

Effects of SGLT2 Inhibition on eGFR and Glomerular and Tubular Damage Markers in Japanese Patients With Type 2 Diabetes

Hiromi Konishi^a, Jun Shirakawa^{a, b}, Kazuki Tajima^a, Tomoko Okuyama^a, Yu Togashi^a, Hikaru Takamine^a, Yoshinobu Kondo^a, Rieko Kunishita^a, Yasuo Terauchi^{a, b}

Abstract

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic drugs that enhances insulin-independent urinary glucose excretion. Recent studies have suggested that SGLT2 inhibitors possess a renoprotective property in type 2 diabetes patients. However, evidence of the effects of SGLT2 inhibition on glomerular and tubular damage markers is lacking. The aim of this study was to examine the effect of SGLT2 inhibitors on renal function, especially on glomerular and tubular damage markers in patients with type 2 diabetes.

Methods: We retrospectively analyzed data from 81 patients who used SGLT2 inhibitors. Next, we investigated whether treatment with SGLT2 inhibitors affected urinary damage markers including N-acetyl- β -D-glucosaminidase (NAG), liver-type fatty acid-binding protein (L-FABP), type IV collagen, and β 2-microglobulin (β 2MG) in patients with type 2 diabetes.

Results: In the retrospective study, SGLT2 inhibition reduced the estimated glomerular filtration rate (eGFR) at 4 and 12 weeks in a manner that was correlated with the baseline eGFR. In the longitudinal study, SGLT2 inhibition tended to increase the urinary damage marker levels with an accompanying decrease in eGFR after 1 month of use. The observed changes in eGFR and urinary damage markers were reversed at 3 months, even though both the HbA1c level and blood pressure were further improved.

Conclusions: These results indicated that SGLT2 inhibition reduces the eGFR in a manner depending on the baseline eGFR levels and transiently increased the glomerular and tubular damage markers in

patients with type 2 diabetes.

Keywords: Glomerular and tubular damage markers; SGLT2 inhibitor; Type 2 diabetes

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic drug that enhances insulin-independent urinary glucose excretion without increasing body weight. Recent evidence suggests that SGLT2 inhibitors reduce the risk of cardiovascular events and exert renoprotective effects [1]. Studies have suggested that the renoprotective actions of SGLT2 -inhibitors are caused by reductions in blood glucose, body weight, and blood pressure levels [2-4], with tubuloglomerular feedback (TGF) playing a particularly important role in the renal effects [5, 6]. Hyperglycemia can enhance glomerular filtration rate (GFR) during the early stage of diabetes, and individuals with glomerular hyperfiltration are thought to be at risk for progression to diabetic nephropathy [7]. Diabetes-induced proximal tubule growth involves an initial hyperplastic growth period and a hypertrophic growth period [8]. Another study also suggested that tubular growth is related to an enhanced proximal tubular fluid reabsorption rate [9]. Thus, in diabetic nephropathy, proximal tubule function is enhanced by tubular growth, and TGF is thought to induce glomerular hyperfiltration. Recent animal studies have reported that an SGLT2 inhibitor improved glomerular hyperfiltration independent of a reduction in blood glucose levels [10], but that tubular growth was inhibited by glycaemic control [6]. Treatment with dapagliflozin resulted in an initial fall in the estimated glomerular filtration rate (eGFR), but this reduction was completely reversible only 1 week after dapagliflozin discontinuation in type 2 diabetes patients [11]. The SGLT2 inhibitor empagliflozin reportedly reduced the GFR in type 1 diabetes patients with hyperfiltration of the normal GFR [5]. The EMPA-REG OUTCOME trial also showed a reduction in eGFR after 4 weeks in patients with type 2 diabetes [1], while canagliflozin decreased the eGFR after 3 weeks of treatment in type 2 diabetes patients with stage 3 chronic kidney disease [12]. A subgroup of Asian pa-

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^aDepartment of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

^bCorresponding Author: Jun Shirakawa, Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: jshira-tyk@umin.ac.jp; Yasuo Terauchi, Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: terauchi-tyk@umin.ac.jp

