Initial dip predicts renal protective effects after the administration of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and chronic kidney disease with normoalbuminuria

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Research

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Original Article

Initial dip predicts renal protective effects after the administration of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and chronic kidney disease with normoalbuminuria

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Abstract

Background: We investigated the renoprotective effects of sodium-glucose cotransporter 2 inhibitors (SGLT2is) on renal function in patients with type 2 diabetes and chronic kidney disease (CKD) with normoalbuminuria.

Methods: A retrospective review of clinical records of Japanese participants with type 2 diabetes and CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) with normoalbuminuria (urine albumin to creatinine ratio < 30 mg/g Cr and/or urinary protein to creatinine ratio < 150 mg/g Cr) was conducted. Participants were categorized into two groups depending on whether they had started using SGLT2is. The main study outcome was a comparison of the change in renal function evaluated by eGFR after 1 year (ΔeGFR + 1 y) between the two groups. Then, we identified predictors that were associated with the outcome.

Results: Among the 48 participants, 21 were treated with SGLT2is (SGLT2 group) and 25 were treated with other antidiabetic medications (control group). Although eGFR was significantly decreased at 1 year in the control group, the decline in eGFR was not observed in the SGLT2 group. The change in eGFR was significantly greater in the SGLT2 group than in the control group (ΔeGFR + 1 year, -4.0 [-7.7 to -0.3] mL/min/1.73 m^2 in the control group, 0.9 [-3.9 to 5.7] mL/min/1.73 m^2 in the SGLT2

group; $P = 0.0231$). Additionally, multiple linear regression analysis showed that an initial dip was an independent factor associated with the worsening of renal function in the SGLT2 group.

Conclusions: Although more favorable effects of SGLT2is on renal function were observed in patients with type 2 diabetes and CKD with normoalbuminuria, the higher initial dip was a possible marker of worsening renal function after the initiation of SGLT2is.

Keywords: Chronic kidney disease, Diabetic kidney disease, Normoalbuminuria, Sodium-glucose cotransporter 2 inhibitor

Background

The incidence and prevalence of diabetes are increasing worldwide, and the ultimate goal of treating diabetes is to prevent or delay the progression of microvascular and macrovascular complications. Dialysis resulting from diabetes is extremely prevalent in Japan [1]. In 2017, the number of patients on chronic dialysis reached 334,505 [1]. Traditionally, it has been thought that typical diabetic nephropathy progresses from normal albuminuria to micro/macroalbuminuria and gradually to decreases in renal function. However, recently, it has been shown that there are atypical diabetic nephropathy cases that already exhibit reduced renal function without micro/macroalbuminuria. Therefore, diabetic kidney disease was proposed as a condition that includes typical and atypical diabetic nephropathy [2].

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) improve glucose tolerance by suppressing renal glucose reabsorption without direct pharmacological action on pancreatic beta cells. Four large prospective clinical trials have shown that SGLT2is decrease the composition renal endpoints such as decline in estimated glomerular filtration rate (eGFR), doubling of the serum creatinine level, new end-stage kidney disease, death from renal or cardiovascular causes, or progression to macroalbuminuria [3-6]. In addition, it has been reported that, in patients with type 2 diabetes and chronic

kidney disease (CKD), SGLT2is prevent the decline in eGFR [7-10]. However, studies on the effects of SGLT2is on renal function in patients with type 2 diabetes and CKD with normoalbuminuria remain limited [8, 9].

In the present study, we investigated the renoprotective effects of SGLT2is on renal function in patients with type 2 diabetes and CKD with normoalbuminuria and identified predictors that were associated with the outcome.

Methods

Study design and participants

The major inclusion criteria were type 2 diabetes and CKD (eGFR < 60 mL/min/1.73 m^2) with normoalbuminuria (urine albumin to creatinine ratio [UACR] < 30 mg/g Cr and/or urinary protein to creatinine ratio [UPCR] < 150 mg/g Cr) at SGLT2is initiation. As a control, patients who were not administered SGLT2is were also included. The exclusion criteria were as follows: type 1 diabetes, use of glucagon-like peptide-1 receptor agonists for type 2 diabetes, endocrine disease, use of steroids or immunosuppressants for autoimmune disease, dialysis, transplantation, liver cirrhosis, and malignancy. Finally, 46 patients were eligible for evaluation. The study was conducted with the approval of the Institutional Review Board of Obihiro Kosei Hospital (2020-017), and registered with the University Hospital Medical Information Network (UMIN; number UMIN000040424).

