Renoprotective effect of chronic treatment with sodium-glucose cotransporter 2 inhibitors and its associated factors in Japanese patients with chronic heart failure and diabetes

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ABSTRACT

Background: Recent clinical trials have shown that sodium-glucose cotransporter 2 (SGLT2) inhibitors have beneficial effects on renal function in heart failure patients. This study confirmed the renoprotective effect of treatment with SGLT2 inhibitors in Japanese patients with chronic heart failure and diabetes and further investigated what cardiac/hemodynamic and noncardiac factors are involved in its effect.

Methods: Eligible 50 outpatients with chronic heart failure and type-2 diabetes mellitus chronically taking SGLT2 inhibitors were enrolled. Annual changing rates of estimated glomerular filtration rate (eGFR) were compared before and after treatment with SGLT2 inhibitors and the associations of the change in eGFR slope after SGLT2 inhibitor administration with changes in various clinical and echocardiographic parameters were evaluated.

Results: The mean follow-up periods before and after SGLT2 inhibitor administration were 2.6 and 1.9 years, respectively. Changing rates of eGFR per year were significantly improved after treatment with SGLT2 inhibitors (5.78 ± 7.67 to 0.43 ± 10.81 mL/min/1.73 m²/year, p = 0.006). The daily doses of loop diuretics were not altered after SGLT2 inhibitor administration. Neither decreased body weight nor increased hematocrit was associated with the change in eGFR slope before and after SGLT2 inhibitor administration. While, the decrease in inferior vena cava diameter and the increase in its respiratory collapsibility were significantly correlated with the improvement of eGFR decline slope after SGLT2 inhibitor administration.

Conclusions: Our findings indicated that chronic treatment with SGLT2 inhibitors ameliorated annual decline in eGFR in Japanese patients with chronic heart failure, suggesting the possibility that the improvement of venous congestion was involved in its renoprotective effect.

1. Introduction

Renal impairment is significantly involved in cardiovascular prognosis. Many studies have shown that renal function is one of the powerful predictors of adverse outcomes in patients with acute and chronic heart failure [1]. Therefore, preservation of renal function is a key to better prognosis in heart failure patients and preventing deterioration of renal function is an important factor to be considered in treatment for heart failure.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed as a unique type of hypoglycemic agent that promotes urinary glucose excretion, have been shown to exert beneficial effects on both cardiovascular and renal outcomes in patients with type-2 diabetes by large-scale overseas randomized controlled trials [2–5]. In addition, subanalyses of these clinical trials have revealed that SGLT2 inhibitors slow the annual decline in estimated glomerular filtration rate (eGFR) in diabetic patients [2–4]. Furthermore, it has recently been demonstrated by clinical trials using empagliflozin and dapagliflozin that such...
renoprotective effects of SGLT2 inhibitors are also observed in patients with chronic heart failure [6–8]. However, in Japanese patients, the effect of SGLT2 inhibitors on renal function remains to be fully elucidated, except for some limited studies in patients with diabetes and/or chronic kidney disease [9–12]. In particular, there has been no study examining their effects in patients with chronic heart failure. Thus, first of all, we confirmed whether SGLT2 inhibitors exert a favorable effect on the preservation of renal function in Japanese patients with heart failure, by comparing serial changes in eGFR for years before and after SGLT2 inhibitor administration. So far, it has not been clearly shown what factors contribute to the renoprotective effect of SGLT2 inhibitors, although previous studies including overseas clinical trials variously discussed hemodynamic and nonhemodynamic factors being involved. Therefore, we further investigated what cardiac/hemodynamic and noncardiac factors were associated with the renoprotective effect of SGLT2 inhibitors.

