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ORIGINAL RESEARCH

The Relationship between Increases in Morning Spot Urinary Glucose Excretion and Decreases in HbA_{1C} in Patients with Type 2 Diabetes After Taking an SGLT2 Inhibitor: A Retrospective, Longitudinal Study

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ABSTRACT

Introduction: Sodium glucose co-transporter 2 (SGLT2) inhibitors increase urinary glucose excretion (UGE) by reducing the renal threshold for glucose excretion, which results in decreased serum glucose concentrations in patients with type 2 diabetes mellitus (T2D). However, no study to date has determined whether larger increases in UGE after SGLT2 inhibitor treatment correspond to larger reductions in glycated hemoglobin (HbA_{1C}).

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Methods: We enrolled participants who were newly prescribed an SGLT2 inhibitor (dapagliflozin 10 mg or ipragliflozin 50 mg, once daily) as an add-on therapy. Patients were tested for HbA_{1C} and first morning spot urinary-creatinine and -glucose concentrations immediately prior to administration of the SGLT2 inhibitor and at a 12-week follow-up appointment. We investigated the relationship between increases in morning spot UGE and decreases in HbA_{1C}.
Results: A total of 101 participants with T2D were enrolled. The median age and diabetes duration were 61.0 and 12.8 years, respectively, and the median HbA_{1C} was 8.10%. SGLT2 inhibitors significantly lowered the HbA_{1C} level, with a median change from baseline to week 12 of -0.60% ($p < 0.001$). Robust increases from baseline were seen for the morning spot urinary glucose-to-creatinine ratio (UGCR), with a median change at week 12 of 47.3 mg/mg. In the correlation analysis, the ΔHbA_{1C} level showed a significant positive correlation with Δmorning spot UGCR ($r = 0.395$, $p < 0.001$). In other words, a greater reduction in HbA_{1C} was correlated with a smaller increase in UGE. After adjusting for confounding variables, ΔHbA_{1C} was significantly associated with Δmorning spot UGCR.
Conclusions: Although SGLT2 inhibitor treatment leads to a reduced HbA_{1C} level by augmenting UGE, larger increases in UGE do not correlate to larger reductions in HbA_{1C}. This suggests that the increase in UGE might not be

an indicator of the degree of reductions in blood glucose.

INTRODUCTION

The renal threshold for glucose excretion (RT_G) is the serum glucose concentration at which tubular reabsorption of glucose begins to saturate and glucose first appears in the urine [1]. The cutoff values of RT_G are dependent on sodium glucose co-transporter 2 (SGLT2), which is the protein responsible for the majority of filtered glucose reabsorption from the proximal renal tubules. Patients with type 2 diabetes mellitus (T2D) have increased expression of SGLT2 and elevated renal glucose absorption, which may contribute to persistent hyperglycemia [2]. The advent of SGLT2 inhibitors, which prevent glucose reabsorption from the proximal renal tubules, thereby promoting urinary glucose excretion (UGE) and decreasing the serum glucose level, adds to the wide range of pharmacotherapeutic options for treating patients with diabetes [3].

In previous studies [4, 5], it was shown that an SGLT2 inhibitor reduces RT_G, increases UGE, and decreases the serum glucose concentration in patients with T2D. Increases in UGE, along with improvements in blood glucose indices, have been deemed pharmacological effects of SGLT2 inhibitors. Furthermore, in multiple-dose clinical studies of both healthy subjects and patients with diabetes, SGLT2 inhibitors dose-dependently decreased RT_G, leading to a dose-dependent increase in UGE [4–9]. However, there are no studies to date as to whether larger increases in UGE after SGLT2 inhibitor treatment translate to larger reductions in glycated hemoglobin (HbA_{1c}).

In this study, we aimed to investigate the relationship between increases in morning spot UGE, which showed good agreement with overnight 8-h UGE in a previous study [10], and decreases in HbA_{1C} in patients with T2D after SGLT2 inhibitor treatment.

