



Blood glucose levels and bodyweight change after dapagliflozin administration

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Keywords

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ABSTRACT

Aims/Introduction: Increased blood glucose or increased weight is often observed in patients who are prescribed sodium–glucose cotransporter 2 inhibitors (SGLT2i). The aim of this study was to determine in advance which patients, among those prescribed a SGLT2i, would be likely to have improved or worsened blood glucose levels and gain or loss of weight through the use of real-world data-based prescriptions.

Materials and Methods: After 3 months of dapagliflozin prescription, patients were divided into four groups: H(+)/W(+) for improved glucose and weight loss; H(+)/W(–) for improved blood glucose and weight gain; H(–)/W(+) for worsened glucose and weight loss; and H(–)/W(–) for worsened glucose and weight gain.

Results: The proportion of patients in the H(+)/W(+) group was 53.5% (325/608 patients), H(+)/W(–) was 19.7% (120/608), H(–)/W(+) was 26.8% (114/608) and H(–)/W(–) was 8.1% (49/608). The odds of proceeding to H(+)/W(–) compared with H(+)/W(+), which served as the reference, were 144% in baseline hemoglobin A1c (HbA1c) 7.0–8.0%, 233% in baseline HbA1c 8.0–9.0% and 359% in baseline HbA1c \geq 9.0% (odds ratio 3.59, $P < 0.05$) compared with the reference. The odds of proceeding to H(–)/W(+) were 29, 13 and 8%, respectively (all $P < 0.05$), and to H(–)/W(–) were 17, 15 and 8%, respectively (all $P < 0.05$), compared with the reference. The results were expected to vary individually, because changes in blood glucose and bodyweight are more affected by diet and exercise than by drugs.

Conclusions: When first prescribing dapagliflozin, a physician should be aware of the weight gain rather than glucose change if the baseline HbA1c is high, and might concentrate on weight-related lifestyle training, such as diet and exercise.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) suppress glucose reabsorption in the kidneys and increase glucose excretion through urine, thereby lowering blood glucose^{1,2}. The biggest advantage of these drugs is that they are also associated with effects such as weight loss and a lower risk of hypoglycemia in addition to lowering blood glucose^{3,4}. In the American Association of Clinical Endocrinologists guidelines⁵ and Korean Diabetes Association guidelines⁶, SGLT2i is the highest priority oral hypoglycemia agent (OHA) that can be administered to patients who are unable to control blood glucose with metformin alone.

SGLT2i are excellent OHAs in terms of their potent glucose-lowering and weight loss effects. As such, many studies with SGLT2i have reported that the group taking SGLT2i showed a consistent weight loss effect compared with the control group⁷. However, there is also a concern that patients taking SGLT2i often gain weight resulting from significant calorie intake due to weight loss. In the actual clinical field, SGLT2i prescription is often associated with weight gain and secondary blood glucose rise.

Some patients might achieve both goals of blood glucose loss and weight loss after SGLT2i prescription^{8,9}. On the contrary, there will certainly be patients with increased blood glucose or weight after SGLT2i administration. The difference in the outcome might be due to the individual characteristics of patients

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who are prescribed and taking the SGLT2i. Thus, it is important to predict which patients, among those prescribed a SGLT2i, would be likely to have improved or worsened blood glucose levels and gain or lose weight. Nevertheless, identification of risk factors affecting patients' blood glucose or weight based on personal information or blood tests evaluated in the hospital is highly valuable to the physicians prescribing SGLT2i. Therefore, in the present study, we assessed changes in body-weight and blood glucose level in patients who were first prescribed with SGLT2i in actual clinical practice. The purpose of the present study was to determine in advance which patients, among those prescribed a SGLT2i, would be likely to have improved or worsened blood glucose levels and gain or loss of weight through the use of real-world data (RWD)-based prescriptions.

MATERIALS AND METHODS

Study population

The present study included patients who were followed up after being diagnosed with type 2 diabetes and were visiting Seoul St. Mary's Hospital (Seoul, Korea) regularly for 2 years from December 2014 to December 2016. Among them, data of all patients who were prescribed dapagliflozin (10 mg), an SGLT2i, for blood glucose control for the first time were extracted. In the case of the first prescription of dapagliflozin, it was determined whether dapagliflozin was added to other OHA prescriptions (or previous lifestyle change management) or whether other OHA prescriptions were changed to dapagliflozin. This research included only cases in which dapagliflozin was added to other OHA prescriptions. Cases with changes in OHA medications other than dapagliflozin or changes from other OHAs to dapagliflozin were excluded from the study. Those with dapagliflozin intake or prescription discontinuation within 3 months of the first prescription of dapagliflozin due to side-effects or other reasons were also excluded.

