Clinical Benefit of Switching from Low-Dose to High-Dose Empagliflozin in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors ameliorate blood glucose levels in patients with type 2 diabetes mellitus (T2DM) by inhibiting the reabsorption of glucose from the kidneys, thus increasing urinary glucose excretion. Most SGLT2 inhibitors have been reported to exert dose-dependent effects. However, little is known about the benefits of increasing the dose of SGLT2 inhibitors in clinical use. The aim of the present study was to investigate the effect of increasing the dose of the SGLT2 inhibitor empagliflozin in T2DM.

Methods: We collected 52 subjects with T2DM with inadequate glycemic control. The dose of empagliflozin was increased from 10 to 25 mg, taken once daily, and the alterations in glycemic control and several other clinical parameters were evaluated.

Results: The increased dose of empagliflozin significantly ameliorated glycemic control. In addition, body weight (BW), body mass index (BMI), triglyceride (TG), and γ-glutamyl-transpeptidase (GGT) were significantly decreased and hematocrit (Hct) was increased. Multivariate logistic regression analyses revealed that baseline diastolic blood pressure (DBP) (odds ratio 1.093, 95% CI 1.019–1.156, \( P = 0.012 \)) and baseline TG (odds ratio 1.012, 95% CI 1.001–1.023, \( P = 0.026 \)) were retained as independent predictors for the improvement of hemoglobin A1c (HbA1c) levels. Moreover, multivariate stepwise regression analyses revealed that changes in high-density lipoprotein cholesterol (\( \beta = 0.264, 95\% \text{ CI} 1.217 \text{ to } 0.000, P = 0.049 \)) and HbA1c (\( \beta = 0.302, 95\% \text{ CI} 0.077–1.096, P = 0.025 \)) were retained as independent predictors for changes in BMI.

Conclusion: Increasing the dose of empagliflozin significantly ameliorated BW, BMI, GGT, TG, fasting plasma glucose and HbA1c and increased Hct in patients with T2DM. Moreover, baseline DBP and TG were independent predictors for the improvement of HbA1c. These findings may provide useful information when considering increasing the dosage of SGLT2 inhibitors in patients with T2DM who have inadequate glycemic control.

Trial Registration: UMIN Clinical Trials Registry (UMIN000041543).
Key Summary Points

Why carry out this study?
Although sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors have been reported to exert dose-dependent effects in clinical use, the benefits of increasing the dose of SGLT2 inhibitors are not well known.

In this study, we investigated the beneficial effect of increasing the dose of empagliflozin, an SGLT2 inhibitor, in patients with type 2 diabetes mellitus (T2DM).

What was learned from the study?
Increasing the dose of empagliflozin significantly ameliorated HbA1c, and baseline diastolic blood pressure and triglyceride were independent predictors for the improvement of HbA1c.

When we are considering increasing the dose of SGLT2 inhibitors in patients with T2DM who have inadequate glycemic control, these findings may provide beneficial information.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a novel class of antidiabetes reagents, have a unique mechanism of action. In the nondiabetic state, glucose can pass through the renal glomeruli, but is completely reabsorbed in the renal tubules by sodium-glucose co-transporter mechanisms [1]. Glycosuria occurs when the renal threshold for glucose (a blood glucose level of approximately 10 mmol/l) is exceeded. Hyperglycemia increases the filtrated and reabsorbed glucose up to two- to threefold [1]. SGLT2 is the main transporter responsible for glucose reabsorption, which is found in the proximal kidney tubule [1]. SGLT2 inhibitors block the SGLT2 system and reduce the reabsorption of renal filtrated glucose, thereby lowering blood glucose levels [1].