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Table 1. Mean Changes From Baseline in Glycemic Control, Lipid Profile, and Renal Function in Patients Receiving SGLT2 Inhibitors for 12 Weeks (N = 81)

	Baseline	4 weeks	12 weeks	P value		
				0 vs. 4 weeks	4 vs. 12 weeks	0 vs. 12 weeks
Body weight (kg)	78.3 (68.0, 90.6)	77.4 (66.7, 90.0)	76.2 (67.0, 89.0)	< 0.0001*	< 0.0001*	< 0.0001*
Body mass index (kg/m ²)	29.3 (26.6, 32.6)	28.4 (26.0, 32.3)	28.4 (25.7, 31.9)	< 0.0001*	< 0.0001*	< 0.0001*
HbA1c (mmol/mol)	65 (57, 75)	62 (55, 70)	58 (53, 67)	< 0.0001*	< 0.0001*	< 0.0001*
HbA1c (%)	8.1 (7.4, 9.0)	7.8 (7.2, 8.6)	7.5 (7.0, 8.3)	< 0.0001*	< 0.0001*	< 0.0001*
BUN (mg/dL)	14.5 (12.0, 16.8)	16.0 (13.0, 19.0)	16.0 (13.0, 19.0)	0.0031*	0.073	< 0.0001*
Cre (mg/dL)	0.74 (0.58, 0.84)	0.79 (0.63, 0.90)	0.76 (0.60, 0.95)	< 0.0001*	0.4	< 0.0001*
eGFR (mL/min/1.73 m ²)	80.0 (69.4, 93.0)	74.7 (63.7, 91.6)	77.3 (65.4, 91.1)	< 0.0001*	0.37	< 0.0001*
CCr (mL/min)	131 (99.3, 178)	120 (87.0, 160)	120 (88.0, 160)	< 0.0001*	0.44	< 0.0001*
LDL-C (mg/dL)	101 (80.8, 130)	98.5 (80.9, 115)	104 (83.8, 127)	0.003*	0.0029*	0.49
HDL-C (mg/dL)	50.0 (41.8, 58.3)	48.5 (42.0, 57.5)	52.0 (43.0, 59.5)	0.28	0.0012*	0.096
TG (mg/dL)	152 (103, 223)	140 (97.5, 218)	145 (94.8, 215)	0.089	0.24	0.099
UA (mg/dL)	5.55 ± 1.29	4.93 ± 1.15	5.07 ± 1.18	< 0.0001*	0.028*	0.0002*

Mean ± standard deviation or medians (25th and 75th percentiles). CCr was calculated by Cockcroft and Gault equation. P values were determined by paired *t*-test or Wilcoxon signed-rank test. *P < 0.05.

tients in the EMPA-REG OUTCOME trial showed reductions in the risk of cardiovascular mortality after treatment with SGLT-inhibitor, and an initial decrease in eGFR was also observed in Asian patients [13]. However, the clinical meaning of the initial reduction in eGFR induced by SGLT2 inhibition remains unclear in terms of glomerular and tubular functional impairment. In the present study, we first evaluated the effects of SGLT2 inhibitor on the changes in eGFR in Japanese type 2 diabetes patients. We also analyzed several glomerular and tubular damage markers, such as urinary N-acetyl-β-D-glucosaminidase (NAG), liver-type fatty acid binding protein (L-FABP), type IV collagen, and β2 microglobulin (β2MG), in a subgroup of patients who were treated with an SGLT-2 inhibitor.

Materials and Methods

Ethics approval and consent to participate

The study was approved by the institutional review board and was registered with the University Hospital Medical Information Network Japan (UMIN) (ID# 000021619). The patients were anonymized to protect their personal information. The study protocol was approved by the Medical Ethics Committee of the Yokohama City University Hospital (Reference No. B151001013 and B151105005), and Yokohama Central Hospital (on July 14, 2016), and the study was performed in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. All subjects of prospective study enrolled gave written informed consent for participation. As a retrospective study, the opt-out method of obtaining informed consent was adopted.

