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Effects of switching from dipeptidyl peptidase 4 inhibitors to oral semaglutide on oxidative stress and glycemic variability in patients with type 2 diabetes: an open-label, prospective, randomized, multicenter, parallel-group comparison study

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Abstract

Background To compare the effects of switching from dipeptidyl peptidase 4 (DPP-4) inhibitors to oral semaglutide on oxidative stress and glucose variability assessed by continuous glucose monitoring in patients with type 2 diabetes mellitus (T2DM).

Methods This was an open-label, prospective, randomized, multicenter, parallel-group comparison study conducted over 24 weeks. Patients with T2DM who had been taking regular doses of DPP-4 inhibitors for at least 12 weeks were enrolled. They were randomly assigned to either continue on DPP-4 inhibitors (DPP-4 inhibitor group) or switch to oral semaglutide at 3 mg/day, with a dose increase to 7 mg/day after 4 weeks (semaglutide group). The primary endpoint was the change in the diacron-reactive oxygen metabolites test, an oxidative stress marker. Secondary endpoints included changes in glucose variability assessed using continuous glucose monitoring, metabolic indices, physical assessments, and Diabetes Treatment Satisfaction Questionnaire scores.

Results Fifty-eight patients with T2DM were randomized to the semaglutide group ($n=30$) and the DPP-4 inhibitor group ($n=28$). Six patients in the semaglutide group and one patient in the DPP-4 inhibitor group dropped out during the study. Ultimately, data from 24 patients in the semaglutide group and 27 patients in the DPP-4 inhibitor group were included for analysis. Switching to oral semaglutide therapy for 24 weeks significantly reduced oxidative stress, glucose variability, and hemoglobin A1c levels compared to continuous treatment with DPP-4 inhibitors. However, there was no significant difference in Diabetes Treatment Satisfaction Questionnaire scores between the two groups. (II)

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Conclusions Our study demonstrated that switching to oral semaglutide therapy from DPP-4 inhibitors significantly improved oxidative stress and glycemic parameters, including glucose variability, in patients with T2DM. Trial registration: jRCT1031210620.

Keywords Continuous glucose monitoring, Glucose variability, Oxidative stress, Type 2 diabetes mellitus, Glucagon-like peptide-1 receptor agonists, Dipeptidyl peptidase 4 inhibitor

Introduction

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD), a leading cause of death in these patients [1]. Therefore, for patients with T2DM, it is crucial to prevent future CVD events and reduce the increased mortality. Injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been shown to decrease glycated hemoglobin (HbA1c) values and body weight (BW), reducing the risk of CVD events in patients with T2DM with established CVD or at high risk for CVD [2–4]. The American Diabetes Association and European Association for the Study of Diabetes Consensus Report now recommend the use of GLP-1RA for treating T2DM patients with atherosclerotic CVD and/or multiple coronary risk factors, regardless of baseline HbA1c values [5]. However, injectable GLP-1RAs have certain disadvantages, including high cost, low tolerability, and the requirement for subcutaneous administration, which may limit their use in patients with T2DM [6]. In recent years, oral semaglutide, the first-in-class oral GLP-1RA offering equipotent hypoglycemic effects to injectable GLP-1RAs with a low risk of hypoglycemia, has been approved for the treatment of T2DM [7, 8], positioning it as a potential therapeutic agent for managing T2DM. Conversely, several clinical trials have shown that dipeptidyl peptidase 4 (DPP-4) inhibitors, another type of oral incretin-based therapy, have a neutral effect on CVD in patients with T2DM [9–11]. DPP-4 inhibitors are one of the most commonly prescribed oral hypoglycemic agents, particularly in Japan, because of their affordability and efficacy, minimal risk of hypoglycemia, and no risk of BW gain [12]. The American Diabetes Association and European Association for the Study of Diabetes Consensus Report recommend the use of DPP-4 inhibitors to maintain glycemic control and achieve optimal BW goals in patients with T2DM [5].

