Scientific Research Publishing

Journal of Diabetes Mellitus, 2025, 15(2), 93-106
https://www.scirp.org/journal/jdm
ISSN Online: 2160-5858
ISSN Print: 2160-5831

Efficacy of Oral Semaglutide after Switching from DPP-4 Inhibitors on Glucose Level and Body Weight Control in Japanese Type 2 Diabetes Patients with Obesity

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How to cite this paper: Okamoto, A., Yokokawa, H., Morimoto, A., Goto, K., Fukuda, H., Hisaoka, T. and Naito, T. (2025) Efficacy of Oral Semaglutide after Switching from DPP-4 Inhibitors on Glucose Level and Body Weight Control in Japanese Type 2 Diabetes Patients with Obesity. *Journal of Diabetes Mellitus*, **15**, 93-106.
https://doi.org/10.4236/jdm.2025.152007

Received: February 20, 2025
Accepted: May 18, 2025
Published: May 21, 2025

Abstract

Background and Objective: Although oral semaglutide may be considered as a suitable treatment option for obese patients with type 2 diabetes mellitus (T2DM) inadequately responsive to dipeptidyl peptidase (DPP)-4 inhibitor–based therapy, evidence from actual clinical settings remains limited. This study aimed to investigate the effect of oral semaglutide in obese patients with T2DM who had an inadequate response to DPP-4 inhibitor–based therapy. **Methods:** This study was a retrospective, single-center study in which outpatients with T2DM were 1) aged 20 years or older at the time of oral semaglutide administration, 2) treated with an existing DPP-4 inhibitor for 3 months and/or longer at the time of oral semaglutide administration, and 3) had a hemoglobin A1c (HbA1c) level of ≥ 6.5% and/or a body mass index (BMI) ≥ 25.0 kg/m^2. The primary endpoints were changes in HbA1c and body weight from baseline to 6 months after oral semaglutide treatment switching from DPP-4 inhibitor. **Results:** In the 48 patients studied, HbA1c was 7.01 ± 0.54%, and BMI was 26.7 ± 3.6 kg/m^2 at baseline. HbA1c significantly decreased by 0.68 ± 0.36%, and body weight significantly decreased by 3.4 ± 2.3 kg ($p < 0.001$ for each). Improvements in indices of lipid metabolism and liver function were observed. Non-serious nausea and loss of appetite were observed in many patients, but these symptoms resolved in approximately 3 months. Mild constipation was also observed. **Conclusion:** Oral semaglutide appears to be a promising alternative to DPP-4 inhibitors as a means of glycemic and weight control in obese T2DM.

Keywords

Semaglutide, Type 2 Diabetes Mellitus, DPP-4 Inhibitors, HbA1c, Body Weight

1. Introduction

Incretin-related medications were introduced in 2009 in Japan, and they are widely used as a drug treatment for type 2 diabetes mellitus (T2DM) in clinical settings. Glucagon-like peptide 1 (GLP-1) belongs to the incretin hormone family and is secreted in the small intestine after a meal to stimulate insulin secretion in a glucose-dependent manner via GLP-1 receptors [1] [2]. GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4), and the half-life of GLP-1 is approximately 2 minutes [3]. As GLP-1 secretion is reduced in T2DM, DPP-4 inhibitors were developed, and sitagliptin was introduced in 2006 for the treatment of T2DM.

DPP-4 inhibitors suppress DPP-4 activity by more than 80% and increase the concentration of biologically active GLP-1 approximately 2-fold [4], resulting in a significant reduction in postprandial blood glucose levels [5] and a reduction in the hemoglobin A1c (HbA1c) level of approximately 0.8% [6]. Another benefit of DPP-4 inhibitors is that they do not increase the risk of hypoglycemia, possibly via potentiating effects on endogenous GLP-1 [7].

GLP-1 receptor agonists (GLP-1 RAs), which exogenously stimulate the GLP-1 receptor, have been developed and are being utilized in clinical settings. As GLP-1 RAs achieve higher than physiological concentrations of GLP-1, GLP-1 RAs show various effects in addition to hypoglycemic effects in the treatment to T2DM. For example, GLP-1 RAs promote weight loss, which is thought to be due to delayed gastric emptying and central appetite suppressive effects [2]. It has also been suggested that delayed gastric emptying is more important than insulin secretion in regulating postprandial hyperglycemia [8].

Semaglutide, a human GLP-1 analogue with 94% structural homology to GLP-1, reportedly exhibits improved binding to albumin through binding of long-chain fatty acids and resistance to degradation by DPP-4 due to partial replacement of amino acids [9]. This modification results in a half-life of approximately 7 days for semaglutide, which can be controlled by administering the drug subcutaneously once a week. Semaglutide was approved for use in the United States in 2017 as a long-acting GLP-1 RA. In a series of Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) studies, subcutaneous semaglutide (0.5 mg or 1.0 mg) was shown to be effective in reducing body weight as well as significantly lowering blood glucose [10] [11].

