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Glucagon-Like Peptide-1 Receptor Agonists Added to Sodium-Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes: A Historical Cohort Study Using the Diabetes Study From the Center of Tokyo Women's Medical University (DIACET)

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Original

Glucagon-Like Peptide-1 Receptor Agonists Added to Sodium-Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes: A Historical Cohort Study Using the Diabetes Study From the Center of Tokyo Women's Medical University (DIACET)

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Background: This study clarifies the effects of adding a glucagon-like peptide-1 receptor agonist (GLP-1RA) to sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy on glycated hemoglobin (HbA1c) and body weight in Japanese patients with type 2 diabetes (T2D).

Methods: This historical cohort study, part of the Diabetes Study from the Center of Tokyo Women's Medical University, included 80 adults with T2D (registered April 2014-July 2020) prescribed SGLT2i for ≥3 months before adding GLP-1RA. HbA1c and weight changes to 12 months after GLP-1RA prescription were assessed, overall and in subgroups based on previous dipeptidyl peptidase-4 inhibitor use, body mass index (BMI), baseline HbA1c levels, and insulin use.

Results: HbA1c was significantly reduced from baseline (mean ± SD: 8.9 ± 1.6%) at all times, including 6 months (primary endpoint: 8.2 ± 1.3%; change: −0.76%, P = 0.002). At 12 months, 21.4% of individuals achieved HbA1c levels <7%. Results were similar in most subgroups. In the BMI ≥30 kg/m^2 subgroup, HbA1c was significantly reduced only at 3 months; 15.2% of individuals achieved HbA1c <7% at 12 months. Significant weight changes were observed only in insulin non-users.

Conclusions: Adding GLP-1RA to SGLT2i therapy reduced HbA1c levels in Japanese people with T2D; obese individuals may require more intensive treatment.

Keywords: combination therapy, glucagon-like peptide-1 receptor agonist, sodium-glucose transporter 2 inhibitor, type 2 diabetes

Introduction

The broad range of antidiabetic drugs available for the treatment of type 2 diabetes (T2D) allows tailoring of therapy based on individual needs. The American Diabetes Association (ADA) has recommended the biguanide metformin as first-line pharmacologic therapy, with addition of a glucagon-like peptide-1 receptor agonist (GLP-1

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RA), sodium-glucose cotransporter 2 inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP-4i), thiazolidine, or sulfonylurea as second-line therapy.[1] The ADA guidelines were recently updated to preferentially recommend prescribing a GLP-1RA or SGLT2i for individuals with heart failure, chronic kidney disease, or cardiovascular disease, as well as those at high risk of cardiovascular disease.[1, 2] This change in guidance was based on accumulating evidence of the beneficial cardiovascular and renal effects of GLP-1RAs and SGLT2is.[3] In contrast, the Japanese clinical guidelines currently do not make specific drug recommendations but encourage clinicians to make treatment choices based on individual factors, such as disease condition, age, and complications, including obesity.[4] In Japanese clinical practice, biguanides and DPP-4is are the most commonly prescribed first-line medications for T2D.[5, 6] Although the use of SGLT2is in Japan has increased markedly since they became available in 2014,[6] prescription of GLP-1RAs, available since 2010, remains low.[5]

In addition to improving glycemic control, both GLP-1RAs and SGLT2is reduce body weight.[7] Evidence also suggests an additive effect on lowering glycated hemoglobin (HbA1c) and body weight when used in combination,[8-12] although combined use of these two drug classes has been uncommon in Japan so far.[5] Although some Japanese studies have examined addition of an SGLT2i to a GLP-1RA[13-18] to our knowledge, no study has investigated GLP-1RAs as add-on therapy to SGLT2is in Japanese people with T2D.

The aim of this historical cohort study was to examine changes in HbA1c and body weight in the 12 months after addition of a GLP-1RA to SGLT2i therapy in Japanese individuals with T2D. These changes were also examined in subgroups of individuals who were previously treated with a DPP-4i and switched to a GLP-1RA and in those who were not previously treated with a DPP-4i, as well as in subgroups based on body mass index (BMI) and baseline HbA1c levels.

Materials and Methods

Study design

This was a historical cohort study conducted as part of the Diabetes Study from the Center of Tokyo Women's Medical University (DIACET) in Japan.[19, 20] DIACET is an ongoing, single-center, prospective, observational cohort registry that includes data on demographics, diagnoses, prescriptions, procedures, and laboratory tests in individuals with diabetes from inpatient and outpatient services. The protocol for this study was approved by the Ethics Committee of Tokyo Women's Medical University (number: 2566-R6 and 2020-0100) and conforms to the provisions of the Declaration of Helsinki. Because this was a retrospective analysis of previously collected, de-identified data, separate informed consent was not required, and individuals could opt out of the registry.

