

# Renoprotective effect of additional sodium–glucose cotransporter 2 inhibitor therapy in type 2 diabetes patients with rapid decline and preserved renal function

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## Keywords

Rapid decliner, Slope of estimated glomerular filtration rate decline, Sodium–glucose cotransporter 2 inhibitor

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## ABSTRACT

**Aims/Introduction:** The slope of estimated glomerular filtration rate (eGFR) decline (eGFR slope) in early-stage type 2 diabetes patients might predict the future risk of end-stage renal disease. Type 2 diabetes patients who show rapid progressive eGFR decline are termed rapid decliners. Several studies of rapid decliners have investigated the efficacy of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in patients with advanced renal dysfunction; however, no studies, to our knowledge, have focused on patients with preserved renal function. Therefore, we investigated the efficacy of SGLT2i in rapid decliners with preserved renal function.

**Materials and Methods:** This study enrolled type 2 diabetes patients with baseline eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> who had been treated with SGLT2i for  $\geq 3$  years. Among these individuals, we defined those with annual eGFR declines  $\geq 5$  mL/min/1.73 m<sup>2</sup> per year before SGLT2i administration as rapid decliners. The primary end-point was the change in eGFR slope after SGLT2i administration.

**Results:** Among 165 patients treated with SGLT2i for  $\geq 3$  years, 21 patients were rapid decliners with preserved renal function. The mean age and eGFR at SGLT2i administration were 58.6 years and 87.1 mL/min/1.73 m<sup>2</sup>, respectively. The mean annual eGFR slope improved significantly in those administered SGLT2i compared with the control group (−1.00 and −4.36 mL/min/1.73 m<sup>2</sup> per year, respectively;  $P < 0.001$ ). Notably, the steeper the eGFR slope before starting SGLT2i administration, the larger the improvement of eGFR slope, which was independent of the reduction of albuminuria.

**Conclusions:** Early intervention with SGLT2i may have renoprotective effects in type 2 diabetes patients with rapid decline and preserved renal function.

## INTRODUCTION

The prevalence of diabetes has increased worldwide, and 425 million adult patients had diabetes in 2017<sup>1</sup>. Similarly, the prevalence of diabetes in Japan has increased, and the number of the patients hit a record high of approximately 10 million, in 2016<sup>2</sup>. The annual number of incident dialyses resulting from diabetes, accounting for the greatest proportion of

incident dialyses in Japan since 1998, was 16,019 in 2019<sup>3</sup>. To reduce the progression from diabetic kidney disease to end-stage renal disease (ESRD), identification and effective screening of high-risk patients, and early therapeutic interventions in these individuals are important<sup>4–6</sup>.

Recently, it has been found that a certain proportion of patients with diabetes show a rapid progressive decline in renal function from preserved baseline estimated glomerular filtration rate (eGFR;  $\geq 60$  mL/min/1.73 m<sup>2</sup>)<sup>7–11</sup>. It has been suggested that the slope of eGFR decline (eGFR slope) of early-stage

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patients with type 2 diabetes might predict the future risk of ESRD<sup>10,11</sup>. According to the Kidney Disease: Improving Global Outcomes guidelines, rapid progression of renal dysfunction is defined as a sustained decline in eGFR of  $\geq 5$  mL/min/1.73 m<sup>2</sup> per year, based on an increased risk of ESRD<sup>12</sup>. A cohort study that aimed to elucidate the characteristics of rapid decliners with eGFR still in the preserved range and to clarify their risk factors was carried out in Japanese patients with type 2 diabetes<sup>11</sup>. In that study, 14% of the participants were identified as rapid decliners, in whom eGFR decreased  $>5$  mL/min/1.73 m<sup>2</sup> per year, consistent with Kidney Disease: Improving Global Outcomes guidelines; specifically, these individuals showed decreases of 29 mL/min/1.73 m<sup>2</sup> within 4 years, a rate expected to result in renal insufficiency<sup>11</sup>.

In a guideline of medical care in diabetes, issued by the American Diabetes Association, sodium–glucose cotransporter 2 inhibitors (SGLT2i) are recommended for type 2 diabetes patients with chronic kidney disease<sup>13</sup>, given that SGLT2i have shown beneficial effects on renal end-points consisting of albuminuria, renal hard end-points including a  $\geq 40\%$  decrease in eGFR to  $<60$  mL/min/1.73 m<sup>2</sup>, new ESRD and death from renal or cardiovascular causes in large clinical trials<sup>14–17</sup>. The effects of SGLT2i on renal outcomes have been shown to be consistent across different levels of albuminuria, with greater effects on the slope of eGFR decline in participants with severely increased albuminuria<sup>18</sup>. Additionally, it has been suggested that the beneficial effect of SGLT2i on eGFR decline is consistent across a range of baseline eGFRs<sup>19</sup>. These results show the renoprotective effect of SGLT2i in patients with various levels of renal function, although there are, to our knowledge, few studies investigating the efficacy of SGLT2i in patients with type 2 diabetes showing a rapid decline in renal function before initiation of SGLT2i.

