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Sodium Glucose Cotransporter-2 Inhibitors as an Add-on Therapy to Metformin Plus Dipeptidyl Peptidase-4 Inhibitor in Patients with Type 2 Diabetes

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Purpose: To date, no study has compared the effects of adding sodium glucose cotransporter-2 (SGLT-2) inhibitors to the combination of metformin plus dipeptidyl peptidase-4 (DPP-4) inhibitors to the effects of adding other conventional anti-diabetic drugs (ADDs) to the dual therapy. We aimed to compare the effect of adding SGLT-2 inhibitors with that of adding sulfonylurea (SU) in type 2 diabetes (T2D) patients inadequately controlled with metformin plus DPP-4 inhibitors.

Materials and Methods: This study was designed to evaluate the non-inferiority of SGLT-2 inhibitor to SU as an add-on therapy to the dual combination of metformin plus DPP-4 inhibitors. A total of 292 T2D patients who started SU or SGLT-2 inhibitors as an add-on therapy to metformin plus DPP-4 inhibitors due to uncontrolled hyperglycemia, defined as glycated hemoglobin (HbA1c) ≥7%, were recruited. After propensity score matching, 90 pairs of patients remained, and 12-week changes in HbA1c levels were reviewed to assess glycemic effectiveness. Data from these patients were analyzed retrospectively.

Results: After 12 weeks of triple therapy, both groups showed significant changes in HbA1c levels, with a mean of -0.9% in each group. The inter-group difference was 0.01% [95% confidence interval (CI): -0.26–0.27], and the upper limit of the 95% CI was within the limit for non-inferiority (0.40%). There were no inter-group differences in the changes of liver enzyme levels and kidney function.

Conclusion: Adding SGLT-2 inhibitors is not inferior to adding SU as a third-line ADD to metformin plus DPP-4 inhibitor combination therapy.

Key Words: Type 2 diabetes mellitus, sodium-glucose cotransporter 2 inhibitors, glycemic control

INTRODUCTION

Type 2 diabetes (T2D) is a progressive, chronic disease characterized by worsening of insulin resistance and β-cell function,[1] and has complex and multifactorial pathogenic mechanisms.[2] Therefore, the majority of T2D patients need combination therapy of two or more anti-diabetic drugs (ADDs). With the introduction of incretin-based therapies and sodium glucose cotransporter-2 (SGLT-2) inhibitors, the number of possible combinations of ADDs for T2D patients has recently increased.

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent rapid degradation of incretin hormones, such as glucagon-like peptide-1, thereby increasing the postprandial secretion of insulin and suppressing the secretion of glucagon.[3] Based on its significant glucose-lowering effect, neutral effect on body weight, and excellent safety profile, this class of ADDs has been frequently prescribed as a dual combination therapy with metformin, the

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first choice of ADDs. However, due to the progressive nature of T2D, patients with T2D often fail to achieve their target glucose level with this dual combination therapy. Most international guidelines recommend triple combination therapy for T2D patients failing to achieve target glycemic goals under dual therapy.[4-6]

Since the approval of dapagliflozin by the European Medicines Agency in 2012, SGLT-2 inhibitors have emerged as an alternative option of ADDs for T2D treatment.[7] This class of ADDs induces glycosuria by inhibiting reabsorption of glucose from the proximal tubule in the kidneys. This class of ADDs has shown cardioprotective results in addition to the glucose-lowering effects.[8] Since the mechanism of SGLT-2 inhibitors is quite different from previous ADDs, SGLT-2 inhibitors were expected to be effective not only as monotherapy but also in combination with other ADDs. In this respect, SGLT-2 inhibitors may also be considered to be a favorable third class of ADDs for patients with poor glycemic control taking metformin and DPP-4 inhibitor. In fact, the triple therapy consisting of metformin, DPP-4 inhibitors, and SGLT-2 inhibitors has shown significant effectiveness in glycemic control and excellent safety.[9-12]

However, previous studies were only designed to compare the effect of adding SGLT-2 inhibitors or DPP-4 inhibitors to the effect of placebo in patients with T2D receiving dual combination therapy, which consisted of metformin plus DPP-4 inhibitors or metformin plus SGLT-2 inhibitors. There has been no study comparing the effects of adding SGLT-2 inhibitors to other classes of ADDs in patients with T2D inadequately controlled by dual combination therapy of metformin plus DPP-4 inhibitors.

Therefore, we designed the present study to compare the glycemic control effectiveness of adding SGLT-2 inhibitors with that of adding sulfonylurea (SU), another widely prescribed ADD, in uncontrolled T2D patients under dual combination therapy of metformin plus DPP-4 inhibitors.