Study population

Individuals were identified from DIACET data collected between April 17, 2014, and July 18, 2020. Individuals were eligible if they had a diagnosis of T2D, were ≥18 years of age, and were prescribed an SGLT2i for ≥3 months before a GLP-1RA was additionally prescribed. SGLT2is included ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin, and GLP-1RAs included dulaglutide, liraglutide, lixisenatide, exenatide, and semaglutide. Individuals were excluded if they had a diagnosis of type 1 diabetes, gestational diabetes, or any other type of diabetes besides T2D at any time, were pregnant, or were undergoing dialysis. Individuals with missing HbA1c and BMI data at baseline and/or missing HbA1c data at 6 months were excluded from the analysis. Within this cohort, DPP-4i use subgroups were identified as follows: the DPP-4i group had used a DPP-4i as add-on to an SGLT2i for ≥3 months before switching to a GLP-1RA as add-on to an SGLT2i on an index date, and the non-DPP-4i group had no previous use of DPP-4i before adding a GLP-1RA to an SGLT2i.

Clinical measures

Data collected from April 17, 2014, to August 31, 2021, were analyzed. The index date was the date when an individual was first prescribed a GLP-1RA as add-on to an SGLT2i that they had been prescribed for ≥3 months. Demographic data were collected at the index date. HbA1c and body weight were assessed at 0, 3, 6, 9, and 12 months after the index date (**Supplementary**

Table 1). The primary outcome was change in HbA1c from the index date to 6 months after the index date. The secondary outcomes were changes in HbA1c from the index date to 3, 9, and 12 months after the index date, and change in body weight from the index date to 3, 6, 9, and 12 months after the index date.

Statistical analysis

The expected sample size was 100 individuals. In the AWARD-10 trial,[11] dulaglutide 0.75 mg added to an SGLT2i resulted in a least squares mean difference in HbA1c change from baseline of 0.66% compared with placebo. Based on this difference, we determined that a sample size of 100 would allow estimation of mean change in HbA1c with 0.3% as half the width of the two-sided 95% confidence interval, assuming a standard deviation (SD) of 1.5%.

All analyses are based on complete case analysis with no imputation of missing values. In addition to the prespecified subgroup analysis by DPP-4i use, subgroup analyses by baseline BMI (<25, 25 to <30, and ≥30 kg/m^2), baseline HbA1c (<8%, 8% to <10%, and ≥10%), and insulin use (insulin users and insulin non-users) were also conducted. Mean (± SD) HbA1c and body weight were calculated at each time point for the overall cohort and for the DPP-4i use, BMI, HbA1c, and insulin use subgroups, and the comparison between baseline and each time point was tested using one-way analysis of variance with Dunnett's test for multiple comparisons for the overall cohort and prespecified DPP-4i use subgroups. No adjustment for multiplicity was conducted for the exploratory analyses of baseline BMI, baseline HbA1c, and insulin use subgroups. A two-tailed P-value <0.05 was considered significant. No statistical comparisons were made between the subgroups, except at baseline (one-way analysis of variance for continuous variables and chi-square test for categorical variables). The proportion of individuals who achieved HbA1c <7% at baseline, 6 months, and 12 months was also calculated. IBM SPSS version 28 (Armonk, NY, USA) was used for statistical analysis.

Results

Baseline characteristics

There were 3,097 adults with T2D who were registered in DIACET between April 17, 2014, and July 18, 2020 (**Figure 1**). Of these, 117 individuals were prescribed both an SGLT2i and a GLP-1RA, and 80 individuals met the eligibility criteria and were included in the analysis. Of these 80 individuals, 18 had switched from a DPP-4i to a GLP-1RA as add-on to an SGLT2i, and 62 had not previously received a DPP-4i. The majority (62.5%) of individuals were male, with a mean age of 53.4 years, mean body weight of 85.4 kg, mean BMI of 30.7 kg/m^2, and mean HbA1c of 8.9% (**Table 1**). Dulaglutide (66.3% of individuals) and ipragliflozin (45.0% of individuals) were the most commonly prescribed GLP1-RA and SGLT2i, respectively (**Table 1**). Many individuals were taking several diabetes medications in addition to GLP-1RAs and SGLT2is, most commonly a biguanide. The DPP-4i use subgroup was taking significantly more oral antidiabetic drugs (OADs) than the non-DPP-4i use subgroup (mean ± SD number: 3.0 ± 0.6 vs. 1.8 ± 1.0 in the DPP-4i and non-DPP-4i use subgroups, respectively; P = 0.004).