Several studies have investigated the efficacy of SGLT2i in rapid decliners with advanced renal dysfunction<sup>5,6,20</sup>, and one has done so in rapid decliners with preserved to advanced renal dysfunction<sup>21</sup>. However, to our knowledge, no studies have focused on rapid decliners with preserved renal function. As there is still no therapeutic drug that can restore renal function once it has declined, it is worthwhile to consider administering SGLT2i to patients whose eGFRs are in the preserved range ( $\geq 60$  mL/min/1.73 m<sup>2</sup>), but are rapidly declining, as this could prevent patients from entering the chronic kidney disease range ( $<60$  mL/min/1.73 m<sup>2</sup>). Therefore, to evaluate the protective effect of SGLT2i on the progression of renal dysfunction from early stages, we investigated the efficacy of SGLT2i in rapid decliners with preserved renal function ( $\geq 60$  mL/min/1.73 m<sup>2</sup>).

## MATERIALS AND METHODS

### Study population

Based on clinical information from hospital medical records, we retrospectively identified patients with type 2 diabetes who had been treated with SGLT2i for  $\geq 3$  years, and whose eGFR

had been measured continuously for 2 years before, and 3 years after, initiation of treatment with SGLT2i. We plotted the measured values of eGFR every 4 months to calculate a linear approximation formula, and identified the slope of the straight line as the slope of eGFR decline (i.e., eGFR slope), which shows the change in eGFR per year (mL/min/1.73 m<sup>2</sup> per year). Among participants, we selected patients with annual eGFR decline before SGLT2i administration  $\geq 5$  mL/min/1.73 m<sup>2</sup> per year; these individuals were identified as rapid decliners. In contrast, patients with annual eGFR decline before SGLT2i administration  $<5$  mL/min/1.73 m<sup>2</sup> per year were identified as moderate decliners. The identification of rapid decliners in the present study was based on the definition of the rapid progression of renal dysfunction as a sustained decline in eGFR  $\geq 5$  mL/min/1.73 m<sup>2</sup> per year in the Kidney Disease: Improving Global Outcomes guidelines<sup>12</sup>. The definition was consistent with the result of the previous study evaluating the characteristics of rapid decliners with eGFR still in the preserved range among Japanese patients with type 2 diabetes<sup>11</sup>. As a control, patients without SGLT2i administration were also included. Those patients who met the exclusion criteria included the following: those with type 1 diabetes, those with type 2 diabetes who were aged  $<20$  years, those with poor adherence or interruption of the medication regimen and those with eGFR  $<60$  mL/min/1.73 m<sup>2</sup> at the point of initiation of SGLT2i.

### Protocol

This was a retrospective, longitudinal and observational study of patients with type 2 diabetes who were newly initiated on SGLT2i with at least 3 years of follow up after initiation. Data were collected between March 2013 and August 2021 at the outpatient center at the Koseiren Tsurumi Hospital and the Bungoono City Hospital in Oita, Japan. Two periods of medical history were reported: before and after the SGLT2i initiation date. The baseline was defined as the date on which SGLT2i was initiated. Outcome data were collected from the patients' medical records every 4 months in the period between 2 years before and 3 years after the baseline. Baseline data for age, sex, bodyweight, body mass index (BMI), systolic and diastolic blood pressure, and medications for diabetes and hypertension were also collected. Samples of blood and urine were collected at each clinic visit, and analyzed in the hospital clinical laboratory to determine levels of glycated hemoglobin (HbA1c), uric acid, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, urinary albumin : creatinine ratio (UACR), and other tests of kidney and liver function.

The primary objective of the present study was to assess the clinical efficacy of SGLT2i on renal function by comparing the eGFR slope after SGLT2i administration between the groups with or without SGLT2i administration. A secondary objective was to analyze the change in eGFR slope after initiation of SGLT2i compared with that before initiation ( $\Delta$ [eGFR slope]), and to investigate the variables associated with  $\Delta$ (eGFR slope) for identifying early stage type 2 diabetes patients in whom

SGLT2i should preferably be initiated. We calculated the  $\Delta$  (eGFR slope) using the following formula:

$$\Delta(\text{eGFR slope}) = (\text{eGFR slope after 3 years of SGLT2i therapy}) - (\text{eGFR slope 2 years before SGLT2i therapy})$$

### Statistical analysis

Data pertaining to normally distributed continuous variables are presented as the mean  $\pm$  standard deviation, whereas those pertaining to non-normally distributed continuous variables are presented as median values (interquartile range). The paired Student's *t*-test, Wilcoxon signed-rank sum test or the  $\chi^2$ -test was used to compare the two paired groups. We used Pearson's correlation analysis to determine which factors were associated with the change of the eGFR slope before and after initiation of SGLT2i. Additionally, we carried out multiple regression analysis to identify which factors independently determined the change of the eGFR slope before and after initiation of SGLT2i. A *P*-value  $<0.05$  was considered statistically significant. Statistical analyses were carried out as two-tailed tests using the Statistical Package for Social software program, version 25 (SPSS Inc.; IBM, Tokyo, Japan).