Study definitions and outcomes

We conducted a retrospective review of the clinical records of all consecutive Japanese outpatients with type 2 diabetes admitted to Obihiro Kosei Hospital in Obihiro from April 2014 to December 2019. The participants were categorized into two groups

97 depending on whether they used SGLT2is: in the SGLT2 group, patients started
98 receiving SGLT2is in addition to their other antidiabetic medication; and in the control
99 group, patients received conventional antidiabetic medications alone. Outcome data
100 were collected from the patients' medical records. Baseline data for age, sex, duration of
101 diabetes, and medications for diabetes and hypertension were also collected. Common
102 measurements, such as body weight, body mass index (BMI), systolic and diastolic
103 blood pressure (SBP and DBP, respectively), plasma glucose (PG) level, glycated
104 hemoglobin (HbA1c) level, kidney and liver function test results, high-density
105 lipoprotein cholesterol (HDL) level, low-density lipoprotein (LDL) level, triglyceride
106 (TG) level, UACR, and/or UPCR, at each clinic visit were collected. The eGFR 1–2
107 months after SGLT2is initiation was also used as an eGFR initial data point. We defined
108 the change in eGFR as the initial dip, as previously reported [7, 10, 11]. These
109 parameters were measured using commercially available assay kits.
110 The primary objective of this study was to assess the clinical effectiveness of
111 SGLT2is on renal function by analyzing the change in eGFR at one year (ΔGFR + 1 y)
112 after initiating SGLT2is, compared with the change after conventional antidiabetic
113 medication. The secondary objective was to investigate the variables associated with
114 ΔGFR + 1 y, to identify suitable patients with type 2 diabetes for the renoprotective

115 effect of SGLT2is. The initial dip and ΔGFR + 1 y were calculated as follows: initial
116 dip = eGFR at 1 or 2 months after starting SGLT2is − eGFR at the start of SGLT2is;
117 ΔGFR + 1 y = eGFR at 1 year − eGFR at baseline.

118 **Statistical analysis**

119 Chi-square test, Mann-Whitney *U*-test, unpaired *t*-test, or paired *t*-test was used to
120 compare between the two groups as appropriate. Results are shown as mean ± standard
121 deviation or median. We used a two-way analysis of variance (ANOVA) followed by
122 post hoc Bonferroni test for repeated measurements. Calculations for correlation
123 coefficients and simple linear regression analyses were performed to test for
124 associations between ΔGFR + 1 y and baseline parameters in the SGLT2 group.
125 Additionally, we performed stepwise multivariate regression analysis to examine which
126 factors independently determined ΔGFR+1y in the SGLT2 group. *P*-values < 0.05 were
127 considered statistically significant. Statistical analyses were performed using JMP 14
128 (SAS Inc., Cary, NC, USA) and Microsoft Excel Statistics 2012 for Windows (SSRI
129 Co. Ltd, Tokyo, Japan).

130

Results

Table 1 shows the underlying diseases present in study patients. Of the 46 patients, the SGLT2 group comprised 21 patients, and the control group comprised 25 patients. There were no differences in most of the baseline parameters between the two groups, except for duration of diabetes, PG, HbA1c, alanine aminotransferase (ALT), or TG. The number of patients with CKD staging among both groups was as follows: SGLT2 group G3a: 15, G3b: 5, and G4: 1; control group G3a: 18, G3b: 5, and G4: 2. As shown in Fig. 1, the eGFR in the control group was significantly decreased after 1 year. However, there was no decrease in eGFR in the SGLT2 group. As shown in Fig. 2, the magnitude of the effect for eGFR was significantly greater in the SGLT2 group than in the control group (ΔeGFR + 1 year: -4.0 (-7.7 to -0.3) mL/min/1.73 m^2 in the control group, 0.9 (-3.9 to 5.7) mL/min/1.73 m^2 in the SGLT2 group; P = 0.0231). Next, to reveal the factors associated with the changes in eGFR at 1 year after starting SGLT2is, we examined the correlations between ΔeGFR + 1 year and the clinical parameters in the SGLT2 group. As shown in Table 2, only the initial dip showed a significant positive correlation (P = 0.0159) with ΔeGFR + 1 year. Moreover, as shown in Table 3, multiple linear regression analysis identified higher initial dip as an independent factor associated with worsening of renal function in the SGLT2 group, after adjusting for age,

BMI, HbA1c level, and eGFR ($P = 0.0166$).