METHODS

Study Participants

This was a retrospective, longitudinal study of the patients with T2D who presented to Severance Hospital Diabetes Center between January 2015 and October 2016 and who were newly prescribed an SGLT2 inhibitor (dapagliflozin 10 mg or ipragliflozin 50 mg, once daily) as an add-on therapy to lower inadequately controlled serum glucose. We enrolled participants who had been tested for blood glucose parameters, including serum fasting glucose and HbA_{1C}, and first morning spot urinary creatinine and glucose concentrations immediately prior to the administration of the SGLT2 inhibitor and at a 12-week follow-up visit. We used the following inclusion criteria: (1) patients who regularly visit the outpatient clinic for blood glucose control and (2) patients who were newly prescribed an SGLT2 inhibitor (dapagliflozin 10 mg or ipragliflozin 50 mg, once daily) as an add-on therapy. Participants who met the following criteria were excluded: (1) <20 years of age; (2) type 1 diabetes; (3) pregnant women; (4) active infectious disease including urinary tract infection; (5) estimated glomerular filtration rate (eGFR) <60 ml/min/ 1.73 m^2.

Age, sex, weight, height, waist circumference, blood pressure, duration of diabetes, and pre-existing use of oral hypoglycemic agents or insulin were recorded. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Compliance with Ethics Guidelines

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The

Institutional Review Board at Severance Hospital approved this study protocol (4-2016-0998). Written informed consent for this study was not required by the Institutional Review Board because the database was only accessed for analysis purposes and personal information was not used.

Measurements of Blood and Urinary Gluco-Metabolic Parameters

To exclude external factors such as food intake on glucose homeostasis, participants were advised to keep fasting after dinner, but could drink water. Following an overnight fast, blood tests for glucose, HbA_{1C}, lipid profiles, and creatinine were performed, and a routine fasting morning urine sample was collected, both immediately prior to the administration of the SGLT2 inhibitor and at a 12-week follow-up visit. The morning urine and blood were sampled on the same day. In our previous study [10], we determined that the overnight 8-h UGE, overnight 8-h urinary glucose-to-creatinine ratio (UGCR), and morning spot UGCR showed good agreement with each other, suggesting that morning spot UGCR can be used as a simple index for estimating overnight amounts of UGE in patients with T2D. HbA_{1C} was measured by an immunoassay using an Integra 800 CTS (Roche, Hercules, CA, USA). Serum glucose and creatinine were measured using the Hitachi 7600 analyzer (Hitachi Ltd., Tokyo, Japan). For serum creatinine, a compensated kinetic Jaffé method (Clinimate CRE, Sekisui Medical Co., Ltd., Tokyo, Japan) was used in which the creatinine concentration was standardized to isotope dilution-mass spectrometry. The eGFR was derived using the guidelines from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [11]. The urinary glucose levels were measured using the hexokinase method with an AU680 chemistry analyzer (Beckman Coulter, Brea, CA, USA). The urinary creatinine levels were measured using the AU680 analyzer (Beckman Coulter, Inc.) with the kinetic Jaffé method. Urinary glucose levels were expressed as UGCR to minimize the influence of variations of kidney function using the following formula: morning spot UGCR (mg/mg) = [first-voided morning spot urine glucose (mg/dl)/first-voided morning spot urine creatinine (mg/dl)].

Statistical Analysis

All statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA). A normality test was performed for all continuous variables. The data are presented as mean ± standard deviation (SD) for normally distributed continuous variables and as median (interquartile range) for non-normally distributed continuous variables. Categorical data are expressed as numbers and percentages. The characteristics of the study participants were analyzed according to the change in HbA_{1C} after 12 weeks of SGLT2 inhibitor treatment using the two-sample Student's t test or the Mann-Whitney U test for continuous variables and Pearson's χ^2 test for categorical variables. The laboratory parameters at baseline and at week 12 of SGLT2 inhibitor treatment were compared using a paired t test or the Wilcoxon signed-rank test. The changes of the major parameters from baseline to 12 weeks were defined as follows: ΔHbA_{1C} (%) = [HbA_{1C} at week 12 (%)—HbA_{1C} at baseline (%)]; Δmorning spot UGCR (mg/mg) = [morning spot UGCR at week 12 (mg/mg)—morning spot UGCR at baseline (mg/mg)]. Correlations between Δmorning spot UGCR and either baseline HbA_{1C} or ΔHbA_{1C} were analyzed using Spearman's correlation coefficient. Multiple linear regression analyses were performed on logarithm-transformed values of Δmorning spot UGCR to model the relationship between the change in urinary glycemic indices and metabolic parameters including ΔHbA_{1C}. All P values <0.05 were considered statistically significant.

