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ORIGINAL RESEARCH

Comparison of the changes in the factors associated with the renal prognosis of non-elderly and elderly subjects treated with empagliflozin- a retrospective observation study in Japanese patients with type 2 diabetes

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Hiroyuki Ito[1]
Suzuko Matsumoto[1]
Takuma Izutsu[1]
Eiji Kusano[1]
Shinya Nishio[1]
Shinichi Antoku[1]
Tomoko Yamasaki[1]
Toshiko Mori[1]
Michiko Togane[1]
Shigenori Ando[2]
Emiko Tsugami[2]

[1]Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital, Tokyo, Japan; [2]Department of Pharmacy, Edogawa Hospital, Tokyo, Japan

Purpose: The factors associated with the renal prognosis over six months after the initiation of empagliflozin were compared between the non-elderly and elderly Japanese patients with type 2 diabetes.

Patients and methods: In total, 132 patients treated with empagliflozin (10 mg, once daily) were studied as the safety analysis set. One hundred ten subjects whose medications were not changed during the observation period were investigated as the full analysis set to assess the effectiveness. The subjects were divided into two groups: non-elderly subjects (n=72) of<65 years of age and elderly subjects (n=38) of≥65 years of age.

Results: Although the body weight and HbA1c, AST, ALT and γ-GTP levels were significantly reduced in both the non-elderly and elderly subjects, blood pressure, eGFR and urinary protein excretion were only significantly decreased in the non-elderly subjects. The hemoglobin, hematocrit and serum HDL-cholesterol levels were significantly elevated in both groups. The change in eGFR showed a significant positive association with the change in blood pressure. The change in urinary protein excretion tended to be correlated with the change in blood pressure.

Conclusion: Although renoprotective effects might be limited, empagliflozin can safely and effectively improve metabolic parameters, even in elderly subjects.

Keywords: sodium-glucose cotransporter 2 inhibitor, empagliflozin, type 2 diabetes mellitus, elderly, renoprotection, renal impairment

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to have weight reduction and blood pressure lowering effects and improve glycemic control in patients with diabetes. Furthermore, several clinical trials have shown that SGLT2 inhibitors suppress the onset of heart failure, cardiovascular disease and end-stage kidney disease in patients with type 2 diabetes.[1–6] Empagliflozin, a SGLT2 inhibitor, is also effective for reducing the risk of major adverse cardiovascular events and the worsening of diabetic nephropathy in Asian type 2 diabetes patients[7,8] whose body mass index (BMI) values are generally lower in comparison to Caucasians. However, the prescription rate of SGLT2 inhibitors for the treatment

Correspondence: Hiroyuki Ito
Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital, 2-24-18, Higashikoiwa, Edogawa-ku, Tokyo 133-0052, Japan
Tel +81 3 3673 1221
Fax +81 3 3673 1229
Email ito@edogawa.or.jp

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for type 2 diabetes has not been high in Japan[9,10] because of concerns about the drug-related adverse events (AEs), including volume depletion and cerebral infarction in elderly subjects,[11] or a deterioration of the glucose-lowering effect in patients with renal impairment. The number of elderly patients with type 2 diabetes continues to increase in Japan.[12] The aging of patients is closely related to frequent renal impairment in individuals with type 2 diabetic[13,14] and such patients are considered to be at high risk for cardiovascular events.[15,16] Thus, dipeptidyl peptidase-4 (DPP-4) inhibitors are commonly used in real-world clinical practice for the treatment of Japanese patients with type 2 diabetes[9,10] because of safety and reliability from the viewpoint of AEs and glycemic control in elderly patients with renal impairment.[17,18] However, there is no clear evidence to support the inhibition of cardiovascular events or diabetic nephropathy by DPP-4 inhibitors,[19–22] although the glucose-lowering efficacy of DPP-4 inhibitors in Asians is better than that in other ethnic groups.[23]

Recently, it was reported that ipragliflozin therapy was well tolerated and reduced surrogate endpoints such as HbA1c, body weight and blood pressure in elderly Japanese patients with type 2 diabetes based on a post-marketing surveillance study.[24,25] However, this study did not compare the results to those in non-elderly patients. It is considered to be necessary to evaluate the differences in the efficacy and safety of SGLT2 inhibitors in non-elderly and elderly subjects. Thus, we investigated the clinical courses, especially the factors associated with the renal prognosis, over six months after the initiation of empagliflozin therapy in elderly Japanese patients with type 2 diabetes.

Patients and methods

Study design and patients

A flow chart of the patient selection process is shown in Figure 1. One hundred seventy-nine Japanese patients with type 2 diabetes who received 10 mg once daily of empagliflozin (Jardiance® tablets, Nippon Boehringer Ingelheim Co., Ltd. Eli Lilly Japan K.K.) at our department in the period from December 2014 to February 2018 were eligible for inclusion in this study. Subjects in whom empagliflozin treatment started with the replacement of other antidiabetic agents (other SGLT2 inhibitors [n=7], glucagon-like peptide-1 [GLP-1] receptor agonists [n=4] and other classes [n=16]), subjects who discontinued treatment or who were transferred to other hospitals during the observation period, and subjects whose antidiabetic or antihypertensive agents were changed during the observation period were excluded from the analysis. In total, 132 patients with type 2 diabetes (male; 70%, 57±12 years of age, patient's age≥65 years; 33%) were studied as the safety analysis set (SAS) in order to analyze the safety of empagliflozin. Further, 110 subjects (male; 73%, 58 ±12 years of age, patient's age≥65 years; 35%) were investigated as the full analysis set (FAS) in order to assess the effectiveness of empagliflozin after the exclusion of subjects for whom the administration of empagliflozin was stopped during the observation period, subjects whose