Empagliflozin, a potent, highly selective SGLT2 inhibitor, is an effective and generally well-tolerated antidiabetes agent approved for the treatment of diabetes mellitus (DM) [2, 3] in the European Union, United States, Japan and other countries. Empagliflozin is also recognized to have weight- and blood-pressure-lowering effects and improves liver disorders, as evaluated by aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or γ-glutamyltranspeptidase (GGT) measurements in patients with type 2 DM (T2DM) [4, 5]. Moreover, clinical trials of empagliflozin have demonstrated efficacy in lowering the incidence of cardiovascular disease (CVD) in T2DM patients, independent of its glucose-lowering ability [6], and have shown reduced progression of diabetic kidney disease (DKD) [7]. Therefore, empagliflozin is considered an antidiabetic drug that is beneficial in the management of T2DM with obesity, hypertension, metabolic syndrome, fatty liver, and a high risk of CVD and/or DKD.

Almost all SGLT2 inhibitors have been reported to have dose-dependent effects. For example, the recommended dosage of empagliflozin is 10 mg once daily before or after breakfast, and combination therapy with several antihyperglycemic drugs has been approved. When its efficacy is insufficient, an increased dose of up to 25 mg once daily is allowed. However, little is known about the clinical benefits of increasing the dose of empagliflozin. Therefore, the aim of the present
study was to investigate the benefit of increasing the dose of empagliflozin in T2DM.

METHODS

Study Subjects

This was a retrospective, longitudinal study of patients with T2DM who presented to Nishinohon Hospital between January 2019 and June 2020. We retrospectively reviewed the medical records and collected various information on participants whose dose of empagliflozin was increased from 10 mg once daily to 25 mg once daily, and who did not receive any additional medications such as antihypertensive or anti-hyperlipidemic drugs, for 6 months. We used the following inclusion criteria: (1) patients who were continuing to visit the hospital for blood glucose control; (2) patients who were already prescribed 10 mg of empagliflozin once daily; and (3) patients from whom blood samples had been collected early in the morning in the fasting state. Participants meeting the following criteria were excluded: (1) < 20 years of age; (2) having type 1 diabetes; (3) pregnancy; (4) active infectious disease including urinary tract infection; (5) severe hepatic disease; and (6) malignancy.

Age, sex, height, weight, blood pressure, and pre-existing use of hypoglycemic agents, antihypertensive agents or anti-hyperlipidemic agents were recorded. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Kidney function was estimated via the estimated glomerular filtration rate (eGFR) on the basis of age, sex and serum creatinine using the equation for Japanese subjects developed by Matsuo et al. [8].

Compliance with Ethics Guidelines

All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Human Ethics Review Committee of Nishinohon Hospital (protocol number: R2-7) and registered at UMIN-CTR (UMIN000041543). All subjects provided written informed consent.

Measurements of Blood and Urinary Parameters

To avoid the influence of external factors on glucose homeostasis measurement, morning blood samples were selected from fasted participants only. Fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), serum total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations as well as AST, ALT and GGT were measured using a Hitachi 7600 analyzer (Hitachi Ltd., Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) concentration was determined using the Friedewald formula [9]. The eGFR was derived using the formula recommended by the Japanese Society of Nephrology [10, 11]. The baseline and changes (Δ) in several factors were evaluated over a period of 24 weeks.

Statistical Analysis

All statistical analyses were performed using SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA). A normality test was performed for all continuous variables using the Shapiro–Wilk test. All data are given as the mean ± standard error of the mean for normally distributed continuous variables. Categorical data are expressed as percentages. The laboratory parameters at baseline and at 4, 12, or 24 weeks after SGLT2 inhibitor treatment were compared using the paired t test or the Wilcoxon signed-rank test. The Spearman correlation coefficient was calculated to examine the relationship between ΔHbA1c and ΔBMI with several plasma factors at baseline and 24 weeks. Multivariate logistic regression analysis was used to investigate independent predictors of improvement in HbA1c after 24 weeks of treatment (≤ 0.0%), and this analysis was constructed by adjusting for factors such as diastolic blood pressure (DBP; baseline), TG.
To investigate independent predictors of BMI, a multivariate stepwise regression analysis was constructed by adjusting for factors such as HbA1c, GTT, HDL-C and TG. All P values < 0.05 were considered statistically significant.