Discussion

In the present study, we showed that additional treatment with SGLT2is prevents the decline in eGFR in the SGLT2 group compared with that in the control group. Although we had previously shown that more favorable effects of SGLT2is on renal function in patients with type 2 diabetes and CKD with normoalbuminuria compared with patients with macroalbuminuria [9], this study did not include a control group. Therefore, this study was able to confirm the renoprotective effects on SGLT2is for patients with type 2 diabetes and CKD with normoalbuminuria compared with non-SGLT2is user.

In addition, using multiple linear regression analysis we showed that the initial dip in the SGLT2 group was useful in predicting the renoprotective effect of SGLT2is. Previously, Miyoshi et al. showed that the decline in eGFR before starting SGLT2is in patients with type 2 diabetes and CKD stages 3-4 was an independent factor associated with renal function outcomes [7]. However, there have been no studies on the predictive factors associated with the worsening of renal function in patients with type 2 diabetes and CKD with normoalbuminuria. This is the first report to identify independent factors associated with the worsening of renal function in patients with type 2 diabetes and CKD with normoalbuminuria.

It has been proposed that one mechanism for the renoprotective effects of SGLT2is

185 is decreasing intraglomerular pressure through tubuloglomerular feedback restoration
186 [12-15]. It has also been reported that empagliflozin reduces the intraglomerular
187 pressure to 6–8 mmHg in patients with type 1 diabetes [16]. In fact, a decrease in eGFR
188 is typically observed within 1 month after initiating SGLT2is therapy [3]. This
189 phenomenon is called the initial dip or initial drop [17]. As other mechanisms, SGLT2is
190 have the renoprotective effect through not only their anti-inflammatory and
191 anti-oxidative stress effects [18, 19], but also increase of hematocrit and
192 β-hydroxybutyrate [15].

193 Pathological findings revealed that tubulointerstitial and vascular lesions were more
194 advanced in patients with type 2 diabetes and CKD with normoalbuminuria than in
195 those with micro/macroalbuminuria [20]. In contrast, glomerular lesions were more
196 advanced in patients with type 2 diabetes and CKD with micro/macroalbuminuria than
197 in those with normoalbuminuria [20]. Previously, it has been shown that the
198 pathological findings in patients with type 2 diabetes and CKD with normoalbuminuria
199 are similar to those in patients with nephrosclerosis [21]. In nephrosclerosis, it is
200 thought that the glomeruli undergo progressive ischemic changes [22], in which
201 intraglomerular pressure can be normal or decreased [23]. Results from the EMPA-REG
202 outcome study demonstrated that the eGFR increases after withdrawing SGLT2i [3].

These data support the idea that the initial dip in GFR after SGLT2is administration is a hemodynamic effect [3]. It seems likely that some patients with type 2 diabetes and CKD with normoalbuminuria who show a high initial dip after SGLT2is initiation have reduced renoprotective effects due to an excessive drop in intraglomerular pressure caused by changes in blood volume or renal perfusion. Future studies will determine whether this result can also be applied to patients with type 2 diabetes and CKD with micro/macroalbuminuria with glomerular lesions.

There are some limitations to the present study. First, this study was retrospective in nature. Second, the sample size was small, which might have limited its statistical power. Third, baseline parameters such as the duration of diabetes, PG levels, and HbA1c levels were unbalanced between the groups, which may have made interpretation difficult. Fourth, this study had a short follow-up period and was conducted in a single center. Larger and longer prospective studies will be required to verify our results in the future.

In conclusion, our study suggests that renoprotective effects of SGLT2is on renal function were observed in patients with type 2 diabetes with CKD and normoalbuminuria. Additionally, patients who show a high initial dip after SGLT2is initiation should be carefully monitored for decline in renal function.