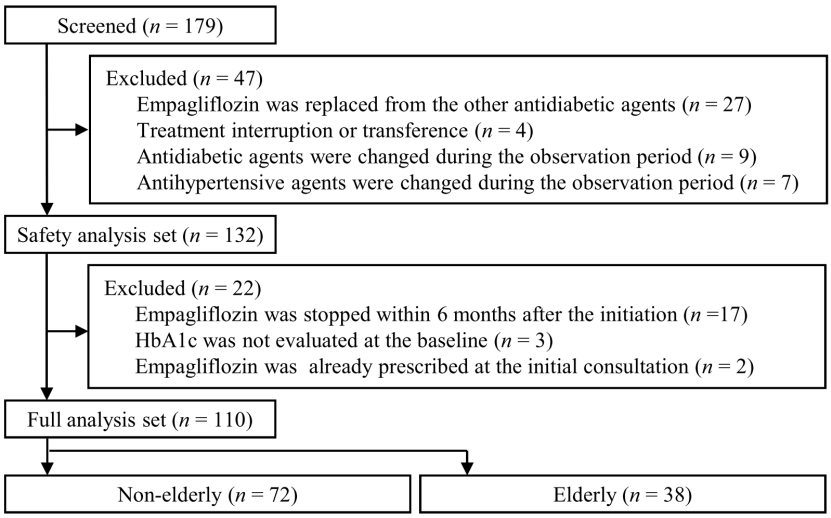

Figure 1 Flowchart of patient selection. The safety of empagliflozin was analyzed in the safety analysis set (n=132) and the effectiveness was investigated in the full analysis set (n=110).

HbA1c levels were not evaluated at the initiation of empagliflozin and subjects who were already prescribed empagliflozin at the initial consultation. Finally, the study subjects were divided into two groups based on the patients' age: non-elderly (n=72) who were less than 65 years of age and elderly (n=38) who were≥65 years of age.

Measurements

The eGFR was calculated using the formula recommended by the Japanese Society of Nephrology.[26] Diabetic nephropathy was defined as a urinary albumin-to-creatinine ratio (ACR) of≥30 mg/g/creatinine in a random spot urine test. The urinary protein excretion was evaluated by the pyrogallol red method using urine test-strips (Uriflet S; ARKRAY, Inc., Kyoto, Japan) and an automatic analyzer (Austin MAX AX 4280; ARKRAY, Inc.). Proteinuria was graded as (±), (1+), (2+) and (3+) corresponding to 15 mg/dL, 50 mg/dL, 150 mg/dL and 325 mg/dL, respectively, according to the median value of the measurement range in the semi-quantitative results.[27–29]

Obese individuals were defined as those with a BMI of ≥25 kg/m^2 according to the criteria set by the Japan Society for the Study of Obesity.[30] Hypertension was defined as a systolic blood pressure of≥140 mmHg and/or a diastolic blood pressure of≥90 mmHg.[31] Participants currently using antihypertensive medications were also classified as being positive for hypertension. Hyper-LDL-cholesterolemia was defined as a serum LDL-cholesterol concentration of≥3.62 mmol/L or the current use of statins or ezetimibe. A current drinker was defined as a person consuming>20 g ethanol equivalent/day. Diabetic retinopathy, peripheral neuropathy, cerebrovascular disease, coronary heart disease and peripheral artery were diagnosed as previously described.[13–16]

The clinical parameters and AEs were retrospectively examined over six months after the initiation of empagliflozin based on the subjects' medical records. When clinical data including the HbA1c level were missing, the appropriate value obtained on the previous visit was used according to the last observational carried forward (LOCF) method.

Ethics conduct

The study was conducted in accordance with the principles expressed in the 2008 Declaration of Helsinki. The Ethics Committee of Edogawa Hospital approved the study protocol and waived the need for written informed consent because the data were analyzed anonymously for this retrospective analysis based on information stored in the hospital (approved number: 2019–20, date: June 20, 2019).

Statistical analyses

All data are presented as the mean ± standard deviations. The χ^2 test was used for between-group comparisons of categorical variables. None of the continuous variables (age, duration of diabetes, body weight, BMI, blood pressure, hemoglobin, hematocrit, serum lipid concentrations, aspartate transaminase [AST], alanine transaminase [ALT], γ-glutamyl transpeptidase [γ-GTP], HbA1c, eGFR, uric acid and urinary protein excretion) showed a normal distribution in the Shapiro-Wilk tests. Thus, Wilcoxon's signed rank test was used to assess the significance of differences in the continuous variables. Wilcoxon's rank sum test was used to assess the significance of differences in body weight, BMI, blood pressure, hemoglobin, hematocrit, serum lipid concentration, AST, ALT, γ-GTP, HbA1c, eGFR, uric acid and urinary protein excretion during the observation period in comparison to baseline values. A least squares model was used to evaluate the associations between the clinical background factors of the patients and the changes at six months after the initiation of empagliflozin therapy in the HbA1c levels (ΔHbA1c), body weight (ΔBW), systolic blood pressure (ΔsBP), diastolic blood pressure (ΔdBP), eGFR (ΔeGFR) and urinary protein excretion (ΔUP). Factors that showed a significant association with changes in each dependent variable in a univariate analysis were included in a multivariate analysis. *P*-values of<0.05 (two-tailed) were considered to indicate statistical significance. The statistical software package JMP version 8.0.1 (SAS Institute, Cary, NC) was used to perform all analyses.

