 3 months—baseline HbA1c: − 0.4 ± 0.9%, $p < 0.0001$; Table 2).

In the analysis of seasonal changes in HbA1c levels 3 months after the start of SGLT2 inhibitors treatment, we found that HbA1c levels were higher in February and March when compared to other months; however, this was not statistically significant (Fig. 2).

Table 1 Clinical characteristics of study subjects

Variables	
Number of patients	275
Male/female	153 (56%)/122 (44%)
Age (years)	54 ± 13
Body mass index (kg/m^2)	31 ± 7
HbA1c (%)	7.8 ± 1.2
Casual blood glucose (mg/dL)	167 ± 57
LDL cholesterol (mg/dL)	113 ± 33
Triglyceride (mg/dL)	212 ± 297
HDL cholesterol (mg/dL)	51 ± 15
Hematocrit (%)	41 ± 5
Serum creatinine (mg/dL)	0.76 ± 0.39
eGFR (ml/min/1.73 m^2)	83 ± 26
Systolic blood pressure (mmHg)	134 ± 16
Diastolic blood pressure (mmHg)	80 ± 12
Co-morbidities	
Hypertension	162 (59%)
Dyslipidemia	141 (51%)
Coronary artery disease	28 (10%)
Stroke	3 (1%)
Antidiabetic drugs	
SGLT2 inhibitors, mean dose	
Ipragliflozin	38 (14%), 45 ± 10 mg
Dapagliflozin	71 (26%), 5.5 ± 1.5 mg
Luseogliflozin	50 (18%), 2.7 ± 0.6 mg
Tofogliflozin	51 (19%), 20 ± 0 mg
Canagliflozin	50 (18%), 100 ± 0 mg
Empagliflozin	15 (5%), 12 ± 5 mg
Other anti-diabetic drugs	
DPP-4 inhibitors	123 (45%)
α-Glucosidase inhibitors	40 (15%)
Sulfonylureas	27 (10%)
Biguanides	131 (48%)
Glinides	27 (10%)
Thiazolidinediones	32 (12%)
Insulin	86 (31%)
GLP-1 receptor agonist	37 (13%)

Unless indicated otherwise, data are presented as mean ± standard deviation

HbA1c glycated hemoglobin A1c, *SGLT2* sodium glucose co-transporter 2, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1

Pharmacodynamic differences among SGLT2 inhibitors due to varying renal thresholds for glucose excretion and/or SGLT1/2 selectivity have been reported; thus, the glucose-lowering effects might also differ by type of SGLT2 inhibitor [6]. However, we did not observe any statistically significant differences in HbA1c levels after 3 months of treatment for the 6 different SGLT2 inhibitors in the ANOVA (Supplemental Fig. 1) nor in the multiple regression analyses adjusted for baseline eGFR (data not shown).

The glucose-lowering effect of SGLT2 inhibitors was greater when SGLT2 inhibitors were used in combination with biguanides when compared to using them without biguanides (without vs. with biguanides: $-0.31 \pm 0.91\%$ vs. $-0.55 \pm 0.94\%$; $p < 0.05$); however, there were no differences in the glucose-lowering effect of SGLT2 inhibitors between the groups with/without other antidiabetic drugs (Fig. 3). In addition, we found no differences in the glucose-lowering effect of SGLT2 inhibitors when SGLT2 inhibitors were used alone ($n = 37$) versus when they were used in combination with other antidiabetic drugs ($n = 238$) (monotherapy vs. combination therapy: $-0.33 \pm 0.97\%$ vs. $-0.44 \pm 0.93\%$; Fig. 3). The proportion of patients who achieved glycemic control of the HbA1c target of $< 7\%$ increased