Other than the number of OADs, there were no significant differences in clinical characteristics between the DPP-4i use subgroups, although the DPP-4i use subgroup tended to have a higher mean baseline HbA1c (9.3% vs. 8.8%), body weight (92.0 vs. 83.5 kg), and BMI (32.1 vs. 30.2 kg/m^2) than the non-DPP-4i use subgroup, respectively (**Table 1**). In addition to differences in body weight and BMI, there was a significant difference in age across the BMI subgroups, with individuals in the ≥30 kg/m^2 subgroup being the youngest and those in the <25 kg/m^2 subgroup being the oldest (**Supplementary Table 2**). There were no significant differences across the HbA1c subgroups other than baseline HbA1c itself (**Supplementary Table 2**). As would be expected, insulin users had a significantly longer duration of diabetes, a significantly higher baseline HbA1c and were significantly less likely to be treated with sulfonylurea compared with insulin non-users (**Supplementary Table 2**).

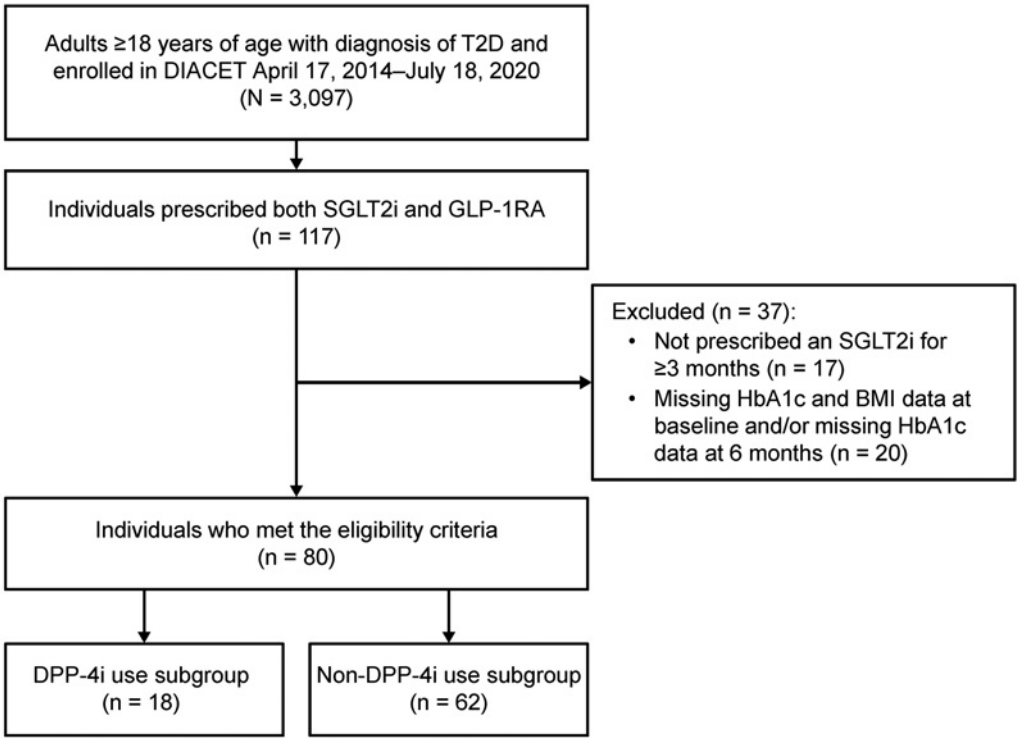

Figure 1. Study flow diagram.
BMI, body mass index; DIACET, Diabetes Study from the Center of Tokyo Women's Medical University; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

Changes in HbA1c

HbA1c was significantly reduced from baseline at all time points in the overall cohort (**Figure 2a-2b**, **Supplementary Table 3**). In the primary analysis, HbA1c decreased from a mean ± SD of 8.9 ± 1.6% at baseline to 8.2 ± 1.3% at 6 months (change from baseline −0.76%, P = 0.002). HbA1c was also significantly reduced from baseline at all time points in both DPP-4i use subgroups (**Figure 2a-2b**, **Supplementary Table 3**). In the DPP-4i use subgroup, HbA1c decreased from a mean ± SD of 9.3 ± 1.0% at baseline to 8.3 ± 0.9% at 12 months (change from baseline −1.05%, P = 0.006). In the non-DPP-4i use subgroup, HbA1c decreased from a mean ± SD of 8.8 ± 1.8% at baseline to 8.1 ± 1.5% at 12 months (change from baseline −0.68%, P = 0.045). In the BMI subgroups, HbA1c was significantly reduced from baseline at all time points in the 25 to < 30 kg/m^2 subgroup, but only at 3 months in the ≥30 kg/m^2 subgroup (**Figure 2c-2d**, **Supplementary Table 3**). Although mean HbA1c decreased in the < 25 kg/m^2 subgroup, the changes were not statistically significant, possibly because of the small number of individuals in this subgroup (n = 11). In the baseline HbA1c subgroups, HbA1c was significantly reduced at all time points in the 8% to <10% and ≥10% subgroups, but not in the <8% subgroup (**Figure 2e-2f**, **Supplementary Table 3**). The largest changes were seen in individuals in the baseline HbA1c ≥10% subgroup, with a decrease from a mean ± SD of 11.5 ± 1.7% at baseline to 9.1 ± 1.3% at 3 months (change from baseline −2.4%, P < 0.001) and 9.4 ± 1.6% at 12 months (change from baseline −2.1%, P = 0.004). HbA1c was significantly reduced from baseline to a similar extent in both the insulin user and non-user subgroups (**Figure 2 g-2 h**, **Supplementary Table 3**).