Results

Baseline characteristics and efficacy

The clinical characteristics of the FAS at the baseline are shown in Table 1. The duration of diabetes in the elderly subjects was significantly longer than that in the non-elderly subjects. The rates of diabetic neuropathy and peripheral artery disease were significantly higher in elderly subjects. While the combined use of sulfonylureas or DPP-4 inhibitors was significantly more frequent in elderly subjects, biguanides were frequently used by non-elderly subjects. Table 2 shows the clinical parameters of the FAS at baseline and at six months after the initiation of empagliflozin. The body weight, diastolic blood pressure,

Table 1 The clinical characteristics of the full analysis set (n=110) at baseline

	Non-elderly	Elderly	*P*
n	38	72	
Male (%)	78	63	0.11
Age (years)	52±10	69±4	<0.01
Duration of diabetes (years)	8±6	14±7	<0.01
Smoking history (%)	65	67	0.88
Current drinker (%)	19	28	0.32
Obesity (%)	86	84	0.81
Hypertension (%)	78	80	0.89
Hyper-LDL-cholesterolemia (%)	67	76	0.29
Diabetic retinopathy (%)[#]	58	53	0.67
Diabetic nephropathy (%)	49	43	0.58
Diabetic neuropathy (%)	28	58	0.01
Cerebrovascular disease (%)	3	5	0.52
Coronary heart disease (%)	32	42	0.29
Peripheral arterial disease (%)	0	11	<0.01
Concomitant anti-diabetic agents (%)			
Sulfonylureas	5	32	<0.01
Biguanides	69	50	0.046
Thiazolidinediones	7	2	0.32
α-glucosidase inhibitors	7	18	0.07
DPP-4 inhibitors	47	74	<0.01
GLP-1 receptor agonists	14	8	0.34
Insulin	31	26	0.64
Antihypertensive agents (%)			
RAS inhibitors[##]	51	63	0.24
Calcium channel blocker	28	34	0.49

Notes: [#]Diabetic retinopathy includes simple, preproliferative and proliferative retinopathy. [##]RAS inhibitors include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
Abbreviations: LDL, low-density lipoprotein; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; RAS, renin-angiotensin system.

eGFR, and hemoglobin and hematocrit levels in the elderly subjects were significantly lower than those in the non-elderly subjects at baseline. The non-elderly subjects included 63 patients with a normal eGFR (≥60 mL/min/1.73 m^2) and 9 patients with a reduced eGFR (<60 mL/min/1.73 m^2). The elderly subjects included 24 patients with a normal GFR and 14 patients with a reduced eGFR. The serum HDL-cholesterol concentration was significantly higher in the elderly subjects. While the body weight, BMI, HbA1c, AST, ALT and γ-GTP levels were significantly reduced in both the non-elderly and elderly subjects, blood pressure, eGFR and urinary protein excretion were only significantly decreased in the non-elderly subjects after the initiation of empagliflozin. The levels of hemoglobin, hematocrit and serum HDL-cholesterol significantly increased in both groups. The prevalence of patients whose HbA1c reached<7.0% was significantly increased in both the non-elderly (7–25%, $P<0.01$) and elderly (5–34%, $P<0.01$) subjects. The prevalence of patients whose HbA1c reached <8.0% was also significantly increased in both the non-elderly (29 to 74%, $P<0.01$) and elderly (29–76%, $P<0.01$) subjects.

Table 3 shows the relationships between the ΔHbA1c, ΔBW, ΔsBP and ΔdBP, and the baseline clinical parameters. The ΔHbA1c showed a significant negative correlation with the HbA1c level at baseline (correlation coefficient=−0.483, $P<0.01$, $R^2=0.44$) according to a multivariate analysis with rennin-angiotensin system (RAS) inhibitor use, hemoglobin, hematocrit and HbA1c included as independent variables. The ΔBW was significantly associated with the BMI at baseline (correlation coefficient=−0.048, $P=0.03$, $R^2=0.18$) according to a multivariate analysis with RAS inhibitor use, BMI, hemoglobin, hematocrit, HbA1c and AST included as independent variables. The ΔsBP was significantly associated with the systolic blood pressure (correlation coefficient=−0.394, $P<0.01$) and the γ-GTP-value (correlation coefficient=0.066, $P<0.01$) at baseline ($R^2=0.27$) according to a multivariate analysis with systolic blood pressure, diastolic blood pressure and γ-GTP levels included as independent variables. The ΔdBP showed a significant negative correlation with the diastolic blood pressure at baseline (correlation coefficient=−0.335, $P<0.01$, $R^2=0.20$) according to a multivariate analysis with male sex, elderly subject, systolic blood pressure and diastolic blood pressure included as independent variables.

Table 4 shows the relationships between the ΔeGFR and ΔUP, and the clinical parameters at baseline. The ΔeGFR showed a significant negative correlation with the eGFR value at baseline ($R^2=0.16$) according to a multivariate analysis with the elderly subject, patient's age, body weight and eGFR values as independent variables. The ΔUP showed a significant negative correlation with the urinary protein excretion at baseline ($R^2=0.50$) according to a multivariate analysis that included diabetic retinopathy, nephropathy, DPP-4 inhibitor use, GLP-1 receptor agonist use, systolic blood pressure, diastolic blood pressure and urinary protein excretion as independent variables.