### Ethical considerations

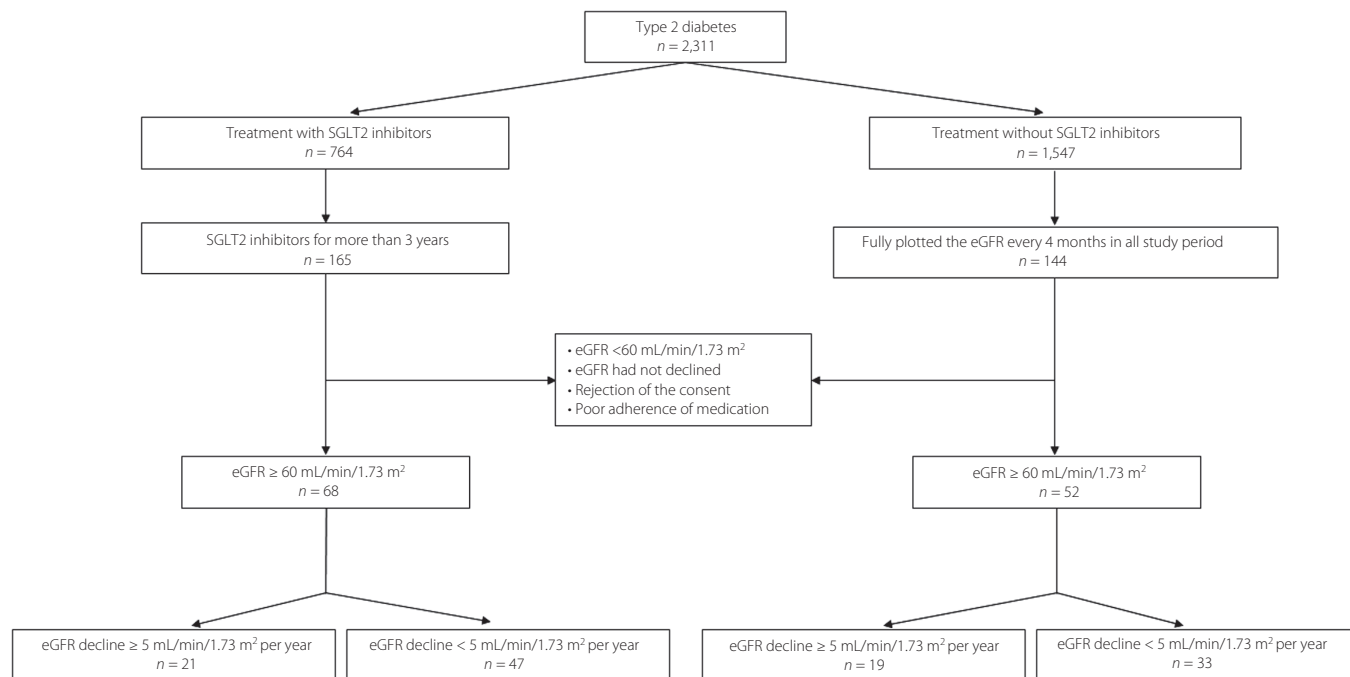
Ethical approval for this study was obtained from the ethics committee of Koseiren Tsurumi Hospital (Approval No. 20-005). Given that this work was a retrospective observational study and not a prospective interventional study, the opt-out consent procedure was used in the study. The study conforms

to the provisions of the Declaration of Helsinki and its subsequent amendments.

### RESULTS

The total number of patients who matched the study requirements was 120 (Figure 1). Among them, 98 patients (81.7%) were from the Koseiren Tsurumi Hospital, and the other 22 patients (18.3%) were from the Bungoono City Hospital. Among 68 type 2 diabetes patients who were treated with SGLT2i for  $\geq 3$  years with a preserved baseline eGFR ( $\geq 60$  mL/min/1.73 m<sup>2</sup>), the annual eGFR decline before SGLT2i administration was  $\geq 5$  mL/min/1.73 m<sup>2</sup> per year in 21 patients (30.9%), who were defined as rapid decliners. The other 47 patients (69.1%) had annual eGFR declines before SGLT2i administration of  $<5$  mL/min/1.73 m<sup>2</sup> per year and were defined as moderate decliners. The control group comprised 19 rapid decliners and 33 moderate decliners without SGLT2i administration (Figure 1).

Baseline characteristics of patients categorized as rapid decliners and moderate decliners are summarized in Table 1. In rapid decliners, the mean age, BMI and HbA1c were 58.6 years, 26.2 kg/m<sup>2</sup> and 8.0%, respectively. There were no significant differences in baseline parameters compared with the control group, with the exceptions of HbA1c, systolic and diastolic blood pressure, and the prevalence of treatment with biguanide and dipeptidyl peptidase-4 inhibitors. In moderate decliners, the mean age, BMI and HbA1c were 63.1 years, 27.7 kg/m<sup>2</sup> and 7.9%, respectively. There were no significant