Table 2 The effects of SGLT2 inhibitors on clinical parameters

Variables	Available data, *n*	Before the treatment	3 month after the treatment	*p* value
HbA1c (%)	275	7.8 ± 1.2	7.4 ± 1.0	< 0.0001
Rate of HbA1c < 7%, *n* (%)	275	76 (28%)	108 (39%)	< 0.0001
Random blood glucose (mg/dL)	271	166 ± 57	153 ± 50	0.0002
Body weight (kg)	242	82 ± 19	80 ± 18	< 0.0001
LDL cholesterol (mg/dL)	217	113 ± 33	110 ± 31	0.12
Triglyceride (mg/dL)	229	212 ± 297	203 ± 193	0.68
HDL cholesterol (mg/dL)	228	51 ± 15	52 ± 14	0.02
Hematocrit (%)	234	41 ± 5	43 ± 5	< 0.0001
Serum creatinine (mg/dL)	255	0.76 ± 0.39	0.79 ± 0.42	< 0.0001
eGFR (ml/min/1.73 m^2)	255	83 ± 26	80 ± 25	0.001
Systolic blood pressure (mmHg)	261	134 ± 16	131 ± 18	0.003
Diastolic blood pressure (mmHg)	261	80 ± 12	78 ± 12	0.019

Unless indicated otherwise, data are presented as mean ± standard deviation
HbA1c glycated hemoglobin, *SGLT2* sodium glucose co-transporter 2, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate

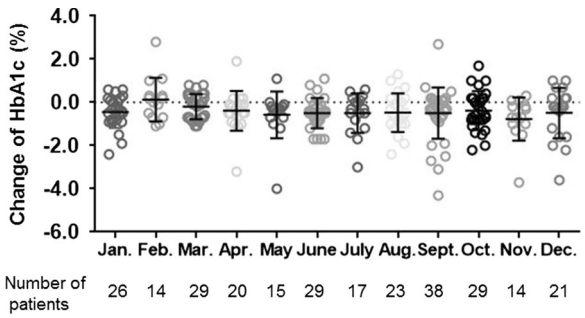

Fig. 2 Seasonal changes in HbA1c levels 3 months after the start of SGLT2 inhibitor treatment

from 28% to 39% within 3 months of SGLT2 inhibitor treatment (Table 2).

Effects of SGLT2 Inhibitors on the Lipid Profile and Renal Function

We noted a significant increase in HDL cholesterol levels (HDL cholesterol at 3 months—baseline HDL cholesterol: 1.2 ± 7.5 mg/dL, $p < 0.05$; Table 2) in response to treatment with SGLT2 inhibitors; however, no such effect was observed for LDL cholesterol or triglyceride levels (Table 2).

We also detected significant increases in serum creatinine levels (serum creatinine at 3 months—baseline serum creatinine: 0.03 ± 0.16 mg/dL, $p < 0.0001$; Table 2) and decreases in eGFRs (eGFR at 3 months—baseline eGFR: − 3.0 ± 29.2 mL/min/1.73 m^2, $p < 0.01$; Table 2); however, no cases of severe renal dysfunction were reported in this study.

Predictors of Decreased HbA1c Levels After SGLT2 Inhibitor Treatment

Single regression analysis showed that the magnitude of changes in HbA1c levels 3 months after the start of treatment (HbA1c at 3 months—baseline HbA1c) was positively associated with age ($p < 0.01$), indicating that younger patients showed greater decreases in HbA1c levels (Table 3). Changes in HbA1c levels 3 months after the start of treatment were also positively associated with changes in HbA1c levels 1 month after the start of treatment