Although the eGFR was significantly decreased at one month after the initiation of empagliflozin in non-elderly subjects, the eGFR was not significantly reduced in the elderly subjects (Figure 2A). The ΔeGFR in the non-elderly subjects was significantly greater than that in the

Table 2 The clinical parameters of the full analysis set (n=110) at baseline and six months after the initiation of empagliflozin

	Non-elderly (n=72)			Elderly (n=38)		
	Baseline	**6 months**	***P***	**Baseline**	**6 months**	***P***
Body weight (kg)	85.1±16.2	83.6±15.8	<0.01	73.8±13.8*	72.4±13.3	<0.01
Body mass index (kg/m^2)	30.2±5.2	29.6±5.0	<0.01	28.7±4.2	28.1±4.2	<0.01
Systolic blood pressure (mmHg)	136±16	129±17	<0.01	133±15	131±14	0.24
Diastolic blood pressure (mmHg)	87±13	81±13	<0.01	75±10*	74±10	0.39
Hemoglobin (g/L)	148±14	152±14	<0.01	138±16*	142±14	<0.01
Hematocrit (%)	43.8±3.8	45.5±3.9	<0.01	41.2±4.6*	42.8±4.1	<0.01
LDL-cholesterol (mmol/L)	2.72±0.64	2.67±0.77	0.33	2.66±0.73	2.50±0.64	0.18
HDL-cholesterol (mmol/L)	1.18±0.24	1.23±0.28	<0.01	1.39±0.27*	1.44±0.30	0.02
HbA1c (%)	8.7±1.2	7.6±0.9	<0.01	8.7±1.4	7.5±1.0	<0.01
Aspartate transaminase (IU/L)	33±27	24±12	<0.01	31±16	26±13	0.01
Alanine transaminase (IU/L)	39±24	29±19	<0.01	33±22	24±14	<0.01
γ-glutamyl transpeptidase (IU/L)	63±57	50±54	<0.01	54±54	45±53	<0.01
eGFR (mL/min/1.73 m^2)	84.5±20.4	79.9±19.6	<0.01	67.2±16.8*	66.1±16.3	0.44
Uric acid (μmol/L)	315±68	312±86	0.56	297±68	277±62	0.06
Urinary protein excretion (mg/dL)	24.6±47.5	13.4±28.9	<0.01	19.4±59.2	17.6±58.6	0.66

Note: *P<0.01 vs. corresponding value in the non-elderly subjects.
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

elderly subjects (−4.6±8.7 mL/min/1.73 m^2 vs. −1.0 ±6.8 mL/min/1.73 m^2, P=0.03). Similarly, the urinary protein excretion at one month after the initiation of empagliflozin was reduced in the non-elderly subjects, while no significant reduction was observed in the elderly subjects (Figure 2B). The ΔUP in the non-elderly was significantly greater than that in the elderly subjects (−11.0±27.6 mg/dL vs −1.8±12.3 mg/dL, P=0.01).

Figure 3 shows the changes in the subgroups according to the eGFR at baseline. In the non-elderly subjects, the eGFR was significantly reduced after the initiation of empagliflozin in the patients with a normal eGFR at baseline, although the eGFR did not decrease in the patients with a reduced eGFR (Figure 3A). In the elderly subjects, the eGFR did not significantly change in either the patients with normal or reduced eGFRs at baseline (Figure 3B). In the FAS, the ΔeGFR showed a significant positive association with the ΔsBP and ΔdBP (Figure 4). Although the ΔUP was not significantly associated with ΔBW, ΔHbA1c or ΔdBP, the ΔUP tended to be positively correlated with the ΔsBP (n=96, r^2=0.03, P=0.08).

Safety

In the SAS, empagliflozin was discontinued in 2 patients because of no effect and in 15 patients (11%) at the onset of AEs, including genital infection (n=7), hypoglycemia (n=1), increased urine volume (n=4), volume depletion (n=1), skin eruption (n=1) and cholelithiasis (n=1) (Figure 1). The AEs recorded during the observation period in the SAS are shown in Table 5. The frequencies of AEs (both overall and individual events) in the non-elderly and elderly subjects did not differ to a statistically significant extent. Although the frequency of AEs in the subjects with a reduced eGFR was higher than that in those with a normal eGFR in both the non-elderly and elderly subjects, the difference was not statistically significant. Eight of the nine subjects who developed genital or urinary tract infection were women. Severe hypoglycemia requiring the assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions was not observed during the observation period.

Discussion

In the present study, the eGFR and urinary protein excretion did not differ significantly after the initiation of empagliflozin in elderly subjects, although the HbA1c level and body weight significantly decreased in both non-elderly and elderly patients with type 2 diabetes. The ΔeGFR was significantly associated with changes in blood pressure levels and the ΔUP also tended to be associated with changes in systolic blood pressure. These results are considered to have been mainly caused by the deterioration of the blood pressure-lowering effect because arterial elasticity is generally reduced in elderly subjects, especially patients with type 2 diabetes.[13] Although Kario et al reported that the addition of empagliflozin to existing antihypertensive and antidiabetic

Table 3 The relationship between the ΔHbA1c, ΔBW, ΔsBP, ΔdBP, and the clinical parameters at baseline in the full analysis set (n=110)