RESULTS

Characteristics of the Study Participants

A total of 101 participants were recruited in this study. The demographics and laboratory

Table 1 Baseline characteristics of the study participants according to change in HbA_{1C} after 12 weeks of treatment with SGLT2 inhibitors ($N = 101$)

Baseline characteristics	Total (N = 101)	Decreased HbA$_{1c}$ (N = 77)	Increased HbA$_{1c}$ (N = 24)	P value
Demographics				
Age (years)	61.0 (51.0–68.0)	58.0 (50.5–67.5)	64.0 (51.3–73.0)	0.133
Male Sex [n (%)]	50 (49.5)	37 (48.1)	13 (54.2)	0.601
BMI (kg/m^2)	26.4 ± 3.66	26.6 ± 3.76	25.9 ± 3.31	0.433
Waist circumference (cm)	92.0 ± 9.47	92.2 ± 9.41	91.5 ± 9.89	0.789
Systolic blood pressure (mmHg)	125.5 (116.0–133.0)	126.0 (115.3–132.8)	124.5 (116.0–135.8)	0.910
Diastolic blood pressure (mmHg)	74.9 ± 9.75	74.9 ± 9.73	74.8 ± 9.99	0.992
Duration of diabetes (years)	12.8 (8.88–17.8)	11.8 (8.88-17.4)	16.8 (9.06–18.5)	0.322
Laboratory indices				
HbA$_{1C}$ (%)	8.10 (7.55–9.05)	**8.30 (7.60–9.45)**	**7.60 (6.63–8.05)**	**<0.001**
Fasting glucose (mg/dl)	150.0 (126.5–180.0)	**155.0 (130.5–191.0)**	**136.5 (111.0–155.8)**	**0.013**
Total cholesterol (mg/dl)	150.0 (126.0–175.0)	**152.0 (132.0–179.0)**	**131.0 (113.5–156.8)**	**0.035**
Triglyceride (mg/dl)	123.0 (83.3–167.0)	**127.0 (89.0–174.0)**	**90.0 (61.0–157.0)**	**0.043**
HDL cholesterol (mg/dl)	43.0 (37.0–52.0)	43.0 (37.0–52.0)	44.5 (36.5–54.8)	0.415
LDL cholesterol (mg/dl)	79.4 ± 38.6	81.3 ± 41.0	73.0 ± 28.9	0.373
BUN (mg/dl)	15.3 ± 3.95	15.2 ± 3.96	15.6 ± 3.98	0.635
Creatinine (mg/dl)	0.73 (0.59–0.87)	0.74 (0.59–0.88)	0.67 (0.60–0.85)	0.641
eGFR CKD-EPI (ml/min/1.73 m^2)	97.1 ± 18.3	96.8 ± 17.6	98.1 ± 20.8	0.766
Urinary glycemic indices				
Morning spot urine glucose (mg/dl)	22.0 (8.50–149.0)	24.0 (8.50–165.0)	16.0 (9.00–123.3)	0.655
Morning spot UGCR (mg/mg)	0.19 (0.08–1.36)	0.19 (0.08–1.51)	0.20 (0.08–1.37)	0.955
Antidiabetic drugs				
Metformin [n (%)]	86 (85.1)	65 (84.4)	21 (87.5)	>0.999
Sulfonylurea [n (%)]	52 (51.5)	38 (49.4)	14 (58.3)	0.490
DPP-IV inhibitor [n (%)]	48 (47.5)	36 (46.8)	12 (50.0)	0.818
Thiazolidinediones [n (%)]	9 (8.90)	**4 (5.20)**	**5 (20.8)**	**0.033**
α-Glucosidase inhibitors [n (%)]	11 (10.9)	7 (9.10)	4 (16.7)	0.286
Insulin [n (%)]	37 (36.6)	30 (39.0)	7 (29.2)	0.471

Continuous variables are described as mean ± SD for parametric variables and median (interquartile range) for nonparametric variables