MATERIALS AND METHODS

Patients and data collection

We conducted a retrospective study using longitudinal data from tertiary level electronic medical records from the university-affiliated Severance Hospital in South Korea. Using the medical records, we recruited T2D patients who started SU (SU group) or SGLT-2 inhibitors (SGLT-2i group) as an add-on therapy to metformin plus DPP-4 inhibitors dual therapy due to their uncontrolled hyperglycemia, defined as glycated hemoglobin (HbA1c) ≥7%. We defined the index date as the first day of SU or SGLT-2 inhibitor prescription. Only the patients who had taken metformin plus DPP-4 inhibitors combination therapy for more than 12 weeks before the index date without any other ADDs were included in this study. We excluded patients whose dosage of metformin or DPP-4 inhibitors was changed after the index date. Patients who started or changed drugs that could influence glucose metabolism during the study period, such as glucocorticoids, levothyroxine, and immunosuppressive drugs, were also excluded.

The study protocol was approved by the Institutional Review Board of Severance Hospital (no. 4-2021-0701). All methods were performed in accordance with relevant guidelines and regulations. Written informed consent was not required in this study, as the database was only retrospectively accessed for analytical purposes and personal information was not used.

Measurements of clinical and laboratory parameters

Baseline demographics, body mass index, and prescription records were identified by reviewing electronic medical records. To evaluate glycemic effectiveness, we assessed the levels of HbA1c and fasting blood glucose. Baseline variables were measured on the day of SGLT-2 inhibitor or SU addition, and the follow-up measurements were conducted after 12 weeks of each triple combination therapy. Baseline C-peptide level was also checked, as it could affect the effect of ADDs.

In addition to the glycemic parameters, we also assessed the results of laboratory measurements from blood samples related to safety or other metabolic influence: liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total bilirubin, blood urea nitrogen (BUN), creatinine, and estimated glomerular filtration rate (eGFR). The eGFR level was calculated using the Modification of Diet in Renal Disease study equation.

Study outcomes

The primary outcome of this study was glycemic control effectiveness assessed by 12-week changes in HbA1c levels. We hypothesized that SGLT-2 inhibitors are not inferior to SU as an add-on therapy to metformin plus DPP-4 inhibitor dual therapy. The secondary outcomes were changes in fasting blood glucose levels and other parameters related to safety, such as liver enzymes and kidney function, during those triple combination therapies.

Statistical analysis

The baseline characteristics, laboratory measurements, and 12-week changes in variables were compared according to the treatment groups, which included the SGLT-2i group and the SU group. Student's t-test or Kruskal-Wallis test was used to compare continuous variables between the two groups, and χ^2 test was used to compare categorical variables. The changes in variables from baseline to week 12 within each group were evaluated using the paired t-test. Propensity score matching was used to minimize the influence of potential confounding factors. Variables included in the matching process were age, sex, T2D duration, and HbA1c.

For testing the non-inferiority of SGLT-2 inhibitors to SU as an add-on therapy to the dual combination of metformin plus

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DPP-4 inhibitors with 80% power, we calculated that 80 patients per treatment group were required, assuming no difference in HbA1c between SGLT-2i group and SU group and a 0.4% margin of non-inferiority with one-sided test of the 95% confidence interval (CI). The standard deviation (SD) of change in HbA1c from baseline to month 3 was assumed to be 0.9.

All statistical analyses were performed using SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean±SD, while categorical variables are expressed as number and percentage (%). *P*-values <0.05 were considered statistically significant.

RESULTS

Study population characteristics

A total of 292 patients were recruited for this study; 184 patients were in the SU group, and the other 108 subjects comprised the SGLT-2i group. The patients in the SU group were older (62.9±11.4 years old vs. 56.0±11.8 years old, $p<0.001$), had longer history of T2D (10.4±7.5 years vs. 8.0±0.6 years, $p=0.002$) and had lower eGFR (86.3±26.3 mL/min/1.73 m^2 vs. 96.1±21.2 mL/min/1.73 m^2, $p=0.001$) than those in the SGLT-2i group (Supplementary Table 1, only online). The mean baseline HbA1c value was slightly higher in the SU group, but the difference was not statistically significant (8.1± 0.7% vs. 8.0±0.8%, $p=0.066$).