	ΔHbA1c		ΔBW		ΔsBP		ΔdBP	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
Male	−0.193	0.35	1.035	0.12	−0.396	0.90	−5.046	0.03
Elderly	−0.070	0.72	−0.346	0.58	4.830	0.11	4.508	0.04
Age (/years)	−0.009	0.24	0.006	0.82	0.097	0.43	0.135	0.13
Duration of diabetes (/years)	−0.003	0.86	0.019	0.67	−0.162	0.46	0.096	0.54
Smoking history	0.010	0.96	0.358	0.57	1.893	0.54	−0.407	0.85
Current drinker	−0.010	0.96	0.668	0.34	2.620	0.46	1.292	0.61
Obesity	−0.222	0.39	−1.962	0.02	1.114	0.80	5.270	0.10
Hypertension	0.182	0.41	−1.441	0.05	−6.148	0.08	−4.175	0.10
Hyper-LDL-cholesterolemia	−0.143	0.47	0.232	0.71	4.400	0.16	2.419	0.28
Diabetic retinopathy[#]	−0.149	0.47	−0.581	0.35	0.048	0.99	−1.417	0.51
Diabetic nephropathy	−0.012	0.95	−0.844	0.16	−0.553	0.85	−0.095	0.96
Diabetic neuropathy	−0.230	0.29	−0.412	0.51	−2.383	0.47	2.670	0.26
Cerebrovascular disease	−0.680	0.16	−0.315	0.83	2.157	0.77	9.365	0.07
Coronary heart disease	−0.007	0.97	0.239	0.70	−0.856	0.78	−0.166	0.94
Peripheral arterial disease	−0.161	0.74	0.904	0.66	−5.392	0.46	−5.740	0.28
Concomitant anti-diabetic agents								
Sulfonylureas	−0.211	0.42	−0.464	0.60	3.013	0.50	−0.769	0.81
Biguanides	0.094	0.62	0.002	0.99	−1.194	0.69	4.210	0.05
Thiazolidinediones	0.374	0.35	−2.219	0.09	−4.620	0.45	−2.759	0.53
α-glucosidase inhibitors	−0.109	0.71	−0.616	0.49	−2.53	0.60	−1.733	0.62
DPP-4 inhibitors	−0.279	0.13	−0.063	0.91	1.491	0.60	3.361	0.10
GLP-1 receptor agonists	0.175	0.54	−0.435	0.63	−2.500	0.56	−3.084	0.32
Insulin	−0.148	0.46	1.233	0.05	−3.143	0.31	−3.018	0.18
Antihypertensive agents								
RAS inhibitors[##]	0.360	0.049	−1.598	<0.01	−2.805	0.33	−1.037	0.62
Calcium channel blocker	0.278	0.16	0.030	0.96	2.781	0.37	2.581	0.25
Body weight (/kg)	−0.007	0.25	−0.020	0.24	−0.008	0.93	−0.050	0.47
Body mass index (/kg/m^2)	−0.031	0.09	−0.113	0.04	0.183	0.58	0.193	0.40
Systolic blood pressure (/mmHg)	−0.000	0.97	−0.013	0.46	−0.381	<0.01	−0.135	0.04
Diastolic blood pressure (/mmHg)	−0.007	0.34	−0.010	0.66	−0.253	0.02	−0.346	<0.01
Hemoglobin (/g/dL)	−0.123	0.04	0.490	0.01	0.329	0.73	−1.250	0.07
Hematocrit (/%)	−0.042	0.049	0.150	0.03	0.120	0.72	−0.437	0.07
LDL-cholesterol (/mmol/)	−0.107	0.45	0.154	0.70	0.005	1.00	−1.994	0.20
HDL-cholesterol (/mmol/L)	0.345	0.34	−0.596	0.56	3.156	0.55	6.404	0.10
HbA1c (/%)	−0.490	<0.01	0.483	0.04	−0.618	0.59	−0.856	0.30
Aspartate transaminase (/IU/L)	−0.003	0.38	−0.026	0.03	0.053	0.38	0.005	0.90
Alanine transaminase (/IU/L)	−0.004	0.34	−0.004	0.72	0.095	0.11	0.009	0.84
γ-glutamyl transpeptidase (/IU/L)	−0.002	0.16	0.002	0.64	0.061	0.02	0.005	0.80
eGFR (/mL/min/1.73 m^2)	0.001	0.84	0.006	0.66	−0.056	0.41	−0.017	0.74
Uric acid (/μmol/L)	−0.001	0.55	0.002	0.69	0.025	0.25	0.001	0.93
Urinary protein excretion (/mg/dL)	−0.002	0.26	−0.009	0.08	−0.002	0.94	−0.010	0.63

Notes: [#]Diabetic retinopathy includes simple, preproliferative and proliferative retinopathy. [##]RAS inhibitors include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Abbreviations: LDL, low-density lipoprotein; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; RAS, renin-angiotensin system; GFR, estimated glomerular filtration rate.

therapy showed significant blood pressure reductions in older diabetic patients using 24 hr ambulatory blood pressure monitoring,[32] there was no significant change in the blood pressure levels of the elderly subjects of the present study. A simple comparison with our results is difficult because their method of measuring blood pressure differed from ours and

Table 4 The relationship between the ΔeGFR and ΔUP, and the clinical parameters at baseline in the full analysis set (n=110)