2. Methods

2.1. Study subjects

A total of 83 chronic heart failure outpatients with type 2 diabetes mellitus for whom both SGLT2 inhibitors and loop diuretics were prescribed at the Department of Cardiovascular Medicine of our hospital during January and March 2020 were enrolled for the screening. Prescribed SGLT2 inhibitors included dapagliflozin, canagliflozin, empagliflozin, tofogliflozin, luseogliflozin, and ipragliflozin. Prescribed loop diuretics included furosemide and azosemide. Laboratory data and medical treatment were longitudinally surveyed from January 2015 to December 2020 at the longest. Thirty-three cases with a short observation period <6 months before (17 cases) and/or after (22 cases) the introduction of an SGLT2 inhibitor were excluded from the study. Ultimately, 50 patients who had been taking SGLT2 inhibitors until the end of the follow-up period and whose eGFR levels were continuously measured for at least ≥6 months both before and after administration of SGLT2 inhibitors were selected as eligible for the present analyses.

Chronic heart failure was diagnosed from clinical symptoms and findings according to the Framingham diagnostic criteria for heart failure [13], which require the simultaneous presence of at least two major criteria, or one major criterion in conjunction with two minor criteria, and requiring treatment with cardiovascular drugs including diuretics.

All procedures of the present study were carried out in accordance with the principles outlined in the Declaration of Helsinki and national ethical guidelines for human studies. The study protocol was approved by the ethics committee of Ishikiriseiki Hospital (Approval number: 21–23).

2.2. Clinical parameters

In this longitudinal observational study, eligible patients were retrospectively followed up as described in Fig. 1. Clinical data such as body weight, blood pressure, heart rate, blood (hematological and biochemical) parameters, echocardiographic parameters, and medical treatment were collected at respective ends of the follow-up periods before and after administration of SGLT2 inhibitors (i.e., exam.1 during follow-up period 1 and exam.2 during follow-up period 2 shown in Fig. 1). Hematocrit, hemoglobin, plasma glucose, hemoglobin A1c, and serum creatinine were determined using standard laboratory measurements. Plasma brain natriuretic peptide (BNP) was measured with a specific immunoradiometric assay for human BNP (ARCHIECT-JP, ABBOT JAPAN Co, Ltd, Tokyo, Japan) [14]. The loop diuretic dose was calculated using a furosemide equivalent, which was defined as 40 mg of furosemide being equivalent to 60 mg of azosemide [15].

2.3. Evaluation of renal function

Based on age, sex, and serum creatinine, eGFR was calculated using a formula taken from the Modification of Diet in Renal Disease Study with a modified equation for Japanese subjects [16]. Fig. 2 shows representative data of annual changes in eGFR in one case. All eGFR values were plotted separately before and after the initiation of SGLT2 inhibitor administration, except hospitalization periods, along the time course axis. The slope of the linear regression curve was calculated as an annual changing rate in eGFR [17].

2.4. Echocardiography

Two-dimensional transthoracic echocardiography was performed using a cardiac ultrasound unit (Vivid 7; General Electric, Milwaukee, Wisconsin, USA) as previously described [17]. Measurements included left atrial (LA) diameter, left ventricular diameters at end-diastole (LVDd) and end-systole (LVDs), and inferior vena cava (IVC) diameters at end-expiratory and end-inspiratory phases (as maximum and minimum IVC diameters, respectively). IVC collapsibility index with respiration was calculated as 100 × (maximum IVC diameter – minimum IVC diameter)/maximum IVC diameter. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (LVEF) were determined by using modified Simpson’s method or the Teichholz correction of the cube formula (in cases without left ventricular regional asynergy). The peak pressure gradient of tricuspid regurgitation (TRPG) was measured using continuous-wave Doppler echocardiography. The peak velocity of early diastolic filling (E) in left ventricular inflow waves and early diastolic mitral annular velocity (e’) in the septal wall were obtained from pulse-wave Doppler and tissue Doppler imaging, respectively, and then the E to e’ ratio (E/e’) was calculated.