Study population

We screened all the patients with a history of SGLT2 inhibitor use at Yokohama City University Hospital. This retrospective study analyzed the medical records data of patients with type 2 diabetes who received SGLT2 inhibitors at Yokohama City University Hospital between April 2014 and November 2016. During these 2 years and 7 months, a total of 166 patients received an SGLT 2 inhibitor at least once (ipragliflozin: 56 patients, dapagliflozin: 32 patients, tofogliflozin: 13 patients, luseogliflozin: 13 patients, canagliflozin: 30 patients, empagliflozin: 22 patients). We analyzed changes in body weight, HbA1c, eGFR, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride and uric acid.

Patients who visited at 4 and 12 weeks after the start of SGLT2 inhibitor treatment, and who underwent blood and urine tests were included in the present study. Patients who did not visit at the predefined intervals and who exhibited poor medication adherence were excluded. Finally, we analyzed data from 81 patients who met the inclusion/exclusion criteria. Based on the results of this retrospective study, we then investigated whether treatment with an SGLT2 inhibitor affected the eGFR and urinary damage markers including NAG, L-FABP, type IV collagen, and β2MG in patients with type 2 diabetes.

Japanese type 2 diabetes patients who had not been previously treated with an SGLT2 inhibitor were recruited from among inpatients or outpatients of Yokohama City University Hospital or Yokohama Central Hospital. Patients with a low eGFR (< 29 mL/min/1.73 m²) or kidney diseases other than diabetic nephropathy were excluded. Twenty-three eligible patients (10 patients for a prospective study and 13 patients for a retrospective observational study) were the subjects of the final analysis. The patients received tofogliflozin (20 mg/day),

and the eGFR, NAG, L-FABP, type IV collagen, and β 2MG levels were assessed at baseline and at the end of the fourth and 12th weeks. The 23 patients were followed up for 4 weeks, and 19 patients (83%) were again followed up at 12 weeks.

Measurements

The HbA1c levels were measured using high-performance liquid chromatography (HPLC) (National Glycohemoglobin Standardization Program (NGSP) values). The urinary concentrations of microalbumin were measured using a turbidimetric immunoassay kit. The β 2MG, NAG, L-FABP, and type IV collagen levels were determined using a latex-enhanced turbidimetric immunoassay kit (Denka Seiken Co., Tokyo, Japan), a 6-methyl-2-pyridyl-N-acetyl-1-thio- β -D-glucosaminide (MPT-NAG) kit (Nittobo Medical CO., Tokyo, Japan), a two-step sandwich enzyme-linked immunosorbent assay kit (CMIC Holdings Co., Tokyo, Japan), and a one-step sandwich enzyme-linked immunosorbent assay kit (Kyowa Pharma Chemical Co., Toyama, Japan), respectively. The estimated glomerular filtration rate was calculated as previously described [14]: $eGFR (mL/min/1.73 m^2) = 194 \times \text{serum creatinine} (-1.094) \times \text{age} (-0.287) \times 0.739$ (if female).

Statistical analysis

Continuous data are presented as the mean \pm standard deviation (SD) or the median and interquartile range. For paired analyses, paired *t*-test for continuous values with a normal distribution was used. A Wilcoxon signed-rank test was used for continuous values that did not follow a normal distribution. For unpaired analysis, we use Mann-Whitney U test for continuous values that did not follow a normal distribution. All the statistical analyses were performed using the Statistical Package for JMP 12.0.1 (SAS Institute Inc., Cary, NC, USA). A two-sided P value < 0.05 was considered statistically significant.

Results

SGLT2 inhibitor transiently attenuated eGFR in patients with type 2 diabetes when examined retrospectively

Table 1 shows the parameters before and after 4 or 12 weeks of treatment with SGLT2 inhibitors in 81 type 2 diabetes patients (44 men and 37 women; mean age, 54.5 ± 12.3 years old; ipragliflozin: 22 patients, dapagliflozin: 14 patients, tofogliflozin: seven patients, luseogliflozin: 12 patients, canagliflozin: 21 patients, empagliflozin: five patients). SGLT2 inhibition reduced body weight, improved HbA1c, and decreased LDL cholesterol and uric acid levels significantly at 4 and 12 weeks (Table 1). The eGFR levels were significantly reduced after treatment with the SGLT2 inhibitor at week 4 (-6.6%, $P < 0.0001$), while the levels of eGFR at week 12 tended to have recovered to the baseline level, compared with the level at week 4 (-3.4% compared with baseline, $P = 0.37$). Univariate and multivariate