Bold denotes statistical significance at $P < 0.05$

HbA$_{1C}$ glycated hemoglobin, *SGLT2* sodium-glucose co-transporter 2, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *UGCR* urinary glucose-to-creatinine ratio, *DPP-IV* dipeptidyl peptidase-IV, *SD* standard deviation

characteristics of the participants are shown in Table 1. The median age and duration of diabetes among the study participants were 61.0 and 12.8 years, respectively. The participants were divided into two groups according to whether HbA_{1C} decreased ($N = 77$) or increased ($N = 24$) after 12 weeks of treatment with SGLT2 inhibitors. The median value of ΔHbA_{1C} [HbA_{1C} at week 12 (%)—HbA_{1C} at baseline (%)] in the two groups was −0.90% and 0.75%, respectively. There were no significant differences in age, sex, BMI, waist circumference, blood pressures, or duration of diabetes between the two groups. The proportions of participants taking oral hypoglycemic agents (except thiazolidinediones) or insulin were similar between the two groups. With respect to laboratory indices, baseline HbA_{1C} and serum fasting glucose were significantly higher in the group with decreased HbA_{1C} than in the group with increased HbA_{1C}. In addition, the baseline HbA_{1C} level showed a significant negative correlation with ΔHbA_{1C} level (Fig. 1), which suggests that patients with higher baseline HbA_{1C} have greater reductions of HbA_{1C} after taking an SGLT2 inhibitor. The eGFR values calculated using the CKD-EPI equation did not significantly differ between the two groups. Regarding urinary glycemic indices, neither the morning spot urine glucose concentration nor morning
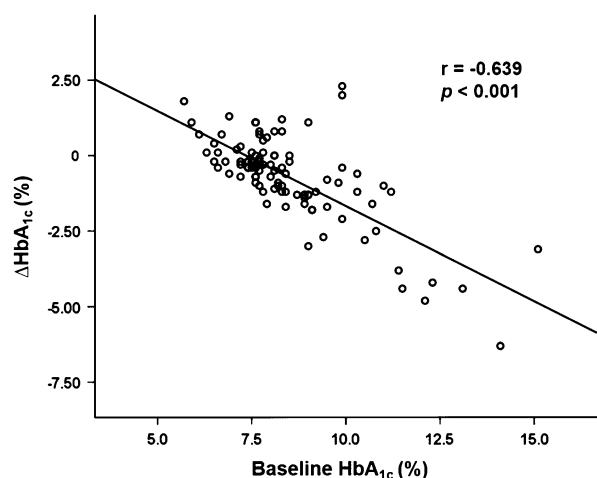
spot UGCR differed significantly between the two groups. In the group with increased HbA_{1C}, only one participant showed a slightly lower morning spot UGCR value after SGLT2 inhibitor treatment compared to baseline (Δmorning spot UGCR = −0.70 mg/mg).

Changes in Laboratory Parameters from Baseline to Week 12

Changes in laboratory parameters from baseline to week 12 of SGLT2 inhibitor treatment are shown in Table 2. SGLT2 inhibitors (i.e., dapagliflozin or ipragliflozin) used as an add-on therapy significantly lowered the HbA_{1C} level, with a median change from baseline to week 12 of −0.60% ($p < 0.001$). Similar to HbA_{1C}, serum fasting glucose was also significantly decreased at week 12 compared to the baseline values, with a median change of −25.0 mg/dl ($p < 0.001$). There was no significant change in the eGFR at week 12 compared to baseline. Robust increases from baseline were seen for both the morning spot urine glucose concentration and morning spot UGCR, with median changes at week 12 of 3837 mg/dl and 47.3 mg/mg, respectively.

Correlations between Change in Urinary Glycemic Indices and Change in HbA_{1C} Level

In the correlation analyses, the baseline HbA_{1C} level (Fig. 2a) showed a significant negative correlation with Δmorning spot UGCR. Regarding the ΔHbA_{1C} level (Fig. 2b), it showed a significant positive correlation with Δmorning spot UGCR. In other words, larger reductions in HbA_{1C} were correlated with smaller increases in UGE.