Study design

Physical information, such as age, sex, height, weight and blood pressure, at the time of the first prescription of dapagliflozin was recorded. The extracted blood tests carried out at the initial prescription were as follows: glucose, blood urea nitrogen/creatinine, Modification of Diet in Renal Disease (MDRD)-estimated glomerular filtration rate (eGFR), total bilirubin (TB), aspartate transaminase/alanine transaminase, alkaline phosphatase, glutamyl transpeptidase, total cholesterol/triglycerides/high-density lipoprotein cholesterol/low-density lipoprotein cholesterol and sodium/potassium tests. After approximately 3 months (2–4 months) since dapagliflozin was first prescribed, values such as weight and hemoglobin A1c (HbA1c) were measured during visits. According to the baseline, and changes in blood glucose and weight after 3 months, cases in which both HbA1c and weight improved were defined as H(+)/W(+), and cases in which both deteriorated were defined as H(-)/W(-). Cases in which HbA1c improved while weight deteriorated

were defined as H(+)/W(-), and cases in which HbA1c deteriorated while weight improved were defined as H(-)/W(+). Cases that had no change in HbA1c or weight were included with the cases in which both were deteriorated.

Protection of privacy

All the extracted data used in this research were anonymous, and encrypted identification numbers were used. Information was saved as an encrypted file on the encrypted computer of the corresponding author. Only the corresponding author was able to access the data. For data quality management or statistic processing, any content that helped identify an individual was deleted. This work proceeded as a retrospective cohort study using electronic medical record (EMR) data of cases in which diagnosis and treatment had been completed. Due to the nature of the present study, and as this study did not influence the patients' physical conditions, patient consent was not necessary. This study was approved by the Institutional Review Board of the Catholic University of Korea.

Statistical analysis

Descriptive statistics are presented as means and standard deviations, or percentages of participants. All patients who were prescribed dapagliflozin were grouped by efficacy (four groups) based on weight and HbA1c change. Continuous variables were assessed by analysis of variance (ANOVA) with the Bonferroni correction, and categorical variables were assessed by the χ^2 -test. To compare the degree of dapagliflozin efficacy and baseline status, analysis was carried out by univariable and multivariable logistic regression. Subgroup analyses between efficacy of dapagliflozin and baseline conditions were carried out by the χ^2 -test or independent *t*-test considering multiple comparisons. Analyses were carried out with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), and two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Among the patients being followed up after being diagnosed with type 2 diabetes at Seoul St. Mary's Hospital from December 2014 to December 2016, there were 1,663 (864 men, 799 women) patients who were prescribed dapagliflozin for blood glucose control for the first time (Figure 1). Among these patients, 39.1% (651/1,663 patients) had dapagliflozin added to the existing OHA (or previous lifestyle change management), and 60.9% (1,012/1,663 patients) had existing OHA changed to dapagliflozin. A total of 43 patients who stopped taking dapagliflozin due to side-effects or other various reasons within 3 months since dapagliflozin was prescribed were excluded. Therefore, the research was carried out using a total of 608 patients who were prescribed dapagliflozin for blood glucose control for the first time.

There were 48.0% men (292/608 patients), and 52.0% women (316/608 patients) in this study (Table 1). With respect to the age distribution, 32.7% of patients (199/608 patients)

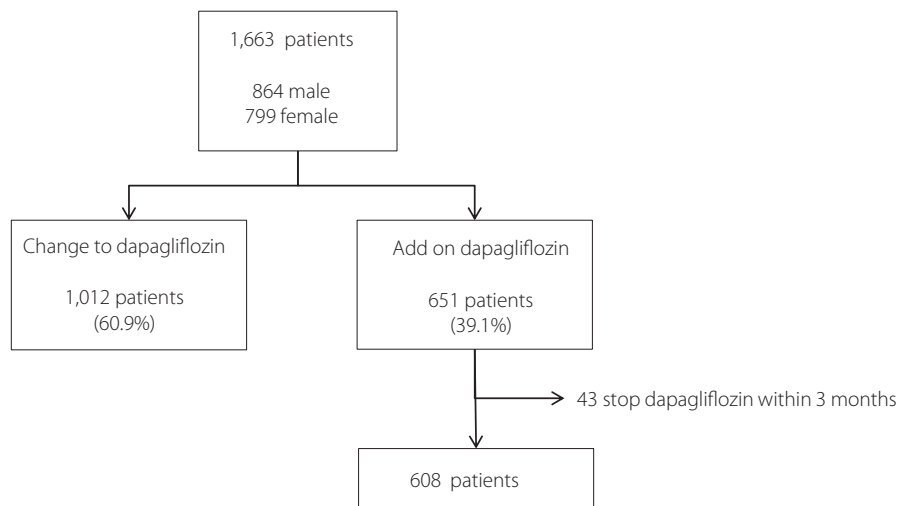


Figure 1 | Trial profile.

were aged in their 50s, 26.0% (158/608 patients) were aged in their 40s and 20.9% (127/608 patients) were aged in their 60s. Patients aged in their 70s with a dapagliflozin prescription comprised 5.9% of the sample (36/608 patients). A baseline HbA1c level of 7.0–7.9% was the highest and observed in 36.8% of the sample (224/608 patients), whereas the next highest level was 8.0–8.9%, observed in 26.3% of the sample (160/608 patients). A baseline HbA1c of 10.0% was in 8.9% (54/608) of the dapagliflozin prescribed patients. As for baseline body mass index (BMI), 51.2% (311/608) of patients had a BMI of 25–30 kg/m², and 26.5% (161/608) of patients had a BMI of >30 kg/m².