### Table 1
Baseline characteristics of patients in the study

| Variable                  | Unit       | Value for all subjects (N = 52) |
|---------------------------|------------|---------------------------------|
| Sex                       | male; %    | 76.9                            |
| Age                       | Years      | 65.1 ± 1.5                      |
| Duration of diabetes      | Years      | 14.6 ± 1.0                      |
| Body weight               | kg         | 70.6 ± 1.6                      |
| Body mass index           | kg/m²      | 25.9 ± 0.5                      |
| Systolic blood pressure   | mmHg       | 127.4 ± 2.1                     |
| Diastolic blood pressure  | mmHg       | 74.3 ± 1.5                      |
| LDL-C                     | mg/dL      | 105.1 ± 4.1                     |
| HDL-C                     | mg/dL      | 51.4 ± 1.9                      |
| TG                        | mg/dL      | 165.8 ± 13.1                    |
| FPG                       | mg/dL      | 146.6 ± 4.7                     |
| HbA1c                     | %          | 7.47 ± 0.10                     |
| eGFR                      | mL/min/1.73m² | 74.5 ± 3.8                   |
| Hematocrit                | %          | 45.7 ± 0.7                      |
| AST                       | U/L        | 23.7 ± 1.6                      |
| ALT                       | U/L        | 30.4 ± 3.2                      |
| GGT                       | U/L        | 41.3 ± 6.2                      |
| Hypertension              | %          | 53.8                            |
| Hyperlipidemia            | %          | 82.7                            |
| CVD                       | %          | 21.2                            |
| Coronary artery disease   | %          | 8.0                             |
| Cerebrovascular disease   | %          | 12.6                            |
| Peripheral artery disease | %          | 6.9                             |
| Diabetic complications    | %          | 63.2                            |
| Retinopathy               | %          | 25.3                            |
| Neuropathy                | %          | 20.7                            |

**Table 1** continued

| Variable                  | Unit       | Value for all subjects (N = 52) |
|---------------------------|------------|---------------------------------|
| Nephropathy               | %          | 48.3                            |
| Medications               |            |                                 |
| Statins                   | %          | 73.1                            |
| Ezetimibe                 | %          | 23.1                            |
| Fibrates                  | %          | 7.7                             |
| ACE inhibitors            | %          | 3.8                             |
| ARBs                      | %          | 40.4                            |
| CCBs                      | %          | 38.5                            |
| Antidiabetic treatments   |            |                                 |
| Sulfonylureas             | %          | 30.8                            |
| Biguanides                | %          | 55.8                            |
| DPP-4 inhibitors          | %          | 75.0                            |
| α-Glucosidase inhibitor   | %          | 13.5                            |
| Glinides                  | %          | 5.8                             |
| Thiazolidinediones        | %          | 13.5                            |
| GLP-1 receptor agonist    | %          | 19.2                            |
| Insulin                   | %          | 15.4                            |

**LDL-C** low-density lipoprotein cholesterol, **HDL-C** high-density lipoprotein cholesterol, **TG** triglyceride, **FPG** fasting plasma glucose, **eGFR** estimated glomerular filtration rate, **AST** aspartate aminotransferase, **ALT** alanine aminotransferase, **GGT** γ-glutamyl transpeptidase, **CVD** cardiovascular disease, **ACE** angiotensin-converting enzyme, **ARBs** angiotensin II receptor blockers, **CCBs** calcium channel blockers, **DPP-4** dipeptidyl peptidase-4, **GLP-1** glucagon-like peptide-1
RESULTS

Characteristics of the Study Participants

A total of 52 participants were recruited in this study, and their baseline characteristics are summarized in Table 1. The median age and HbA1c of the study participants were 64.9 years and 7.46%, respectively. More than half of the patients were being treated with biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors and statins, and there were no further changes to medications after the dose of empagliflozin was increased during the 6-month trial period. During the observation period, no adverse events were observed.

