Renoprotective effects of sodium glucose cotransporter 2 inhibitors in type 2 diabetes patients with decompensated heart failure

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Abstract

Background

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) reduces the risk of the composite renal endpoint and weakens the progressive decline in renal function in patients with chronic heart failure (HF). However, a detailed mechanism of SGLT2i on renal function and outcome remains uninvestigated.

Methods

We prospectively included 40 type 2 diabetic mellitus (T2DM) patients (median 68 years old, 29 male) who were hospitalized for decompensated HF and received SGLT2i during the index hospitalization. Of them, 24 patients had increases in estimated glomerular filtration rate (eGFR) at 12-month follow-up and 16 had decreases in eGFR. We investigated the factors associating with the improvement in renal function of SGLT2i therapy in participants.

Results

Lower plasma B-type natriuretic peptide (BNP) level and the use of renin-angiotensin system inhibitor (RASI) were independently associated with increases in eGFR during the follow-up period (p < 0.05 for both). Patients with both low plasma BNP levels and uses of RASI had significant increases in eGFR irrespective of the HbA1c levels.

Conclusions

Lower plasma BNP level and the use of RASI at baseline were associated with the renoprotective effect of SGLT2i among patients with decompensated HF and T2DM.

Background

Patients with heart failure (HF) have a high risk of mortality and morbidity, particularly when they have concomitant kidney impairment [1, 2]. Impaired renal function is common in patients with HF and reduced ejection fraction (HFrEF) and up to 50% have chronic kidney disease (CKD) [3]. Patients with CKD also commonly develop HF, and their dominant cause of death is a cardiovascular event.

The currently approved medication to protect kidney function in patients with type 2 diabetes mellitus (T2DM) is renin-angiotensin system inhibitor (RASI) [4, 5]. Sodium-glucose cotransporter 2 inhibitor (SGLT2i), which ameliorates hyperglycemia by suppressing renal glucose reabsorption, has been demonstrated to have favorable effects on the kidney and cardiovascular outcomes in large clinical trials involving patients with T2DM [6–8]. The EMPEROR-Reduced trial further demonstrated that SGLT2i was
associated with a lower risk of composite renal outcome and a slower progressive decline in renal function in patients with chronic HFrEF, irrespective of the existence of T2DM [9]. These studies suggest that the renal benefit of SGLT2i appears to be independent of their blood glucose-lowering effects. However, a detailed mechanism remains uninvestigated. Detailed assessments of the renoprotective effect of SGLT2i would be a key to more clarify the clinical implication and optimal patient selection for the SGLT2i therapy. In this study, we investigated the factors associating with the renoprotection of SGLT2i therapy in patients with HF and T2DM.

Methods

The present study was a single-center, non-randomized, open-labeled, prospective registry study designed to assess the factors associating with the renoprotection of SGLT2i therapy for HF patients with T2DM. The Institutional Ethics Board of Toyama University Hospital approved the study protocol (#Rin 29–94), which complied with the Declaration of Helsinki. Written informed consent was obtained from all of the patients beforehand.

Study population

This study involved consecutive T2DM patients who had received SGLT2i for the first time during their index hospitalization for decompensated HF, which was diagnosed according to the Framingham criteria, at our institute between February 2016 and September 2019. All patients had New York Heart Association (NYHA) class III/IV symptoms upon admission for HF. Among canagliflozin (100mg/day), dapagliflozin (5mg/day), and empagliflozin (10mg/day), one SGLT2i was non-randomly selected and administered. All patients had HbA1c level of 6.1% or higher and received guideline-directed medical therapy for HF.

Exclusion criteria were as follows: type 1 diabetes mellitus, end-stage renal failure (estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m²), use of any mechanical circulatory supports, pregnancy or breastfeeding in the study period, history of hypersensitivity to the study drugs, severe ketosis, diabetic coma or precoma, and suspension of SGLT2i during the observation period.

Study design and data collection

Baseline characteristics including demographics and laboratory data were obtained at index discharge. In this study, eGFR at baseline and 6 and 12 months after discharge was retrospectively retrieved. A primary endpoint was defined as any increases in eGFR at 12 months after discharge compared with eGFR at index discharge (achievement of renoprotection). The eGFR was calculated using the guidelines from the Chronic Kidney Disease Epidemiology Collaboration.