Grouping according to changes in weight and HbA1c

Among 608 patients who participated in the research, 73.2% of patients had improved HbA1c values (445/608 patients), but 26.8% of patients showed deteriorated HbA1c (163/608 patients; Table 2). The H(+)/W(+) group, which had both positive effects of blood glucose improvement and weight loss, included 53.5% (325/608) of the patients, whereas the H(+)/W(–) group was 19.7% (120/608 patients), H(–)/W(+) was 26.8% (114/608 patients) and H(–)/W(–) was 8.1% (49/608 patients; Figure 2).

Significant intergroup differences were found with regard to sex, baseline HbA1c, glucose, TB, aspartate transaminase/alanine transaminase, high-density lipoprotein, sodium and potassium. In the case of H(+)/W(–), in which weight was deteriorated compared with H(+)/W(+), the baseline BMI was significantly low (28.0 ± 3.7 vs 27.1 ± 3.6 , $P < 0.05$), and baseline HbA1c was significantly high (8.2 ± 1.3 vs 8.7 ± 1.5 , $P < 0.01$). The occurrence of H(–)/W(+), in which HbA1c was rather deteriorated compared with H(+)/W(+), was more frequent in men (51.0 vs 36.1%, $P < 0.05$), as well as with lower

Table 1 | Baseline characteristics of patients who were prescribed dapagliflozin

Sex, <i>n</i> (%)	
Male	292 (48.0%)
Female	316 (52.0%)
Age, <i>n</i> (%)	
<20 years	3 (0.5%)
20–29 years	25 (4.1%)
30–39 years	60 (9.9%)
40–49 years	158 (26.0%)
50–59 years	199 (32.7%)
60–69 years	127 (20.9%)
≥70 years	36 (5.9%)
HbA1c, <i>n</i> (%)	
<7.0%	107 (17.6%)
7.0–7.9%	224 (36.8%)
8.0–8.9%	160 (26.3%)
9.0–9.9%	63 (10.4%)
≥10%	54 (8.9%)
BMI, <i>n</i> (%)	
<23 kg/m ²	51 (8.4%)
23–25 kg/m ²	85 (14.0%)
25–30 kg/m ²	311 (51.2%)
≥30 kg/m ²	161 (26.5%)
Antidiabetic medication before SGLT2i prescription	
No medication	42 (6.9%)
Metformin	397 (65.3%)
Sulfonylurea	118 (19.4%)
DPP4i	167 (27.5%)
Thiazolidinedione	10 (1.7%)
Insulin	104 (17.1%)

Total *n* = 608. BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitor; HbA1c, hemoglobin A1c; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

Table 2 | Baseline characteristics of patients who were first prescribed dapagliflozin

	H(+)/W(+) group	H(+)/W(-) group	H(-)/W(+) group	H(-)/W(-) group	P-value
	325	120	114	49	
Age (years)	51 ± 12	53 ± 14	53 ± 11	54 ± 11	0.262
Sex (male), n (%)	230 (51.0%)	98 (56.3%)	53 (36.1%)**	24 (38.7%)	0.001
BMI (kg/m ²)	28.0 ± 3.7	27.1 ± 3.6*	28.1 ± 3.6	27.8 ± 3.9	0.099
SBP (mmHg)	124 ± 12	127 ± 11	124.58 ± 9.10	128 ± 12	0.141
DBP (mmHg)	78 ± 9	80 ± 9	76 ± 10	79 ± 11	0.086
HbA1c (%)	8.2 ± 1.3	8.7 ± 1.5**	7.4 ± 0.9**	7.3 ± 1.0*	<0.001
Glucose (mg/dL)	167 ± 49	172 ± 53	149 ± 50**	146 ± 35*	<0.001
BUN (mg/dL)	15 ± 5	15 ± 5	15 ± 4	16 ± 5	0.342
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.785
MDRD-eGFR (mL/min/1.73 m ²)	88.2 ± 17.1	89.2 ± 20.3	85.2 ± 19.0	84.6 ± 18.6	0.205
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.2**	0.6 ± 0.2	0.003
AST (U/L)	32 ± 21	29 ± 16*	29 ± 17	24 ± 11*	0.018
ALT (U/L)	44 ± 33	36 ± 21	38 ± 26	33 ± 24**	0.017
ALP (U/L)	59 ± 18	64 ± 21	59 ± 20	61 ± 33	0.256
γGTP (U/L)	58 ± 44	55 ± 52	46 ± 30*	46 ± 34	0.168
Total cholesterol (mg/dL)	166 ± 39	169 ± 43	166 ± 73	165 ± 37	0.941
Triglyceride (mg/dL)	168 ± 103	197 ± 171	166 ± 331	152 ± 90	0.372
HDL cholesterol (mg/dL)	44 ± 10	43 ± 11	47 ± 10*	48 ± 9**	0.002
LDL cholesterol (mg/dL)	91 ± 30	90 ± 32	87 ± 31	86 ± 25	0.508
Sodium (mEq/L)	141 ± 2	141 ± 3*	141 ± 3	141 ± 2	0.047
Potassium (mEq/L)	4.4 ± 0.3	4.7 ± 0.4	4.4 ± 0.3	4.5 ± 0.3*	0.046
HbA1c change (%)	-1.1 ± 0.1	-1.3 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	
Weight change (kg)	-3.2 ± 0.1	1.4 ± 0.3	-2.9 ± 0.2	1.1 ± 0.3	