Switching to a High Dose of Empagliflozin Ameliorates Several Parameters in Patients with Type 2 DM

Changes in clinical parameters were investigated after the dose of empagliflozin was increased from 10 to 25 mg for 6 months (Table 2, Fig. 1). Diabetic markers including FPG and HbA1c were significantly improved by –12.7 mg/dL and –0.13%, respectively. In addition, body weight (BW), BMI, TG and GGT were significantly decreased by –0.6 kg, –0.2 kg/m², –22.1 mg/dL and –6.6 U/L, respectively, and hematocrit (Hct) was significantly increased by 0.9% after 3 months.

Table 2 Clinical parameters of all subjects in this study at baseline, 4 weeks, 12 weeks and 24 weeks after increasing the dose of empagliflozin

|                | Baseline     | After 4 weeks | After 12 weeks | After 24 weeks |
|----------------|--------------|---------------|----------------|---------------|
| BW (kg)        | 70.5 ± 1.6   | 70.6 ± 1.6    | 70.2 ± 1.6     | 69.9 ± 1.6*   |
| BMI (kg/m²)    | 25.9 ± 0.5   | 26.0 ± 0.5    | 25.8 ± 0.5     | 25.7 ± 0.5*   |
| SBP (mmHg)     | 127.4 ± 2.1  | 124.8 ± 2.9   | 128.6 ± 2.3    | 127.6 ± 2.4   |
| DBP (mmHg)     | 74.3 ± 1.5   | 74.3 ± 1.7    | 74.2 ± 1.6     | 74.2 ± 1.5    |
| LDL-C (mg/dL)  | 105.1 ± 4.1  | 106.1 ± 4.0   | 105.4 ± 4.2    | 104.0 ± 4.1   |
| HDL-C (mg/dL)  | 51.4 ± 1.9   | 51.1 ± 2.1    | 51.7 ± 1.9     | 52.2 ± 1.8    |
| TG (mg/dL)     | 165.8 ± 13.1 | 172.7 ± 18.7  | 168.4 ± 13.6   | 143.7 ± 11.7* |
| FPG (mg/dL)    | 146.6 ± 4.7  | 157.0 ± 7.1   | 145.2 ± 5.8    | 133.9 ± 3.6*  |
| HbA1c (%)      | 7.47 ± 0.10  | 7.49 ± 0.10   | 7.44 ± 0.10    | 7.32 ± 0.09*  |
| eGFR (mL/min/1.73m²) | 74.5 ± 3.8 | 73.1 ± 3.7 | 75.6 ± 4.1 | 73.9 ± 3.7 |
| Hct (%)        | 45.7 ± 0.7   | 46.0 ± 0.7    | 46.6 ± 0.8*    | 45.8 ± 0.8    |
| AST (U/L)      | 23.7 ± 1.6   | 23.1 ± 1.3    | 23.3 ± 1.3     | 22.2 ± 1.5    |
| ALT (U/L)      | 30.4 ± 3.2   | 29.6 ± 2.4    | 28.8 ± 2.6     | 26.3 ± 2.7    |
| GGT (U/L)      | 41.3 ± 6.2   | 35.0 ± 4.4*   | 37.6 ± 5.3     | 34.7 ± 4.2*   |

BW body weight, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, Hct hematocrit, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT γ-glutamyl transpeptidase

*P < 0.05 vs. baseline
Independent Predictors for the Improvement of HbA1c and the Reduction of BMI