Statistical analyses

Continuous variables were expressed as the median and interquartile unless any specific statements. Categorical variables were expressed as absolute numbers and percentages. Wilcoxon test was applied to compare continuous parameters, and Pearson's χ² test was applied for comparison of categorical
variables. Univariable and multivariable analyses with logistic regression models were performed to calculate the adjusted odds ratio (OR) to assess the influence of various parameters on the renoprotective effect of SGLT2i. Variables significant with p < 0.05 in the univariate analyses were included in the multivariate analyses. A cut-off of plasm B-type natriuretic peptide (BNP) concentration for any increases in eGFR after SGLT2i initiation was calculated using receiver operating characteristic analysis. Multivariate analysis of variance was applied to investigate the differences in changes in eGFR over time between the two groups stratified by predictor of efficacy for renal function. The statistical analysis was performed by using JMP® 15 (SAS Institute Inc., Cary, NC, USA). The level of significance was defined as p < 0.05.

**Results**

**Baseline Characteristics**

A total of 111 patients were considered to be included in this study (Fig. 1). Of them, 65 patients continued SGLT2i without suspension for 12 months. 18 patients who were lost to follow-up or had no biochemical tests were excluded. Cardiovascular death occurred in 4 patients and non-cardiovascular death occurred in 3 patients. A total of 40 patients (median 68 years old, 29 male) were finally included in this study.

The baseline characteristics are summarized in Table 1. The participants were divided into two groups according to the achievement of primary endpoint: any increases in eGFR at 12-month follow-up: an increased group (N = 26) and a decreased group (N = 14). The median value of changing eGFR (eGFR at month 12 - eGFR at baseline) in the two groups was + 5.5 and − 7.5, respectively (Fig. 2).
| Characteristic                                      | Total (N = 40) | Increased eGFR (N = 26) | No-increased eGFR (N = 14) | P value |
|----------------------------------------------------|---------------|------------------------|---------------------------|---------|
| Age, years                                         | 68 (57–75)    | 68 (55–72)             | 71 (61–79)                | 0.177   |
| Male, N                                            | 29 (73)       | 19 (73)                | 10 (71)                   | 0.911   |
| Body weight, kg                                    | 62 (51–73)    | 66 (54–76)             | 54 (47–71)                | 0.112   |
| Body mass index, kg/m²                              | 23.9 (19.6–27.2) | 24.7 (21.9–27.9) | 20.4 (19.0–24.9)          | 0.076   |
| Systolic blood pressure, mmHg                       | 108 (95–119)  | 110 (100–119)          | 100 (90–120)              | 0.173   |
| Heart rate, beats per minutes                       | 70 (63–81)    | 69 (63–83)             | 74 (64–79)                | 0.570   |
| HbA1c, %                                           | 6.8 (6.6–7.6) | 6.7 (6.6–7.7)          | 7.0 (6.6–7.2)             | 0.776   |
| Fasting blood sugar, mg/dL                          | 110 (96–129)  | 102 (86–128)           | 122 (107–130)             | 0.076   |
| Left ventricular ejection fraction, %               | 42 (27–56)    | 39 (28–58)             | 42 (26–55)                | 0.966   |
| Ischemic etiology, N                               | 19 (48)       | 12 (46)                | 7 (50)                    | 0.816   |
| Atrial fibrillation, N                              | 8 (20)        | 5 (19)                 | 3 (21)                    | 0.868   |
| Hemoglobin, g/dL                                   | 12.9 (11.5–15.6) | 13.6 (16.0–11.7) | 12.4 (11.1–14.2)          | 0.223   |
| Hematocrit, %                                      | 38.5 (34.2–44.9) | 40.6 (35.2–45.6) | 37.6 (33.5–41.4)          | 0.192   |
| Serum albumin, g/dL                                | 3.7 (3.5–3.8) | 3.7 (3.5–3.9)          | 3.6 (3.2–3.7)             | 0.107   |
| Serum sodium, mEq/L                                | 138 (136–140) | 140 (138–140)          | 137 (135–140)             | 0.094   |
| Serum potassium, mEq/L                             | 4.4 (4.1–4.6) | 4.4 (4.1–4.6)          | 4.4 (4.2–4.5)             | 0.943   |
| eGFR, mL/minute/1.73m²                              | 53.0 (36.1–74.5) | 54.5 (40.0–73.5) | 50.1 (31.6–80.4)          | 0.712   |
| Plasma BNP, pg/mL                                  | 94 (54–251)   | 86 (50–175)            | 205 (75–374)              | 0.059   |
| Plasma NT-proBNP, pg/mL                            | 864 (260–1819) | 740 (251–1424)        | 1479 (356–3057)           | 0.242   |
| Heart failure therapies                             |               |                       |                           |         |
| Beta-blockers, N                                    | 37 (93)       | 23 (89)                | 14 (100)                  | 0.186   |
| ACEI/ARB, N                                        | 37 (93)       | 26 (100)               | 11 (79)                   | 0.014   |
|                          | Total (N = 40) | Increased eGFR (N = 26) | No-increased eGFR (N = 14) | P value |
|--------------------------|----------------|-------------------------|---------------------------|---------|
| Loop diuretics, N        | 19 (48)        | 11 (42)                 | 8 (57)                    | 0.370   |
| Furosemide, mg/day       | 0 (0–20)       | 0 (0–20)                | 20 (0–40)                 | 0.158   |
| MRA, N                   | 27 (68)        | 17 (65)                 | 10 (71)                   | 0.697   |
| Thiazides, N             | 2 (5)          | 2 (8)                   | 0 (0)                     | 0.287   |
| Anti-diabetic agents     |                |                         |                           |         |
| Sulfonylureas, N         | 3 (8)          | 2 (8)                   | 1 (7)                     | 0.950   |
| DPP-4i, N                | 20 (50)        | 14 (54)                 | 6 (43)                    | 0.741   |
| Biguanides, N            | 8 (20)         | 5 (19)                  | 3 (21)                    | 0.868   |
| Insulin, N               | 5 (12)         | 5 (19)                  | 0 (0)                     | 0.079   |

HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; BNP, b-type natriuretic peptide; NT-proBNP, N-terminal pro-b-type natriuretic peptide; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; DPP-4i, dipeptidyl peptidase-4 inhibitors

Continuous variables were expressed as median (25%-75% percentile) and categorical variables were expressed as number (%)

There were no significant differences in most of the demographic data between the two groups. The prescription rate of RASI was higher in the increased eGFR group. The proportions of participants taking oral hypoglycemic agents were statistically not different between the two groups. Baseline plasma BNP level tended to be lower in the increased eGFR group. Of note, the baseline eGFR value was not statistically different between the two groups.

**Association between the SGLT2i therapy and renoprotection**

In univariate logistic regression analysis, body mass index, plasma BNP level, usage of RASI, and insulin administration were significantly associated with the renoprotective effect of SGLT2i (p < 0.05 for all; Table 2). Lower plasma BNP level (0.26 of odds ratio, 95% confidence interval 0.08–0.79) and the use of RASI were independently associated with the renoprotective effect of SGLT2i (p < 0.05 for both). Of note, no patients achieved the primary endpoints without RASI.
Table 2
Logistic regression analyses for any increases in eGFR

| Variables                               | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | 95% CI              | Odds ratio | p value  | 95% CI        | Odds ratio | p value |
| Age                                     | -                   | -          | 0.154    | -              | -          | 0.265   |
| Male                                    | -                   | -          | 0.912    | -              | -          | 0.265   |
| Body mass index                         | 0.99–1.39           | 1.17       | 0.041    | -              | -          | 0.265   |
| Systolic blood pressure                 | -                   | -          | 0.145    | -              | -          | 0.265   |
| Heart rate                              | -                   | -          | 0.671    | -              | -          | 0.265   |
| HbA1c                                   | -                   | -          | 0.520    | -              | -          | 0.265   |
| Fasting blood sugar                     | -                   | -          | 0.311    | -              | -          | 0.265   |
| Left ventricular ejection fraction      | -                   | -          | 0.797    | -              | -          | 0.265   |
| Ischemic etiology                       | -                   | -          | 0.816    | -              | -          | 0.265   |
| Atrial fibrillation                     | -                   | -          | 0.869    | -              | -          | 0.265   |
| Hemoglobin                              | -                   | -          | 0.199    | -              | -          | 0.265   |
| Hematocrit                              | -                   | -          | 0.176    | -              | -          | 0.265   |
| Serum albumin                           | -                   | -          | 0.068    | -              | -          | 0.265   |
| Serum sodium                            | -                   | -          | 0.062    | -              | -          | 0.265   |
| Serum potassium                         | -                   | -          | 0.685    | -              | -          | 0.265   |
| eGFR                                    | -                   | -          | 0.897    | -              | -          | 0.265   |
| BNP (per 163 pg/mL increase)            | 0.16–0.88           | 0.37       | 0.016    | 0.08–0.79      | 0.26       | 0.007   |
| NT-proBNP                               | -                   | -          | 0.163    | -              | -          | 0.265   |