	ΔeGFR				ΔUP			
	Univariate		Multivariate		Univariate		Multivariate	
	correlation coefficient	*P*	correlation coefficient	*P*	correlation coefficient	*P*	correlation coefficient	*P*
Male	−2.254	0.20			−3.332	0.54		
Elderly	3.538	0.03	2.716	0.23	4.738	0.07		
Age (/years)	0.133	0.049	−0.157	0.15	0.252	0.24		
Duration of diabetes (/years)	0.084	0.49			0.103	0.79		
Smoking history	0.914	0.59			−3.746	0.48		
Current drinker	−2.407	0.22			−1.745	0.77		
Obesity	−2.663	0.24			4.399	0.57		
Hypertension	−0.426	0.82			−5.375	0.37		
Hyper-LDL-cholesterolemia	2.340	0.17			3.674	0.49		
Diabetic retinopathy[#]	3.078	0.07			−19.413	<0.01	−4.062	0.53
Diabetic nephropathy	1.097	0.50			−15.654	<0.01	−0.985	0.87
Diabetic neuropathy	0.895	0.61			−3.554	0.56		
Cerebrovascular disease	5.041	0.23			4.724	0.70		
Coronary heart disease	2.351	0.15			−7.725	0.15		
Peripheral arterial disease	6.040	0.15			8.542	0.55		
Concomitant anti-diabetic agents								
Sulfonylureas	−0.405	0.86			0.315	0.97		
Biguanides	3.021	0.06			0.824	0.87		
Thiazolidinediones	0.416	0.91			−2.715	0.79		
α-glucosidase inhibitors	0.867	0.73			−6.778	0.43		
DPP-4 inhibitors	1.245	0.44			13.156	<0.01	5.929	0.18
GLP-1 receptor agonists	−1.898	0.44			−19.244	<0.01	−6.293	0.32
Insulin	−1.421	0.42			−3.692	0.48		
Antihypertensive agents								
RAS inhibitors[##]	0.478	0.76			0.227	0.96		
Calcium channel blocker	−3.031	0.08			−0.551	0.92		
Body weight (/kg)	−0.104	0.03	−0.090	0.08	−0.137	0.36		
Body mass index (/kg/m^2)	−0.198	0.22			0.176	0.74		
Systolic blood pressure (/mmHg)	−0.038	0.47			−0.516	<0.01	−0.316	0.05
Diastolic blood pressure (/mmHg)	−0.101	0.11			−0.666	<0.01	−0.169	0.36
Hemoglobin (/g/dL)	−1.795	0.13			−1.701	0.29		
Hematocrit (/%)	−0.207	0.27			−0.573	0.31		
LDL-cholesterol (/mmol/L)	−0.623	0.61			2.696	0.47		
HDL-cholesterol (/mmol/L)	−4.012	0.20			14.713	0.12		
HbA1c (/%)	0.158	0.80			−1.460	0.44		
Aspartate transaminase (/IU/L)	0.000	0.99			0.098	0.34		
Alanine transaminase (/IU/L)	0.038	0.26			0.038	0.71		
γ-glutamyl transpeptidase (/IU/L)	0.009	0.53			−0.038	0.40		
eGFR (/mL/min/1.73 m^2)	−0.138	<0.01	−0.150	<0.01	−0.026	0.83		
Uric acid (/μmol/L)	0.009	0.47			−0.032	0.42		
Urinary protein excretion (/mg/dL)	0.013	0.43			−0.302	<0.01	−0.234	<0.01

Notes: [#]Diabetic retinopathy includes simple, preproliferative and proliferative retinopathy. [##]RAS inhibitors include angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Abbreviations: LDL, low-density lipoprotein; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; RAS, renin-angiotensin system; GFR, estimated glomerular filtration rate.

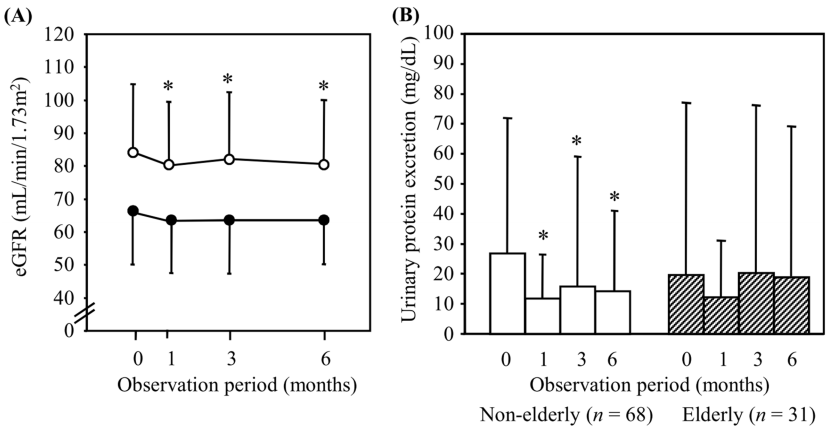

Figure 2 Changes in the eGFR (**A**) and urinary protein excretion (**B**) in non-elderly and elderly subjects. The open (n=72) and closed (n=38) circles indicate non-elderly and elderly subjects, respectively. The open (n=68) and shaded (n=31) bars indicate non-elderly and elderly subjects, respectively. *P<0.01 vs baseline (0 month) value.