In the overall cohort, 18.8% and 21.4% of individuals achieved HbA1c 7% at 6 and 12 months, respectively (**Figure 3a**). The HbA1c <7% achievement rate was numerically lower in the DPP-4i use subgroup (11.1% and 12.5% at 6 and 12 months, respectively) than in the non-DPP-4i use subgroup (21.0% and 24.1% at 6 and

Table 1. Demographics, clinical characteristics, and diabetes medications

Variable	All (n = 80)	Non-DPP-4i use subgroup (n = 62)	DPP-4i use subgroup (n = 18)	P-value (DPP-4i vs. non-DPP-4i)
Age (years)	53.4 ± 10.5	54.1 ± 10.9	50.7 ± 8.3	0.23
Male sex	50 (62.5)	37 (59.7)	13 (72.2)	0.53
Duration of diabetes (years)	13.6 ± 8.4	13.1 ± 8.4	15.2 ± 8.1	0.35
Time from SGLT2i initiation to GLP-1RA initiation (days)	643 ± 482	666 ± 499	563 ± 420	0.43
BMI (kg/m^2)	30.7 ± 5.4	30.2 ± 5.1	32.1 ± 6.0	0.18
Body weight (kg)	85.4 ± 17.2	83.5 ± 16.2	92.0 ± 19.6	0.07
HbA1c (%)	8.9 ± 1.6	8.8 ± 1.8	9.3 ± 1.0	0.25
SBP (mmHg)	132.0 ± 15.8 [n = 67]	132.7 ± 16.4 [n = 51]	129.8 ± 13.7 [n = 16]	0.53
DBP (mmHg)	78.4 ± 9.7 [n = 67]	79.5 ± 10.2 [n = 51]	74.9 ± 7.0 [n = 16]	0.10
Number of OADs	2.1 ± 1.0	1.8 ± 1.0	3.0 ± 0.6	0.004
GLP-1RA				0.17
Dulaglutide	53 (66.3)	43 (69.4)	10 (55.6)	
Liraglutide	23 (28.8)	15 (24.2)	8 (44.4)	
Exenatide	4 (5.0)	4 (6.5)	0 (0.0)	
Concomitant diabetes medications at index date				
SGLT2i				0.77
Canagliflozin	8 (10.0)	6 (9.7)	2 (11.1)	
Dapagliflozin	14 (17.5)	12 (19.4)	2 (11.1)	
Empagliflozin	14 (17.5)	12 (19.4)	2 (11.1)	
Ipragliflozin	36 (45.0)	27 (43.5)	9 (50.0)	
Luseogliflozin	2 (2.5)	1 (1.6)	1 (5.6)	
Tofogliflozin	6 (7.5)	4 (6.5)	2 (11.1)	
Biguanide	57 (71.3)	44 (71.0)	13 (72.2)	0.92
Sulfonylurea	35 (43.8)	27 (43.5)	8 (44.4)	0.95
Thiazolidinedione	16 (20.0)	12 (19.4)	4 (22.2)	0.79
α-glucosidase inhibitor	13 (16.3)	8 (12.9)	5 (27.8)	0.13
Glinide	1 (1.3)	1 (1.6)	0 (0.0)	0.59
Insulin	28 (35.0)	22 (35.5)	6 (33.3)	0.87

Data are mean ± standard deviation or n (%).

BMI, body mass index; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter 2 inhibitor.

12 months, respectively) (**Figure 3a**). The HbA1c <7% achievement rate was lower in individuals with higher BMI than in individuals with lower BMI, and only 13.2% and 15.2% of individuals with BMI ≥30 kg/m^2 had achieved HbA1c <7% at 6 and 12 months, respectively (**Figure 3b**). Although 53.3% of individuals with baseline HbA1c <8% achieved HbA1c <7% by 12 months, only 7.7% of individuals with baseline levels ≥10% met this target (**Figure 3c**).

Changes in body weight

Small reductions (mostly <2 kg) in body weight were seen in the overall cohort and in most of the subgroups, and most of the changes were not statistically significant compared with baseline (**Figure 4**, **Supplementary Table 4**). The exception was the insulin non-user subgroup, which showed a significant decrease in body weight over time (mean change at 12 months = −2.2 kg), whereas weight was stable or increased (but not statistically significantly) in the insulin user subgroup (**Figure 4h**, **Supplementary Table 4**).