The addition of a fatty acid derivative, N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), improved the gastrointestinal absorption of semaglutide and made it possible to administer the drug orally [12]. The once-daily oral formulation of semaglutide was evaluated for hypoglycemic effects in a series of Peptide Innova-

tion for Early Diabetes Treatment (PIONEER) studies [13] [14]. In the PIONEER 3 trial, oral semaglutide (7 mg and 14 mg/day) showed a significant decrease in HbA1c compared to the DPP-4 inhibitor sitagliptin (100 mg/day) in patients with T2DM inadequately responsive to metformin, while at the same time promoting a significant decrease in body weight [15].

Although these findings suggest that oral semaglutide may be a suitable treatment option for obese T2DM patients inadequately responsive to DPP-4 inhibitor–based therapy, evidence from actual clinical settings remains limited. In the present study, we investigated the effectiveness of oral formulation of semaglutide switching from a DPP-4 inhibitor in actual clinical practice.

2. Methods

2.1. Study Design

This was a retrospective, single-center study conducted at the Okamoto Internal Medicine Clinic, Tokyo, Japan, from April 1, 2021, to October 31, 2021. The follow up duration was 6 months after the initiation of oral semaglutide.

The study subjects were patients with T2DM who visited the Okamoto Internal Medicine Clinic for treatment of diabetes mellitus every month. Among them, eligible participants were prescribed semaglutide switching from a DPP-4 inhibitor due to HbA1c ≥ 6.5% and/or a body mass index (BMI) ≥ 25.0 kg/m^2 during the study period. Othe eligibility criteria were: 1) age ≥ 20 years at the time of oral semaglutide administration, and 2) treated with an existing DPP-4 inhibitor for 3 months or longer at the time of oral semaglutide administration. Exclusion criteria were: 1) patients with a history of pancreatitis, 2) patients with severe gastrointestinal disorders, such as severe gastroparesis, 3) patients who experienced severe hypoglycemia with conventional therapy, 4) pregnant or lactating patients, 5) patients with severe renal dysfunction, and 6) patients being treated with a GLP-1 RA.

Oral semaglutide was started at a dose of 3 mg once daily and increased to 7 mg once daily after 4 weeks. If 7 mg of oral semaglutide once daily for 4 weeks or longer was not effective, the dose was increased to 14 mg once daily. The dosages and administration of antihyperglycemic drugs that had been administered before oral semaglutide were increased or decreased depending on the status of glycemic control in each patient.

2.2. Evaluation Parameters

The starting date of oral semaglutide was recognized as baseline. Age, sex, and height at baseline were recorded. Overnight fasting blood samples and urine samples, along with body weight, blood pressure measurements, and heart rate, were collected at baseline and 6 months after oral semaglutide administration. BMI was calculated as weight (kg) divided by height (m) squared. HbA1c was measured using high-performance liquid chromatography (HPLC) and expressed as National Glycohemoglobin Standardization Program (NGSP) levels. Creatinine, uric

acid, triglycerides, total cholesterol (TC), high-density-lipoprotein (HDL) cholesterol (HDL-C), and low-density-lipoprotein (LDL) cholesterol (LDL-C) were measured as evaluation parameters. LDL-C was estimated using the Friedewald equation ([TC] – [HDL-C] – [TG/5]) [16]. In addition, aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (*γ*-GTP), white blood cell count, red blood cell count, hemoglobin content, hematocrit, albumin, and urea nitrogen were measured to investigate the safety of semaglutide oral formulation. Estimated glomerular filtration rate (eGFR) was calculated using the following formula [17].

Male: eGFR = 194 × serum creatinine − 1.094 × age − 0.287.

Female: Male × 0.739.

2.3. Endpoints

The primary endpoints were changes in HbA1c and body weight from baseline to 6 months after oral semaglutide administration. The secondary endpoint was achieving HbA1c < 6.5% after oral semaglutide treatment. Changes in the dosage and administration of concomitant hypoglycemic drugs were also assessed as secondary endpoints. The discontinuation and dosage reduction of insulin secretagogues was considered based on participants' improvement of the glycemic control during the observation period. For safety assessment, adverse events (including changes in laboratory test values) for which a relationship to oral semaglutide could not be ruled out were defined as adverse drug reactions.

2.4. Statistical Analysis

Continuous variables in the text or tables are expressed as mean ± standard deviation (SD), and non-normally distributed data are expressed as median and interquartile ranges. Comparisons of values between baseline and 6 months after oral semaglutide were made using paired *t*-tests or Wilcoxon rank sum tests. Comparisons between patient populations were made using unpaired *t*-tests or Mann-Whitney *U* tests. Pearson's correlation coefficients were also obtained for changes in HbA1c and body weight. The analysis was based on R Commander's Easy R (EZR) ver. 1.4. Mediating 1 and R ver. 3.5. 2 (The R Foundation for Statistical Computing, Vienna, Austria) were used for this study [18], and a two-sided p value of < 0.05 was considered statistically significant.