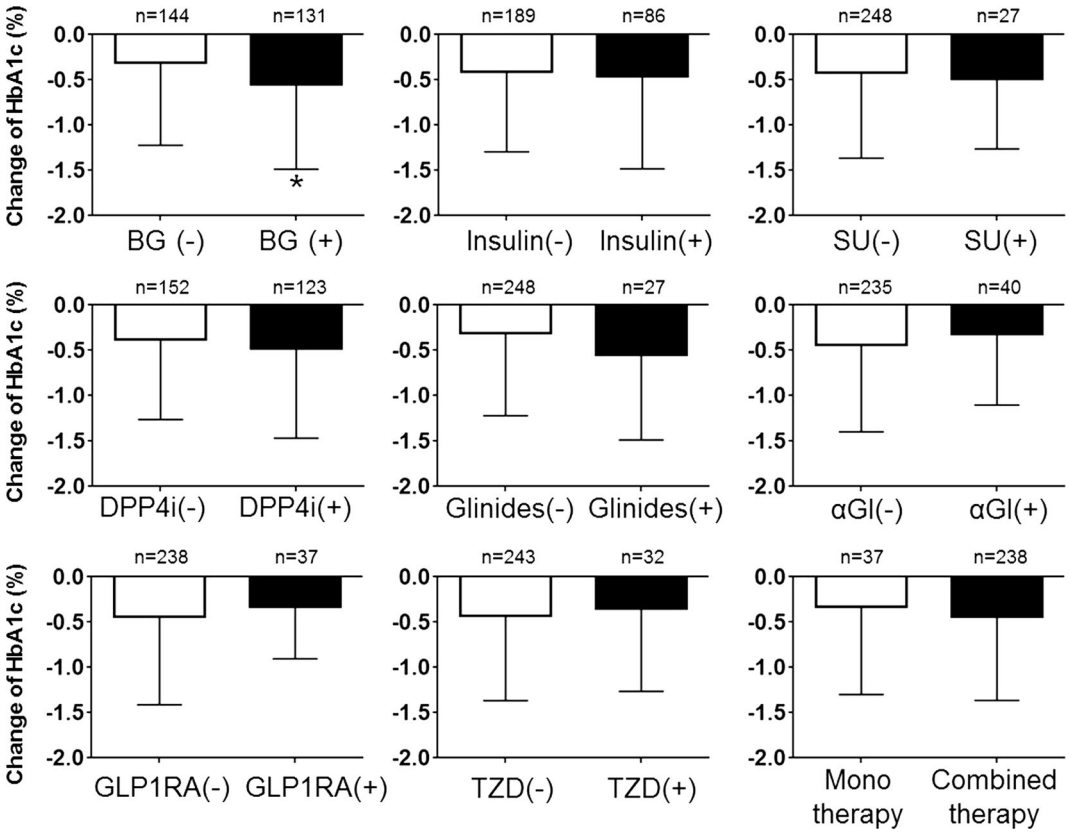

Fig. 3 Glucose-lowering effect of SGLT2 inhibitors as monotherapy or in combination with other anti-diabetic drugs (*$p < 0.05$). Antidiabetic drugs included biguanides (*BG*), insulin, sulfonylureas (*SU*), DPP-4 inhibitors (*DPP-4i*), glinides, α-glucosidase inhibitors (*β-GI*), GLP-1 receptor agonist (*GLP-1RA*), and thiazolidinediones (*TZD*)

(HbA1c at 1 months—baseline HbA1c) ($p < 0.001$). Moreover, we detected negative associations with baseline (pre-treatment) HbA1c levels ($p < 0.001$; Table 3; Fig. 4) and baseline eGFRs ($p < 0.001$; Table 3; Fig. 5). The greatest decrease in HbA1c levels associated with SGLT2 inhibitor treatment was observed among patients with an eGFR ≥ 100 mL/min/1.73 m^2 (Fig. 5). No association was found between changes in HbA1c levels and BMI (Table 3; Fig. 6).

We then performed a multiple regression analysis adjusting for age and sex to clarify the independent determinants for changes in HbA1c levels 3 months after the start of treatment (Table 3). This analysis showed that baseline HbA1c levels ($p < 0.0001$), baseline eGFR ($p < 0.05$), and changes in HbA1c levels 1 month after the start of treatment ($p < 0.001$) were predictors for changes in HbA1c levels after 3 months of treatment. The multiple regression analysis adjusting for age, sex and concomitant antidiabetic drugs also showed that those three factors are predictors for changes in HbA1c levels after 3 months of treatment (Supplemental Table 1). These indicate that decreases in HbA1c levels were greater in patients with high baseline HbA1c levels, high baseline eGFRs, and greater initial responses to SGLT2 inhibitor treatment.

DISCUSSION

We show that SGLT2 inhibitors are effective in decreasing HbA1c levels after 3 months of treatment with no severe side effects. The predictors for the effects of SGLT2 inhibitor

Table 3 Determinants of change in HbA1c after 3 months treatment

Variables	Univariate		Multivariate					
	β (95% CI)	*p* value	Model 1		Model 2		Model 3	
			β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Age	0.12 (0.03, 0.21)	< 0.01	0.04 (− 0.05, 0.12)	0.39	0.04 (− 0.07, 0.16)	0.48	0.02 (− 0.05, 0.09)	0.61
Male	0.83 (− 0.46, 2.13)	0.20	0.59 (− 0.55, 1.73)	0.31	0.59 (− 0.74, 1.92)	0.38	0.20 (− 0.80, 1.20)	0.69
BMI	− 0.04 (− 0.23, 0.16)	0.73						
Beseline HbA1c	− 0.43 (− 5.18, − 3.33)	< 0.001	− 4.14 (− 5.10, − 3.19)	< 0.0001				
Baseline eGFR	− 0.09 (− 0.14, − 0.04)	< 0.001			− 0.07 (− 0.13, − 0.01)	0.02		
Change in HbA1c after 1 month	0.2 (0.05, 0.35)	< 0.001					0.89 (0.76, 1.02)	< 0.001