**Figure 1** | Flow diagram of the study. eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose cotransporter 2.

**Table 1** | Clinical characteristics of the patients at baseline

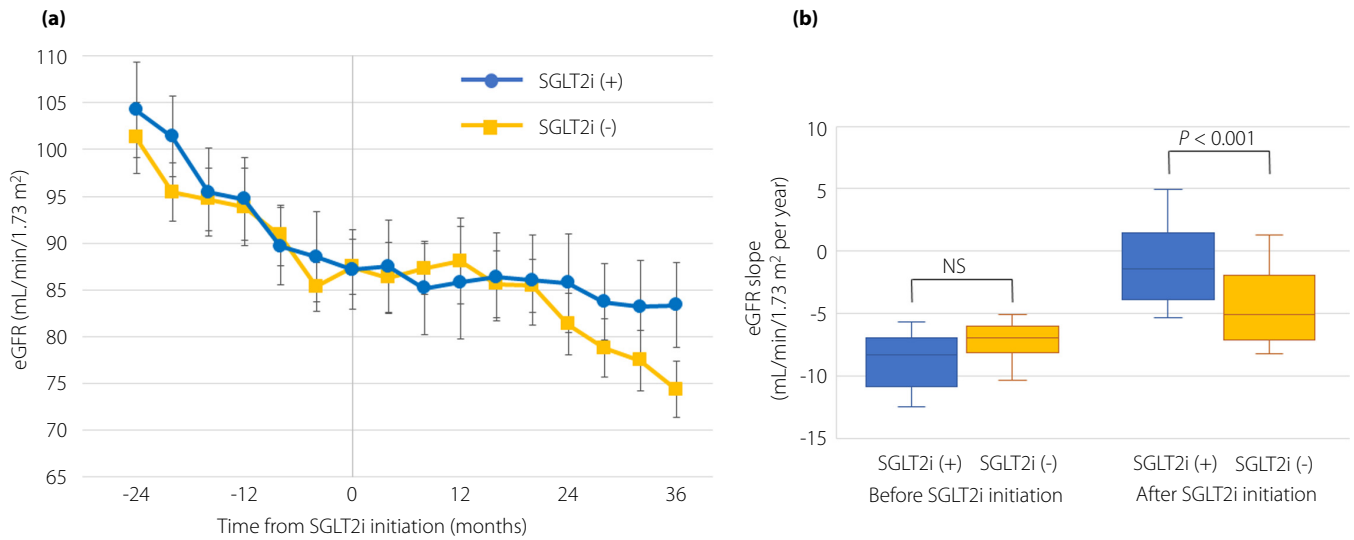
	Rapid decliners		P-value	Moderate decliners		P-value
	SGLT2i (+) (n = 21)	SGLT2i (-) (n = 19)		SGLT2i (+) (n = 47)	SGLT2i (-) (n = 33)	
Sex, male (%)	15 (71.4)	11 (58.0)	0.370	27 (57.4)	22 (66.7)	0.405
Age (years)	58.6 ± 9.5	63.9 ± 9.4	0.094	63.1 ± 10.8	65.0 ± 8.9	0.403
BMI (kg/m <sup>2</sup> )	26.2 ± 2.9	24.8 ± 3.5	0.227	27.7 ± 3.9	24.7 ± 3.4	0.002
HbA1c (%)	8.0 ± 0.6	6.9 ± 0.7	<0.001	7.9 ± 0.9	6.9 ± 0.8	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	87.1 ± 19.8	87.4 ± 12.8	0.962	76.2 ± 12.8	75.8 ± 11.2	0.909
eGFR slope before initiation of SGLT2i (mL/min/1.73 m <sup>2</sup> per year)	-9.4 ± 4.1	-7.5 ± 1.9	0.081	-2.5 ± 1.3	-2.3 ± 1.3	0.464
UACR (mg/g) (n = 14 and 16)	102.9 ± 158.4	16.9 ± 27.7	0.075	72.1 ± 104.9	26.9 ± 38.6	0.089
Systolic BP (mmHg)	137.7 ± 18.0	125.2 ± 11.8	0.019	136.1 ± 16.8	129.6 ± 13.6	0.085
Diastolic BP (mmHg)	79.4 ± 12.5	70.9 ± 7.5	0.018	77.7 ± 13.3	74.7 ± 10.4	0.302
Concomitant medication						
ACE-I or ARB (%)	11 (52.4)	7 (36.8)	0.324	31 (66.0)	15 (45.5)	0.068
Diuretics (%)	3 (14.2)	0 (0.0)	0.233	8 (17.0)	2 (6.1)	0.184
Oral hypoglycemic agent						
SGLT2i (%)						
Canagliflozin	2 (9.5)	-	-	10 (21.3)	-	-
Dapagliflozin	10 (47.6)	-	-	20 (42.6)	-	-
Empagliflozin	3 (14.3)	-	-	2 (4.3)	-	-
Ipragliflozin	5 (23.8)	-	-	12 (25.5)	-	-
Luseogliflozin	0 (0.0)	-	-	0 (0.0)	-	-
Tofogliflozin	1 (4.8)	-	-	3 (6.4)	-	-
α-GI (%)	4 (19.0)	2 (10.5)	0.664	10 (21.3)	2 (6.1)	0.109
Biguanide (%)	16 (76.1)	8 (42.1)	0.028	35 (74.5)	16 (48.5)	0.017
DPP-4i (%)	18 (85.7)	7 (36.8)	0.001	43 (91.5)	17 (51.5)	<0.001
Glinide (%)	2 (9.5)	0 (0.0)	0.488	3 (6.4)	2 (6.1)	1.000
Sulfonylurea (%)	7 (33.3)	2 (10.5)	0.133	25 (59.6)	6 (18.2)	0.002
Thiazolidine (%)	6 (28.5)	1 (5.3)	0.095	9 (19.1)	5 (15.2)	0.643
Insulin (%)	3 (14.3)	1 (5.3)	0.607	4 (8.5)	4 (12.1)	0.711
Glucagon like peptide-1 receptor agonist (%)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-