2.5. Ethics Approval and Consent to Participate

The study protocol was approved by the Clinic Committee of Okamoto Internal Medical Clinic, and the study was conducted in compliance with the Declaration of Helsinki [19] and the Japanese Ethical Guidelines for Medical Research Involving Human Subjects [20]. The research protocol was reviewed and approved by the Ethics Committee of Juntendo University (no. E21-0347), and written, informed consent was obtained from all participants.

3. Results

A total of 48 patients were observed for up to 6 months after switching from DPP-4 inhibitors to oral semaglutide (Table 1). There were 30 males and 18 females, aged 60.9 ± 10.1 years (35 to 78 years). Duration of diabetes was 12.2 years ± 4.5 years. Throughout the observation period, there were no participants to discontinue oral semaglutide due to adverse drug reactions. Before switching to oral semaglutide, the mean HbA1c was 7.01 ± 0.54%, and BMI was 26.7 ± 3.6 kg/m^2. DPP-4 inhibitors before switching to oral semaglutide included linagliptin in 22 patients, sitagliptin in 15 patients, vildagliptin in 9 patients, and alogliptin and teneligliptin in 1 patient each. When the standard daily dose of each DPP-4 inhibitor was assumed to be titer 1, it was 1.02 ± 0.14 in all patients. The oral dose of semaglutide per day was 8.38 ± 2.97 mg after 6 months. Sodium glucose co-transporter 2 (SGLT-2) inhibitors were administered to all patients before oral semaglutide administration.

Two patients received insulin therapy.

Table 1. Patient characteristics at baseline (n = 48).

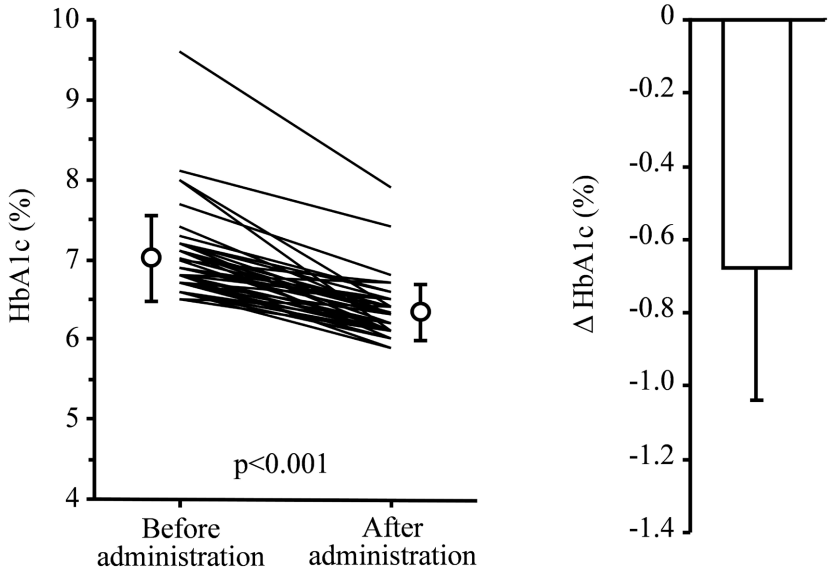
Variable	Mean (SD[a]) or n[b] (%)	
Male/Female	30/18	
Age (years)	60.9	(10.1)
Duration of diabetes (years)	12.2	(4.5)
Body mass index (kg/m^2)	26.67	(3.61)
Body weight (kg)	74.3	(11.8)
Hemoglobin A1c (%)	7.01	(0.54)
eGFR[c] (mL/min/1.73m^2)	76.43	(16.01)
Medication		
Alogliptin (25 mg)	1	(2.1)
Linagliptin (5 mg)	22	(45.8)
Sitagliptin (50 mg)	14	(29.2)
Sitagliptin (100 mg)	1	(2.1)
Teneligliptin (20 mg)	1	(2.1)
Vildagliptin (100 mg)	9	(18.8)

[a]Data are presented as n (%) for categorical variables or mean (standard deviation [SD]). [b]Number. [c]eGFR, estimated glomerular filtration rate.

3.1. Changes in HbA1c and Body Weight

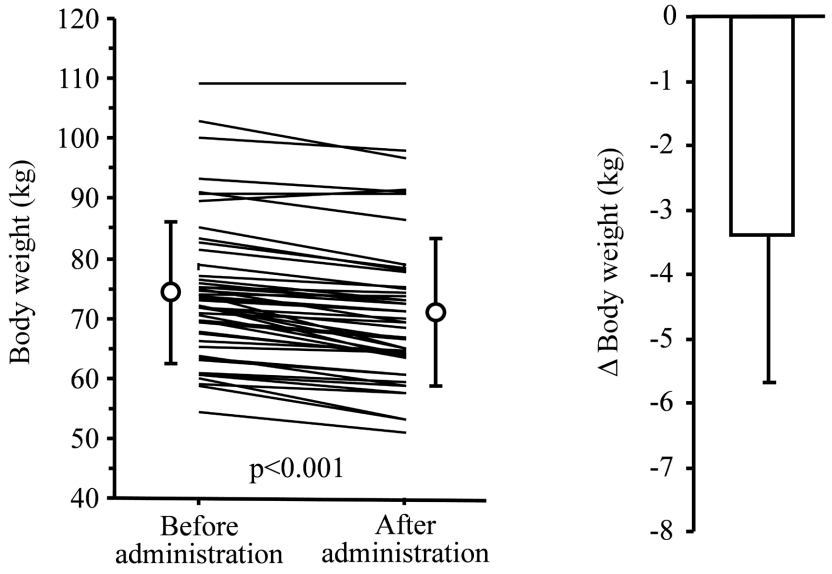
HbA1c decreased significantly from 7.01% ± 0.54% at baseline to 6.33% ± 0.39% after 6 months ($p < 0.001$, Figure 1), a decrease of 0.68% ± 0.36%. Body weight also decreased significantly by 3.4 ± 2.3 kg, from 74.3 ± 11.8 kg at baseline to 70.9 ± 12.3 kg 6 months after oral semaglutide initiation ($p < 0.001$, Figure 2). Body weight decreased by 5% or more was 42% (20 of 48 patients) and by 10% or more