| Beta-blockers                           | -                   | -          | 0.100    | -              | -          | 0.265   |
| ACEI/ARB                                | NA                  | NA         | 0.009    | NA             | NA         | 0.002   |
| Loop diuretics                          | -                   | -          | 0.370    | -              | -          | 0.265   |
| Furosemide (per 10 mg/day increase)     | -                   | -          | 0.077    | -              | -          | 0.265   |
| All patients (N = 40) |
|----------------------|
| MRA                  | - | - | 0.696 |
| Thiazides            | - | - | 0.182 |
| Sulfonylureas        | - | - | 0.950 |
| DPP-4i               | - | - | 0.507 |
| Biguanides           | - | - | 0.869 |
| Insulin              | NA | NA | 0.030 | - | - | 0.103 |

HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; BNP, b-type natriuretic peptide; NT-proBNP, N-terminal pro-b-type natriuretic peptide; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; DPP-4i, dipeptidyl peptidase-4 inhibitors.

Odds ratio were not calculated in several variables due to statistical divergence.

**Stratification of the primary endpoint using BNP and RASI use**

A cut-off of baseline plasma BNP level to predict the primary endpoint was 192 pg/mL (0.684 of area under the curve, 0.808 of sensitivity, and 0.643 of specificity; Fig. 3).

Twenty-three patients satisfied plasma BNP < 192 pg/mL and RASI use (double-positive group). eGFR increased significantly during the 12-month follow-up in the double-positive group, whereas eGFR remained unchanged in the no double positive group (p for interaction < 0.01; Fig. 4).

As sub-analyses, similar trends were observed irrespective of the eGFR levels stratified by 60 mL/min/1.73m² (Fig. 5AB) and the HbA1c levels stratified by 7.0% (Fig. 5CD).

**Discussion**

We investigated the factors associating with the renoprotection of SGLT2i therapy in patients with HF and T2DM. The major finding of the present study was that lower plasma BNP level and the use of RASI at baseline were associated with the renoprotective effect of SGLT2i. Those with lower plasma BNP levels and the use of RASI had greater eGFR during the 12-month follow-up period over those without both of them irrespective of the eGFR levels and the HbA1c levels at baseline.

**SGLT2i and BNP**

Both EMPEROR-Reduced trial and DAPA-HF trial demonstrated that SGLT2i prevented the occurrence of worsening HF in patients with chronic HFrEF [9, 10]. The EMPEROR-Reduced trial further demonstrated that empagliflozin was associated with a lower risk of renal outcome and a slower progressive decline in
renal function. Several large placebo-controlled trials using SGLT2i suggested that they might exert a beneficial effect on the renal outcome as a class effect [11–13]. On the contrary, the DAPA-HF trial, which used dapagliflozin, did not demonstrate the improvement of renal outcome [14].

The pattern of inconsistent findings in renal outcomes might be explained by the differences in the distribution of NYHA functional class in each trial. More patients with NYHA class II were enrolled in the EMPEROR-Reduced trial compared to the DAPA-HF trial. SGLT2i might have renoprotective effect particularly for those with less sick HF, as we also found in this study. In a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials, HFrEF patients with NYHA class II also had a lower risk of composite cardiovascular outcome compared to those with NYHA class III–IV symptoms [15]. These findings appear to be due to direct cardioprotective and nephroprotective effects, which may be related to actions on sodium balance, energy homeostasis, and mitigation of cellular stress [16]. The detailed mechanism remains uncertain, but the existence of renal congestion, indicated by the elevated BNP level, might suppress the improvement in renal function.