BMI body mass index, *HbA1c* glycated hemoglobin, *eGFR* estimated glomerular filtration rate

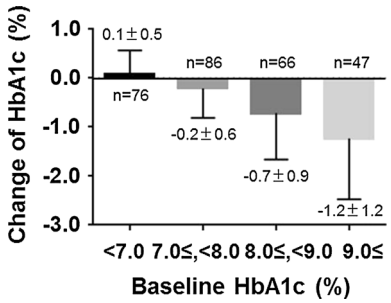

Fig. 4 Effects of SGLT2 inhibitor treatment on changes in HbA1c levels, stratified by baseline HbA1c levels

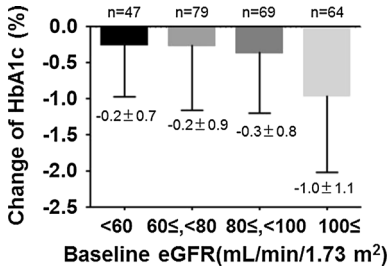

Fig. 5 Effects of SGLT2 inhibitor treatment on changes in HbA1c levels, stratified by estimated glomerular filtration rates (eGFR)

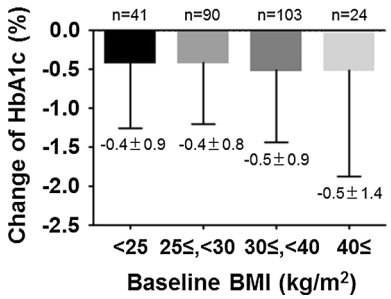

Fig. 6 Effects of SGLT2 inhibitor treatment on changes in HbA1c levels, stratified by baseline body mass index (BMI)

treatment were high baseline HbA1c levels, a high eGFR, and greater decreases in HbA1c levels after 1 month of treatment.

It has not yet been established which patients are ideal candidates for SGLT2 inhibitor treatment in terms of glucose lowering. The ASSIGN-K study showed that SGLT2 inhibitors were more effective in patients with high baseline HbA1c levels and a shorter duration of diabetes, while age, sex, and BMI were not

associated with a decrease in HbA1c levels 12 weeks after the start of ipragliflozin treatment [7]. Meta-regression analysis showed that high baseline glycemia increased the glucose-lowering effect of other oral agents such as sulfonylureas, glinides, biguanides, thiazolidinediones, α-glucosidase inhibitors, and DPP4 inhibitors [8–10]. Consistent with previous studies, our results show that decreased HbA1c levels are associated with baseline HbA1c levels. The fraction of filtered glucose excreted by SGLT2 inhibitors increases along with an increase in plasma glucose concentration [11]. This explains why the glucose-lowering effect of SGLT2 inhibitors was greater in subjects with high HbA1c levels when compared to those with low HbA1c levels.

It is known that SGLT2 inhibitors decrease body weight through caloric elimination, and that they are a suitable treatment option for obese diabetic patients [12]. However, our study shows that SGLT2 inhibitors decreased HbA1c levels regardless of baseline BMI, indicating that BMI is not a predictor of lowering HbA1c levels [13, 14].

SGLT2 inhibitors stimulate food intake as a compensation for the energy loss due to glycosuria. It has been reported that SGLT2 inhibition may increase food intake in an animal model of obesity [15]. Thus, if patients quite caloric restriction, a rebound of hyperglycemia may occur. In addition, for antidiabetics such as sulfonylurea, rebound of the glucose-lowering effect or secondary failure due to desensitization of insulin secretion has been reported [16]. However, previous trials showed that SGLT2 inhibitors have a constant effect on lowering HbA1c levels without a glucose-lowering rebound [2, 17]. Consistent with earlier studies, we show that decreased HbA1c levels after 3 months of treatment were associated with decreased HbA1c levels after 1 month of treatment. This suggests that the 3-month glucose-lowering effect of SGLT2 inhibitor treatment can be predicted by the initial effects of the treatment.