was 6% (3 of 48 patients). Body weight decreased by 3.1 ± 2.2 kg (4.0% ± 2.8%) in men and by 3.9 ± 2.5 kg (5.8% ± 3.5%) in women. There was no statistical difference in gender.



HbA1c: hemoglobin A1c, DPP-4: dipeptidyl peptidase 4; Comparison of HbA1c between baseline and 6 months after oral semaglutide was made using paired t-test.

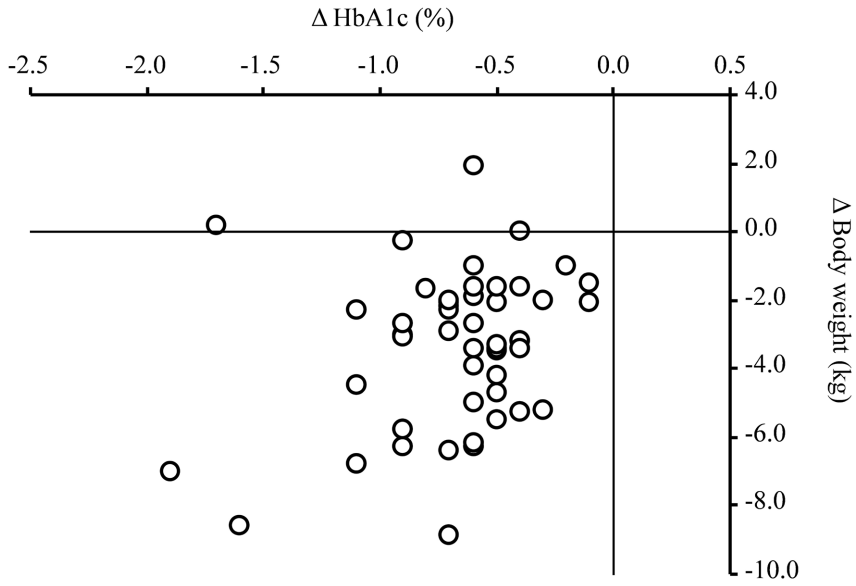
Figure 1. Decreased change in HbA1c after switching to oral semaglutide from a DPP-4 inhibitor.



DPP-4: dipeptidyl peptidase 4; Comparison of body weight between baseline and 6 months after oral semaglutide was made using paired t-test.

Figure 2. Decreased change in body weight after switching to oral semaglutide from a DPP-4 inhibitor.

HbA1c decreased in all patients, and body weight decreased in 45 of 48 patients after oral semaglutide administration. The relationship between the changes in HbA1c and body weight is shown in Figure 3. There was no significant relationship between the changes in these two parameters (r = 0.282). All patients had HbA1c > 6.5% before switching to semaglutide oral formulation, and 36 patients (75.0%) achieved HbA1c < 6.5% after treatment with oral semaglutide.



HbA1c: hemoglobin A1c; Correlation coefficient with 0.282 for changes in HbA1c and body weight was calculated by Pearson's correlation coefficient.

Figure 3. Significant relationship between changes in HbA1c and body weight.

3.2. Changes in Dosage of Concomitant Hypoglycemic Drugs

The insulin secretagogues glinide or sulfonylurea were used in 39 of 48 patients (81.3%) in addition to DPP-4 inhibitors and SGLT-2 inhibitors at baseline. The dose of concomitant insulin secretagogues was reduced in 13 patients, and these drugs were discontinued in 12 patients after treatment with oral semaglutide (Table 2). Two patients received insulin therapy, and their dosage of insulin was reduced from 14 to 10 units per day and from 12 to 9 units per day, respectively.

Table 2. Change in dose of co-administered insulin secretagogues.

	Before administration (mg)		After administration (mg)	
	Mean (SD[a])			
Gliclazide (n = 3)	33.3	(11.5)	0	(0)
Glimepiride (n = 9)	1.3	(0.8)	0.3	(0.4)
Repaglinide (n = 13)	0.9	(0.4)	0.4	(0.4)

[a]Data are presented as mean (SD).