**SGLT2i and RASI**

RASI were the only classes of medication that have been shown to slow a decline in kidney function [4, 5]. The use of RASI was also associated with the renoprotective effect in the present study. Although few studies have investigated the combined effects of RASI and SGLT2i, several previous studies of SGLT2i have identified a minimal increase in plasma renin activity [17, 18]. SGLT2i can cause diuresis, natriuresis, and associated body fluid loss, resulting in renin activation. Although a reduction in plasma volume by SGLT2i would be expected to activate renin-angiotensin-aldosterone system, RASI may counterbalance this effect. Hence, RASI may have played an important role in renal protection in the present study.

Conversely, several studies in animal models or humans have confirmed unchanged activity in the renin-angiotensin-aldosterone system following the SGLT2i administration [19, 20]. An increase in GFR associating with long-term SGLT2i therapy is thought to be secondary to tubuloglomerular feedback, which is also a response of the macula densa to the increased salt delivery via inhibition of sodium transport proximally [21]. Furthermore, an increase in sodium chloride delivery to the macula densa may suppress the renin-angiotensin-aldosterone system. These different effects of SGLT2i may explain the inconsistent data regarding the responses of renin-angiotensin-aldosterone system to SGLT2i.

Consequently, the association between SGLT2i and systemic renin-angiotensin-aldosterone system activation is not straightforward. However, since plasma renin activity is significantly higher in patients with HF compared to healthy people [22], it is plausible that the renin-angiotensin-aldosterone system is activated in participants in the present study. This hypothesis may explain the finding that the use of RASI was associated with the renoprotective effect of SGLT2i in the present study.

**Limitations**

The sample size was small and the observation period was only one year. Given the low event number, the number of potential confounders included in the multivariate analyses was restricted. The one-year
observation period may be insufficient to reveal changes in eGFR after SGLT2i administration. A large-scale multicenter study with a longer follow-up period is required. Although there was a difference in renal outcome between EMPEROR-Reduced trial and DAPA-HF trial, the multiple types of SGLT2i were used in the present study. Therefore, it remains unclear whether the renal beneficial effect is consistent across any SGLT2is. Lastly, the EMPEROR-Reduced trial revealed that SGLT2i reduced the risk of the composite renal endpoint, independently of diabetes status [23]. We also indicated that increases in eGFR during the observation period were independent of the HbA1c levels, whereas we did not include patients without T2DM in this study. Further studies are warranted to clarify the mechanism of SGLT2i on renal function and outcome.

**Conclusions**

Lower plasma BNP level and the use of RASI at baseline were associated with the renoprotective effect of SGLT2i among patients with HF and T2DM.

**Abbreviations**

HF  
heart failure  
HFrEF  
heart failure and reduced ejection fraction  
CKD  
chronic kidney disease  
T2DM  
type 2 diabetes mellitus  
RASI  
renin-angiotensin system inhibitor  
SGLT2i  
sodium-glucose cotransporter 2 inhibitor  
NYHA  
New York Heart Association  
eGFR  
estimated glomerular filtration rate  
OR  
odds ration  
BNP  
B-type natriuretic peptide

**Declarations**

*Ethics approval and consent to participate*
The Institutional Ethics Board of Toyama University Hospital approved the study protocol (#Rin 29-94), which complied with the Declaration of Helsinki. Written informed consent was obtained from all of the patients beforehand.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Not applicable

**Authors’ contributions**

TI analyzed and interpreted the patient data regarding the renal function and SGLT2i therapy, and was a major contributor in writing the manuscript. All authors have made substantial contributions to the conception and design of this study. All authors read and approved the final manuscript.

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Figures

Figure 1

Enrollment and Follow-up.
Figure 2

Distribution of the changes in estimated glomerular filtration rate (eGFR).
Figure 3

Receiver operating characteristic (ROC) curve of baseline plasma BNP level.

BNP cut-off: 192 pg/mL
Figure 4

Changes in estimated glomerular filtration rate (eGFR) during the one-year observational period. Variables were expressed as mean and standard deviations.
Figure 5

Changes in estimated glomerular filtration rate (eGFR) during the one-year observational period stratified by baseline eGFR. Variables were expressed as mean and standard deviations.
Figure 6

Changes in estimated glomerular filtration rate (eGFR) during the one-year observational period stratified by baseline glycated hemoglobin (HbA1c) levels. Variables were expressed as mean and standard deviations.