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; PG, plasma glucose; SBP, systolic blood pressure; SGLT2is, sodium-glucose cotransporter 2 inhibitors; TG, triglyceride; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein to creatinine ratio.

Declarations

Ethics approval and consent to participate: This study was conducted with approval from the Institutional Review Board of the Obihiro Kosei Hospital (2020-017), and registered with the University Hospital Medical Information Network (UMIN; number UMIN000040424).

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: AN has obtained research support from Mitsubishi Tanabe

Pharma, Daiichi Sankyo, MSD, Novo Nordisk Pharma, Novartis Pharma, AstraZeneca, LifeScan Japan, Nippon Boehringer Ingelheim, and Taisho Pharmaceutical.

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Authors' contributions: KT and AN contributed to writing the manuscript. KT and SF contributed to data analysis. KT, AN, and SF contributed to the discussion, and reviewed and edited the manuscript. KT is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors have read and approved the final manuscript.

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Figure legend

Fig. 1

Changes in eGFR in patients with or without SGLT2is administration. Data are presented as mean ± standard deviation (SD). $^{**}P < 0.01$: two-way analysis of variance followed by post hoc Bonferroni test, 0 year *vs*. 1 year in the control group. eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose cotransporter 2 inhibitors.

Fig. 2

Comparison of changes in eGFR in patients with or without SGLT2is administration. The Wilcoxon rank-sum test was used for statistical analysis. $^{*}P < 0.05$. eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose cotransporter 2 inhibitors.

344 Table 1. Baseline characteristics of the 46 participants

	Control (n=25)	SGLT2 (n=21)	*P* value
Age (years)	67.9 ± 9.1	67.4 ± 7.9	0.8333
Man/Woman (n)	12/13	11/10	0.7672
Duration of diabetes (years)	7.0 (2.0 to 13.5)	12.5 (7.3 to 24.0)	0.0429
Weight (kg)	65.3 ± 14.5	69.9 ± 12.1	0.2810
BMI (kg/m^2)	25.5 ± 4.2	27.9 ± 4.7	0.0967
PG (mg/dl)	146.8 ± 47.4	206.1 ± 79.6	0.0032
HbA1c (%)	7.1 ± 1.0	8.0 ± 1.1	0.0058
eGFR (mL/min/1.73 m^2)	49.3 ± 10.9	49.7 ± 9.1	0.9014
AST (U/L)	22.0 (18.5 to 28.0)	26.0 (20.0 to 42.0)	0.0898
ALT (U/L)	23.0 (13.0 to 30.0)	29.0 (20.0 to 38.0)	0.0310
HDL (mg/dL)	45.1 ± 13.0	49.7 ± 15.1	0.2875
LDL (mg/dL)	109.7 ± 33.4	106.1 ± 26.2	0.6995
TG (mg/dL)	170.5 (126.3 to 222.8)	121.0 (92.0 to 163.5)	0.0224
Stage of diabetic nephropathy	III 23/ IV 2	III 20/ IV 1	0.6577
Chronic kidney disease	IIIa 18/IIIb 5/ IV 2	IIIa 15/ IIIb 5/ IV 1	0.8780
UACR (mg/g Cr)	13.0 (7.3 to 16.9)	12.6 (8.0 to 16.5)	0.8838
UPCR (mg/g Cr) (n = 1 and 4)	50.8	115.21 ± 21.7	-
SBP (mmHg)	126.3 ± 22.0	127.2 ± 10.8	0.9058
DBP (mmHg)	73.5 ± 14.5	70.91 ± 9.1	0.6085
Treatment with ARB or ACEI (%)	56.0	47.6	0.5708
Diuretics (%)	24.0	14.3	0.4081
SGLT2i (%)			
Empagliflozin	0	28.6	
Ipragliflozin	0	14.3	
Luseogliflozin	0	0	
Dapagliflozin	0	19.1	
Tofogliflozin	0	0	
Canagliflozin	0	38.1	
Antidiabetic drugs (%)			
Sulfonylureas (%)	16.0	4.8	0.2226
Metformin (%)	32.0	33.3	0.9235
Thiazolidinedione (%)	0	0	-
Alpha-glucosidase inhibitor (%)	4.0	23.8	0.0469
Glinide (%)	8.0	19.1	0.2678

Dipeptidyl peptidase-4 inhibitor (%)	84.0	71.4	0.3032
Insulin (%)	24.0	28.6	0.7251
Glucagon like peptide-1 receptor agonist (%)	0	0	-

Values are shown as means ± standard deviation, median, n, or %.