3.3. Comparison of Metabolic Parameters and Renal Function

Levels of serum creatinine, serum uric acid, triglycerides, HDL-C, and LDL-C after switching to oral semaglutide from DPP-4 inhibitor are shown in Table 3. Six months after oral semaglutide administration, the serum uric acid level tended to decrease, and LDL-C, TC, and triglyceride levels decreased significantly. A slight decrease in HDL-C level was also observed. By contrast, no changes were observed in creatinine level and eGFR.

Table 3. Comparison of renal function and metabolic parameters before and after administration of semaglutide.

	Before administration (n = 47)		After Administration (n = 47)		p value
	Mean (SD)[a] and median (range)[a]				
BUN[b] (mg/dL)	16.91	(3.80)	15.57	(4.15)	0.010
Creatinine (mg/dL)	0.760	(0.189)	0.753	(0.173)	0.566
eGFR[c] (mL/min/1.73 m^2)	76.43	(16.01)	76.57	(14.76)	0.955
Serum uric acid (mg/dL)	5.06	(1.08)	4.81	(1.14)	0.053
TC[d] (mg/dL)	220.2	(48.6)	196.1	(37.8)	<0.001
HDL-C[e] (mg/dL)	58.6	(12.5)	54.3	(12.5)	<0.001
LDL-C[f] (mg/dL)	87.7	(25.0)	76.3	(18.5)	<0.001
TG[g] (mg/dL)	108.0	[86.0, 162.5]	91.0	[76.0, 132.5]	0.016

[a]Data are presented as mean (SD) or median (25 th percentile, 75 th percentile). [b]Blood urea nitrogen. [c]eGFR, estimated glomerular filtration rate. [d]Total cholesterol. [e]High-density-lipoprotein cholesterol. [f]Low-density-lipoprotein cholesterol. [g]Triglycerides; Comparisons of values between baseline and 6 months after oral semaglutide were made using paired t-tests or Wilcoxon rank sum tests.

3.4. Safety

A comparison of liver function and blood test–related items is shown in Table 4. Six months after oral semaglutide administration, the γ-GTP level decreased significantly, and small but significant decreases were observed in red blood cell count, hemoglobin, hematocrit, albumin, and blood urea nitrogen levels. In addition, 10 of the 48 patients experienced nausea and decreased appetite during the period of treatment with 3 mg oral semaglutide, and when the dose was increased further to 7 mg, an additional 21 patients complained of nausea and decreased appetite. However, after approximately 3 months, these gastrointestinal symptoms abated in many patients. Constipation was also reported by 18 patients. There was no patient who discontinued semaglutide due to adverse events. For patients enrolled in this study, extrapancreatic enzymes (amylase, lipase and trypsin) were checked, and there was no patient who experienced "acute pancreatitis".

Table 4. Comparison of hepatic and blood test parameters before and after administration of semaglutide.

	Before administration (n = 47)		After administration (n = 47)		p value
	Mean (SD)[a]				
Albumin (g/dL)	4.55	(0.33)	4.47	(0.31)	0.019
AST[b] (IU/L)	23.1	(7.7)	22.7	(8.0)	0.685
ALT[c] (IU/L)	26.0	(16.3)	23.7	(15.6)	0.139
γ-GTP[d] (IU/L)	28.5	(19.9)	22.7	(11.2)	0.003
White blood cells (μL)	6231.9	(1546.5)	6161.7	(1972.1)	0.655
Red blood cells (10^4/μL)	484.0	(52.8)	471.5	(57.2)	0.004
Hemoglobin (g/dL)	14.49	(1.47)	14.13	(1.70)	0.003
Hematocrit (%)	45.29	(3.79)	44.14	(4.42)	0.005

[a]Data are presented as mean (SD), [b]Aspartate aminotransferase. [c]Alanine transaminase. [d]γ-Glutamyl transpeptidase; Comparisons of values between baseline and 6 months after oral semaglutide were made using paired t-tests or Wilcoxon rank sum tests.

4. Discussion

Our results show that switching to oral semaglutide from a DPP-4 inhibitor contributes to better glycemic control and results in significant body weight loss. The improvement in HbA1c with oral semaglutide was greater in patients with higher initial HbA1c, regardless of the type of DPP-4 inhibitor administered before oral semaglutide.

In the 2021 tabulation by the Diabetes Data Management Study Group, the average HbA1c level in 53,533 patients with T2DM was 7.11%, and 49% of patients had an average HbA1c < 7.0% [21]. The difficulty in maintaining good glycemic control in T2DM may be due to multiple interrelated factors associated with T2DM, treatment inertia leading to delays in treatment intensification, inadequate lifestyle changes, and poor adherence to treatment [22] [23]. If control is suboptimal after 3 to 6 months from the initial treatment, intensification with alternative hypoglycemic therapies is necessary and must be addressed individually to meet the needs of the patient [23].