HbA1c is considered the gold standard biomarker for assessing glycemic control and is strongly linked to the future risk of diabetic vascular complications [13]. Furthermore, many clinical trials have demonstrated that improvement of HbA1c reduces CVD event risk in diabetic patients [14–16]. However, several clinical trials have demonstrated that intensive glycemic control based on HbA1c values does not necessarily reduce the risk of CVD in patients with T2DM [17, 18]. This could partly be explained by the fact that HbA1c reflects long-term overall glycemic control and may not accurately capture glucose variability, including postprandial hyperglycemia and hypoglycemia [19]. Indeed, it has been reported that in patients with type 2 diabetes, glucose variability is more correlated with brachial-ankle pulse wave velocity [20], a surrogate marker of CVD risk, than with HbA1c itself [21]. In addition, we have previously found that glucose-lowering therapies that reduce daily and day-to-day glucose variability could decrease the levels of diacron-reactive oxygen metabolites (d-ROMs), a surrogate marker of oxidative stress, in patients with T2DM [22]. Given that glucose variability has been associated with endothelial dysfunction and oxidative stress, both of which contribute to the development and progression of CVD [23–25], improving glucose variability—something that cannot be accurately assessed using HbA1c values—may represent a novel therapeutic target for managing T2DM.

In the PIONEER 3 trial, oral semaglutide was found to be more effective than sitagliptin, a DPP4 inhibitor, in reducing HbA1c values and BW in patients with T2DM [26]. Recently, Furusawa et al. reported that switching from DPP4 inhibitors to oral semaglutide improved HbA1c [27]. However, to the best of our knowledge, there is a lack of clinical studies comparing the impact of oral semaglutide and DPP4 inhibitors on oxidative stress and glucose variability in patients with T2DM. Therefore, the aim of this study was to compare the effects of oxidative stress and glucose variability using continuous glucose monitoring (CGM) in patients with T2DM.

Methods

Study design

The present study was designed as an open-label, prospective, randomized, multicenter, parallel-group comparison study for 24 weeks at Showa University Hospital, Tokatsu Hospital, Seino Internal Medicine Clinic, and Jiyugaoka Medical Clinic in Japan between February 2022 and May 2023. Figure 1 summarizes the study protocol. Patients were randomly assigned to either the DPP-4 inhibitors group (maintaining regular doses of DPP-4 inhibitors for 12 weeks) or the semaglutide group (replacing DPP-4 inhibitors with oral semaglutide at 3 mg/day, with a dose increase to 7 mg/

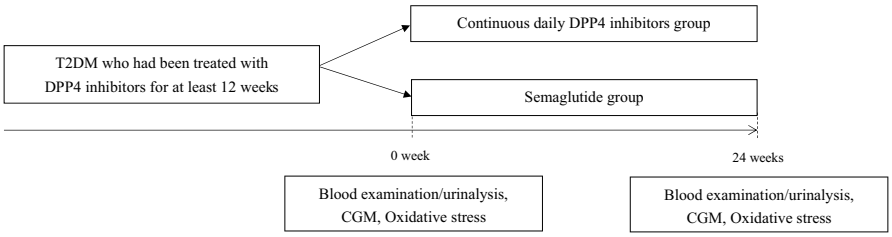


Fig. 1 Study protocol. Outpatients with type 2 diabetes mellitus (T2DM) who had been on regular doses of dipeptidyl peptidase 4 inhibitors for at least 12 weeks were randomly assigned to either a maintenance therapy group receiving dipeptidyl peptidase 4 inhibitors or a group whose treatment was switched to oral semaglutide

day after 4 weeks). Randomization was performed using the Mujinwari online computer-generated system (URL:https://mujinwari.biz/users/login). Allocation factors included sex (male, female), age (<65, ≥65 years), and HbA1c (<7.5%, ≥7.5%). At baseline and 24 weeks after the intervention, clinical and laboratory parameters were measured before breakfast on Day 1 of CGM, as previously described [28]: BW, blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, fasting plasma glucose (FPG), and HbA1c. All clinical data (age, diabetes duration, smoking habit, and gender) were retrieved from medical records. Diabetes treatment remains essentially unchanged unless there is a risk of hypoglycemia. Patients were instructed not to change their lifestyle or alter the dose of any concomitant drugs. The study protocol was approved by the Ethics Committee of Showa University (approval no. 21–128-A) and adhered to the principles of the Declaration of Helsinki and current legal regulations in Japan. After thoroughly explaining the study protocol, informed consent was obtained from all participants. This study was registered with the Japan Registry of Clinical Trials (jRCT1031210620).