2.5. Statistical analysis

Statistical analysis was performed using a standard statistical package (JMP 9.0, SAS Institute, Cary, North Carolina, USA). Values were expressed as mean ± SD. The significance of differences in various parameters before and after treatment with SGLT2 inhibitors was evaluated with a paired t-test. The comparison of annual changing rates of eGFR before and after administration of SGLT2 inhibitors was also performed by the non-parametric method using Wilcoxon signed-rank test. An unpaired Student’s t-test was used for comparison between the two groups. The relation between variables was assessed using univariate linear regression analyses and Pearson’s correlation

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**Follow-up period 1**

Visit to outpatient clinic (Before SGLT2 inhibitor administration)

Initiation of SGLT2 inhibitor administration

Exam. 1

**Follow-up period 2**

Visit to outpatient clinic (After SGLT2 inhibitor administration)

Exam. 2

Fig. 1. A simple schema of patient follow-up before and after sodium-glucose cotransporter 2 (SGLT2) inhibitor administration in the present retrospective longitudinal observational study.
A value of $p < 0.05$ was accepted as statistically significant.

### 3. Results

The clinical characteristics of the present subjects are summarized in Table 1. The mean age was 68 years old and the ratio of men was 70 %. The mean level of eGFR just before the initiation of SGLT2 inhibitor administration was 55 mL/min/1.73 m$^2$. As causes of heart failure, ischemic heart disease (44 %) was the most common, followed by valvular heart disease (20 %) and cardiomyopathy (10 %). The rate of patients with atrial fibrillation was 40 %. In this retrospective longitudinal observational study, the mean follow-up periods before and after the introduction of treatment with SGLT2 inhibitors were 939 and 686 days (2.6 and 1.9 years), respectively.

Medical drugs prescribed at respective ends of the follow-up periods before and after administration of SGLT2 inhibitors are shown in Table 2.

#### Table 1

Clinical characteristics of the present subjects ($n = 50$).

| Variable                        | Age, years | Sex, men/women | Body mass index, kg/m$^2$ | eGFR, mL/min/1.73 m$^2$ | Ischemic heart disease | Valvular heart disease | Cardiomyopathy | Arrhythmia-related | Hypertensive | Others/unknown |
|---------------------------------|------------|----------------|--------------------------|-------------------------|------------------------|-----------------------|----------------|-------------------|--------------|----------------|
| Age, years                      | 68.0 ± 11.3| 35/15          | 27.0 ± 5.3               | 55.4 ± 18.8             | 22 (44 %)              | 10 (20 %)             | 5 (10 %)       | 4 (8 %)            | 4 (8 %)      | 5 (10 %)       |

#### Table 2

Comparison of medical treatment before and after administration of SGLT2 inhibitors.

| Variable                        | Before administration | After administration | $p$ |
|---------------------------------|-----------------------|----------------------|-----|
| Loop diuretics (daily dose)     |                       |                      |     |
| Furosemide dose, mg/day         | 9.8 ± 10.8            | 9.4 ± 14.3           | 0.8084 |
| Azosemide dose, mg/day          | 21.6 ± 29.7           | 26.1 ± 25.5          | 0.1527 |
| Loop diuretic dose, mg/day*     | 24.2 ± 14.9           | 26.8 ± 15.6          | 0.2881 |

#### Notes

*Furosemide equivalent dose; i.e., azosemide 60 mg was considered equivalent to furosemide 40 mg.
SGLT2, sodium-glucose cotransporter 2; MR, mineralocorticoid receptor; ARB, angiotensin II receptor blocker; ACE, angiotensin converting enzyme; DOAC, direct oral anticoagulant; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1.
Table 2. The daily doses of furosemide, azosemide, and overall loop diuretics (furosemide equivalent dose) did not change before and after SGLT2 inhibitor administration. As for cardiovascular drugs other than loop diuretics, the percentages of the use of Ca channel blockers and direct oral anticoagulants were significantly increased after SGLT2 inhibitor administration. Concerning antidiabetic drugs other than SGLT2 inhibitors, the rates of the use of dipeptidyl peptidase 4 inhibitors and metformin were increased during the follow-up periods after SGLT2 inhibitor administration.