Total n = 608. Compared with H(+)/W(+). H(+)/W(+), both hemoglobin A1c (HbA1c) and weight improved; H(+)/W(-), HbA1c improved while weight deteriorated; H(-)/W(+), HbA1c deteriorated while weight improved; H(-)/W(-), both HbA1c and weight deteriorated. *P < 0.05; **P < 0.01. γGTP, glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; MDRD-eGFR, Modification of Diet in Renal Disease-estimated glomerular filtration rate; SBP, systolic blood pressure.

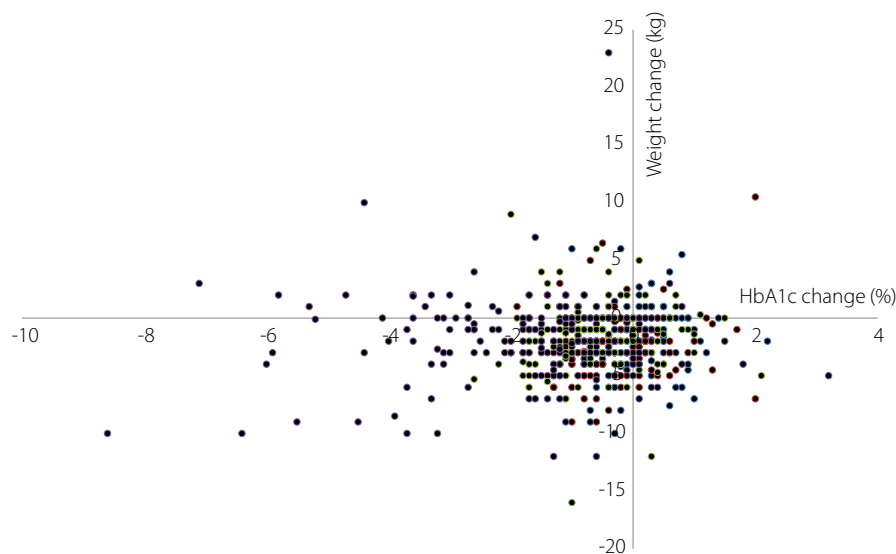


Figure 2 | Scatter plot showing the relationship between the change of hemoglobin A1c (HbA1c) and weight.

HbA1c (8.2 ± 1.3 vs 7.4 ± 0.9 , $P < 0.01$), glucose (167 ± 49 vs 149 ± 50 , $P < 0.01$), total bilirubin (0.7 ± 0.3 vs 0.6 ± 0.2 , $P < 0.01$), glutamyl transpeptidase (58 ± 44 vs 46 ± 30 , $P < 0.05$) values and higher high-density lipoprotein (44 ± 10 vs 47 ± 10 , $P < 0.05$) values. In comparison with H(+)/W(+), the occurrence of H(-)/W(-), in which HbA1c and weight were both deteriorated, HbA1c (8.2 ± 1.3 vs 7.3 ± 1.0 , $P < 0.05$), glucose level (167 ± 49 vs 146 ± 35 , $P < 0.01$), aspartate transaminase (32 ± 21 vs 24 ± 11 , $P < 0.05$) and alanine transaminase (44 ± 33 vs 33 ± 24 , $P < 0.01$) levels were low, and the high-density lipoprotein (44 ± 10 vs 48 ± 9 , $P < 0.01$) level was high.

We found that after dapagliflozin prescription, when the patients were women (odds ratio [OR] 0.45, $P = 0.001$) and had a BMI >25 kg/m² (OR 0.11, $P < 0.001$) or higher triglycerides level (≥ 150 mg/dL; OR 0.50, $P = 0.006$), they were more likely to proceed to H(-)/W(+) rather than H(+)/W(+) status. In other words, sex, BMI and triglycerides level showed an effect when HbA1c was deteriorated accompanied by weight loss (Table 3). There were no significant variables for proceeding to H(+)/W(+) and H(+)/W(-). In other words, although HbA1c was improved, there was no difference in the values in terms of weight gain or loss. When the baseline HbA1c was higher, the possibility to proceed to H(-)/W(-) was approximately 95% lower than for H(+)/W(+).

