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Original

Changing from a Dipeptidyl Peptidase (DPP)-4 Inhibitor to Oral Semaglutide in Patients with Poorly Controlled Type 2 Diabetes Mellitus: An Observational Study

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Summary

Aims: The aim of the present study was to evaluate the effect of changing from a dipeptidyl peptidase (DPP)-4 inhibitor to oral semaglutide on glycemic control, as reflected by hemoglobin A1c (HbA1c), occasional plasma glucose (PG) and glycoalbumin (GA), and body weight (BW) in routine clinical practice.

Patients and Methods: A search of electronic medical records was performed for patients treated with a DPP4 inhibitor for diabetes mellitus and who were then changed to oral semaglutide because of relatively poor glycemic control from December 2021 to March 2022. A total of 19 patients met these inclusion criteria. Data for these patients were evaluated until the end of August 2022.

Results: HbA1c and occasional PG were significantly decreased compared to baseline (the time of changing treatment) at 4 months and at the final visit (a mean of about 6 months). GA was significantly decreased from baseline at 1 month, 4 months, and at the final visit. BW was also significantly decreased from baseline at 4 months and the final visit. There were no statistically significant changes in low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) or estimated glomerular filtration rate (eGFR).

Conclusion: These results of the present study show that changing from a DPP4 inhibitor to oral semaglutide significantly improved glycemic control, as reflected by HbA1c, occasional PG and GA, and led to a significant reduction in BW after an observational period of over 4 months.

Key Words: oral semaglutide, DPP4 inhibitor, type 2 diabetes

Introduction

Strict glycemic control by intensive therapy with antidiabetic medications, in addition to diet and exercise therapy, can prevent progression of complications of type 2 diabetes mellitus, including microangiopathies such as neuropathy, retinopathy and nephropathy, and cardiovascular disease, including ischemic heart disease, stroke and peripheral arterial disease[1-3].

Glucagon-like peptide-1 (GLP-1) is an intestinal incretin hormone that suppresses the rapid increase of circulating postprandial glucose by promoting insulin se-

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cretion by pancreatic β cells, decreasing release of glucagon by pancreatic α cells, delaying gastric emptying, and inhibiting food intake[4-7]. GLP-1 receptor agonists (GLP-1RAs) that mimic the effects of GLP-1 are now widely used clinically and are beneficial for treatment of patients with type 2 diabetes mellitus. As with other peptide-based drugs, GLP-1RAs have very low bioavailability and need to be injected due to degradation by proteolytic enzymes and the low pH in the gastrointestinal tract[8].

Semaglutide is a long-acting GLP-1RA that has 95% homology with human native GLP-1 and is administered by subcutaneous injection once weekly[9]. An oral form of semaglutide has recently been developed as a coformulation with a permeation enhancer, sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC), which promotes absorption of semaglutide in the stomach. Oral semaglutide has as strong a glucose-lowering effect as subcutaneous GLP-1RAs[10-12] and also has a protective effect against cardiovascular events, especially for cardiovascular mortality when given at a high dose (14 mg daily)[13].

Oral semaglutide has a stronger glucose-lowering effect than dipeptidyl peptidase (DPP)-4 inhibitors (DPP4-Is) such as sitagliptin, which inhibit degradation of GLP-1, resulting in the elevation of circulating active GLP-1 levels[14]. Therefore, changing from a DPP4-I to oral semaglutide may be clinically beneficial for patients with poor glycemic control. Oral semaglutide was released in February 2021 in Japan and long-term prescriptions, which allows for easier administration in a greater number of patients, have been permitted since December 2021. In this observational study, the effects of changing from a DPP4-I to oral semaglutide on glycemic control and body weight (BW) were examined in routine clinical practice by observing changes in patients who had already made this change in therapeutic strategy.

Patients and Methods

Outpatients with type 2 diabetes mellitus who received regular treatment for glycemic control from the same physician (K.T.: first author) at Dokkyo Medical University Saitama Medical Center were eligible for the study. A search of electronic medical records (EMRs) from December 2021 to March 2022 was used to identify patients who had received a DPP4-I for diabetes and had then changed to oral semaglutide because of relatively poor glycemic control, based on the judgement of the managing physician. A total of 19 patients (8 men, 11 women) met the inclusion criteria and were enrolled in the present study. Most of the patients (n = 16) had changed from sitagliptin 50 mg once daily to oral semaglutide, 2 had changed from anagliptin 100 mg twice daily, and one from teneligliptin 20 mg once daily.