Concerning antidiabetic drugs other than SGLT2 inhibitors, the rates of the use of dipeptidyl peptidase 4 inhibitors and metformin were increased during the follow-up periods after SGLT2 inhibitor administration. As for cardiovascular drugs other than SGLT2 inhibitors, the rates of the use of diuretics were increased during the follow-up periods after SGLT2 inhibitor administration.

Fig. 3 shows the comparison of individual annual changing rates of eGFR before and after administration of SGLT2 inhibitors. In a total of 50 patients, changing rates of eGFR per year were significantly ameliorated after treatment with SGLT2 inhibitors (Fig. 3A, −5.78 ± 7.67 to −0.43 ± 10.81 mL/min/1.73 m²/year, p = 0.0061 by paired t-test). Even when these values were thought to be non-normally distributed ones and median values were analyzed by the non-parametric method, annual changing rates of eGFR were significantly improved after SGLT2 inhibitor administration (median (25, 75 percentiles), −4.24 (−8.99, −0.62) to 0.13 (−4.35, 5.23) mL/min/1.73 m²/year, p = 0.0014 by Wilcoxon signed-rank test). Next, to eliminate the possibility that the difference was biased toward significant by including cases with a marked increase or decrease in annual changing rate of eGFR, we re-evaluated after excluding 7 cases who had a remarkably decreased or increased annual changing rate of eGFR (<−20 or >20 mL/min/1.73 m²/year) either before (3 cases) or after (4 cases) administration of SGLT2 inhibitors. As a result, the amelioration of annual changing rates of eGFR after SGLT2 inhibitor administration remained significant (Fig. 3B, −4.51 ± 5.99 to 1.14 ± 6.77 mL/min/1.73 m²/year, p = 0.0002 by paired t-test).

Clinical data and echocardiographic findings collected at respective ends of the follow-up periods before and after administration of SGLT2 inhibitors are shown in Table 3. Body weight was significantly decreased and the levels of hematocrit and hemoglobin were significantly increased after SGLT2 inhibitor administration. Systolic and diastolic blood pressures, heart rate, plasma glucose, hemoglobin A1c, and BNP levels did not alter before and after SGLT2 inhibitor administration. In echocardiographic parameters, LVdD and LVEDV significantly decreased after SGLT2 inhibitor administration, whereas other parameters such as LA diameter, LVDs, LVEF, E/e′, TRPG, and IVC diameters including its collapsibility did not change before and after treatment with SGLT2 inhibitors.

We investigated what factors were associated with the improvement of eGFR decline rate by treatment with SGLT2 inhibitors. As shown in Table 4, dose changes in loop diuretics were not significantly associated with the degrees of changes in eGFR slope before and after SGLT2 inhibitor administration. In clinical parameters, body weight decreased and hematocrit and hemoglobin increased after SGLT2 inhibitor administration, as mentioned above (Table 3). However, neither change was significantly associated with the change in eGFR slope before and after administration of SGLT2 inhibitors.
SGLT2 inhibitor administration (Table 4 and Fig. 4). In addition, the slope (i.e., annual changing rate of eGFR) before and after administration of sodium-glucose cotransporter 2 (SGLT2) inhibitors.

The change in BNP and that in the E/e’ ratio tended to correlate negatively with the change in eGFR slope before and after SGLT2 inhibitor administration (Table 4).