Discussion

This is the first study to evaluate the effect of adding a GLP-1RA to SGLT2i therapy on clinical outcomes in people with T2D in real-world Japanese clinical practice. In individuals who had been treated with an SGLT2i for ≥3 months, addition of a GLP-1RA significantly reduced HbA1c, and the effect was sustained over the 12-month observation period. Previous studies have demonstrated that adding an SGLT2i to a GLP-1RA improves

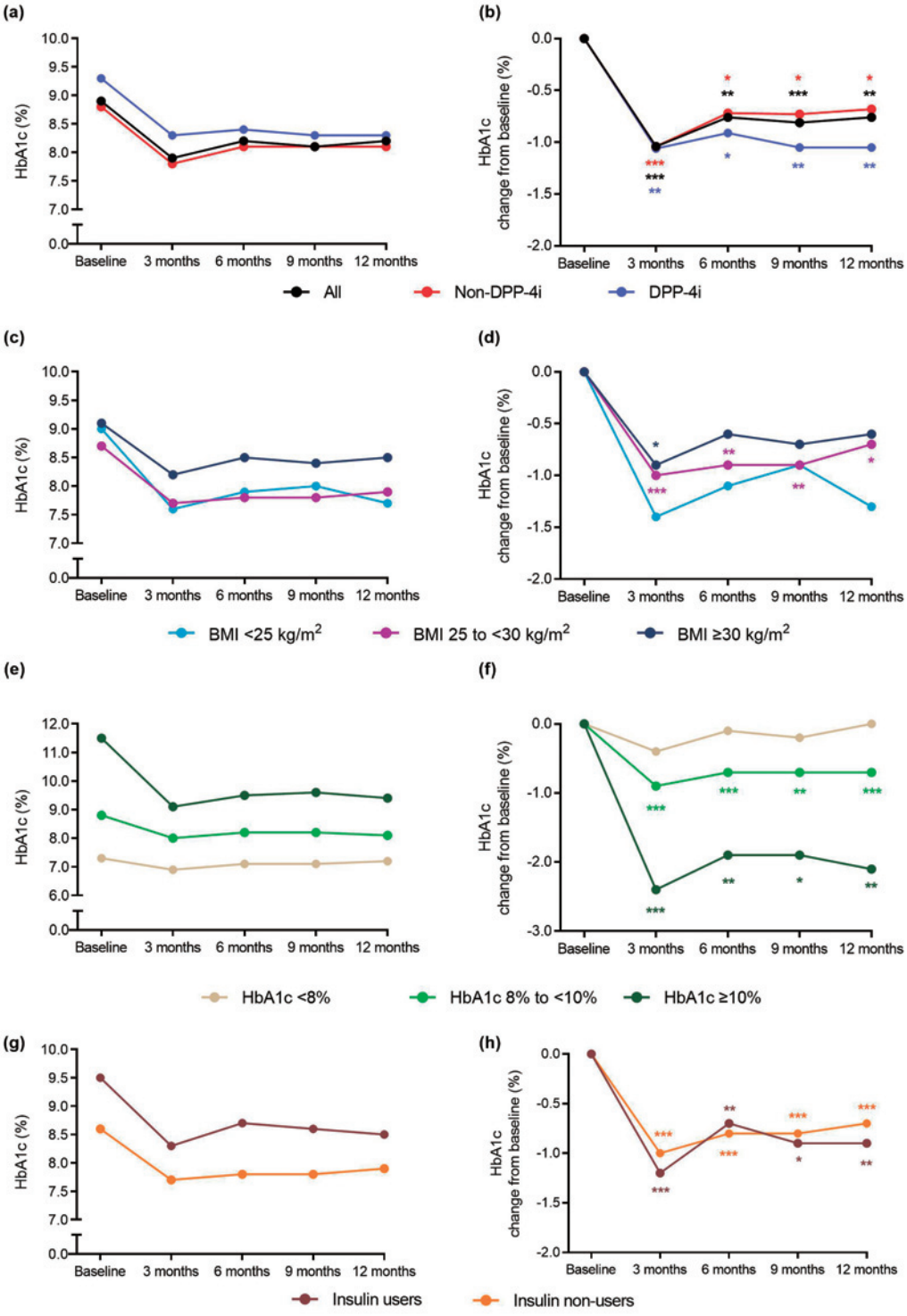

Figure 2. Changes in glycated hemoglobin (HbA1c) levels over 12 months after adding a glucagon-like peptide-1 receptor agonist (GLP-1RA) to a sodium-glucose cotransporter 2 inhibitor (SGLT2i). (**a**) HbA1c levels and (**b**) change from baseline HbA1c levels for all individuals (black; n = 80), the dipeptidyl peptidase-4 inhibitor (DPP-4i) use subgroup (blue; n = 18), and the non-DPP-4i use subgroup (red; n = 62). (**c**) HbA1c and (**d**) change from baseline HbA1c for the body mass index (BMI) <25 kg/m^2 subgroup (light blue; n = 11), the BMI 25 to <30 kg/m^2 subgroup (purple; n = 31), and the BMI ≥30 kg/m^2 subgroup (dark blue; n = 38). (**e**) HbA1c and (**f**) change from baseline HbA1c for the baseline HbA1c <8% subgroup (tan; n = 20), the baseline HbA1c 8% to <10% subgroup (light green; n = 45), and the baseline HbA1c ≥10% subgroup (dark green; n = 15). (**g**) HbA1c and (**h**) change from baseline HbA1c for the insulin user subgroup (brown; n = 28) and the insulin non-user subgroup (orange; n = 52). *P < 0.05; **P < 0.01; ***P ≤ 0.001 vs. baseline.

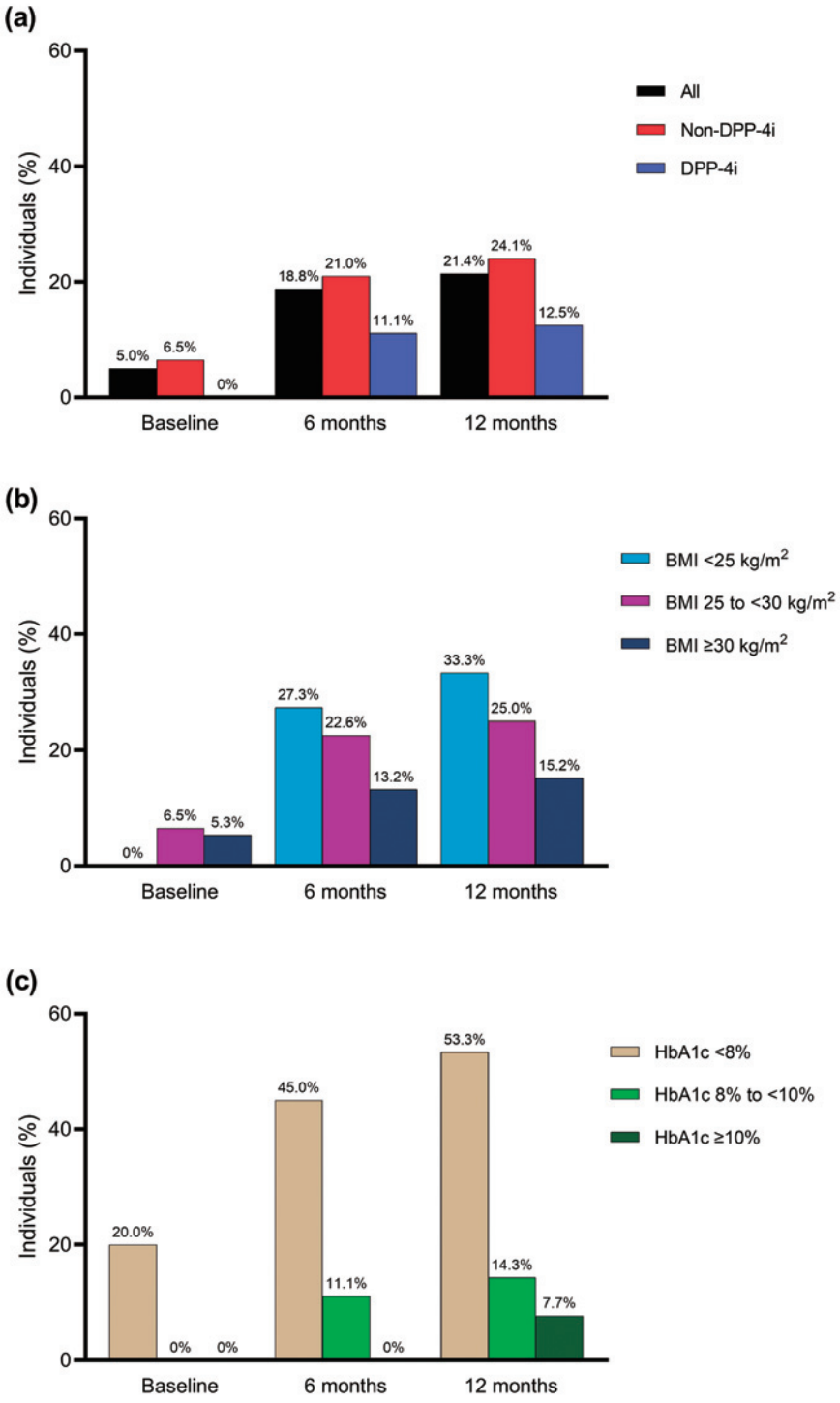

Figure 3. Proportion of individuals with glycated hemoglobin (HbA1c) levels <7% at baseline and at 6 and 12 months after adding a glucagon-like peptide-1 receptor agonist (GLP-1RA) to a sodium-glucose cotransporter 2 inhibitor (SGLT2i).