Table 2. Linear Regression Analysis Between Δ eGFR and Variables (Between Before and 4 Weeks or 12 Weeks

	Between baseline and 4 weeks after SGLT-2 inhibitor treatment				Between baseline and 12 weeks after SGLT-2 inhibitor treatment						
	Univariate regression model		Multivariate regression model		Univariate regression model		Multivariate regression model				
	β	P value	β	P value	β	P value	β	P value			
Age (years)	0.091	0.068	0.18	0.18	0.082	0.92	0.14	0.080	0.083	0.087	0.72
Sex	-0.15	0.85	0.86	0.86	0.86	0.82	-0.97	1.00	0.33	-0.89	0.31
Body weight change (kg)	0.78	0.48	0.11	0.65	0.46	0.16	-0.21	0.34	0.55	-0.45	0.13
Basal eGFR (mL/min/1.73 m ²)	-0.076	0.032	0.018*	-0.13	0.043	0.0046*	-0.16	0.034	< 0.0001*	-0.19	< 0.0001*
ACE inhibitor / ARB	-0.86	0.84	0.31	-0.4	0.86	0.64	-1.46	0.99	0.14	-0.22	0.80

*P < 0.05.

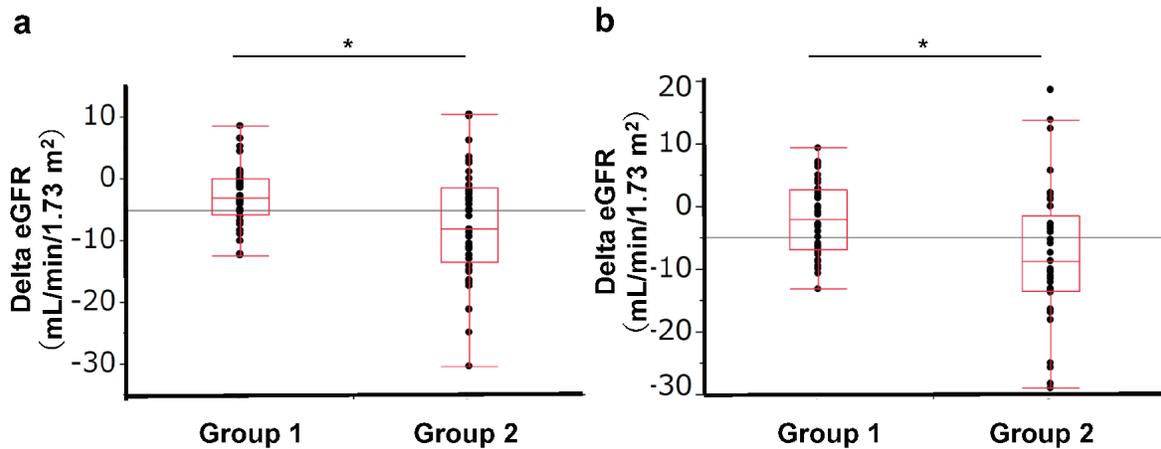


Figure 1. Change in eGFR according to baseline eGFR group. Group 1: eGFR < 80.0 mL/min/1.73 m², Group 2: eGFR ≥ 80 mL/min/1.73 m². (a) Change in eGFR from baseline to 4 weeks. (b) Change in eGFR from baseline to 12 weeks.

analyses showed that the changes in eGFR were not affected by age, sex, body weight change, or the use of ACE inhibitor or ARB and were correlated with the eGFR at baseline (Table 2). We divided the patients into two groups according to the median baseline eGFR (80.0 mL/min/1.73 m²): Group 1 was defined as those with a baseline eGFR below 80 mL/min/1.73 m², while subjects with a baseline eGFR of more than 80 mL/min/1.73 m² were assigned to Group 2. No significant differences in the baseline characteristics were observed between the two groups except for renal functions (BUN, Cr, eGFR, and CCr) (Supplementary Table 1) (www.jofem.org). Group 2 had a greater reduction in eGFR at 4 weeks than that in Group 1 (Fig. 1). Although Group 2 showed a significant improvement in HbA1c compared with Group 1 at 4 weeks, no significant difference was observed at 12 weeks (Table 3). The lipid parameters (LDL-cho, HDL-cho, and TG) and uric acid

value were not significantly different between the two groups at either 4 or 12 weeks.