Data for glycemic control and related blood chemistry tests were evaluated at several time points: the final visit before the change to semaglutide, baseline (the time of the change from a DPP4-I to oral semaglutide), 1 month and 4 months after baseline, and at the final visit (5-8 months after baseline). All patients underwent examination at each of these time points. Data from EMRs were evaluated until the end of August 2022. The mean interval between the final visit before the change to semaglutide and baseline was 2.7 ± 0.6 months. The periods from baseline to the final visit were 5 (n = 6), 6 (n = 6), 7 (n = 5), and 8 (n = 2) months, with a mean of 6.2 ± 1.0 months.

All patients except one changed from a DPP4-I to 3 mg of oral semaglutide for the first month, after which the dose was increased to 7 mg. The dose was subsequently increased to 14 mg at 6 months after baseline in two patients due to an insufficient effect; both of these patients had received sitagliptin. One patient who changed from anagliptin took oral semaglutide 3 mg for 5 months due to transient mild appetite loss; subsequently, the dose was increased to 7 mg. The clinical characteristics of all 19 patients at baseline are shown in the Table.

When the change from DPP4-I to oral semaglutide was made, all patients were required to confirm and strengthen diet and exercise therapy, as possible. Recommended diet and exercise therapy includes: recommended daily calorie intake amount is $[\text{height(m)}/100]^2 \times 22 \times 30$ as a general rule (if the patient's BMI was 25 or more, the patient first aimed to achieve a 3% reduction of current BW), with carbohydrate being approximately 60% of the entire caloric intake and a handful of vegetables. Recommended exercise is walking 40-60 min daily at approximately 80 m/min (exercise may be reduced or suspended according to physi-

Table Clinical features and laboratory data at baseline in patients with Type 2 Diabetes Mellitus

Number (male/female)	19 (8/11)
Age (years)	63.9 ± 12.7
BMI (kg/m^2)	26.8 ± 5.0
Duration of diabetes, years (n)	
0-4	2
5-9	6
10-14	5
> 15	6
HbA1c (%)	9.5 ± 0.8
GA (%)	23.8 ± 5.0
PG (mg/dL)	261.7 ± 53.5
LDL-C (mg/dL)	125.3 ± 34.8
TG (mg/dL)	177.4 ± 59.8
eGFR (ml/min/1.73 m^2)	68.5 ± 15.6
Weight (kg)	69.9 ± 15.8
Diabetic therapy (n)	
Sulfonylureas and glinides	16
Metformin	16
Pioglitazone	0
αGI	2
SGLT2-I	4
DPP4-I	19
Insulin	0

Data are expressed mean ± standard deviation.
Baseline: first visit during December 2021 and March 2022
n: number of the patients
BMI: body mass index, HbA1c: hemoglobin A1c, GA: glycoalbumin, PG: occasional plasma glucose, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate
Diabetic therapy: αGI: α glucosidase inhibitors, DPP4-I: dipeptidyl peptidase 4 inhibitors, SGLT2-I: sodium glucose cotransporter 2 inhibitors
In therapies, most patients were receiving combination therapy for diabetes.

cal condition).

Ethical considerations

The study was approved by the Institutional Ethics Committee at Dokkyo Medical University Saitama Medical Center with a 5-month opt-out period (no. 22004, date: 3/26/2022).

Statistical analysis

Differences in hemoglobin A1c (HbA1c), occasional plasma glucose (PG), glycoalbumin (GA), BW, low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and estimated glomerular filtration rate (eGFR) before administration and at baseline, at one month, 4 months and at the final visit were evaluated using repeated measures analysis of variance (ANOVA) with a *post-hoc* Holm test. Correlation of changes in HbA1c, GA and BW before and after the change to oral semaglutide were evaluated using Pearson correlation analysis. All analyses were performed using BellCurve for Excel software (Social Survey Research Information Co., Ltd, Tokyo, Japan). A two-sided $P < 0.05$ was taken to indicate statistical significance.