Multiple Linear Regression Analysis for Factors Affecting Changes in Urinary Glycemic Indices

To determine which factors predicted changes in urinary glycemic indices after SGLT2 inhibitor treatment, we performed multiple linear regression analyses (Table 3) using

Fig. 1 Correlation between baseline HbA_{1C} and ΔHbA_{1C} ($N = 101$). ΔHbA_{1C} (%) = [HbA_{1C} at week 12 (%)—HbA_{1C} at baseline (%)]. *HbA_{1C}* glycated hemoglobin

Table 2 Changes in laboratory parameters from baseline to week 12 ($N = 101$)

	Baseline	Week 12	*P*
HbA$_{1C}$ (%)	**8.10 (7.55–9.05)**	**7.50 (7.05–8.25)**	**<0.001**
Fasting glucose (mg/dl)	**150.0 (126.5–180.0)**	**125.0 (108.5–148.0)**	**<0.001**
eGFR CKD-EPI (ml/min/1.73 m^2)	96.4 ± 17.3	95.9 ± 18.3	0.415
Morning spot urine glucose (mg/dl)	**22.0 (8.50–149.0)**	**3859.0 (2581.0–5158.5)**	**<0.001**
Morning spot UGCR (mg/mg)	**0.19 (0.08–1.36)**	**47.5 (30.6–66.3)**	**<0.001**

Continuous variables are described as mean ± SD for parametric variables and median (interquartile range) for nonparametric variables

Bold denotes statistical significance at $P < 0.05$

HbA$_{1C}$ glycated hemoglobin, *eGFR* estimated glomerular filtration rate, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *UGCR* urinary glucose-to-creatinine ratio

log-transformed Δmorning spot UGCR as the dependent variable. In the univariate model, age and eGFR were significantly associated with Δmorning spot UGCR. After adjusting for age, sex, eGFR, baseline morning spot UGCR, and ΔHbA$_{1C}$, both eGFR and ΔHbA$_{1C}$ were significantly associated with Δmorning spot UGCR.

DISCUSSION

Despite numerous reports on the clinical efficacy and safety of SGLT2 inhibitors, a debate remains regarding the direct causality between the pharmacologic efficacy of SGLT2 inhibitors in UGE and their clinical effectiveness in lowering the glucose level as assessed by several glycemic indices since few observational studies based on routine care have been performed. We hypothesized that the increased glucose excretion into the urine might decrease glycemic parameters, such as HbA$_{1C}$ or glycated albumin, in the blood. Based on these hypotheses, this study aimed to investigate the relationship between increases in morning spot urine glucose parameters and decreases in HbA$_{1C}$ in patients with T2D after taking SGLT2 inhibitors.

In this retrospective, observational study of SGLT2 inhibitors in Korean patients with poorly controlled T2D, we demonstrated three main findings. First, based on the increased urinary glucose levels after starting SGLT2 inhibitor

therapy, the pharmacological mode of action of SGLT2 inhibitors on renal tubules is intact and active. Second, based on the HbA$_{1C}$ results, we determined that, despite the pharmacological activity of SGLT2 inhibitors, there are responders and non-responders among the subjects with T2D. Third, based on the increased morning spot urine glucose parameters and decreased HbA$_{1C}$, the relation between morning spot urine glucose parameters and HbA$_{1C}$ is not as simple as hypothesized.