Effects of SGLT2 inhibition on eGFR and glomerular and tubular damage markers in patients with type 2 diabetes in a longitudinal study

Next, we investigated the changes in glomerular damage markers after treatment with SGLT-2 inhibitors in type 2 diabetes patients. The urinary NAG, L-FABP, type IV collagen, and β2MG levels were measured in 23 of the 81 above-mentioned patients. Supplementary Table 2 (www.jofem.org) shows the results after 4 weeks of SGLT-2 inhibitor treatment in 23 type 2 diabetes patients (14 men and nine women; mean age, 51.7 ± 11.9 years old; mean duration of diabetes, 9.78 ± 7.34 years) with nor-

Table 3. Mean Changes From Baseline in Glycemic Control, Lipid Profile, and Renal Function in Patients Receiving SGLT2 Inhibitors for 12 Weeks by Baseline eGFR Group (N = 81)

	Baseline - 4weeks			Baseline - 12weeks		
	Group 1	Group 2	P value	Group 1	Group 2	P value
Delta Body weight (kg)	-1.0 (-2.0, 0)	-1.0 (-2.3, 0)	0.50	-1.30 (-3.0, -0.45)	-1.90 (-4.0, -0.125)	0.36
Delta HbA1c (mmol/mol)	-2.0 (-5.0, 0)	-5.0 (-9.0, -1.0)	0.016*	-5.5 (-9.8, 1.0)	-7.0 (-14, -2.5)	0.12
Delta HbA1c (%)	-0.20 (-0.40, 0)	-0.40 (-0.80, -0.1)	0.016*	-0.50 (-0.88, 0.10)	-0.60 (-1.30, -0.25)	0.11
Delta BUN (mg/dL)	0 (-2.0, 2.0)	1.0 (-1.0, 4.0)	0.095	2.0 (0, 3.0)	1.0 (-1.0, 4.0)	0.83
Delta Cre (mg/dL)	0.03 (0, 0.088)	0.04 (0.01, 0.09)	0.54	0.015 (-0.03, 0.11)	0.05 (0.0005, 0.08)	0.37
Delta eGFR (mL/min/1.73 m ²)	-3.05 (-5.9, 0)	-8.2 (-13.6, -1.5)	0.0075*	-2.05 (-6.9, 2.65)	-8.80 (-13.6, -1.40)	0.0009*
Delta CCr (mL/min)	-5.25 (-8.18, -0.14)	-14.8 (-25.6, -1.56)	0.0021*	-4.61 (-11.1, -3.28)	-14.6 (-30.3, -5.91)	0.0005*
Delta LDL (mg/dL)	-5.4 (-13.0, 7.05)	-7.6 (-15.6, 5.35)	0.38	5.8 (-10.2, 13.8)	-2.9 (-8.75, 12.8)	0.87
Delta HDL (mg/dL)	0 (-2.0, 2.5)	-1.0 (-4.0, 2.0)	0.12	2.0 (-3.0, 8.2)	0 (-3.0, 5.0)	0.43
Delta TG (mg/dL)	-6.0 (-31.0, 25.0)	-19.0 (-52.5, 24.0)	0.28	5.0 (-24.0, 26.0)	-17.0 (-67.0, 9.0)	0.052
Delta UA (mg/dL)	-0.65 (-1.25, 0)	-0.7 (-1.2, 0)	0.94	-0.6 (-1.1, 0.2)	-0.5 (-1.1, 0.05)	0.65

Medians (25th and 75th percentiles). CCr was calculated by Cockcroft and Gault equation. P values were determined by Mann-Whitney U test. *P < 0.05.