Semaglutide is the only GLP-1 RA available in both injectable and oral formulations. It was suggested that oral formulations are more convenient, leading to greater acceptability and adherence to GLP-1 RA therapy, which may provide an additional option to facilitate achieving glycemic control, especially in patients who are reluctant to receive injectable treatment [24]. Semaglutide oral formulation was compared with sitagliptin, empagliflozin, and liraglutide in a series of PIONEER studies [15] [25]-[27]. In these studies, oral semaglutide showed a decrease in HbA1c of > 1.0%, which was superior to that of the comparator. In addition, the oral semaglutide formulation showed a significant body weight loss compared to the comparator, with a significantly greater decrease in body weight

of > 1 kg for oral semaglutide compared to 1.8 mg liraglutide.

Pharmacokinetic and exposure-response analyses of oral semaglutide compared to subcutaneous semaglutide based on data from the SUSTAIN and PIONEER studies have also been reported [28]. Dose-dependent efficacy (decrease in HbA1c and body weight) and tolerability (occurrence of nausea and vomiting) were revealed. The authors reported that switching to subcutaneous semaglutide from other GLP-1 RAs is useful [29]. In our real-world study, switching from a DPP-4 inhibitor to oral semaglutide also resulted in a significant decrease in HbA1c and significant weight loss. Regardless of route of administration, the data indicates that semaglutide is a beneficial option for treating T2DM.

In the present study, switching from DPP-4 inhibitor to oral semaglutide resulted in a reduction or discontinuation of insulin secretagogues. In addition, the insulin dosage was reduced in one patient. Better glycemic control and the ability to reduce or discontinue insulin secretagogues may also be a major factor in improving patients' burdens to diabetes treatment.

We observed improvements in deviations in liver enzyme levels, possibly due to increased weight loss. T2DM is often associated with abnormalities in uric acid or lipid metabolism, and these patients have a higher risk of developing cardiovascular diseases. With regard to the physiological effects of GLP-1, treatment with GLP-1 RAs, which improve not only glycemic control but also lipid metabolism, is of great value, and treatment with oral semaglutide is particularly effective.

A similar previous studies in T2DM patients treated with DPP-4 inhibitors reported that switching from DPP-4 inhibitors to oral semaglutide showed better HbA1c and body weight reductions, and improvement of liver function enzymes (AST and γ-GTP) compared to continuous DPP-4 inhibitors treatment [30] [31]. This study also confirmed that switching from DDP-4 inhibitors to oral semaglutide resulted in a decrease in HbA1c and body weight in T2DM patients with obesity under treatment with DPP-4 inhibitors. Although the efficacy of oral semaglutide against DPP-4 inhibitors was similar in the previous study and this study, the evidence on the clinical position of oral semaglutide in T2DM patients under treatment with DPP-4 inhibitors is needed to be accumulated in the actual clinical setting.

Gastrointestinal adverse drug reactions are a potential impediment to treatment with oral semaglutide. In the present study, minor nausea, decreased appetite, or constipation were observed at low doses, but the frequency of these symptoms increased with increasing dose. However, many of these symptoms disappeared approximately 3 months after onset in many patients; thus, it may be necessary to take measures such as reducing the dose if symptoms are severe, based on discussion with the patient and careful observation.

This study has several limitations worth noting. First, there may have been selection bias given the small sample size and the fact that patients were recruited from one medical institution that specializes in diabetes treatment. In addition, the study lacked a control group, and participants were receiving a heterogeneous

group of concomitant glucose-lowering drugs. Therefore, application of the results to actual clinical settings could be limited. A large-scale, multicenter, controlled study will be needed to better compare our data to those from studies in other medical settings. Second, important factors such as fasting blood glucose levels, serum insulin, C-peptide, proinsulin, glucagon, proinsulin-to-insulin ratio, insulin resistance assessment (HOMA of β-cell function), and health-related behaviors were not evaluated but should be addressed in future studies. Third, the follow-up period of 6 months was relatively short. As a next step, cohort studies with longer follow-up periods should be conducted to assess long-term outcomes, including glycemic control. Finally, there was no limitation on the type of DPP-4 inhibitor in terms of switching, and there were no restrictions on the type of SGLT-2 inhibitors used in the patients. Therefore, how the differences in switched drugs or concomitant drugs affected the outcome of this study is unclear.

5. Conclusion

This retrospective, single-center study showed significant improvement in HbA1c and body weight after patients were switched to oral semaglutide from a DPP-4 inhibitor. Oral semaglutide appears to be a promising drug for managing glycemic status and body weight in obese patients with T2DM, although additional validation is needed.

Acknowledgment

The authors thank all the patients who participated in this study and all of the staff of the Okamoto Internal Medicine Clinic for their excellent assistance.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AO and HY. The first draft of the manuscript was written by AO and HY, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

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

Conflicts of Interest

The authors declare that they have no competing interests.

References

[1] McLean, B.A., Wong, C.K., Campbell, J.E., Hodson, D.J., Trapp, S. and Drucker, D.J.