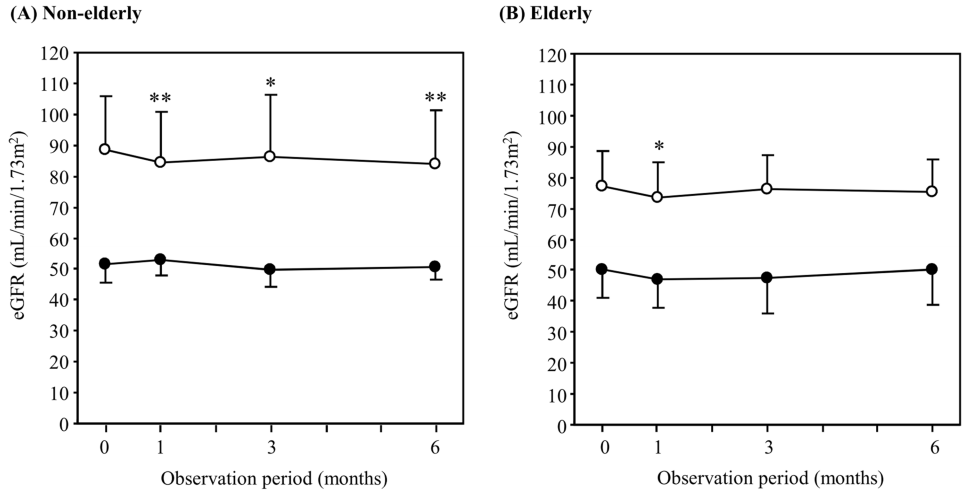

Figure 3 Changes in the eGFR in subgroups according to the eGFR at baseline in non-elderly (**A**) and elderly (**B**) subjects. The closed and open circles indicate subjects with a normal eGFR (eGFR≥60 mL/min/1.73 m^2) and those with a reduced eGFR (eGFR <60 mL/min/1.73 m^2), respectively. *P<0.05 and **P<0.01 vs baseline (0 month) value.

because no data were obtained from non-elderly subjects in their study. However, it is necessary to consider the possibility that the renoprotective effect induced by empagliflozin through blood pressure reduction is limited in elderly patients. It is known that a relatively rapid decrease of eGFR, so-called the initial dip, is observed in the initial phase after the administration of SGLT2 inhibitors.[1–3] After this initial dip, the eGFR tended to return toward the baseline value and remain stable thereafter.[1–3]

Sinclair et al noted that early transient decreases from baseline in the eGFR were seen with canagliflozin, a SGLT2 inhibitor, within the first 3–6 weeks of treatment, these changes subsequently stabilized or became attenuated over the 26-week treatment period, even in elderly patients with type 2 diabetes, similarly to non-elderly patients based on a pooled analysis of 4 clinical studies.[33] This result is considered not to conflict with ours because their data were obtained from elderly subjects whose eGFR was≥50 (the mean ranged from 75.9 to 77.4) mL/min/1.73 m^2. Perkovic et al also noted that changes in the eGFR in a phase 3 study of canagliflozin in older patients (55–80 years) with type 2 diabetes[34] were similar to those seen in other placebo-controlled studies over 26 weeks.[35] This result is seems to be close to our own data in subjects with a normal eGFR, regardless of the age subgroups, as the mean age and eGFR of their subjects was 63.6 years and 77.5 mL/min/1.73 m^2, respectively.

These phenomena are considered to suggest that the cancellation of glomerular hyperfiltration induces long-term stability of the eGFR. Although we did not observe long-term changes in eGFR in the present study, our results demonstrate that the reduction of the systemic blood pressure contributed to the initial dip in the eGFR,

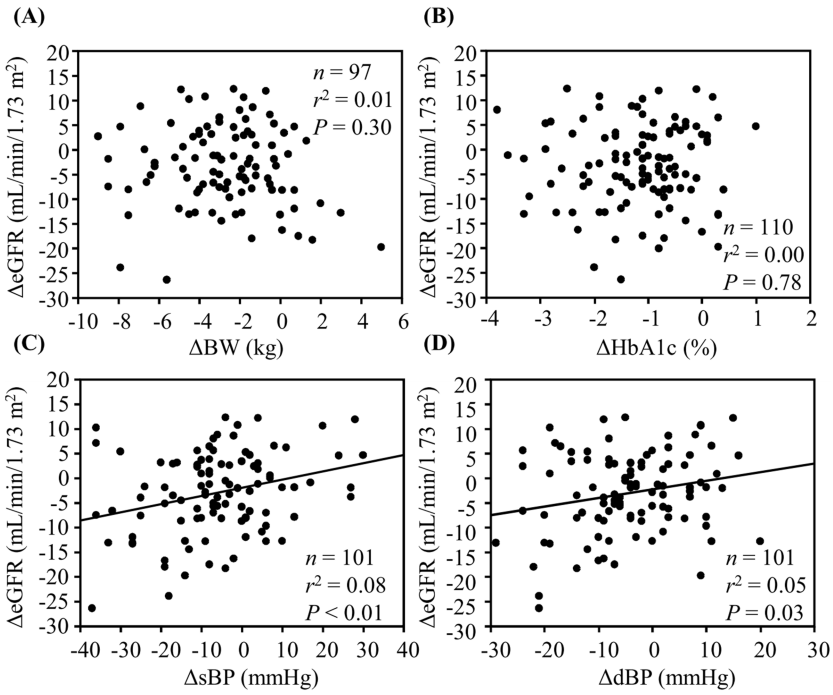

Figure 4 The relationships between the changes in the eGFR and the changes in body weight (**A**), HbA1c (**B**), systolic blood pressure (**C**) and diastolic blood pressure (**D**) in the full analysis set.