In previous studies [6, 8], SGLT2 inhibitors induced sustained glycosuria and improvements in blood glucose. In a study of the addition of dapagliflozin treatment for patients with T2D that was inadequately controlled on pioglitazone [8], the beneficial effects of dapagliflozin on hyperglycemia were maintained for almost 1 year and were consistent with a sustained pharmacodynamic activity toward glycosuria. Consistent with these previous reports, our study participants also showed a significant increase in morning spot UGCR, indicating that controlled glycosuria was induced after 12 weeks of SGLT2 inhibitor treatment. However, of the 101 participants, 8 had negative Δmorning spot UGCR values after SGLT2 inhibitor treatment. This suggests that the glycosuria can be divided into two categories. The first category is natural-overflow glycosuria, where UGE is caused by elevated blood glucose and glomerular-filtered glucose levels. The other category is chemically induced glycosuria for
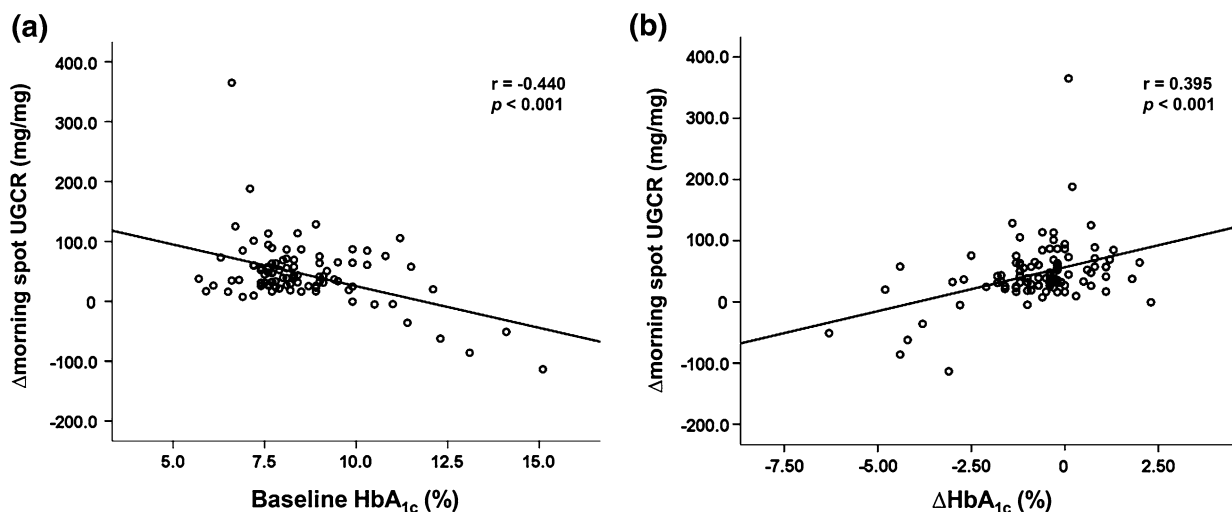
Fig. 2 Correlations between Δmorning spot UGCR and baseline HbA$_{1C}$ (**a**) or ΔHbA$_{1C}$ (**b**) ($N = 101$). Δmorning spot UGCR (mg/mg) = [morning spot UGCR at week 12 (mg/mg)—morning spot UGCR at baseline (mg/mg)]; ΔHbA$_{1C}$ (%) = [HbA$_{1C}$ at week 12 (%)—HbA$_{1C}$ at baseline (%)]. *UGCR* urinary glucose-to-creatinine ratio, *HbA$_{1C}$* glycated hemoglobin

Table 3 Multiple linear regression models for change in morning spot UGCR ($N = 101$)

Variables	Univariate		Multivariate	
	STD β	P	STD β	P
ΔHbA$_{1C}$ (%)	0.177	0.098	**0.269**	**0.007**
Age (years)	**−0.308**	**0.003**	0.000	0.999
Male sex	−0.069	0.518	−0.045	0.633
eGFR CKD-EPI (ml/min/1.73 m^2)	**0.464**	**<0.001**	**0.501**	**0.001**
Baseline morning spot UGCR (mg/mg)	0.024	0.820	−0.030	0.747

Logarithm-transformed values of Δmorning spot UGCR were used as the dependent variable

ΔHbA$_{1C}$ (%) = [HbA$_{1C}$ at week 12 (%)—HbA$_{1C}$ at baseline (%)]; Δmorning spot UGCR (mg/mg) = [morning spot UGCR at week 12 (mg/mg)—morning spot UGCR at baseline (mg/mg)]

Bold denotes statistical significance at $P < 0.05$

UGCR urinary glucose-to-creatinine ratio, *HbA$_{1c}$* glycated hemoglobin, *eGFR* estimated glomerular filtration rate, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *STD* standardized

managing hyperglycemia using an SGLT2 inhibitor. In this study, those eight patients who had negative Δmorning spot UGCR values had very high baseline HbA$_{1C}$ levels of more than 9.90% with mean 12.2% (Table S1 for details). Therefore, we postulate that, in patients with very high HbA$_{1C}$ levels, the initial total glycosuria (natural overflow plus chemically induced glycosuria) might be more augmented by SGLT2 inhibitor treatment, resulting in decreased serum glucose levels. After the stable state of

pharmacologic efficacy of SGLT2 inhibitor, the decreased levels of serum glucose in turn decreased the urinary glucose excretion. The net degree of chemically induced glycosuria caused by the SGLT2 inhibitors might be lower than the initial natural-overflow glycosuria.