In the case of H(+)/W(+), in which HbA1c and weight were both improved at the same time, the OR was obtained when defining the case of HbA1c $<7.0\%$ as a reference (Table 4). The given ORs are for values that were adjusted by sex, age, BMI, blood pressure and glucose level. Baseline HbA1c was analyzed with values divided into four groups that consisted of <7.0 , 7.0–8.0, 8.0–9.0 and $\geq 9.0\%$. After 3 months since dapagliflozin prescription, the odds to proceed to H(+)/W(-) with only HbA1c improvement compared with the reference H(+)/W(+) were 144% in baseline HbA1c 7.0–8.0%, 233% in baseline HbA1c 8.0–9.0% and 359% in baseline HbA1c $\geq 9.0\%$; statistical significance was found for HbA1c $\geq 9.0\%$ (OR 3.59, 95% confidence interval 1.39–9.29, $P < 0.05$). The higher the value of baseline HbA1c, the higher the OR obtained. After 3 months since dapagliflozin prescription, the odds to proceed to H(-)/W(+) with only improvement in weight compared with H(+)/W(+), which were references, were 29, 13 and 8%, respectively (all $P < 0.05$), compared with the reference. Furthermore, after 3 months since dapagliflozin prescription, the odds to proceed to H(-)/W(-), with improvements in neither HbA1c nor weight compared to H(+)/W(+), which were references, were 17, 15 and 8%, respectively (all $P < 0.05$), compared with the reference.

DISCUSSION

The extent of hypoglycemic effect and whether there will be an increase in weight are two concerns of physicians when prescribing OHAs to diabetes patients. Usually, physicians have found the answers to the above concerns empirically. Naturally,

the changes in blood glucose level and weight will be largely influenced by the patient's living environment outside the hospital, especially with eating or exercising habits. Nevertheless, customized prescriptions that can roughly estimate the hypoglycemic effect and weight changes in patients are now an important part of treatment.

Many studies are currently under way on customized treatments that produce good glucose-lowering effects and few side-effects^{10,11}. A significant amount of RWD that has already accumulated in EMR is advantageous in the implementation of high-risk group screening for increased blood glucose levels or increased weight, or their predictive models¹².

Of the patients included in the present study, $\geq 85\%$ were aged in their 40s and over, and approximately 80% were obese patients with a BMI of 25 kg/m² or higher; this is common for patients in ambulatory care¹³ (Table 1). Compared with the most ideal scenario of H(+)/W(+) with reduced blood glucose and weight loss, H(+)/W(-) had a relatively low baseline BMI and high baseline HbA1c. In the H(-)/W(+) group where only blood glucose deteriorated, a relatively high proportion of patients were women, and had significantly lower baseline fasting blood sugar and HbA1c levels. The least desirable outcome was H(-)/W(-), with blood glucose deterioration and weight gain, and was also relatively low in terms of baseline fasting blood sugar and HbA1c. In other words, it was relatively difficult to obtain a meaningful hypoglycemic effect in the 7.0% HbA1c range compared with 8.0% HbA1c.

In a study comparing dipeptidyl peptidase-4 inhibitors, another type of OHA used for treating diabetes, and SGLT2i, when HbA1c was $>8.0\%$, SGLT2i had a better hypoglycemic effect than did dipeptidyl peptidase-4 inhibitors, where in patients with HbA1c <8.0 – 8.5% , dipeptidyl peptidase-4 inhibitors' hypoglycemic effect was better¹⁴. When prescribing SGLT2i, physicians have to consider factors, such as baseline HbA1c, renal function and age. The aforementioned results can be interpreted as being similar to the results obtained in the present study, and it can be inferred that baseline HbA1c is closely related to the expectations of the hypoglycemic effect. Renal function and age did not differ significantly by group in this study, and it is assumed that most GFRs were assessed for patients with relatively superior eGFR values of >60 mL/min/1.73 m².

The probability of developing H(-)/W(+) and H(-)/W(-), where blood glucose deteriorated after dapagliflozin was prescribed, was statistically significantly lower with all baseline HbA1c levels than in H(+)/W(+) (Table 3), which might be interpreted as a reasonable result because of dapagliflozin's glucose-lowering effect. In contrast, the probability of becoming H(+)/W(-) was 1.44-fold higher for baseline HbA1c 7.0–8.0%, and 2.33-fold higher for baseline HbA1c 8.0–9.0% than for H(+)/W(+), and was statistically significant for baseline HbA1c values $>9.0\%$ (3.59-fold higher). In other words, if the HbA1c value is $>9.0\%$, blood glucose can be significantly improved, but the effects of weight loss are not very predictable. The

Table 3 | Analysis of independent risk factors affecting change of glucose level and weight