Table 5 Adverse events during the observation period in the safety analysis set (n=132)

	Non-elderly			Elderly		
	Total	eGFR≥60	eGFR<60	total	eGFR≥60	eGFR<60
	(n=89)	(n=79)	(n=10)	(n=43)	(n=25)	(n=18)
Genital infections	4 (4%)	3	1	4 (9%)	3	1
Hypoglycemia	2 (2%)	2	0	0	0	0
Urinary tract infections	1 (1%)	1	0	0	0	0
Increased urine volume	11 (12%)	7	4	2 (5%)	1	1
Volume depletion	2 (2%)	2	0	3 (7%)	2	1
Skin itching/eruption	5 (6%)	5	0	1 (2%)	1	0
Renal impairment	0	0	0	0	0	0
Gastrointestinal symptoms[#]	6 (%)	6	0	4 (9%)	1	3
Others	16 (18%)	14	2	12 (28%)	7	6
Total	47 (53%)	40 (51%)	7 (70%)	26 (60%)	15 (60%)	12 (67%)

Note: [#]Gastrointestinal symptoms include nausea, vomiting, abdominal fullness, abdominal pain, constipation and diarrhea.

resulting in renoprotection, especially in non-elderly subjects. Alternatively, the initial dip in the eGFR may be a potential predictor of a reduction in the blood pressure through the natriuretic action of SGLT2 inhibitors. SGLT2 inhibitors can cause the reflux activation of renal RAS secondary to natriuresis and possible extracellular volume depletion.[36] Although the use of RAS at baseline was not associated with the changes in the blood pressure, eGFR or urinary protein excretion after the initiation of empagliflozin in the present study, it should be noted that the concomitant use of RAS inhibitors may contribute to the prognostic improvement.[37,38]

However, the renal prognosis remains unclear in the elderly subjects and non-elderly subjects with a reduced eGFR at baseline whose eGFR did not show an initial dip. Because it is possible that SGLT2 inhibitors can be used without concern regarding a rapid decline of the kidney function in such patients, further studies are required to

identify patients in whom SGLT2 inhibitor treatment can be expected to have renoprotective effect. Furthermore, regarding the initial dip of the eGFR, it should be noted that the decreased skeletal muscle mass due to the administration of empagliflozin may lead to the overestimation of the eGFR value by the formula, which includes the serum creatinine level, and mask the initial dip in elderly subjects, although weight reduction due to fat loss is reported to be greater than that due to skeletal muscle loss in patients treated with SGLT2 inhibitors.[39,40] Thus, it is desirable to evaluate the cystatin C-based eGFR in order to correctly examine the changes in the kidney function after the initiation of SGLT2 inhibitors.

In the present study, the concomitant use of sulfonylureas was significantly more frequent in the elderly subjects than in the non-elderly subjects at baseline. This drug class can cause fluid retention,[41] thus leading to weight gain or increased blood pressure. Because the use of sulfonylureas was not associated with any change in the body weight or blood pressure based on the univariate analysis, we did not include it as an independent variable in the multivariate analyses in order to determine the factors associated with the changes in the body weight or blood pressure.

Apart from the factors associated with the renal prognosis, SGLT2 inhibitor treatment was found to be effective in the elderly patients of the present study. Increased hemoglobin and hematocrit values in the peripheral blood without an elevation of blood pressure, reduction of transaminase or elevation of serum HDL-cholesterol concentration were observed in both the non-elderly and elderly patients of the present study, similarly to previous studies.[24,42,43] The accumulation of these benefits in addition to the reduction of HbA1c and body weight is considered to contribute to the prolongation of life expectancy by empagliflozin treatment; although the life expectancy of elderly subjects is shorter than that of non-elderly subjects.[44] Furthermore, the frequency of AEs in non-elderly and elderly patients with type 2 diabetes did not differ to a statistically extent in the present study. Although there has been concern that volume depletion and cerebral infarction may occur when SGLT2 inhibitors are used by elderly patients,[11] the incidence of these AEs was not increased. However, it should be noted that the elderly diabetic patients in the current study were not randomly selected for empagliflozin treatment because the present study was based on a retrospective analysis. The attending physician might have selected patients who were considered unlikely to develop such AEs when prescribing empagliflozin. The significance of our study is that it shows that empagliflozin can be used safety, even by elderly subjects with type 2 diabetes, when patients are appropriately selected.

The present study was associated with several limitations. First, the present study was a retrospective observational investigation of a relatively small number of diabetic patients. Thus, it is necessary to note the possibility that changes in clinical parameters, such as blood pressure, urinary protein excretion and eGFR, occurred incidentally due to the low statistical power. Further investigations in a larger number of patients should be performed to confirm our results. Furthermore, the selection of study subjects, especially in the elderly patients, might have been biased, as already mentioned, because the attending physician might have administered empagliflozin to patients who were unlikely to develop AEs. Second, the urinary protein excretion was determined by a semi-quantitative measurement, without correction of the urinary creatinine level in spot urine samples. The diagnostic accuracy might have affected the ΔUP and the determination of factors such as changes in blood pressure associated with the ΔUP. In the present study, the urinary protein excretion in elderly subjects was lower than that in non-elderly subjects at baseline, although the difference was not statistically significant. The ΔUP was significantly associated with the urinary protein excretion at baseline. If the elderly subjects showed more urinary protein excretion at baseline, the empagliflozin administration might have induced a significant improvement of proteinuria. Third, the efficacy of empagliflozin may have been overestimated because the patients who required treatment intensification due to limited glycemic control, even after the initiation of empagliflozin administration, were excluded from the FAS. Fourth, AEs may have been underestimated, as the present analysis was performed based on medical records. Thus, physicians should be sufficiently careful about the potential development of AEs when administering empagliflozin, especially in elderly patients with type 2 diabetes. However, even with these limitations, we believe that empagliflozin is effective for improving various metabolic parameters and is clinically safe for elderly patients with type 2 diabetes when patients are appropriately selected.

Conclusion

The eGFR, urinary protein excretion and blood pressure did not change significantly in the elderly patients with

type 2 diabetes after the initiation of empagliflozin. Although renoprotective effects might be limited in elderly patients, empagliflozin can safely and effectively improve various metabolic parameters.

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