SGLT2, sodium-glucose cotransporter 2; BMI, body mass index; PG, plasma glucose; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride; UACR, urine albumin-to-creatinine ratio; UPCR, urinary protein to creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

369 Table 2. Relationship between ΔeGFR + 1 y and baseline parameters examined in

370 SGLT2 group

	Correlation coefficient	*P* value
Duration of diabetes (years)	0.1701	0.4735
Age (years)	−0.0839	0.7178
Weight (kg)	−0.2120	0.3983
BMI (kg/m^2)	−0.2047	0.4153
PG (mg/dl)	0.0562	0.8089
HbA1c (%)	0.2048	0.3731
eGFR (mL/min/1.73 m^2)	−0.1697	0.4621
initial dip (mL/min/1.73 m^2)	0.5448	0.0159
AST (U/L)	0.1409	0.5649
ALT (U/L)	0.0723	0.7688
HDL (mg/dL)	−0.1405	0.5436
LDL (mg/dL)	0.2012	0.4089
TG (mg/dL)	0.1953	0.3963
UACR (mg/g Cr)	−0.3991	0.0813
SBP (mmHg)	0.5605	0.0729
DBP (mmHg)	0.4721	0.1426

371 ΔeGFR + 1 y, the change in estimated glomerular filtration rate at one year after starting

372 sodium-glucose cotransporter 2 inhibitor; SGLT2, sodium-glucose cotransporter 2;

373 BMI, body mass index; PG, plasma glucose; HbA1c, glycated hemoglobin; eGFR,

374 estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine

375 aminotransferase; HDL, high-density lipoprotein cholesterol; LDL, low-density

376 lipoprotein; TG, triglyceride; UACR, urine albumin to creatinine ratio; SBP, systolic

377 blood pressure; DBP, diastolic blood pressure.

378

379 Table 3. Multiple regression analysis for ΔeGFR + 1 y and baseline parameters in the

380 SGLT2 group

	Standardized partial regression coefficient	*P* value
Initial dip (mL/min/1.73 m^2)	0.7073	0.0166

381 R^2=0.2793. A multiple regression with stepwise selection was performed considering

382 age, BMI, HbA1c, eGFR, and initial dip. ΔeGFR + 1 y, the change in estimated

383 glomerular filtration rate one year after starting sodium-glucose cotransporter 2

384 inhibitor; SGLT2, sodium-glucose cotransporter 2; BMI, body mass index; HbA1c,

385 glycated hemoglobin; eGFR, estimated glomerular filtration rate.