Association of changes in loop diuretic dose, clinical parameters, and echocardiographic parameters with changes in eGFR slope before and after SGLT2 inhibitor administration.

|                  | Δ eGFR slope | r     | p     |
|------------------|--------------|-------|-------|
| Loop diuretic dose |              |       |       |
| Δ furosemide dose  | –0.0774      | 0.5934|       |
| Δ azonamide dose   | –0.1551      | 0.2822|       |
| Δ loop diuretic dose | –0.1847     | 0.1992|       |
| Clinical parameters |              |       |       |
| Δ body weight      | –0.2097      | 0.2415|       |
| Δ systolic blood pressure | 0.1555 | 0.2808|       |
| Δ diastolic blood pressure | –0.0388 | 0.7892|       |
| Δ heart rate       | –0.0645      | 0.6564|       |
| Δ hematocrit        | 0.0139       | 0.9235|       |
| Δ hemoglobin       | 0.0760       | 0.5997|       |
| Δ glucose          | –0.1599      | 0.2673|       |
| Δ hemoglobin A1c   | –0.0817      | 0.5729|       |
| Δ BNP              | –0.2831      | 0.0659|       |

Echocardiographic parameters

|                          | Δ eGFR slope | r     | p     |
|--------------------------|--------------|-------|-------|
| Δ LA diameter            | –0.2002      | 0.1981|       |
| Δ LVIDd                  | 0.0213       | 0.8921|       |
| Δ LVIDs                  | –0.1471      | 0.3466|       |
| Δ LVEDV                  | 0.0133       | 0.9326|       |
| Δ LVESV                  | –0.1649      | 0.2905|       |
| Δ LVEF                   | 0.0999       | 0.5238|       |
| Δ E/e’                   | –0.3216      | 0.0558|       |
| Δ TRPG                   | –0.1263      | 0.4765|       |
| Δ Maximum IVC            | –0.4279      | 0.0042|       |
| Δ Minimum IVC            | –0.4069      | 0.0068|       |
| Δ IVC collapsibility index | 0.4140     | 0.0058|       |

Δ represents each value after minus before SGLT2 inhibitor administration.

Δ eGFR slope, mL/min/1.73 m²; Δ LA, left atrial diameter; LA, left atrium; LVIDd, left ventricular diameter at end-diastole; LVIDs, left ventricular diameter at end-systole; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; E/e’, the ratio of early diastolic transmitral velocity to early diastolic tissue velocity; TRPG, tricuspid regurgitation pressure gradient; IVC, inferior vena cava.

Table 4

Comparison by treatment without or with respective drugs of changes in eGFR slope before and after SGLT2 inhibitor administration.

| Drug                        | Group treated without the drug* | Group treated with the drug* | p     |
|-----------------------------|--------------------------------|------------------------------|-------|
| Ca channel blocker          |                               |                              |       |
| N                           | 30                             | 20                           |       |
| Δ eGFR slope, mL/min/1.73 m²| 5.94 ± 12.05                  | 4.46 ± 15.04                 | 0.7014|
| DOAC                        | N                              |                              |       |
| N                           | 39                             | 11                           |       |
| Δ eGFR slope, mL/min/1.73 m²| 5.64 ± 13.04                  | 4.31 ± 14.32                 | 0.7712|
| DPP4 inhibitor              | N                              |                              |       |
| N                           | 8                              | 42                           |       |
| Δ eGFR slope, mL/min/1.73 m²| 2.15 ± 9.21                   | 5.96 ± 13.83                 | 0.4597|
| Metformin                   | N                              | 14                           |       |
| N                           | 26                             | 14                           |       |
| Δ eGFR slope, mL/min/1.73 m²| 5.01 ± 13.07                  | 6.22 ± 13.97                 | 0.7727|

Δ eGFR slope, estimated glomerular filtration rate; SGLT2, sodium-glucose cotransporter 2; Δ eGFR slope, slope (i.e., annual changing rate of eGFR) after minus before SGLT2 inhibitor administration; DOAC, direct oral anticoagulant; DPP4, dipeptidyl peptidase 4.

Grouping was based on prescribing or not of each drug at the end of the follow-up period 2 (after SGLT2 inhibitor administration).

Values are means ± SD.

4. Discussion

It is known that the natural course of the decline in eGFR over time in patients with chronic kidney disease is generally linear until end-stage renal failure or eventually accelerating [18-20]. In the present study, we demonstrated that annual decline rates in eGFR were significantly ameliorated after continuous administration of SGLT2 inhibitors in outpatients with chronic heart failure and diabetes, suggesting that chronic treatment with SGLT2 inhibitors has a renoprotective effect in heart failure patients.