Results

HbA1c (n = 19) showed a significant increase from the visit before changing to oral semaglutide to baseline, and then decreased from baseline to 4 months and at the final visit (Fig. 1A). Occasional PG (n = 19) showed a similar significant reduction from baseline to 4 months and at the final visit (Fig. 1B). GA (n = 17) did not differ significantly at baseline compared to the last visit before changing, but significantly decreased from baseline to one month, 4 months and at the final visit (Fig. 1C). There were no significant differences in LDL-C (n = 18), TG (n = 18) and eGFR (n = 19) at all time points (Fig. 1D-F). There was also a significant decrease of BW (n = 19) from baseline to 4 months and at the final visit (Fig. 1G).

In a subset analysis including only patients who changed from sitagliptin to oral semaglutide (n = 16), HbA1c levels were respectively, 9.6 ± 0.9, 9.1 ± 0.9, 7.1 ± 1.0, 7.2 ± 1.0% at baseline, 1, 4 months and at the final visit; a significant decrease was noted at 4 months and at the final visit ($P < 0.001$ and $P < 0.001$). Of the 2 patients who changed from anagliptin to oral semaglutide, one received semaglutide at 3 mg for 5 months before the dose was increased to 7 mg until the final visit. In this patient, HbA1c decreased from 9.2% at baseline to 7.5% at 4 months and 7.1% at the final visit. In the other patient who changed from anagliptin, HbA1c similarly decreased from 9.6% at baseline to 8.0% at 4 months and 6.5% at the final visit. The patient who changed from teneligliptin to semaglutide had a HbA1c of 9.7%, 9.7% and 8.6% at baseline, 4 months and the final visit, respectively. There were no