(2021) Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation. *Endocrine Reviews*, **42**, 101-132. https://doi.org/10.1210/endrev/bnaa032

[2] Andersen, A., Lund, A., Knop, F.K. and Vilsbøll, T. (2018) Glucagon-Like Peptide 1 in Health and Disease. *Nature Reviews Endocrinology*, **14**, 390-403. https://doi.org/10.1038/s41574-018-0016-2

[3] Deacon, C.F., Pridal, L., Klarskov, L., Olesen, M. and Holst, J.J. (1996) Glucagon-Like Peptide 1 Undergoes Differential Tissue-Specific Metabolism in the Anesthetized Pig. *American Journal of Physiology-Endocrinology and Metabolism*, **271**, E458-E464. https://doi.org/10.1152/ajpendo.1996.271.3.e458

[4] Ahrén, B., Landin-Olsson, M., Jansson, P., Svensson, M., Holmes, D. and Schweizer, A. (2004) Inhibition of Dipeptidyl Peptidase-4 Reduces Glycemia, Sustains Insulin Levels, and Reduces Glucagon Levels in Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 2078-2084. https://doi.org/10.1210/jc.2003-031907

[5] Herman, G.A., Bergman, A., Stevens, C., Kotey, P., Yi, B., Zhao, P., *et al.* (2006) Effect of Single Oral Doses of Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, on Incretin and Plasma Glucose Levels after an Oral Glucose Tolerance Test in Patients with Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, **91**, 4612-4619. https://doi.org/10.1210/jc.2006-1009

[6] Craddy, P., Palin, H. and Johnson, K.I. (2014) Comparative Effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison. *Diabetes Therapy*, **5**, 1-41. https://doi.org/10.1007/s13300-014-0061-3

[7] Nauck, M.A., Vilsbøll, T., Gallwitz, B., Garber, A. and Madsbad, S. (2009) Incretin-based Therapies. *Diabetes Care*, **32**, S223-S231. https://doi.org/10.2337/dc09-s315

[8] Nauck, M.A., Niedereichholz, U., Ettler, R., Holst, J.J., Ørskov, C., Ritzel, R., *et al.* (1997) Glucagon-Like Peptide 1 Inhibition of Gastric Emptying Outweighs Its Insulinotropic Effects in Healthy Humans. *American Journal of Physiology-Endocrinology and Metabolism*, **273**, E981-E988. https://doi.org/10.1152/ajpendo.1997.273.5.e981

[9] Kapitza, C., Nosek, L., Jensen, L., Hartvig, H., Jensen, C.B. and Flint, A. (2015) Semaglutide, a Once-Weekly Human GLP-1 Analog, Does Not Reduce the Bioavailability of the Combined Oral Contraceptive, Ethinylestradiol/Levonorgestrel. *The Journal of Clinical Pharmacology*, **55**, 497-504. https://doi.org/10.1002/jcph.443

[10] Goldenberg, R.M. and Steen, O. (2019) Semaglutide: Review and Place in Therapy for Adults with Type 2 Diabetes. *Canadian Journal of Diabetes*, **43**, 136-145. https://doi.org/10.1016/j.jcjd.2018.05.008

[11] Aroda, V.R., Ahmann, A., Cariou, B., Chow, F., Davies, M.J., Jódar, E., *et al.* (2019) Comparative Efficacy, Safety, and Cardiovascular Outcomes with Once-Weekly Subcutaneous Semaglutide in the Treatment of Type 2 Diabetes: Insights from the SUSTAIN 1–7 Trials. *Diabetes & Metabolism*, **45**, 409-418. https://doi.org/10.1016/j.diabet.2018.12.001

[12] Buckley, S.T., Bækdal, T.A., Vegge, A., Maarbjerg, S.J., Pyke, C., Ahnfelt-Rønne, J., *et al.* (2018) Transcellular Stomach Absorption of a Derivatized Glucagon-Like Peptide-1 Receptor Agonist. *Science Translational Medicine*, **10**, eaar7047. https://doi.org/10.1126/scitranslmed.aar7047

[13] Rasmussen, M.F. (2020) The Development of Oral Semaglutide, an Oral GLP-1 Analog, for the Treatment of Type 2 Diabetes. *Diabetology International*, **11**, 76-86. https://doi.org/10.1007/s13340-019-00423-8

[14] Thethi, T.K., Pratley, R. and Meier, J.J. (2020) Efficacy, Safety and Cardiovascular Outcomes of Once-Daily Oral Semaglutide in Patients with Type 2 Diabetes: The PIONEER Programme. *Diabetes, Obesity and Metabolism*, **22**, 1263-1277. https://doi.org/10.1111/dom.14054

[15] Rosenstock, J., Allison, D., Birkenfeld, A.L., Blicher, T.M., Deenadayalan, S., Jacobsen, J.B., *et al.* (2019) Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults with Type 2 Diabetes Uncontrolled with Metformin Alone or with Sulfonylurea. *JAMA*, **321**, 1466-1480. https://doi.org/10.1001/jama.2019.2942

[16] Warnick, G.R., Knopp, R.H., Fitzpatrick, V. and Branson, L. (1990) Estimating Low-Density Lipoprotein Cholesterol by the Friedewald Equation Is Adequate for Classifying Patients on the Basis of Nationally Recommended Cutpoints. *Clinical Chemistry*, **36**, 15-19. https://doi.org/10.1093/clinchem/36.1.15