Many overseas clinical studies including large-scale randomized controlled trials have shown that SGLT2 inhibitors not only improve cardiovascular and renal outcomes but also contribute to the preservation of renal function by slowing the annual rate of decline in eGFR in chronic heart failure patients.

As shown in Table 2, prescription rates of Ca channel blockers, direct oral anticoagulants, dipeptidyl peptidase 4 inhibitors, and metformin were significantly increased during the follow-up periods after SGLT2 inhibitor administration. However, the degrees of changes in eGFR slope before and after SGLT2 inhibitor administration were not affected by prescribing or not of these drugs (Table 5).

Fig. 4. Correlations of changes in inferior vena cava (IVC) diameter and its respiratory collapsibility with changes in estimated glomerular filtration rate (eGFR) slope (i.e., annual changing rate of eGFR) before and after administration of sodium-glucose cotransporter 2 (SGLT2) inhibitors. Δ represents each value after minus before SGLT2 inhibitor administration.
patients with diabetes and/or chronic kidney disease [2-4,21-23]. Furthermore, recent three overseas randomized controlled trials evaluating mainly the effects of empagliflozin or dapagliflozin on cardiovascular prognosis in heart failure, that is, EMPORER-Reduced, EMPORER-Preserved, and DAPA-HF, have revealed that the slowing of the rate of decline in eGFR by SGLT2 inhibitors was also observed in chronic heart failure patients with and without diabetes [6-8,24]. As for Japanese patients, the favorable effects of SGLT2 inhibitors on renal function have been shown in patients with diabetes and/or chronic kidney disease in some limited investigations including retrospective, open-label prospective, and registry studies [9-12]. In addition, there were two previous studies evaluating the change in eGFR for one year after SGLT2 inhibitor administration in patients with heart failure and diabetes [25,26]. However, neither of the two studies has directly proved the effect of SGLT2 inhibitors on changes in renal function by comparing eGFR decline rates with control groups or by evaluating eGFR decline slopes of the same patients over time before and after SGLT2 inhibitors administration. Therefore, this study was the first to serially investigate changes in eGFR over several years before and after treatment with SGLT2 inhibitors and to demonstrate its beneficial effect on renal function in Japanese patients with chronic heart failure.

There were a variety of SGLT2 inhibitors prescribed in the present study, such as dapagliflozin, canagliflozin, empagliflozin, tofogliflozin, luseogliflozin, and ipragliflozin. As noted above, the renoprotective effects of SGLT2 inhibitors in chronic heart failure patients have been demonstrated, particularly with empagliflozin and dapagliflozin [6-8,24]. However, recent Japanese studies using a nationwide real-world dataset have shown that not only cardiovascular but also kidney outcomes (including eGFR decline rate) of diabetic patients were comparable between individual SGLT2 inhibitors, i.e., empagliflozin, dapagliflozin, canagliflozin, and other ones (ipragliflozin, tofogliflozin, and luseogliflozin) [27,28]. Therefore, it may be reasonable to assume that the renoprotective effect of SGLT2 inhibitors in heart failure patients is also a class effect.

Although conventional diuretics including loop diuretics are essential to manage heart failure patients with symptoms of fluid overload, overdoses of loop diuretics cause deterioration of renal function [29]. Hence, reducing the use of loop diuretics through administration of SGLT2 inhibitors may help to preserve renal function. In fact, some of the previous studies for patients with chronic heart failure showed that continuous administration of SGLT2 inhibitors was associated with reduced doses of loop diuretics or less new loop diuretic use, although they contained somewhat inconsistent findings [30-33]. In the present study, however, the daily doses of furosemide, azosemide, and overall loop diuretics did not change before and after SGLT2 inhibitor administration. Thus, the protective effect of SGLT2 inhibitors against the progression of renal dysfunction observed in this longitudinal study was not attributable to a reduction in doses of loop diuretics.