Data are presented as the mean ± standard deviation or as median values (interquartile range). α-GI, alpha-glucosidase inhibitor; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SGLT2i, sodium-glucose cotransporter 2 inhibitors; UACR, urinary albumin : creatinine ratio.

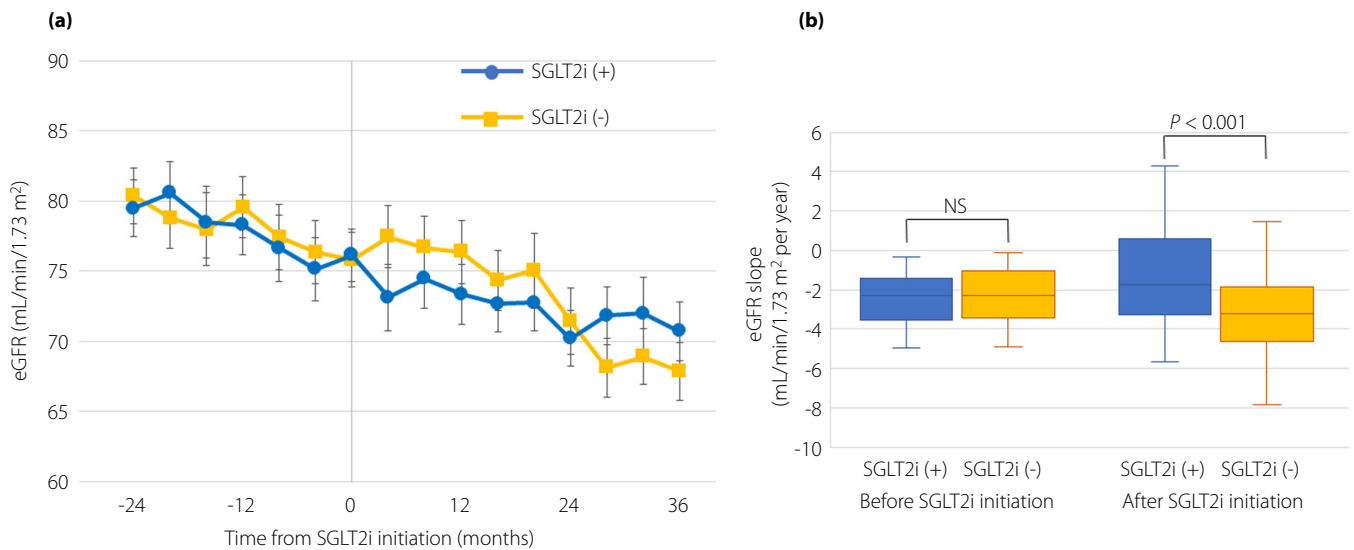
differences in baseline parameters compared with the control group, with the exceptions of BMI, HbA1c, and the prevalence of treatment with biguanide, dipeptidyl peptidase-4 inhibitors, and sulfonylurea.

The serial values of eGFR before and after SGLT2i administration in rapid decliners are shown in Figure 2a. In rapid decliners, the mean annual eGFR slope was significantly improved with administration of SGLT2i compared with the control group (-1.00 and -4.36 mL/min/1.73 m<sup>2</sup> per year, respectively; *P* < 0.001; Figure 2b). The serial values of eGFR before and after initiation of SGLT2i in moderate decliners are shown in Figure 3a. The mean annual eGFR slope was also significantly improved in moderate decliners with administration of SGLT2i compared with the control group (-1.42 and -3.48 mL/min/1.73 m<sup>2</sup> per year, respectively; *P* < 0.001; Figure 3b).