386

387

Figures

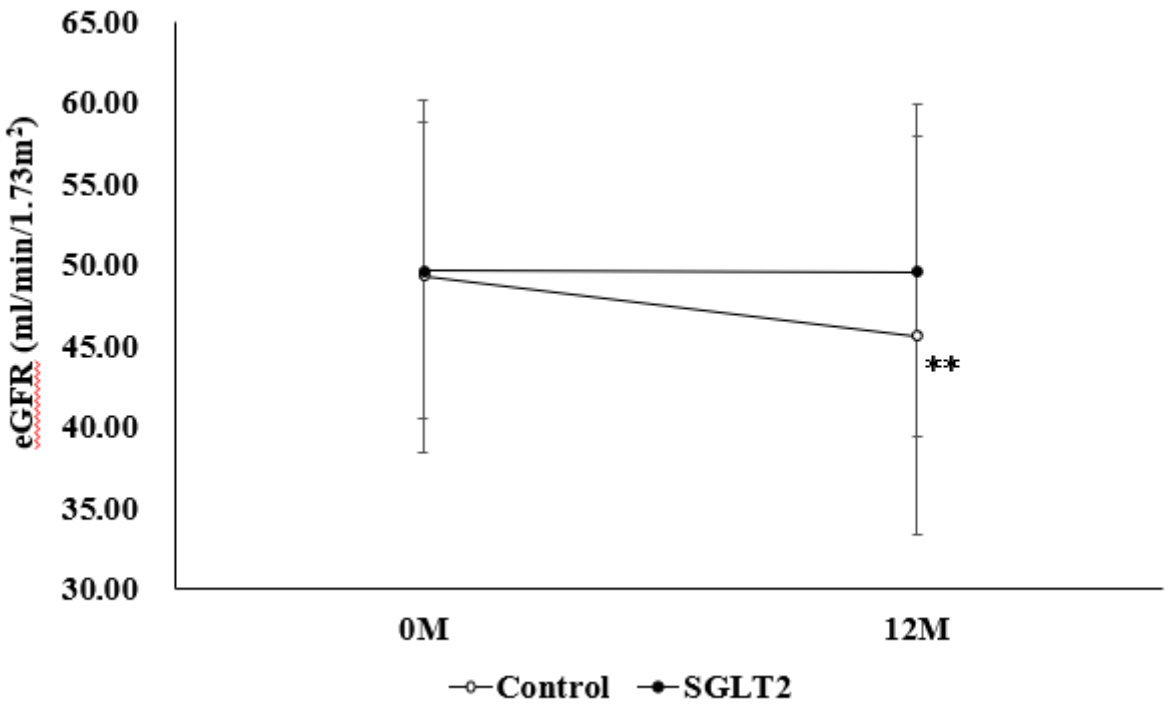

Figure 1

Changes in eGFR in patients with or without SGLT2is administration. Data are presented as mean ± standard deviation (SD). **P < 0.01: two-way analysis of variance followed by post hoc Bonferroni test, 0 year vs. 1 year in the control group. eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose cotransporter 2 inhibitors.

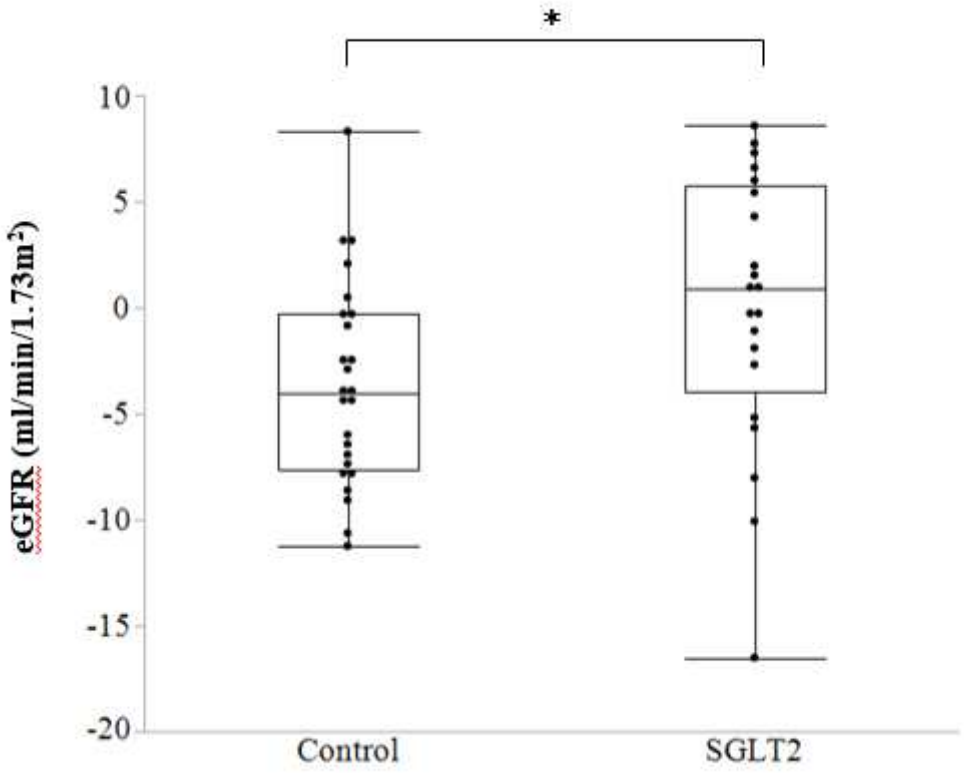

Figure 2

Comparison of changes in eGFR in patients with or without SGLT2is administration. The Wilcoxon rank-sum test was used for statistical analysis. *P < 0.05. eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose cotransporter 2 inhibitors.