Multiple mechanisms are suggested to contribute to the renoprotective effects of SGLT2 inhibitors in patients with diabetes, chronic kidney disease, and heart failure. These include reduced glomerular hypertension through the restoration of tubuloglomerular feedback, decreased activation of the intra-renal renin-angiotensin-aldosterone system, utilization of energy substrates such as ketone bodies, improvement in anemia by increased renal production of erythropoietin, anti-inflammatory and anti-fibrotic effects, and so on [34-36]. Among these possible mechanisms, significantly increased levels of hematocrit and hemoglobin after SGLT2 inhibitor administration were observed in the present study, consistent with the previous findings [37,38]. The findings reported recently in the sub-analysis of the EMPA-REG OUTCOME trial have shown that changes in hematocrit and hemoglobin are associated with decreased heart failure events (hospitalization or death) in diabetic patients [39]. However, since the increased levels of hematocrit and hemoglobin obtained in our study were not significantly correlated with the change in eGFR slope before and after SGLT2 inhibitor administration, we could not find the direct evidence that the increase in such hematological parameters by SGLT2 inhibitors might contribute to the preservation of renal function in heart failure patients.

Venous congestion is thought to be a major hemodynamic factor for the deterioration of renal function in patients with heart failure, particularly those with advanced decompensated heart failure [40], because elevated central venous pressure leads to renal congestion, which is probably involved in lowering GFR through the following possible mechanisms [41]. Renal congestion increases renal interstitial pressure that has effects on the entire capillary bed and the tubules, and potentially induces local hypoxia. Tubular compression increases luminal pressure and attenuates the transglomerular pressure gradient, which can lead to lowering GFR. In essentially compensated patients with chronic heart failure of the present study, the mean level of IVC diameter in the overall subjects did not change significantly before or after SGLT2 inhibitor administration. However, the decrease in IVC diameter and the increase in IVC collapsibility index were both correlated with the improvement of eGFR decline rate after treatment with SGLT2 inhibitors. Better fluid control during outpatient visits following the introduction of SGLT2 inhibitors was linked to central venous pressure decrease, which acted in a renal protective manner via improvement of renal congestion and may have induced the favorable effect on renal function in this study, although it is only our speculation because we did not directly assess renal congestion by examining intrarenal venous flow patterns or otherwise [42].

There are several limitations in this study. First, the present findings were derived from retrospective longitudinal observation. Thus, the decision of administration of SGLT2 inhibitors was left to each physician’s discretion. In addition, there might be a selection bias that patients who discontinued treatment within a short period due to any reason after SGLT2 inhibitor administration were not included, since only subjects chronically receiving SGLT2 inhibitors were enrolled. Second, because of a small sample size, it was difficult to reevaluate the present findings obtained from univariable analyses by using multivariable analyses. Furthermore, this study did not set a conventional therapy group, as a control, treated without SGLT2 inhibitors. On the contrary, it can be a strength of our study that the effect of SGLT2 inhibitors on renal function was assessed longitudinally in the same individuals, by comparing annual changes in eGFR before and after SGLT2 inhibitor administration. Third, the effect of SGLT2 inhibitors on proteinuria or albuminuria, which is an important factor influencing the acceleration of renal function decline, was not assessed in this study. Finally, the present subjects included only diabetic patients with chronic heart failure, although SGLT2 inhibitors have currently been able to be administered irrespective of the existence of diabetes mellitus. Therefore, the findings obtained in this study cannot be applicable to heart failure patients without diabetes.

In conclusion, the present study clearly has shown that chronic treatment with SGLT2 inhibitors ameliorates annual decline in eGFR in Japanese patients with chronic heart failure and diabetes, suggesting that the improvement of venous congestion, at least in part, may be involved in its renoprotective effect. This conclusion should be confirmed in a future prospective study, incorporating the assessment of renal congestion if possible.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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