The changes in glucose metabolic parameters and clinical variables after 3 years of treatment with SGLT2i in rapid decliners and moderate decliners are shown in Table 2. In rapid decliners, the levels of HbA1c were nominally decreased (from 8.0% to 7.8%), although the change was not statistically significant. These patients showed a significant decrease in bodyweight and BMI. Systolic blood pressure and diastolic blood pressure were nominally decreased from 137.7 mmHg to 134.5 mmHg, and from 79.4 mmHg to 77.5 mmHg, respectively, although the changes were not statistically significant. In contrast, hematocrit and hemoglobin levels were significantly increased in patients receiving SGLT2i treatment. SGLT2i therapy nominally decreased serum uric acid levels from 5.3 mg/dL to 5.1 mg/dL, and aspartate aminotransferase levels from 26.7 IU/L to 23.9 IU/L, although these changes were not statistically significant. In contrast, alanine



**Figure 2** | Changes in estimated glomerular filtration rate (eGFR) slope in rapid decliners with (+) or without (–) treatment with sodium–glucose cotransporter 2 inhibitors (SGLT2i). (a) Serial changes in eGFR before and after the baseline. Data are presented as the mean ± standard error. (b) The mean eGFR slope after SGLT2i administration. In the box and whisker plots, lines within boxes represent median values; the top and bottom lines of the boxes represent the 75th and 25th percentiles, respectively; and the top and bottom bars on the whiskers represent the 90th and 10th percentiles, respectively. NS, not significant.



**Figure 3** | Changes in estimated glomerular filtration rate (eGFR) slope in moderate decliners with (+) or without (–) treatment with sodium–glucose cotransporter 2 inhibitors (SGLT2i). (a) Serial changes in eGFR before and after the baseline. Data are presented as the mean ± standard error. (b) The mean eGFR slope after SGLT2i administration. In the box and whisker plots, lines within boxes represent median values; the top and bottom lines of the boxes represent the 75th and 25th percentiles, respectively; and the top and bottom bars on the whiskers represent the 90th and 10th percentiles, respectively. NS, not significant.

aminotransferase levels and  $\gamma$ -glutamyl transpeptidase levels were significantly decreased in patients receiving SGLT2i treatment. We did not find any marked changes in triglycerides, high-density lipoprotein cholesterol or low-density lipoprotein cholesterol.

In moderate decliners, significant decreases in the levels of HbA1c, bodyweight, BMI and systolic blood pressure were seen. Diastolic blood pressure was nominally decreased from 77.7 mmHg to 75.8 mmHg, although this change was not statistically significant. Hematocrit and hemoglobin levels were

**Table 2** | Changes in glucose metabolic parameters and clinical variables before and after sodium–glucose cotransporter 2 inhibitor therapy

	Rapid decliners (n = 21)			Moderate decliners (n = 47)			P value
	Baseline	After 3 years	Absolute change	Baseline	After 3 years	Absolute change	
	Bodyweight (kg)	72.1 ± 9.8	69.0 ± 10.2	-3.1 ± 3.3	72.6 ± 13.9	68.8 ± 14.1	
Body mass index (kg/m <sup>2</sup> )	26.2 ± 2.9	24.9 ± 3.0	-1.2 ± 1.3	27.7 ± 3.9	26.3 ± 4.0	-1.6 ± 1.1	<0.001
Systolic blood pressure (mmHg)	137.7 ± 18.0	134.5 ± 16.1	-3.2 ± 19.7	136.1 ± 16.8	131.5 ± 11.1	-5.0 ± 14.0	0.034
Diastolic blood pressure (mmHg)	79.4 ± 12.5	77.5 ± 8.6	-1.9 ± 9.3	77.7 ± 13.3	75.8 ± 12.3	-1.9 ± 9.2	0.226
Pulse rate (b.p.m.)	77.5 ± 10.9	78.2 ± 10.1	0.7 ± 7.8	77.4 ± 10.7	76.2 ± 10.6	-1.2 ± 9.6	0.484
HbA1c (%)	8.0 ± 0.6	7.8 ± 0.8	-0.3 ± 0.6	7.9 ± 0.9	7.6 ± 0.8	-0.3 ± 0.9	0.040
UACR (mg/g)	114.1 ± 168.3 (n = 12)	102.0 ± 164.2 (n = 12)	-12.1 ± 97.6	75.7 ± 104.9 (n = 21)	48.6 ± 61.9 (n = 21)	-27.1 ± 97.5	0.229
Uric acid (mg/dL)	5.3 ± 1.2	5.1 ± 1.4	-0.2 ± 0.7	5.6 ± 1.4	5.3 ± 1.4	-0.2 ± 1.0	0.149
Hemoglobin (g/dL)	14.1 ± 1.8	15.1 ± 1.9	1.0 ± 0.9	14.3 ± 1.4	14.9 ± 1.8	0.6 ± 0.9	<0.001
Hematocrit (%)	42.6 ± 4.3	45.6 ± 4.4	3.1 ± 2.9	42.8 ± 3.8	44.9 ± 4.7	2.1 ± 2.7	<0.001
Aspartate aminotransferase (IU/L)	26.7 ± 11.0	23.9 ± 9.7	-2.9 ± 12.8	31.3 ± 19.5	26.0 ± 18.3	-5.3 ± 10.7	0.002
Alanine aminotransferase (IU/L)	34.4 ± 17.3	25.9 ± 10.6	-8.6 ± 13.5	38.4 ± 22.4	30.5 ± 22.7	-7.9 ± 16.7	0.003
γ-Glutamyl transpeptidase (IU/L)	32.0 (24.0 - 76.0)	24.5 (20.3 - 41.0)	-7.0 (-15.5 to -2.0)	34.0 (24.0 - 55.0)	26.0 (17.0 - 43.0)	-4.0 (-16.0 to -0.0)	<0.001
Triglyceride (mg/dL)	108.0 ± 49.1	121.0 ± 54.5	13.0 ± 33.0	171.5 ± 130.5	168.3 ± 82.7	-3.2 ± 124.0	0.863
High-density lipoprotein cholesterol (mg/dL)	52.5 ± 11.3	54.7 ± 12.7	2.65 ± 8.7	48.3 ± 9.8	50.4 ± 9.9	2.1 ± 4.8	0.005
Low-density lipoprotein cholesterol (mg/dL)	102.6 ± 22.6	103.3 ± 22.6	0.7 ± 17.7	95.6 ± 25.2	94.2 ± 33.0	-1.4 ± 24.1	0.707