In multiple-dose clinical studies of SGLT2 inhibitors in both healthy subjects and patients with diabetes, SGLT2 inhibitors provided dose-dependent reductions in RT$_G$ and increases in UGE [4–9]. A study comparing 50-, 100-, and

300-mg doses of canagliflozin showed that the mean 24-h RT_G values decreased in a dose-dependent manner in T2D patients [9]. In healthy euglycemic subjects, canagliflozin dose-dependently decreased mean 24-h RT_G and increased mean 24-h UGE [7]. However, the association between the dose of SGLT2 inhibitor and the degree of improvement in blood glucose is not consistent in previous studies. In a study of five dapagliflozin doses in T2D patients [6], changes in fasting serum glucose were dose-related; however, there was little evidence of a dose response for either postprandial glucose or HbA_{1C} level. In a study of canagliflozin as an add-on to metformin treatment [5], reductions in HbA_{1C} and fasting serum glucose showed dose-dependent patterns. However, no study to date has determined whether larger increases in UGE after SGLT2 inhibitor treatment correlate with larger reductions in HbA_{1C}. We hypothesized that the increased UGE might cause decreased glycemic parameters, such as HbA_{1C} or glycated albumin, in the blood. In the correlation and regression analyses, unlike our hypothesis, the ΔHbA_{1C} level and Δmorning spot UGCR showed significant positive correlations. In other words, a larger reduction in HbA_{1C} was correlated with a smaller increase in UGE. We postulate that the pharmacological effects of SGLT2 inhibitors result in increases in chemically induced UGE and improvements in blood glucose, and these improved blood glucose levels trigger less chemically induced UGE and markedly decrease natural-overflow glycosuria.

Our study has some potential limitations. Because the cutoff point for maximum glucose reabsorption in the renal tubules (maximal reabsorptive capacity, T_{mG}) is not abrupt [12], assessing RT_G was impossible in this study design. Therefore, we could not demonstrate a clear relationship between the plasma glucose concentration and urinary glucose amount. Also, we did not collect information about the time, type, or last meal consumed by the participants, which might have an influence on UGCR and glucagon levels. When serum glucose levels are decreasing during fasting state, glucagon is secreted from pancreatic α-cells and signals the liver or kidney to increase glucose output through gluconeogenesis [13]. Furthermore, in subjects with diabetes, it was reported that SGLT2 inhibitor increased endogenous glucose and raised levels of the glucagon hormone, which prompts the body to produce glucose [14]. The participants in our study were newly prescribed an SGLT2 inhibitor as an add-on therapy, and preexisting oral hypoglycemic agents or insulin was maintained throughout study period in each participant. Therefore, improvement in blood glucose was thought to be mainly caused by SGLT2 inhibitor treatment. However, further studies are needed to be investigated on the potential underlying pathophysiology on urinary glucose homeostasis and pharmacologic influences of SGLT2 inhibitors including glucagon levels and food effects on UGCR in accurate research settings for better management in T2D.

CONCLUSION

Although SGLT2 inhibitor treatment leads to reduced HbA_{1C} levels by augmenting UGE (i.e., medication efficacy), larger increases in UGE after SGLT2 inhibitor treatment do not correlate to larger reductions in HbA_{1C} (i.e., effectiveness). This suggests that the relation between morning spot urine glucose parameters and HbA_{1C} is not as simple as hypothesized and increases in UGE might not be an indicator of the degree of reductions in blood glucose.

ACKNOWLEDGEMENTS

Compliance with Ethics Guidelines. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board at Severance Hospital approved this study protocol (4-2016-0998). Written informed consent for this study was not required by the Institutional Review Board because the database was only accessed for analysis purposes and personal information was not used.

Data Availability. All data generated or analyzed during this study are included in this published article.

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