(**a**) All individuals (black; n = 80), dipeptidyl peptidase-4 inhibitor (DPP-4i) use subgroup (blue; n = 18), and non-DPP-4i use subgroup (red; n = 62). (**b**) Body mass index (BMI) <25 kg/m^2 subgroup (light blue; n = 11), BMI 25 to <30 kg/m^2 subgroup (purple; n = 31), and BMI ≥30 kg/m^2 subgroup (dark blue; n = 38). (**c**) Baseline HbA1c <8% subgroup (tan; n = 20), baseline HbA1c 8% to <10% subgroup (light green; n = 45), and baseline HbA1c ≥10% subgroup (dark green; n = 15).

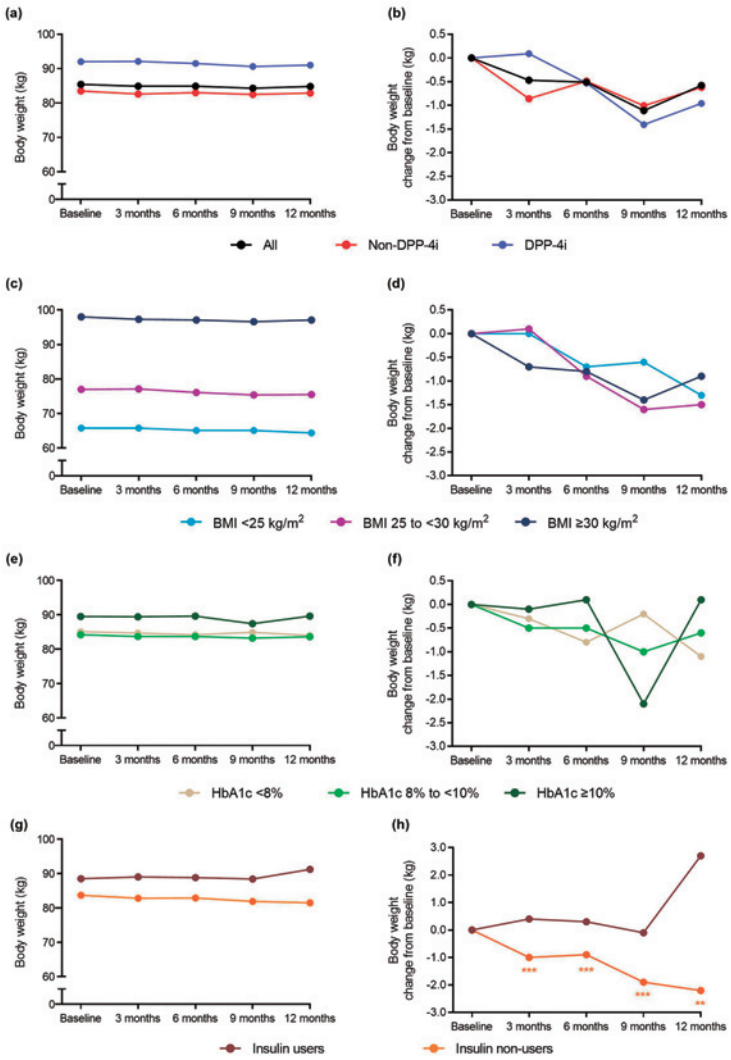

Figure 4. Body weight changes over 12 months after adding a glucagon-like peptide-1 receptor agonist (GLP-1RA) to a sodium-glucose cotransporter 2 inhibitor (SGLT2i).
(**a**) Body weight and (**b**) change from baseline body weight for all individuals (black; n = 80), the dipeptidyl peptidase-4 inhibitor (DPP-4i) use subgroup (blue; n = 18), and the non-DPP-4i use subgroup (red; n = 62). (**c**) Body weight and (**d**) change from baseline body weight for the body mass index (BMI) <25 kg/m^2 subgroup (light blue; n = 11), the BMI 25 to <30 kg/m^2 subgroup (purple; n = 31), and the BMI ≥30 kg/m^2 subgroup (dark blue; n = 38). (**e**) Body weight and (**f**) change from baseline in body weight for the baseline glycated hemoglobin (HbA1c) <8% subgroup (tan; n = 20), the baseline HbA1c 8% to <10% subgroup (light green; n = 45), and the baseline HbA1c ≥10% subgroup (dark green; n = 15). (**g**) HbA1c and (**h**) change from baseline HbA1c for the insulin user subgroup (brown; n = 28) and insulin non-user subgroup (orange; n = 52). **P < 0.01; ***P ≤ 0.001 vs. baseline.