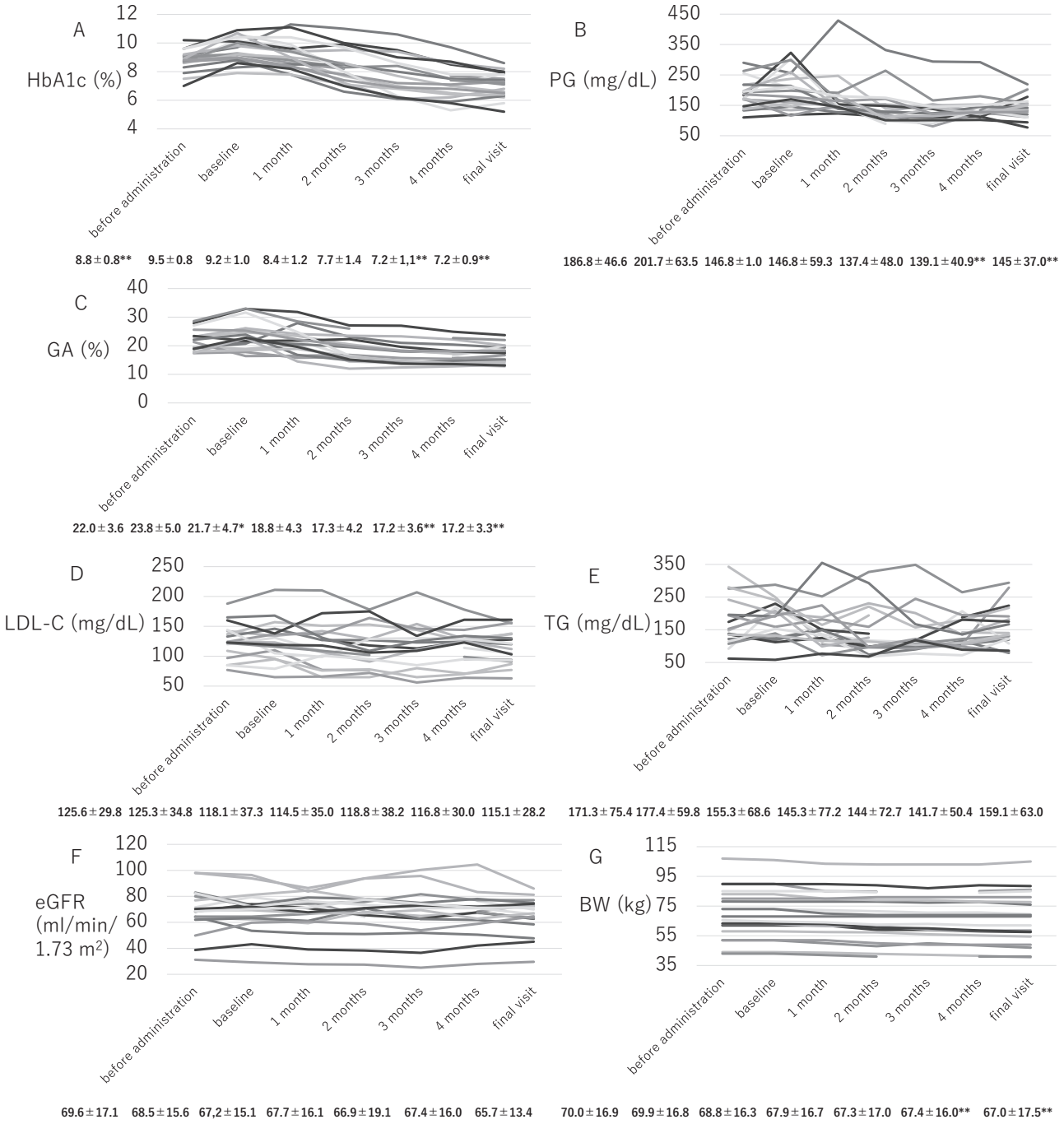

Figure 1 Changes in HbA1c (A), occasional PG (B), GA (C), LDL-C (D), TG (E), eGFR (F), BW (G) in the observational period. *P <0.05, **P <0.001. HbA1c: hemoglobin A1c, PG: plasma glucose, GA: glycoalbumin, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, BW: body weight

significant correlations between the difference in HbA1c at baseline and 4 months and that of BW (R = 0.219, P = 0.2254), and as well as that of GA and BW (R = 0.3783, P = 0.1343). A significant positive correlation was noted between the difference of HbA1c at baseline and 4 months and that of GA (R = 0.8715, P < 0.001; Fig. 2).

Discussion

In this study, HbA1c at the time of changing to semaglutide (baseline) was significantly elevated compared with that at the final visit before starting oral semaglutide. This is a reasonable result because the DPP4-I was changed to oral semaglutide for patients

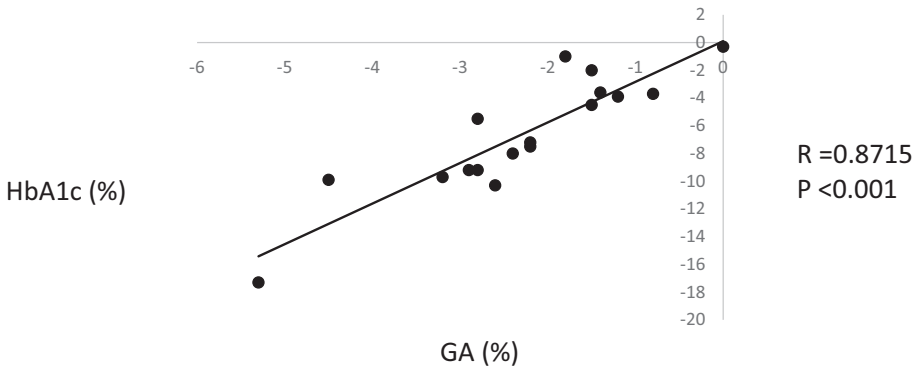

Figure 2 Correlation between the changes of HbA1c from baseline to 4 months and those of GA. HbA1c: hemoglobin A1c, GA: glycoalbumin