	Reference = H(+)/W(+) group					
	vs H(-)/W(+) group			vs H(+)/W(-) group		
	Univariable	Multivariable	P-value	Univariable	Multivariable	P-value
	OR (95% CI)	OR (95% CI)	P-value	OR (95% CI)	OR (95% CI)	P-value
Age	1.01 (1.00–1.03)		0.144	1.01 (0.99–1.03)		0.186
Sex (male)	0.46 (0.29–0.71)	0.45 (0.28–0.71)	0.001	1.04 (0.69–1.59)		0.848
BMI (≥ 25 kg/m ²)	1.05 (0.62–1.78)	0.11 (0.04–0.29)	<0.001	0.70 (0.43–1.13)		0.143
HbA1c ($\geq 6.5\%$)	0.14 (0.05–0.34)		<0.001	2.62 (0.32–21.51)		0.370
Glucose (≥ 126 mg/dL)	0.46 (0.28–0.75)		0.002	1.02 (0.58–1.79)		0.949
BUN (> 20)	0.63 (0.30–1.34)		0.231	0.89 (0.46–1.73)		0.734
Creatinine (> 1.5)	NA			1.36 (0.12–15.10)		0.804
MDRD-eGFR (< 90)	1.33 (0.86–2.07)		0.206	0.88 (0.58–1.34)		0.551
Total bilirubin (> 1.2)	0.51 (0.19–1.35)		0.173	0.58 (0.23–1.44)		0.242
AST	0.82 (0.49–1.37)		0.442	0.61 (0.36–1.05)		0.077
ALT	0.64 (0.41–0.99)		0.047	0.84 (0.55–1.29)		0.432
Total cholesterol (mg/dL)	0.74 (0.39–1.43)		0.373	1.22 (0.70–2.15)		0.481
Triglyceride (mg/dL)	0.49 (0.31–0.79)	0.50 (0.31–0.82)	0.006	1.42 (0.93–2.16)		0.103
HDL cholesterol (mg/dL)	0.51 (0.32–0.82)		0.006	1.11 (0.73–1.70)		0.634
LDL cholesterol (mg/dL)	0.79 (0.49–1.28)		0.340	0.95 (0.60–1.50)		0.828
Sodium	0.57 (0.07–4.90)		0.606	1.64 (0.39–6.98)		0.502
Potassium	NA			N/A		

Backward elimination method was used to perform multivariable logistic regression. H(+)/W(+), both hemoglobin A1c (HbA1c) and weight improved; H(+)/W(-), HbA1c improved while weight deteriorated; H(-)/W(+), HbA1c deteriorated while weight improved; H(-)/W(-), both HbA1c and weight deteriorated. ALT, alanine aminotransaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; HDL, high-density lipoprotein; MDRD-eGFR, Modification of Diet in Renal Disease-estimated glomerular filtration rate; LDL, low-density lipoprotein; NA, not applicable.

Table 4 | Odds ratio for changes in weight and blood glucose according to baseline hemoglobin A1c

HbA1c (Reference <7.0%)	Reference = H(+)/W(+) group					
	H(+)/W(-) group		H(-)/W(+) group		H(-)/W(-) group	
7.0–8.0%	1.44 (0.55–3.74)	NS	0.29 (0.16–0.53)	<0.05	0.17 (0.08–0.38)	<0.05
8.0–9.0%	2.33 (0.90–6.05)	NS	0.13 (0.07–0.28)	<0.05	0.15 (0.06–0.37)	<0.05
≥9.0%	3.59 (1.39–9.29)	<0.05	0.08 (0.03–0.20)	<0.05	0.08 (0.02–0.28)	<0.05

Adjusted by sex, age, body mass index, blood pressure and glucose level. Odds ratio when defining the case of hemoglobin A1c (HbA1c) <7.0% as a reference in the case of H(+)/W(+) in which HbA1c and weight were both improved at the same time. For example, in the case of patients whose baseline HbA1c is 9.5%, and only weight is improved after 3 months since taking dapagliflozin, the patients proceeded to H(-)/W(+), with only a possibility of 8% compared with the patients that proceeded to H(+)/W(+). The patients that proceeded to H(-)/W(-) had only a possibility of 8% compared with the patients that proceeded to H(+)/W(+). The patients that proceeded to H(+)/W(-) had a 250% higher possibility of occurring compared with the patients that proceeded to H(+)/W(+). HbA1c was analyzed not only as a categorical variable, but also as a continuous variable; therefore, it was confirmed that there was a trend increase or decrease. H(+)/W(+), both HbA1c and weight improved; H(+)/W(-), HbA1c improved while weight deteriorated; H(-)/W(+), HbA1c deteriorated while weight improved; H(-)/W(-), both HbA1c and weight deteriorated. NS, not significant.

higher the baseline HbA1c, the higher the probability of improving HbA1c; however, the weight might remain unchanged or increase. In fact, in many other studies, the higher the blood glucose level, the stronger the hypoglycemic effect¹⁵.