glycemic control in Japanese patients with T2D;[13-18] however, until now, there was no evidence that adding a GLP-1RA to SGLT2i therapy was beneficial in people from Japan, as has been shown in people from other countries.[8, 11, 12, 21]

Significant and sustained decreases in HbA1c were seen in the BMI 25 to <30 kg/m^2 subgroup; in contrast, in the higher BMI (≥30 kg/m^2) subgroup, the significant decrease at 3 months was not seen at subsequent time points. Similar results were seen in a Japanese open-label pilot study of switching from sitagliptin to dulaglutide, in which BMI was inversely correlated with change in HbA1c at 6 months.[22] The current results suggest that Japanese people with T2D and high BMI do not respond adequately to dual GLP-1RA and SGLT2i therapy and may require more intensive treatment approaches. For example, during most of the observation period of this study, the approved maximum doses of the GLP-1RAs

dulaglutide (0.75 mg/week) and liraglutide (0.9 mg/day until May 2019; 1.8 mg/day after May 2019) in Japan were half the doses approved in many other countries, which may not have been sufficient for achieving adequate glycemic control in obese individuals. Further, the limited effectiveness of dual therapy in this subgroup may be related to the lack of significant weight loss in these individuals.

The reduction in HbA1c was observed in both the subgroup of individuals who switched from a DPP-4i to a GLP-1RA and in the subgroup of individuals who had not received previous DPP-4i therapy. The DPP-4i class is generally more effective in Asian populations than in non-Asian populations, primarily because of differences in BMI,[23] and these drugs are prescribed more frequently in Japan than in the United States.[6, 24] Notably, on average, the individuals in this study, particularly in the DPP-4i use subgroup, were younger, had a higher BMI, and had a higher baseline HbA1c level than typical Japanese people with T2D.[6, 25] This difference reflects the study population of individuals on SGLT2i therapy because, in Japan, SGLT2is are preferentially prescribed to those with a higher BMI.[6] These people are often treatment resistant,[26] and this possibility is supported by the high number of OADs used in the DPP-4i use subgroup (mean of 3.0 per person), indicating that most of these individuals could not achieve HbA1c targets despite triple oral therapy.[26] Therefore, these people may be considered good candidates for GLP-1RA therapy, partly because GLP-1RAs are associated with greater weight loss than other antidiabetic medications.[27] In the absence of SGLT2i, switching from a DPP-4i to a GLP-1RA has been shown to effectively reduce HbA1c in individuals with a mean BMI >30 kg/m^2, including in Japanese people.[28-30] Although switching from a DPP-4i to a GLP-1RA was associated with weight loss in non-Japanese patients,[28, 29] no significant change in body weight was observed in Japanese individuals despite reductions in HbA1c,[30] similar to what was observed in our study. The results of this real-world observational study indicate that significant improvements in glycemic control can be achieved by adding a GLP-1RA to an SGLT2i, even in the absence of weight loss.

In this study, addition of a GLP-1RA to an SGLT2i was effective in significantly reducing HbA1c in the baseline HbA1c ≥8% subgroup. HbA1c decreased most markedly in the baseline HbA1c ≥10% subgroup, where large decreases of >2% were observed. Clinically meaningful decreases in HbA1c (−0.7%) were also seen in the subgroup of individuals with baseline levels of 8% to <10%. The relationship between baseline HbA1c level and the magnitude of improvement is not unexpected and is consistent with a subgroup analysis of data from a previous randomized trial of liraglutide as add-on to SGLT2i therapy.[31] Similarly, in a Japanese open-label pilot study of switching from sitagliptin to dulaglutide, baseline HbA1c was correlated with change in HbA1c after 6 months.[22] In our study, although HbA1c did not decrease significantly in the subgroup with lower baseline HbA1c (<8%), the proportion of individuals in this subgroup who reached the HbA1c target of <7% increased from 20% at baseline to 53.3% at 12 months, indicating that further improvements can be achieved even in those whose baseline HbA1c is close to the target.

This is the first real-world analysis of the clinical effects of adding a GLP-1RA to an SGLT2i in people with T2D in Japan. This study used a well-established diabetes database that has been collecting data for more than a decade. However, because the database is from a single medical center, the sample size was limited, especially for some of the subgroups in the analysis, and the target sample size was not reached. In addition, there was an unexpected imbalance in the number of individuals in the DPP-4i use subgroups, making it difficult to interpret the effects of switching from a DPP-4i to a GLP-1RA.

Conclusions

Addition of a GLP-1RA to SGLT2i therapy reduces HbA1c levels in Japanese individuals with T2D, regardless of previous DPP-4i use. However, significant improvements in HbA1c levels could not be sustained in the subgroup of individuals with BMI ≥30 kg/m^2, suggesting that these people may require more intensive treatment to achieve long-term glycemic control.

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