It is known that SGLT2 inhibitors do not decrease HbA1c levels more than placebos in patients with moderate renal impairment of eGFR < 45 mL/in/1.73 m^2 [12]. However, it has not been determined whether the glucose-lowering efficacy of SGLT2 can be predicted by baseline eGFR. We revealed that another predictor of SGLT2 inhibitor response is baseline high eGFR. SGLT2, which is located in the brush border membrane of the renal proximal tubule, is inhibited extracellularly from the lumen of the proximal tubule after SGLT2 inhibitors are filtered by the glomerulus [18]. Therefore, the glucose-lowering effect of SGLT2 inhibitors depends on the capacity of glucose filtration represented by the eGFR.

HbA1c values exhibited a seasonal change in Japanese patients with type 2 diabetes [19]. It has been reported that HbA1c values were highest in March and lowest in October, with a difference of 0.30% [20]. Consistent with this study, HbA1c levels were highest in February and March in our data. The reasons for the higher HbA1c levels during these months might be decreased physical activity due to cold weather and increased dietary calorie intake in winter [19].

When comparing the glucose-lowering effects of the 6 different SGLT inhibitors used in this study, no statistically significant difference was detected, although tofogliflozin had the greatest effect. The similarity in chemical structures of these SGLT2 inhibitors likely explains their class effects for glucose lowering [21, 22].

The glucose-lowering effect of SGLT2 inhibitors is independent of insulin, including beta-cell function and insulin sensitivity [23]. Therefore, the prevalence of hypoglycemia is rare, especially in the absence of insulin secretagogues and insulin. SGLT2 inhibitor-related serious adverse effects have been reported previously [24]. We experienced 10 cases of SGLT2 inhibitor-related adverse effects (itching, frequent urination, urinary tract infection, fainting, feeling thirsty, and lower limb numbness) leading to a discontinuation of SGLT2 inhibitor treatment (Fig. 1). SGLT2 inhibitor treatment was discontinued within 4 weeks in 9 of these cases. No cases of ketosis/ketoacidosis were observed, although urinary ketone tests were positive in 8 of 233 patients after SGLT2 inhibitor treatment (Supplemental Table 1). No study has thus far reported predictors for the adverse effects of SGLT2 inhibitors. Therefore, to avoid serious adverse effects, it is crucial to

identify suitable patients for SGLT2 inhibitor treatment by following the recommendation for the appropriate use of SGLT2 inhibitors by the Japanese Diabetes Society (http://www.jds.or.jp), and to carefully follow-up patients after administration of SGLT2 inhibitors, particularly during the first 4 weeks of treatment [24].

The present study has several limitations. First, we only analyzed patients who had been treated with SGLT2 inhibitors for at least 3 months at our hospitals; thus, our study has an inherent patient selection bias. Second, this was a retrospective study with a small sample size. Third, the observation period was relatively short; therefore, we could not analyze the long-term effects of SGLT2 inhibitor treatment. Fourth, 87% of the patients were undergoing combination therapy with SGLT2 inhibitors and other antidiabetic drugs. Thus, we could not exclude the effects of concomitant antidiabetic drugs. Large clinical cohort studies with a longer observation period are needed to clarify the reliable predictors in type 2 diabetes patients of the effect of SGLT2 inhibitors for lowering HbA1c levels.

CONCLUSIONS

In conclusion, we show that high baseline HbA1c levels and a high baseline eGFR were predictors for the effect of SGLT2 inhibitors of lowering HbA1c levels after 3 months of treatment. Moreover, the effect of SGLT2 inhibitors could be predicted by the level of decrease in HbA1c levels after 1 month of treatment (i.e., the initial response to treatment). This suggests that patients with type 2 diabetes who receive the greatest glucose-lowering effect with SGLT2 inhibitor treatment are those with preserved renal function and high HbA1c levels regardless of BMI. Moreover, SGLT2 inhibitor treatment efficacy can be predicted by the patients' initial response to treatment.

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Compliance with Ethics Guidelines. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study protocol was approved by the Ethics Committee of Tokushima University Hospital (No. 2432) and Shikoku Central Hospital (No. 25).

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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