In the present study, when age and sex were adjusted, and when age, sex, and BMI were both adjusted and analyzed, the results were almost the same. Physicians can expect to assume outcomes in the order of H(+)/W(-), H(+)/W(+) and H(-)/W(+) or H(-)/W(-) when prescribing dapagliflozin for patients with a baseline HbA1c level of 9.0% or higher. In the present study, when blood glucose improved with the value of HbA1c, the occurrence of weight change was somewhat predictable. However, it was difficult to estimate whether there were any significant differences in weight changes in the case of deteriorating blood glucose.

In the analysis of independent risk factors affecting weight and blood glucose, the risk of developing into H(+)/W(-) compared with H(+)/W(+) was not statistically significant (Table 4). In other words, if blood glucose improved, no risk factors affecting weight gain or loss were identified. In the case of H(-)/W(+), the risk was higher for women with higher BMI.

A study that examined changes in HbA1c after prescribing dapagliflozin in Korea showed excellent hypoglycemic effects regardless of the BMI value, although the highest hypoglycemic effect was for BMI <25 kg/m²¹⁶. Our study found that obesity had better effects on weight loss, whereas the effect on blood glucose was not optimal. Perhaps because our study was a short-term evaluation for 3 months, it did not include a secondary effect on blood glucose reduction due to subsequent weight loss. As the worst result, H(-)/W(-) also showed a lower risk when HbA1c was higher, than for H(+)/W(+). In other words, a higher level of HbA1c can lead to a greater hypoglycemic effect. In fact, a typical factor influencing blood glucose values in many existing studies is eGFR¹⁷. However, in the present study, eGFR values did not significantly affect blood

glucose and weight changes. It is already well known that the higher the eGFR, the better the hypoglycemic effect. Therefore, the baseline eGFR value is very important in administering dapagliflozin. In Korea, dapagliflozin is not recommended for patients with eGFR values <60 mL/min/1.73 m². The average eGFR in the present study was approximately 84–89 mL/min/1.73 m², and thus, did not seem to have a significant impact on the results.

It is worth taking into account more seriously that blood glucose increased in approximately 26.8% of patients, and weight gains occurred in approximately 27.8% of patients, despite the additional prescription of dapagliflozin (Table 2). In fact, many other studies have shown that the glucose-lowering effect seen in real-world evidence (RWE) studies is relatively low compared with conventional randomized controlled trials (RCTs), even if the same drugs are used¹⁸. As this study was an RWE study, it is expected that the clinical effects observed in this study might decrease, unlike in a strictly controlled RCT environment^{14,19}. Nevertheless, the 26.8% rise in blood glucose was quite high.

Rather than due to the reduced effectiveness of dapagliflozin, the drug's acceptance level and the patients' dietary/exercise habits might have had a greater impact on this result. Weight is also interpreted. As a prescription for SGL2i, the glucose lost in urine is approximately 90 g per day, equivalent to an average consumption of 280 kcal per day. Theoretically, patients with SGLT2i can expect to lose 1 kg in 3 weeks.

A 52-week study carried out with canagliflozin showed an average weight loss of 4 kg, but increased appetite proportional to weight loss was also observed²⁰. The intake of additional calories was stimulated by reduced weight. For this reason, the theoretical effects of weight loss after the SGLT2i prescription might not meet expectations. Food consumption would eventually play an important role, as the caloric intake was estimated to be approximately 100 kcal a day per 1-kg weight loss. Therefore, weight loss induced by prescription medication, such as

with SGLT2i, increases appetite and leads to the possibility of weight gain^{21–23}. The weight gain will lead to a secondary rise in blood glucose, which explains the rise in blood glucose level after dapagliflozin prescription.

The present study was an RWE study using RWD; however, it had several limitations, because it used a relatively small sample size for an RWE. First, the probability of an occurrence due to a low sample size tends to be overly skewed, and requires validation through further analysis. Second, the lack of information contained in the EMR was another limitation. The duration of diabetes was not properly recorded in the EMR; therefore, it could not be included in the study. In addition, there were no data to calculate insulin resistance or insulin sensitivity before and after dapagliflozin administration. Therefore, various factors affecting blood glucose and weight change due to dapagliflozin use were not included in the study.

Finally, disruption variables, such as sex, age, BMI and blood pressure, were adjusted, but the various important disruption variables for diet (especially appetite) and exercise, which affect blood glucose and weight, were not adjusted. This is one of the biggest drawbacks of RWE studies; hence, causality is difficult to explain^{24,25}. Therefore, we were careful in interpreting the present findings, and described the minimum conclusions through discussions of findings made by various clinical experts. This will need to be confirmed through large-scale RCT studies in the future. We believe that this study has played an important role as precedent research before such a large RCT.