Data are presented as mean ± standard deviation or as median values (interquartile range). HbA1c, glycated hemoglobin; UACR, urinary albumin : creatinine ratio.



**Table 3** | Multiple regression analysis for the change in estimated glomerular filtration rate slope after initiation of sodium–glucose cotransporter 2 inhibitors compared with that before initiation as the dependent variable

Parameter	Standardized partial regression coefficient	P-value
Age	0.047	0.707
Sex	−0.024	0.812
BMI	0.021	0.848
Systolic BP	−0.102	0.507
Diastolic BP	−0.197	0.233
HbA1c	−0.014	0.886
eGFR	−0.225	0.086
UACR	−0.122	0.222
eGFR slope in 2 years before the initiation of SGLT2i	−0.868	<0.001

BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SGLT2i, sodium–glucose cotransporter 2 inhibitors; UACR, urinary albumin : creatinine ratio.

significantly increased in patients receiving SGLT2i treatment. Uric acid levels were nominally decreased from 5.6 mg/dL to 5.3 mg/dL, although the changes were not statistically significant. Aspartate aminotransferase levels, alanine aminotransferase levels and  $\gamma$ -glutamyl transpeptidase levels were significantly decreased in patients receiving SGLT2i treatment. We did not find any marked changes in triglycerides or low-density lipoprotein cholesterol, whereas high-density lipoprotein cholesterol was significantly increased in patients receiving SGLT2i treatment.

Additionally, we investigated the variables associated with  $\Delta$  (eGFR slope) in the patients with SGLT2i administration; this analysis used a bivariate analysis, and incorporated age; sex; baseline and change in HbA1c; blood pressure; and bodyweight; baseline kidney and liver function tests; baseline UACR; and medications. The eGFR slope in the 2 years preceding the initiation of SGLT2i was inversely correlated with the  $\Delta$ (eGFR slope) ( $P < 0.001$ ). Based on the multiple regression analysis for  $\Delta$ (eGFR slope) as the dependent variable, the eGFR slope in the 2 years preceding the initiation of SGLT2i was the only associated and independent determinant of the  $\Delta$ (eGFR slope) ( $P < 0.001$ ; Table 3).

## DISCUSSION

The present study showed that add-on treatment with SGLT2i resulted in clinically relevant improvement in the eGFR slope for over 3 years in both rapid and moderate eGFR decliners whose pre-treatment renal function was in the preserved range (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>). The time required to reverse the eGFR levels of the SGLT2i treatment group to above those of the no SGLT2i group was shorter in the rapid decliners than that in the moderate decliners. These data might show that

administration of SGLT2i in the early stage of type 2 diabetes protects the patients from progressive eGFR decline by extending the period of preserved renal function, leading to a decrease in the number of patients progressing to ESRD.

These results have several important implications. First, in both rapid and moderate decliners with preserved renal function (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>), the mean annual eGFR slope was significantly improved with administration of SGLT2i compared with without. Given that similar effects of SGLT2i have been shown in patients with advanced renal dysfunction in previous studies<sup>5,6,20</sup>, early intervention with SGLT2i might be more beneficial for diabetic kidney disease. The present data were derived from real-world clinical practice, meaning that the baseline glycemic control was worse in patients with SGLT2i therapy than in those without, in both rapid and moderate decliners (Table 1). Furthermore, administration of SGLT2i significantly improved the HbA1c levels in the moderate decliners, but not in the rapid decliners. Although this difference in the change in HbA1c might be influenced by the difference in the number of patients between the rapid decliners and moderate decliners, the present data showed that treatment with SGLT2i provided an improved eGFR slope in patients with preserved renal function (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>); the renoprotective effect likely applies irrespective of the status of glycemic control. Notably, although a previous study enrolled rapid decliners with more advanced renal dysfunction than those in the present study, the improvement of the eGFR slope after initiation of SGLT2i again was more robust in patients who were rapid decliners<sup>5,6</sup>. Taken together, the previous and present data show that administration of SGLT2i has renoprotective effects in patients with preserved eGFR levels, as well as in those with advanced renal dysfunction. In addition, the renoprotective effects of SGLT2i were more pronounced in patients who were rapid decliners.