Univariate and multivariate logistic regression analyses for predicting the improvement of HbA1c with the increased dose of empagliflozin are presented in Table 3. Univariate analyses revealed that baseline DBP, baseline LDL-C, baseline TG, ΔTG, ΔAST, ΔALT, and baseline GGT and ΔGGT were significantly correlated with improvement of HbA1c. Multivariate logistic regression analyses revealed that baseline DBP (odds ratio 1.093, 95% CI 1.019–1.156, \( P = 0.012 \)) and baseline TG (odds ratio 1.012, 95% CI 1.001–1.023, \( P = 0.026 \)) were retained as independent predictors for the improvement of HbA1c. Next, univariate and multivariate stepwise regression analyses for predicting the ΔBMI are presented in Table 4. Univariate analyses revealed that ΔHDL-C, baseline TG, ΔHbA1c and ΔGGT were significantly correlated with ΔBMI. Multivariate stepwise regression analyses revealed that ΔHDL-C (\( \beta = -0.264, 95\% \text{ CI} -1.217–0.000, \ P = 0.049 \)) and ΔHbA1c (\( \beta = 0.302, 95\% \text{ CI} 0.077–1.096, \ P = 0.025 \)) were retained as independent predictors for the ΔBMI. Since the baseline HbA1c and BMI were thought to be typically the factors that are the most powerful predicting variables, we reperformed these analyses while adding in these factors. However, there was no change in each explanatory variable (data not shown).

DISCUSSION

To our knowledge, this is the first study to investigate the clinical benefits of increasing the dose of the SGLT2 inhibitor empagliflozin in patients with T2DM. In this retrospective, observational study, we revealed that increasing the dose of empagliflozin from 10 to 25 mg once daily significantly decreased BW, BMI, GGT, FPG and HbA1c and increased Hct in Japanese patients with T2DM. Moreover, multivariate logistic regression analyses revealed that baseline DBP and TG were independent predictors for the improvement of HbA1c, and multivariate stepwise regression analyses indicated that ΔHDL-C and ΔHbA1c were independent predictors for ΔBMI.

The results of randomized clinical trials using empagliflozin are summarized in Table 5. Several trials [12–24] have shown significant reductions of HbA1c and BW with empagliflozin. Increasing the empagliflozin dose from 10 to 25 mg consistently caused a further reduction in HbA1c (13/16 trials, see Table 5). However, this increase in the empagliflozin dose caused a further reduction of BW in only half the studies (8/16 trials, see Table 5). A meta-analysis of randomized controlled trials of empagliflozin reported that the reduction of HbA1c by 25 mg empagliflozin [weighted mean difference (WMD) –0.66%; 95% confidence interval (CI) –0.76 to –0.57%] was greater than that caused by 10 mg empagliflozin [WMD –0.62%; 95% CI –0.68 to –0.57%] [25]. However, it was also reported that the reduction of BW by 25 mg empagliflozin [WMD –1.84 kg; 95% CI –2.30 to –1.38 kg] was almost the same as that caused by 10 mg empagliflozin [WMD –1.85 kg; 95% CI –2.09 to –1.60 kg] [25].

Recently, many network meta-analyses have been performed to distinguish the effects of different agents. For example, Shi et al. found the difference in the effect on heart failure between 10 mg dapagliflozin and 10 mg empagliflozin using network meta-analyses, and they concluded that 10 mg dapagliflozin may be more beneficial for heart failure compared to 10 mg empagliflozin [26]. On the other hand, there are two reports of network meta-analyses based on randomized control trials of empagliflozin. Wu et al. reported that the reduction of HbA1c by 25 mg empagliflozin was greater than that caused by 10 mg empagliflozin, but this was not a significant difference [25 mg vs. 10 mg: effect size –0.04%; 95%CI –0.19 to 0.10]) [27]. They also reported that the
Table 3 Univariate and multivariate logistic regression analyses for the factors associated with improved HbA1c in empagliflozin dose-increasing therapy