Table 4. Mean Changes From Baseline in Glycemic Control, Blood Pressure, Lipid Profile, and Renal Function in Patients Receiving SGLT-2 Inhibitors for 4 Weeks and 12 Weeks (N = 19)

	Standard value	Baseline	4 weeks	12 weeks	P value		
					0 vs. 4 weeks	4 vs. 12 weeks	0 vs. 12 weeks
Body weight (kg)		82.0 ± 15.3	81.6 ± 15.7	79.6 ± 16.1	0.53	0.0098*	0.0039*
Body mass index (kg/m ²)		28.8 ± 3.51	28.6 ± 3.38	27.9 ± 3.67	0.44	0.0094*	0.0043*
HbA1c (mmol/mol)		68.6 ± 16.4	60.8 ± 9.28	54.6 ± 8.86	0.0022*	0.012*	0.0031*
HbA1c (%)		8.43 ± 1.50	7.71 ± 0.86	7.15 ± 0.82	0.0021*	0.012*	0.0031*
eGFR (mL/min/1.73 m ²)		78.5 (67.1, 88.4)	75.0 (70.1, 79.0)	73.4 (66.8, 82.8)	0.027*	0.27	0.41
CCr (mL/min)		127 ± 26.7	122 ± 29.5	120 ± 29.7	0.12	0.37	0.048*
SBP (mm Hg)		135 ± 19.6	130 ± 16.0	128 ± 15.7	0.073	0.43	0.024*
DBP (mm Hg)		81.6 ± 14.3	80.7 ± 11.6	78.7 ± 10.9	0.51	0.61	0.27
LDL-C (mg/dL)		81.0 (72.2, 110)	74.8 (64.0, 83.2)	76.8 (64.2, 91.4)	0.074	0.28	0.52
HDL-C (mg/dL)		50.9 ± 15.0	51.9 ± 12.5	54.0 ± 14.6	0.46	0.15	0.079
TG (mg/dL)		177 (95, 289)	169 (94, 225)	139 (89, 247)	0.64	0.99	0.26
UA (mg/dL)		5.69 ± 1.39	5.00 ± 1.19	4.92 ± 1.28	0.0068*	0.56	0.0023*
Urinary albumin (mg/g Cre)	≤ 18.6	12.0 (6.6, 56.2)	12.1 (7.5, 28.7)	13.3 (6.3, 30.5)	0.52	0.059	0.078
Urinary NAG (U/g Cre)	≤ 5.6	5.97 (2.67, 7.79)	6.33 (5.31, 9.34)	5.83 (4.73, 7.88)	0.11	0.096	0.52
Urinary L-FABP (μg/g Cre)	≤ 8.4	2.70 (1.30, 5.80)	2.91 (1.90, 4.00)	2.30 (1.30, 4.16)	0.4	0.65	0.77
Urinary type IV collagen (μg/g Cre)	≤ 7.3	5.40 (2.00, 7.20)	5.30 (3.80, 6.70)	4.60 (3.70, 6.50)	0.19	0.52	0.71
Urinary β2MG (μg/g Cre)	†	78.6 (40.0, 181)	111 (65.9, 173)	133 (100, 243)	0.95	0.12	0.12

Mean ± standard deviation or medians (25th and 75th percentiles). CCr was calculated by Cockcroft and Gault equation. †The reference value of β2 microglobulin was 11 - 253 μg/day in our hospital. We used the spot urine sample and the urinary excretion levels of β2 microglobulin were described as micrograms per gram of creatinine. P values were determined by paired t-test or Wilcoxon signed-rank test. NAG: N-acetyl-β-D-glucosaminidase; L-FABP: liver-type fatty acid binding protein; β2MG: β2 microglobulin. *P < 0.05.

moalbuminuria (n = 16), microalbuminuria (n = 3), or macroalbuminuria (n = 4). The HbA1c, eGFR, CCr, and UA levels were significantly reduced after treatment with the SGLT2 inhibitor at week 4 (Supplementary Table 2) (www.jofem.org). Of note, the urinary NAG (P = 0.053), L-FABP (P = 0.10), type IV collagen (P = 0.024), and β2MG (P = 0.57) levels showed a tendency to be elevated. Nineteen (12 men and seven women; mean age, 52.6 ± 11.0 years old; mean duration of diabetes, 10.8 ± 7.42 years) of the 23 above-mentioned patients were also followed up after 12 weeks of treatment (Table 4). The previously observed trends in the eGFR and glomerular and tubular damage markers at 4 weeks of treatment had almost recovered to the baseline levels after 12 weeks of treatment, although the body weight, HbA1c, SBP and UA levels were still significantly reduced by the SGLT2 inhibitor at week 12 (Table 4).