After 1:1 propensity score matching, 90 pairs of patients remained in this study (Table 1). There were no significant differences in baseline characteristics, including age, duration of T2D, HbA1c and C-peptide levels, between the SU and SGLT-2i groups. The mean age of the patients was approximately 59 years in both groups. The average duration of T2D was 8.6 years in the SU group and 8.7 years in the SGLT-2i group. The mean HbA1c levels of both groups were about 8.0% (8.0±0.6% vs. 8.1±0.9%, $p=0.789$); and other laboratory measurements, such as liver enzymes and eGFR, were well-matched between the two groups. The doses and types of ADDs in this study are summarized in Supplementary Table 2 (only online).

Glycemic control effectiveness

In the initially recruited 292 patients, the changes in HbA1c during the 12-week treatment were -1.1% in the SU group and -0.9% in the SGLT-2i group, with no statistically significant differences ($p=0.115$).

The changes of HbA1c or fasting glucose from baseline to week 12 in the propensity score-matched subjects are shown in Table 2. Both groups showed significant reductions in HbA1c levels during the 12 weeks of treatment (-0.9±0.9% in SU group, -0.9±0.9% in SGLT-2i group, $p<0.001$ by paired t-test in each group). The inter-group difference was 0.01% (95% CI: -0.26–0.27; $p=0.954$). The upper limit of the 95% CI was within the limit for non-inferiority (0.40%). In addition, the SDs of change in HbA1c from baseline until month 3 (0.9 in both groups) were similar to our estimation (0.9). Given the sufficient number of subjects per group (≥80), the results demonstrated the non-inferiority of adding SGLT-2 inhibitor compared to adding SU to metformin plus DPP-4 inhibitor combination therapy.

The proportion of patients achieving the HbA1c target of less than 7.0% was 46.7% in the SU group and 38.9% in the SGLT-2i group; the difference was not significant ($p=0.292$). When we set the target HbA1c to less than 6.5%, no statistical difference was observed between the two groups (21.1% vs. 12. 2%, $p=0.110$). In addition, there were no significant differences between the two

Table 1. Baseline Characteristics by Treatment Group after Propensity Score Matching

Variables	SU group (n=90)	SGLT-2i group (n=90)	*p* value
Age (yr)	59.1±11.1	58.8±10.3	0.877
Male	56 (62.2)	52 (57.8)	0.543
BMI (kg/m^2)	25.8±7.2	26.2±3.1	0.646
T2D duration (yr)	8.6±6.7	8.7±5.6	0.888
HbA1c (%)	8.0±0.6	8.1±0.9	0.789
Fasting glucose (mg/dL)	179.5±42.2	173.2±42.8	0.322
C-peptide* (ng/mL)	2.9±1.6	3.7±2.8	0.694
BUN (mg/dL)	16.5±4.9	15.4±3.9	0.101
Creatinine (mg/dL)	0.8±0.2	0.8±0.2	0.121
eGFR (mL/min/1.73 m^2)	91.3±26.4	93.7±20.0	0.512
AST (IU/L)	28.1±19.7	33.3±22.0	0.102
ALT (IU/L)	32.9±23.8	39.4±30.6	0.112
Total bilirubin (mg/dL)	0.8±0.3	0.8±0.3	0.654

SU, sulfonylurea; SGLT-2i, sodium glucose cotransporter-2 inhibitor; BMI, body mass index; T2D, type 2 diabetes; HbA1c, glycated hemoglobin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Continuous variables are expressed as means±SD. Categorical variables are expressed as n (%). $p<0.05$ indicates statistical significance.
*Only 18 subjects in SU group and 7 subjects in SGTL-2i group had baseline C-peptide measurements.

Table 2. Effects of Adding SU vs. SGLT-2i on HbA1c at 12 Weeks

Variables	SU group (n=90)	SGLT-2i group (n=90)	*p* value
HbA1c, baseline (%)	8.0±0.6	8.1±0.9	0.789
HbA1c, 12 weeks (%)	7.1±0.8	7.2±0.7	0.738
Change of HbA1c from baseline	-0.9±0.9	-0.9±0.9	0.954
Inter-group difference (95% CI)	0.01 (-0.26–0.27)		
Fasting glucose, baseline (mg/dL)	179.5±42.2	173.2±42.8	0.322
Fasting glucose, 12 weeks (mg/dL)	139.8±40.1	144.6±39.9	0.434
Change of fasting glucose from baseline	-39.7±53.5	-28.6±47.1	0.151
HbA1c <7% at 12 weeks	42 (46.7)	35 (38.9)	0.292
HbA1c <6.5% at 12 weeks	19 (21.1)	11 (12.2)	0.110
Change of HbA1c ≤-1% at 12 weeks	43 (47.8)	35 (38.9)	0.229

SU, sulfonylurea; SGLT-2i, sodium glucose cotransporter-2 inhibitor; HbA1c, glycated hemoglobin; CI, confidence interval.
Continuous variables are expressed as means±SD. Categorical variables are expressed as n (%). $p<0.05$ indicates statistical significance.

groups in the proportion of patients with a decrease in HbA1c of 1% or more (47.8% vs. 38.9%, p=0.229). The changes in fasting blood glucose were also similar in the two groups (-39.7±53.5 vs. -28.6±47.1, p=0.151).