with worsened glycemic control. The semaglutide dose was 3 mg during the first month and 7 mg in the next 3 months, except for one patient who received 3 mg of semaglutide for 5 months and subsequently received a dose of 7 mg. The dose was increased to 14 mg after 6 months in two patients. HbA1c significantly decreased from a mean of 9.5% at baseline to 7.2% at 4 months and at the final visit at a mean of about 6 months. All patients in the present study were changed to oral semaglutide from a DPP4-I, rather than addition of semaglutide, but the extent of reduction of HbA1c of 2.3% was larger than that of 1.7% found in the PIONEER10 trial at 26 weeks with 7 mg of oral semaglutide. This is notable because in the PIONEER10 trial in Japanese patients with type 2 diabetes mellitus, oral semaglutide or a control (dulaglutide) was added, rather than changing from the previously administered medication[15]. The difference in reduction of HbA1c may be due to the fact that the baseline HbA1c of 9.5% in patients in the present study is higher than the 8.3% in the PIONEER10 trial (and also higher than that of 7.4 ± 1.1% in all outpatients examined by the first author[16]). Therefore, it is likely that the high baseline HbA1c in the present study resulted in a greater reduction compared with that in the PIONEER10 trial. In addition, all patients in the present study were asked to increase their diet and exercise therapy after the change to oral semaglutide, and this increased motivation for diet and exercise may have enhanced the effect of semaglutide.

Changing to oral semaglutide significantly reduced PG from baseline to 4 months and at the final visit. Unlike fasting PG, which was measured in the PIONEER 10 trial, occasional PG was evaluated in this study. Therefore, it is difficult to accurately evaluate the effect of oral semaglutide on PG in the present study because the time to the blood test after breakfast appears to have been irregular in most patients. Occasional PG levels generally show large fluctuations, which can cause difficulty in determining statistical significance. Thus, the significant reduction in occasional PG may reflect the strong glucose-lowering effect of oral semaglutide. However, an additional prospective study, in which the time from breakfast to the blood test is controlled, would be warranted to assess this effect more closely. We also investigated the effect of oral semaglutide on GA levels. These results are of particular interest because few studies have examined this effect. The change to oral semaglutide significantly reduced GA from baseline at one and 4 months and at the final visit. The significant change in GA at 1 month, in contrast to that for HbA1c, is reasonable because the GA level reflects shorter-term glycemic control over 2-4 weeks, whereas HbA1c levels reflect changes over 2-3 months[17,18]. The findings for GA at 1 month suggests that semaglutide can improve glycemic control from a time before the effect is reflected by HbA1c levels.

BW was also significantly reduced at 4 months and at the final visit after changing to oral semaglutide. This is consistent with the results of the PIONEER10 trial, although the extent of reduction is larger in the present study compared with that in the PIONEER10 trial, despite similar BWs of approximately 70 kg at baseline in the two studies. We speculate that this may have been at least partially due to a possible change in

motivation for diet and exercise therapy after changing the medication. However, changing to oral semaglutide had no significant effect on lipid levels such as LDL-C and TG, or on renal function reflected by eGFR. The findings of the latter are consistent with the results of the PIONEER5 trial, in which oral semaglutide also had no effect on eGFR[19].

The limitations of the current study include the small number of patients and the relatively short observation period. Thus, a study of more patients and for a longer observational period is needed. Due to the observational design, a control group was not used. The change in blood pressure by changing to oral semaglutide could not be evaluated due to lack of an accurate description of data on blood pressure in EMRs in most patients. It may have been interesting if the correlation between the changes in blood pressure by oral semaglutide and those of BW were assessed because a significant reduction of BW was observed. This is also one of the limitations in the present study. However, changing from a DPP4-I to oral semaglutide mainly at a dose of 7 mg provides a good match to routine clinical practice. The results may show a compound effect of oral semaglutide and greater motivation for diet and exercise therapy based on the change of drug, and these findings may be particularly informative for clinicians.

In conclusion, in this study of patients with poorly controlled type 2 diabetes, changing from a DPP4-I to oral semaglutide significantly improved glycemic control, as reflected by HbA1c, occasional PG and GA, after 4 months. The change to oral semaglutide also significantly reduced BW after a similar time interval.

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Compliance with Ethical Standards

Informed consent: Information on this retrospective study was posted during a 5-month opt-out period.

Ethical approval: The study was approved by the institutional ethics committee at Dokkyo Medical University Saitama Medical Center: Approval no. 22004, date 3/26/2022.

Conflict of interest statement: None of the authors have a conflict of interest to declare.

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