|                  | Univariate |                | Multivariate |                |
|------------------|------------|----------------|--------------|----------------|
|                  | r          | P              | Odds         | 95% CI         | P              |
| Sex (male)       | 0.131      | 0.35           |              |                |                |
| Age              | -0.120     | 0.40           |              |                |                |
| Duration         | -0.009     | 0.83           |              |                |                |
| BMI (baseline)   | 0.188      | 0.18           |              |                |                |
| ΔBMI             | 0.196      | 0.16           |              |                |                |
| SBP (baseline)   | 0.189      | 0.18           |              |                |                |
| ΔSBP             | 0.016      | 0.91           |              |                |                |
| DBP (baseline)   | 0.344      | 0.013*         | 1.093        | 1.019–1.156    | 0.012          |
| ΔDBP             | -0.108     | 0.45           |              |                |                |
| LDL-C (baseline) | 0.186      | 0.18           |              |                |                |
| ΔLDL-C           | 0.173      | 0.22           |              |                |                |
| HDL-C (baseline) | -0.097     | 0.49           |              |                |                |
| ΔHDL-C           | 0.025      | 0.86           |              |                |                |
| TG (baseline)    | 0.377      | 0.006*         | 1.012        | 1.001–1.023    | 0.026          |
| ΔTG              | 0.294      | 0.065          |              |                |                |
| FPG (baseline)   | -0.036     | 0.80           |              |                |                |
| ΔFPG             | 0.136      | 0.34           |              |                |                |
| HbA1c (baseline) | 0.295      | 0.034*         |              |                |                |
| ΔHbA1c           |           |                |              |                |                |
| eGFR (baseline)  | 0.193      | 0.17           |              |                |                |
| ΔeGFR            | 0.212      | 0.13           |              |                |                |
| Hct (baseline)   | 0.150      | 0.30           |              |                |                |
| ΔHct             | -0.074     | 0.61           |              |                |                |
| AST (baseline)   | 0.266      | 0.057          |              |                |                |
| ΔAST             | 0.306      | 0.028*         |              |                |                |
| ALT (baseline)   | 0.262      | 0.06           |              |                |                |
| ΔALT             | 0.380      | 0.005*         |              |                |                |
| GGT (baseline)   | 0.368      | 0.007*         |              |                |                |

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A network meta-analysis performed by Zaccardi et al. demonstrated the results of using two other SGLT2 inhibitors, canagliflozin and dapagliflozin. In that report, the reduction of HbA1c by 100 mg canagliflozin was significantly greater than that caused by 10 mg canagliflozin [300 mg vs. 100 mg: effect size – 0.10%; 95% CI – 0.21 to – 0.02] [28]. On the other hand, the reduction of HbA1c by 10 mg dapagliflozin was greater than that caused by 5 mg dapagliflozin, but this was not significant difference [10 mg vs. 5 mg: effect size – 0.04%; 95% CI – 0.00 to – 0.02] [28]. The reduction of BW by 10 mg dapagliflozin was reported to be significantly greater than that caused by 5 mg dapagliflozin [10 mg vs. 5 mg: effect size – 0.60 kg; 95% CI – 1.00 to – 0.19] [28]. To summarize the above, the effects of increasing the dose of the SGLT2 inhibitor on HbA1c tends to differ with each agent, but the effect on body weight may be consistent across agents.

Because several reports have demonstrated that treatment with SGLT2 inhibitors ameliorated not only HbA1c and BW but also blood pressure, lipid profile and liver injury in patients with T2DM [3, 4], we expected that switching to higher doses of empagliflozin would improve these parameters. Indeed, we found in the present study that increasing the dose of empagliflozin had additive effects on the reduction of serum TG and GGT levels. To clarify the causal relationship between these changes and the effects on HbA1c, we divided the patients into two groups: an improved HbA1c group and a nonimproved HbA1c group, and performed multivariate logistic regression analysis of various factors we suspected of being related. Interestingly, our study revealed that improvement of HbA1c was positively correlated with baseline DBP, baseline TG, ΔTG, ΔAST, ΔALT, baseline GGT and ΔGGT, and that baseline DBP and baseline TG were independent predictors for the improvement of HbA1c. As these factors

| ΔGGT  | 0.289 | 0.037* |
|-------|-------|--------|

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, Hct hematocrit, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT γ-glutamyl transpeptidase