Changes in safety parameters

During the 12 weeks of study period, the blood levels of liver enzymes were significantly decreased in both treatment groups (AST, from 28.1±19.7 to 24.8±12.8 IU/L in the SU group and from 33.3±22.0 to 26.9±18.6 IU/L in the SGLT-2i group; ALT, from 32.9±23.8 to 29.3±20.0 IU/L in the SU group and from 39.4 ±30.6 to 28.8±19.7 IU/L in the SGLT-2i group). There were no differences in the changes of liver enzyme between the two groups (Table 3). The mean BUN level was slightly increased in the SGLT-2i group, probably due to its diuretic effect (15.4 ± 3.9 to 17.7±5.2 mg/dL, p-value from paired t-test<0.001). Serum creatinine levels and eGFR did not change significantly during the treatment period in both groups (creatinine, from 0.8±0.2 to 0.8±0.2 mg/dL in both groups; eGFR, from 91.3± 26.4 to 91.0±26.5 mL/min/1.73 m^2 in the SU group and from 93.7±20.0 to 93.7±24.6 mL/min/1.73 m^2 in the SGLT-2i group).

DISCUSSION

In this retrospective non-inferiority study, adding SGLT-2 inhibitors as a third-line ADD to patients with T2D who were inadequately controlled with metformin plus DPP-4 inhibitor showed significant glycemic control effectiveness that was not inferior to SU addition to the metformin plus DPP-4 inhibitor combination therapy. During the 3 months of triple therapy, both treatment groups showed a 0.9% decrease in HbA1c levels and improved liver enzyme levels.

Table 3. Effects of Adding SU vs. SGLT-2i on Kidney Function and Liver Enzymes

Variables	SU group (n=90)	SGLT-2i group (n=90)	p value
AST, baseline (IU/L)	28.1±19.7	33.3±22.0	0.102
AST, 12 weeks (IU/L)	24.8±12.8	26.9±18.6	0.385
Change of AST from baseline	-3.3±10.7*	-6.8±21.3*	0.172
ALT, baseline (IU/L)	32.9±23.8	39.4±30.6	0.112
ALT, 12 weeks (IU/L)	29.3±20.2	28.8±19.7	0.886
Change of ALT from baseline	-3.6±15.9*	-11.4±27.7*	0.033
Total bilirubin, baseline (mg/dL)	0.8±0.3	0.8±0.3	0.654
Total bilirubin, 12 weeks (mg/dL)	0.7±0.3	0.7±0.3	0.549
Change of total bilirubin from baseline	-0.05±0.3	-0.04±0.2	0.817
BUN, baseline (mg/dL)	16.5±4.9	15.4±3.9	0.101
BUN, 12 weeks (mg/dL)	15.8±4.9	17.7±5.2	0.015
Change of BUN from baseline	-0.7±4.7	2.1±4.2*	<0.001
Creatinine, baseline (mg/dL)	0.8±0.2	0.8±0.2	0.121
Creatinine, 12 weeks (mg/dL)	0.8±0.2	0.8±0.2	0.333
Change of creatinine from baseline	0.01±0.1	0.002±0.08	0.579
eGFR, baseline (mL/min/1.73 m^2)	91.3±26.4	93.7±20.0	0.512
eGFR, 12 weeks (mL/min/1.73 m^2)	91.0±26.5	93.7±24.6	0.497
Change of eGFR from baseline	-0.3±11.8	1.8±13.9	0.281

SU, sulfonylurea; SGLT-2i, sodium glucose cotransporter-2 inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.
Continuous variables are expressed as means±SD. p<0.05 indicates statistical significance.
*p<0.05 by paired t-test in each group.

The glycemic control effectiveness of SGLT-2 inhibitors as a third-line ADD in this study, which was shown as a mean HbA1c change of -0.9% of from baseline, was similar to the results of previous studies. In the phase 3 trial of triple therapy with dapagliflozin added on to metformin plus saxagliptin, the addition of dapagliflozin improved the mean HbA1c levels by -0.82% over 24 weeks.[13] When the treatment period was extended to 52 weeks by the same research team, adding dapagliflozin to metformin plus saxagliptin combination therapy decreased HbA1c levels by 0.74%.[9] When empagliflozin, another SGLT-2 inhibitor, was prescribed to T2D patients who were inadequately controlled by metformin and linagliptin, the mean HbA1c levels decreased by 0.65% over 24 weeks.[11] These results, including those of our study, suggest that the addition of SGLT-2 inhibitors provides a significant additional glucose-lowering effect in patients who did not achieve their target glucose levels with metformin plus DPP-4 inhibitors.