SGLT2i has many additional effects besides producing an excellent hypoglycemic effect, the most positive effect of which is weight loss. Ultimately, the question is whether blood glucose level can be expected to increase or decrease in some patients, and whether weight gain or loss can be roughly estimated in others, in advance.

The results of the present study will certainly vary individually, because changes in blood glucose and bodyweight are more influenced by diet and exercise than by drugs. However, by comparing W(+) and W(–) in the H(+) group with the same improved blood glucose level, it would be helpful in measuring the difference.

RWE studies using RWD are one of the latest trends, especially targeting personalized medications in the form of clinical studies that favor high-risk screening and predictive models, such as with specific diseases and drug side-effects. Such studies contribute to the evolution of safer and more efficient prescriptions. Although RWE studies, such as the present study, are not yet reliable enough to replace RCTs, the high-risk screening or predictive models from RWE studies continue to develop and accumulate experience.

In this study, when prescribing dapagliflozin in diabetes patients, high baseline HbA1c might have a drop in blood glucose, but also brings to attention the change in bodyweight. Therefore, if the physician is able to focus more on weight-related lifestyle education, such as diet and exercise, when

prescribing dapagliflozin, the hypoglycemic effects due to prescription of dapagliflozin are expected to be maximized. However, validation with a larger sample size is required, and the hypoglycemic effect of dapagliflozin also needs to be studied continuously through RCTs.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Wright EM Renal Na(+)-glucose cotransporters. *Am J Physiol Renal Physiol* 2001; 280: F10–F18.
2. Jung CH, Jang JE, Park JY A novel therapeutic agent for type 2 diabetes mellitus: SGLT2 inhibitor. *Diabetes Metab J* 2014; 38: 261–273.
3. Strojek K, Yoon KH, Hrubá V, *et al.* Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab* 2011; 13: 928–938.
4. Wilding JP, Woo V, Soler NG, *et al.* Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med* 2012; 156: 405–415.
5. Garber AJ, Abrahamson MJ, Barzilay JL, *et al.* Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm: 2017 executive summary. *Endocr Pract* 2017; 23: 207–238.
6. Ko SH, Hur KY, Rhee SY, *et al.* Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean diabetes association. *Diabetes Metab J* 2017; 41: 337–348.
7. Bailey CJ, Gross JL, Pieters A, *et al.* Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; 375: 2223–2233.
8. Ferrannini E, Ramos SJ, Salsali A, *et al.* Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* 2010; 33: 2217–2224.
9. Bolinder J, Ljunggren O, Kullberg J, *et al.* Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. *J Clin Endocrinol Metab* 2012; 97: 1020–1031.

10. Standards of medical care in diabetes. *Diabetes Care* 2017; 40: S1–S135.
11. Erratum. Pharmacologic approaches to glycemic treatment. Sec. 8. In standards of medical care in diabetes—2017. *Diabetes Care* 2017; 40: S64–S74.
12. Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records. *J Korean Med Sci* 2018; 33: e213.
13. Won JC, Lee JH, Kim JH, *et al.* Diabetes fact sheet in Korea, 2016: an appraisal of current status. *Diabetes Metab J* 2018; 42: 415–424.
14. Goldenberg RM. Choosing dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, or both, as add-ons to metformin: patient baseline characteristics are crucial. *Clin Ther* 2017; 39: 2438–2447.
15. Ji L, Ma J, Li H, *et al.* Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther* 2014; 36: 84–100.
16. Lee JY, Kim G, Kim SR, *et al.* Clinical parameters affecting dapagliflozin response in patients with type 2 diabetes. *Diabetes Metab* 2017; 43: 191–194.
17. Yale JF, Bakris G, Cariou B, *et al.* Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Obes Metab* 2014; 16: 1016–1027.
18. Edelman SV, Polonsky WH. Type 2 diabetes in the real world: the elusive nature of glycemic control. *Diabetes Care* 2017; 40: 1425–1432.
19. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002; 359: 248–252.
20. Polidori D, Sanghvi A, Seeley RJ, *et al.* How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake. *Obesity (Silver Spring)* 2016; 24: 2289–2295.
21. Terami N, Ogawa D, Tachibana H, *et al.* Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. *PLoS One* 2014; 9: e100777.
22. Jurczak MJ, Lee HY, Birkenfeld AL, *et al.* SGLT2 deletion improves glucose homeostasis and preserves pancreatic beta-cell function. *Diabetes* 2011; 60: 890–898.
23. Kojima N, Williams JM, Takahashi T, *et al.* Effects of a new SGLT2 inhibitor, luseogliflozin, on diabetic nephropathy in T2DN rats. *J Pharmacol Exp Ther* 2013; 345: 464–472.
24. Kim HS, Kim JH. Proceed with caution when using real world data and real world evidence. *J Korean Med Sci* 2019; 34: e28.
25. Kim HS, Kim DJ, Yoon KH. Medical big data is not yet available: why we need realism rather than exaggeration. *Endocrinol Metab (Seoul)* 2019; 34: 349–354.