Second, we investigated the eGFR slope as a renal outcome, given that the patients in the present study showed preserved renal function (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>). Notably, the steeper the eGFR slope before starting SGLT2i administration, the larger the  $\Delta$ (eGFR slope); that is, the larger the improvement of eGFR slope. This observation might be due to higher levels of SGLT2 in the rapid decliners than in the moderate decliners; specifically, the time required to reverse the eGFR levels in the SGLT2i treatment group to above those of the no SGLT2i group was shorter in the rapid decliners than in the moderate decliners (16 months vs 28 months).

Third, we discuss the potential mechanisms of the renoprotective effects of SGLT2i. Multiple mechanisms of SGLT2i have been shown, including those involving hemodynamics, diuresis, metabolism, decreased sympathetic nervous system activity and increased erythropoietin production. In type 2 diabetes, SGLT2 accumulates to higher levels, and reabsorption of glucose and sodium is increased in the proximal tubule cells, thus leading to decreased delivery of glucose and sodium to the macula densa, which is followed by dilation of the afferent arteriole

(tubuloglomerular feedback). The hemodynamic changes in type 2 diabetes result in elevation of intraglomerular pressure and albuminuria/proteinuria. Decreased albuminuria/proteinuria, therefore, would be expected with administration of SGLT2i. In the present study, 92.9% (13/14) of rapid decliners and 95.2% (20/21) of moderate decliners had UACR in microalbuminuric ranges, and the UACR values were not significantly improved after 3 years of treatment with SGLT2i. Based on the UACR data, the renoprotective effects of SGLT2i were likely independent of hemodynamic changes associated with SGLT2i. In fact, an initial dip in eGFR levels is often seen when intraglomerular pressure decreases with SGLT2i administration; however, such an initial dip was not evident in the rapid decliners in the present study, and only a slight initial dip was seen in the moderate decliners in the present work (Figures 2a and 3a).

In contrast, significant increases in hematocrit and hemoglobin levels were observed in both the rapid and moderate decliners. Administration of SGLT2i leads to decreased energy expenditure in the proximal tubule cells, given that reabsorption of glucose and sodium through SGLT2 is coupled to activity of the  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase. The improvement in tubular energy balance might result in increased erythropoietin production in the proximal tubule cells<sup>22</sup>. Therefore, we considered that the renoprotective effect on type 2 diabetes patients with normoalbuminuria or microalbuminuria might be related to the reduction of energy expenditure in proximal tubular cells, which could be reflected in the increased hematocrit levels. Recently, the pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial showed that beneficial renal outcomes were dependent not only on decreases in albuminuria, but also on the other effects of SGLT2i<sup>23,24</sup>. A previous study evaluated patients with type 2 diabetes, dividing them into two groups: those with  $\geq 30\%$  reduction in UACR after SGLT2i administration (defined as responders) and those with  $< 30\%$  reduction in UACR (defined as non-responders)<sup>25</sup>. Given that most of the patients in that study had eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and microalbuminuria, the characteristics of non-responders were close to those in the present study. In that study, the renoprotective effects of SGLT2i were seen in both responders and non-responders, and it was more pronounced in the non-responders, which is likewise consistent with the results of the present study.

Fourth, 47.6% (10/21) of rapid decliners and 42.6% (20/47) of moderate decliners were administered dapagliflozin in the present study, although other types of SGLT2i were also administered. Therefore, the beneficial effects on renal function in the present study were likely to be class effects of SGLT2i.

The present study had several limitations. First, the present study was carried out retrospectively, and the study protocol was not prospectively controlled. Second, the sample size of this study was relatively small for a more definite conclusion, because SGLT2i was administered in lower proportions of type 2 diabetes patients than were other hypoglycemic drugs.

Prospective, large-scale clinical trials on SGLT2i have been carried out with larger sample sizes calculated to ensure meaningful results<sup>23,26–28</sup>. Thus, future prospective, detailed and larger studies for rapid decliners with a multicenter design should be carried out. Nevertheless, the strength of the present study lies in the fact that the observation period was relatively longer (2 years pre-treatment plus 3 years post-treatment) than those of previous studies evaluating the efficacy of SGLT2i. We also focused on the effects of SGLT2i in type 2 diabetes patients whose renal function was preserved (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>). We showed that add-on treatment with SGLT2i resulted in clinically relevant improvement in the eGFR slope for over 3 years in both rapid and moderate eGFR decliners.

In the present study, it was newly revealed that treatment with SGLT2i provided a renoprotective effect in rapid decliners whose renal function remained in the preserved range (eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>). This finding suggests that initiation of SGLT2i in the early stage of type 2 diabetes protects patients from progressive eGFR decline and extends the period of preserved renal function, leading to a decrease in the number of patients who progress to ESRD. In conclusion, we suggest that it will be beneficial to identify those patients showing a rapid progressive eGFR decline in the early phase of type 2 diabetes, and to provide these individuals with SGLT2i therapeutic intervention.

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## DISCLOSURES

The authors declare no conflict of interest.

Approval of the research protocol: The Ethics Committee of Koseiren Tsurumi Hospital, Oita, Japan.

Informed consent: The opt-out consent procedure was used in this study.

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