Discussion

In this study, we investigated the effects of SGLT-2 inhibition on the eGFR and other glomerular damage markers in Japanese type 2 diabetes patients. Our data showed that the initial reduction in eGFR induced by treatment with SGLT2 inhibitors was greater in the subjects who had a higher baseline eGFR. Similar to previous reports, the initial reduction in

eGFR tended to recover to the baseline level at 12 weeks after SGLT2 inhibitor treatment. NAG, L-FABP, type IV collagen, and β2MG also showed a tendency to increase transiently after the start of SGLT-2 inhibition in type 2 diabetes patients.

In type 2 diabetes patients with hypertension receiving renin-angiotensin blockers, the initial reduction in eGFR in subjects receiving dapagliflozin was completely reversible after the discontinuation of treatment [11]. Therefore, the initial fall in eGFR as a result of SGLT-2 inhibitor treatment was not thought to reflect a reduction in the number of functioning nephron GFR. In this study, a higher eGFR at baseline was correlated with a greater reduction in eGFR at both 4 and 12 weeks after the start of SGLT2 inhibitor treatment, compared with the lower eGFR group, independent of the changes in HbA1c and uric acid. This result possibly suggested that the baseline eGFR affects the renoprotective action of SGLT2 inhibitors in the context of correcting hyperfiltration.

Experimental studies have suggested that SGLT2 inhibitors ameliorate glomerular hyperfiltration and reduce albuminuria, kidney hypertrophy and inflammation in animal models of type 1 and type 2 diabetes [3, 15]. The results of the EMPAREG OUTCOME trial suggested that SGLT2 inhibition provides renoprotection by decreasing hyperfiltration [6], arterial stiffness [16, 17], vascular resistance [17], serum uric acid levels [18], and systemic and renal neurohormonal systems [16,

19] in type 2 diabetes patients, despite a reduction in the eGFR. The initial reduction in eGFR induced by SGLT2 inhibitors is thought to be associated with a reduction in blood pressure, an osmotic diuretic effect, and TGF [1, 20]. The present study also showed an initially significant decrease in eGFR, blood pressure, and uric acid levels after 4 weeks of treatment. While empagliflozin has a protective effect on inflammatory and fibrotic marker expressions in human proximal tubular cells [4], our results showing a transient increase in glomerular and tubular damage markers because of SGLT2 inhibition is a new observation for this emerging diabetes treatment. Even if the transient increase in glomerular and tubular damage markers reflects glomerular and tubulointerstitial injuries, the changes observed in this study were almost within the normal range. Therefore, the clinical significance of these transient changes might be minimal, and the changes may reflect a transitory change in eGFR. Further consideration should be given to the transient changes in renal function markers during treatment with SGLT2 inhibitors.

The limitations of this study include a small sample size and a relatively short follow-up period. Furthermore, a control group was not examined, and the biomarker data did not exhibit normal distributions and had large degrees of variance.

In summary, the results of our investigation suggested that SGLT2 inhibition reduces the eGFR over the short term, is correlated with the baseline eGFR level, and tends to have recovered to the baseline level after 12 weeks of treatment in type 2 diabetes patients. SGLT2 inhibition may increase glomerular and tubular damage markers initially, but these markers eventually recover to their baseline levels. Further studies are needed to evaluate the effects of SGLT2 inhibitors on renal functions.

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Conflict of Interest

None of the authors has any potential conflict of interest associated with this research.

Abbreviations

SGLT2 inhibitors: sodium-glucose cotransporter 2 inhibi-

tors; eGFR: estimated glomerular filtration rate; TGF: tubuloglomerular feedback; NAG: N-acetyl- β -D-glucosaminidase; L-FABP: liver-type fatty acid binding protein; β 2MG: β 2 microglobulin; LDL-cholesterol: low-density lipoprotein-cholesterol; HDL-cholesterol: high-density lipoprotein-cholesterol

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