[17] Matsuo, S., Imai, E., Horio, M., Yasuda, Y., Tomita, K., Nitta, K., *et al.* (2009) Revised Equations for Estimated GFR from Serum Creatinine in Japan. *American Journal of Kidney Diseases*, **53**, 982-992. https://doi.org/10.1053/j.ajkd.2008.12.034

[18] Kanda, Y. (2012) Investigation of the Freely Available Easy-to-Use Software 'EZR' for Medical Statistics. *Bone Marrow Transplantation*, **48**, 452-458. https://doi.org/10.1038/bmt.2012.244

[19] Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science and Technology (2013) Ethical Guideline for Epidemiological Studies. http://www.mhlw.go.jp/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/dl/02-02.pdf

[20] World Medical Association (2013) WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net//policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[21] Japan Diabetes Clinical Data Management Study Group (2021) Basic Tabulation Data in 2021 (in Japanese). http://jddm.jp/public-information/index-2021/

[22] Davies, M.J., Aroda, V.R., Collins, B.S., Gabbay, R.A., Green, J., Maruthur, N.M., *et al.* (2022) Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, **45**, 2753-2786. https://doi.org/10.2337/dci22-0034

[23] Rosenthal, M., Arnold, A., Salkar, M., Patelb, S., Harrell, E., Aldridge, H., *et al.* (2022) Patient Centered Studies Focused on Type 2 Diabetes Management, Education, and Family Support: A Scoping Review. *Current Diabetes Reviews*, **18**, e171121197989. https://doi.org/10.2174/1573399818666211117113026

[24] Nauck, M.A. and Meier, J.J. (2019) Pioneering Oral Peptide Therapy for Patients with Type 2 Diabetes. *The Lancet Diabetes & Endocrinology*, **7**, 500-502. https://doi.org/10.1016/s2213-8587(19)30182-2

[25] Pieber, T.R., Bode, B., Mertens, A., Cho, Y.M., Christiansen, E., Hertz, C.L., *et al.* (2019) Efficacy and Safety of Oral Semaglutide with Flexible Dose Adjustment versus Sitagliptin in Type 2 Diabetes (PIONEER 7): A Multicentre, Open-Label, Randomised, Phase 3a Trial. *The Lancet Diabetes & Endocrinology*, **7**, 528-539. https://doi.org/10.1016/s2213-8587(19)30194-9

[26] Rodbard, H.W., Rosenstock, J., Canani, L.H., Deerochanawong, C., Gumprecht, J., Lindberg, S.Ø., *et al.* (2019) Oral Semaglutide versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care*, **42**, 2272-2281. https://doi.org/10.2337/dc19-0883

[27] Pratley, R., Amod, A., Hoff, S.T., Kadowaki, T., Lingvay, I., Nauck, M., *et al.* (2019) Oral Semaglutide versus Subcutaneous Liraglutide and Placebo in Type 2 Diabetes (PIONEER 4): A Randomised, Double-Blind, Phase 3a Trial. *The Lancet*, **394**, 39-50. https://doi.org/10.1016/s0140-6736(19)31271-1

[28] Overgaard, R.V., Hertz, C.L., Ingwersen, S.H., Navarria, A. and Drucker, D.J. (2021) Levels of Circulating Semaglutide Determine Reductions in HbA1c and Body Weight in People with Type 2 Diabetes. *Cell Reports Medicine*, **2**, Article 100387. https://doi.org/10.1016/j.xcrm.2021.100387

[29] Okamoto, A., Yokokawa, H., Nagamine, T., Fukuda, H., Hisaoka, T. and Naito, T. (2021) Efficacy and Safety of Semaglutide in Glycemic Control, Body Weight Management, Lipid Profiles and Other Biomarkers among Obese Type 2 Diabetes Patients Initiated or Switched to Semaglutide from Other GLP-1 Receptor Agonists. *Journal of Diabetes & Metabolic Disorders*, **20**, 2121-2128. https://doi.org/10.1007/s40200-021-00899-9

[30] Furusawa, S., Nomoto, H., Yokoyama, H., Suzuki, Y., Tsuzuki, A., Takahashi, K., *et al.* (2023) Glycaemic Control Efficacy of Switching from Dipeptidyl Peptidase-4 Inhibitors to Oral Semaglutide in Subjects with Type 2 Diabetes: A Multicentre, Prospective, Randomized, Open-Label, Parallel-Group Comparison Study (SWITCH-SEMA 2 Study). *Diabetes, Obesity and Metabolism*, **26**, 961-970. https://doi.org/10.1111/dom.15393

[31] Yoneda, C., Kobayashi, J. and Kuribayashi, N. (2024) Efficacy and Safety of Switching from a Dipeptidyl Peptidase-4 Inhibitor to Oral Semaglutide in Japanese Patients with Type 2 Diabetes Mellitus. *Diabetology International*, **15**, 569-576. https://doi.org/10.1007/s13340-024-00734-5