*P < 0.05
Table 4: Univariate and multivariate stepwise regression analyses for the factors associated with change of BMI (ΔBMI) in empagliflozin dose-increasing therapy

| Univariate | Multivariate |
|------------|--------------|
|            |    |          | β  |    |     | P     |
|            | r     | P     | 95% CI | Upper/lower P |
| Age        | −0.120 | 0.40  |        |        |      |
| Duration   | −0.087 | 0.54  |        |        |      |
| SBP (baseline) | −0.096 | 0.50  |        |        |      |
| ΔSBP       | 0.149  | 0.29  |        |        |      |
| DBP (baseline) | 0.004  | 0.98  |        |        |      |
| ΔDBP       | 0.009  | 0.95  |        |        |      |
| LDL-C (baseline) | 0.015  | 0.92  |        |        |      |
| ΔLDL-C     | 0.090  | 0.53  |        |        |      |
| HDL-C (baseline) | −0.058 | 0.69  |        |        |      |
| ΔHDL-C     | −0.280 | 0.045*|        | −0.264 | −0.051/0.000 | 0.049 |
| TG (baseline) | 0.301  | 0.03* |        |        |      |
| ΔTG        | 0.136  | 0.34  |        |        |      |
| FPG (baseline) | −0.090 | 0.53  |        |        |      |
| ΔFPG       | 0.178  | 0.21  |        |        |      |
| HbA1c (baseline) | 0.072  | 0.61  |        |        |      |
| ΔHbA1c     | 0.316  | 0.023*|        | 0.302  | 0.077/1.096 | 0.025 |
| eGFR (baseline) | 0.029  | 0.84  |        |        |      |
| ΔeGFR      | −0.119 | 0.40  |        |        |      |
| Hct (baseline) | −0.184 | 0.20  |        |        |      |
| ΔHct       | −0.250 | 0.08  |        |        |      |
| AST (baseline) | 0.028  | 0.85  |        |        |      |
| ΔAST       | −0.065 | 0.65  |        |        |      |
| ALT (baseline) | 0.051  | 0.72  |        |        |      |
| ΔALT       | −0.019 | 0.89  |        |        |      |
| GGT (baseline) | 0.260  | 0.062 |        |        |      |
| ΔGGT       | 0.277  | 0.047*|        |        |      |

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, FPG fasting plasma glucose, eGFR estimated glomerular filtration rate, Hct hematocrit, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT γ-glutamyl transpeptidase