As a monotherapy, the glycemic efficacy of SU is superior to SGTL-2 inhibitors.[4] However, in this study, SGLT-2 inhibitors as a third-line ADD were not inferior to SU. This result was in line with a previous long-term study which compared empagliflozin to glimepiride as a second-line treatment option for T2D not controlled by metformin.[14] In that study, the mean changes of HbA1c at week 52 was -0.73% in the empagliflozin group and -0.66% in the glimepiride group, demonstrating the non-inferiority of empagliflozin add-on therapy. The results at week 102 were also not inferior in the empagliflozin group when compared to the glimepiride group as a second-line ADD; the change in HbA1c from baseline was -0.66% vs. -0.55%. Later, the same research team further analyzed the data up to week 208, and reported that this trend was maintained.[15] This may be due to the unique insulin-independent mechanism of SGLT-2 inhibitors; therefore, when used as a combination therapy, SGLT-2 inhibitors may cover various pathophysiological mechanisms of T2D more widely and effectively.

In addition to the non-inferiority of the glycemic control effectiveness of the triple therapy, SGLT-2 inhibitors are considered to be superior to SU in terms of weight loss and low incidence of hypoglycemia. As expected, in the aforementioned studies, patients to whom SGLT-2 inhibitors were added to metformin showed a more pronounced weight loss and fewer hypoglycemic events compared to those in whom SU was added to metformin.[14,15] Due to the limitations of retrospective medical record review, we could not include the data regarding changes in body weight or the incidence of hypoglycemia in this study. However, considering the characteristics of the ADDs, we ex-

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pect that the SGLT-2i group would show a distinct weight loss and a lower incidence of hypoglycemic events compared to the SU group. Considering the long-term prognosis, SGLT-2 inhibitors, unlike SU, have significant preventive effects on cardiovascular diseases and renal diseases.[16] Therefore, from a long-term perspective, choosing SGLT-2 inhibitors as a third-line ADD rather than SU can be considered to be more beneficial for T2D patients whose hyperglycemia is not adequately controlled with metformin and DPP-4 inhibitors.

The present study had several limitations. First, this was a retrospective analysis with a relatively small sample size of subjects. Therefore, the results may have been influenced by potential confounding factors related to the retrospective design of this study. However, by using propensity score matching, we aimed to minimize the interference of other characteristics. Second, this study lacked data in certain areas, such as body weight at every visit, adverse events of ADDs, and differences or changes in patient lifestyle. Third, due to the short duration of the study period, the long-term effects of triple therapy including metformin, DPP-4 inhibitors, and SGLT-2 inhibitors could not be confirmed in this study. Large-scale, long-term prospective studies are required to demonstrate the effects of SGLT-2i add-on to metformin plus DPP-4 inhibitors compared to SU or other ADD add-on therapies. Despite these limitations, this study is still valuable in that it is the first to compare the glycemic control effectiveness between SGLT-2 inhibitors and SU as a third-line ADD in T2D not controlled by metformin and DPP-4 inhibitors.

In conclusion, the glycemic control effectiveness of adding SGLT-2 inhibitors as a third-line ADD to metformin plus DPP-4 inhibitors was not inferior to that of adding SU. Considering the additional benefits of SGLT-2 inhibitors, such as weight loss, low incidence of hypoglycemia, and cardiovascular protection, SGLT-2 inhibitors may be a better option than SU for patients with T2D that is inadequately controlled by metformin and DPP-4 inhibitors.

AUTHOR CONTRIBUTIONS

Conceptualization: Jaehyun Bae and Eun Seok Kang. Data curation: Jaehyun Bae. Formal analysis: Jaehyun Bae. Funding acquisition: Eun Seok Kang. Investigation: Jaehyun Bae. Methodology: Jaehyun Bae and Eun Seok Kang. Project administration: Jaehyun Bae, Young-eun Kim, and Eun Seok Kang. Resources: Jaehyun Bae and Eun Seok Kang. Software: Jaehyun Bae. Supervision: Minyoung Lee, Yong-ho Lee, Byung-Wan Lee, Bong-Soo Cha, and Eun Seok Kang. Validation: Jaehyun Bae and Eun Seok Kang. Visualization: Jaehyun Bae. Writing—original draft: Jaehyun Bae. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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