*P < 0.05
| Treated patients, P/ 10 mg/ 25 mg, N | Intervention method | Intervention period (weeks) | Change of HbA1c (%) | Change of body weight (kg) | Reference(s) |
|-------------------------------------|---------------------|-----------------------------|---------------------|--------------------------|--------------|
|                                     |                     |                             | $P$ 10 mg 25 mg     | $P$ 10 mg 25 mg          |              |
| 82/81/82                            | Monotherapy         | 12                          | $-0.1$ $-0.5$ $-0.6$ | $-0.75$ $-2.33$ $-2.03$ | [12]         |
| 228/224/244                         | Monotherapy         | 24                          | $+0.08$ $-0.66$ $-0.78$ | $-0.33$ $-2.26$ $-2.48$ | [13]         |
| 228/224/244                         | Monotherapy         | 76                          | $+0.13$ $-0.65$ $-0.76$ | $-0.4$ $-2.2$ $-2.5$ | [14]         |
| 207/217/213                         | With Met            | 24                          | $-0.13$ $-0.7$ $-0.77$ | $-0.45$ $-2.08$ $-2.46$ | [15, 16]    |
| 207/217/213                         | With Met            | 76                          | $-0.01$ $-0.62$ $-0.74$ | $-0.46$ $-2.39$ $-2.65$ | [16]         |
| 71/71/70                            | With Met ± one other oral AA | 12                        | $+0.15$ $-0.56$ $-0.55$ | $-1.2$ $-2.7$ $-2.6$ | [17]         |
| 225/225/216                         | With Met + SU       | 24                          | $-0.17$ $-0.82$ $-0.77$ | $-0.39$ $-2.16$ $-2.39$ | [18]         |
| 225/225/216                         | With Met + SU       | 76                          | $+0.0$ $-0.7$ $-0.7$ | $-0.6$ $-2.4$ $-2.3$ | [19]         |
| 165/165/168                         | With Pio ± Met      | 24                          | $-0.11$ $-0.59$ $-0.72$ | $+0.34$ $-1.62$ $-1.47$ | [20]         |
| 165/165/168                         | With Pio ± Met      | 76                          | $-0.01$ $-0.61$ $-0.7$ | $+0.5$ $-1.5$ $-1.2$ | [21]         |
| 95/98/97                            | With other AA       | 24                          | $+0.06$ $-0.46$ $-0.63$ | $-0.33$ $-1.76$ $-2.33$ | [22]         |
| 95/98/97                            | With other AAs      | 52                          | $+0.06$ $-0.57$ $-0.6$ | $-0.44$ $-2.0$ $-2.6$ | [22]         |
| 170/169/155                         | With insulin        | 18                          | $+0.0$ $-0.6$ $-0.7$ | $+0$ $-1.7$ $-0.9$ | [23]         |
| 170/169/155                         | With insulin        | 78                          | $+0.0$ $-0.5$ $-0.6$ | $+0.7$ $-2.2$ $-2.0$ | [23]         |
| 90/86/90                            | With insulin        | 16                          | $±0.00$ $-0.92$ $-1.0$ | $+0.12$ $-1.67$ $-1.62$ | [24]         |
| 90/86/90                            | With insulin        | 52                          | $+0.01$ $-0.89$ $-0.95$ | $+0.22$ $-1.56$ $-1.70$ | [24]         |

$P$ placebo, Met metformin, SU sulfonylurea, Pio pioglitazone, AA antidiabetic agent
are components of metabolic syndrome, increasing the dose of empagliflozin may be effective in T2DM patients with insulin resistance. We also revealed that ΔBW was correlated with ΔHDL-C, ΔHbA1c and ΔGGT, and that the independent predictors for the improvement of BMI were ΔHDL-C and ΔHbA1c, suggesting that HbA1c and HDL-C are related factors that respond well to ΔBW.

This study has some limitations. First, our study was conducted in a single center and the sample size was relatively small. Second, because this was a retrospective study, the dosing of antidiabetic agents was uncontrolled. However, we selected patients who did not change their intakes of other drugs, including antidiabetes agents, statins, fenofibrate, anti-hypertensive agents, and other agents during the follow-up period. Third, this study consisted only of Japanese patients. Further studies are needed to apply the results of this study to other populations.

CONCLUSIONS

We demonstrated in the present study that increasing the dose of empagliflozin from 10 to 25 mg once daily significantly decreased BW, BMI, GGT, FPG and HbA1c and slightly increased Hct in patients with T2DM. Moreover, baseline DBP and TG were independent predictors for the improvement of HbA1c, and ΔHDL-C and ΔHbA1c were independent predictors for ΔBMI. These findings may provide useful information when considering whether to increase the dose of SGLT2 inhibitors in patients with type 2 diabetes who have inadequate glycemic control.

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Disclosures. Takeshi Matsumura, Tomoko Makabe, Seiko Ueda, Yuki Fujimoto, Kayo Sadahiro, Shiori Tsuruyama, Yuma Ookubo, Tatsuya Kondo and Eiichi Araki have nothing to disclose.

Compliance with Ethics Guidelines. The study was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice, the Ethical Guidelines for Epidemiological Research of Japan, the ethical standards of the responsible committee on human experimentation (institutional and national), and the Helsinki Declaration of 1964, as revised in 2013. The study protocol was reviewed and approved by institutional ethics committees at Nishinihon Hospital and recorded at the UMIN Clinical Trials Registry (UMIN000041543). All participants provided written informed consent.

Data Availability. The datasets generated during and/or analyzed during the current
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