Participants

This study enrolled outpatients with T2DM who had been on regular doses of DPP-4 inhibitors for at least 12 weeks. The patients were aged 20 years or older, had HbA1c values of 7.0% or higher, and had been receiving DPP-4 inhibitor therapy for 12 weeks or more. Exclusion criteria were (1) treatment with steroid and/or anti-inflammatory drugs; (2) diabetic ketosis and/or coma within 3 months prior to the study; (3) severe infection, trauma, or perioperative period; (4) estimated glomerular filtration rate of 30 mL/min/1.73 m^2 or lower by the Cockcroft-Gault formula; (5) malignancy; (6) pregnancy; (7) deemed inappropriate for inclusion by their physicians; and (8) use of implantable medical devices such as cardiac pacemakers.

Procedures and measurements

A FreeStyle Libre Pro CGM device (Abbott Japan, Tokyo, Japan) was subcutaneously inserted into each patient on Day 1 and removed on Day 14. Glucose variability was calculated from Day 3 to Day 12 to ensure accurate results. The coefficient of variation was determined by dividing the standard deviation (SD) of the glucose levels by the mean glucose level (MGL) and multiplying by 100 [29]. To assess daily glucose variability, the mean amplitude of glucose excursion (MAGE) was calculated [30]. The mean daily difference of blood glucose (MODD) was calculated as the mean of the absolute difference between the corresponding glucose values [31]. Furthermore, time above range (TAR) indicated the percentage of time spent above 180 mg/dL, time in range (TIR) represented the percentage of time within the target range of 70–180 mg/dL over a 24-h period, and time below range reflected the percentage of time spent below 70 mg/dL [32].

Laboratory measurements

Oxidative stress was assessed using the d-ROMs test, as previously described [33, 34]. This test assesses free radical activity by measuring serum levels of hydroperoxides, and its results are reported in Caratelli Units (U.CARR), where 1 U.CARR is equivalent to the oxidant capacity of 0.08 mg/dL H_2O_2 solution, with a normal range of 250–300 U.CARR. Moreover, clinical variables were measured using an automated analyzer (BM6070; Japan Electron Optics Laboratory, Tokyo, Japan). Plasma glucose levels were measured using the glucose oxidase method, and HbA1c percentages were measured via high-performance liquid chromatography [35].

Diabetes treatment satisfaction

To assess treatment satisfaction, the Diabetes Treatment Satisfaction Questionnaire (DTSQ), an eight-item self-administered questionnaire, was utilized [36, 37]. Scores were calculated at baseline and 24 weeks after the intervention. The total treatment satisfaction score

was calculated by summing the scores of six satisfaction items: "current treatment," "convenience," "flexibility," "understanding," "recommend," and "continue." The remaining two items, "perceived hyperglycemia" and "perceived hypoglycemia," were assessed individually.

Endpoints and assessments

The primary endpoint of the study was the change in d-ROMs from baseline after the 24-week treatment intervention. Secondary endpoints included changes in glucose variability using CGM, metabolic indices such as FPG, HbA1c, lipid profile, liver and renal function and urine albumin excretion, physical assessments such as BW and blood pressure, and DTSQ scores.

Sample size calculation

As mentioned, no clinical studies have compared the effects of GLP-1RA and DPP-4 inhibitors on oxidative stress and glucose variability. Therefore, the sample size was calculated from two perspectives. First, the degree of improvement in HbA1c values was assessed from baseline with oral semaglutide (7 mg/day) and sitagliptin, a DPP-4 inhibitor, at a dose of 50 mg/day at a regular dose of −1.5% and −0.65%, respectively, with a significance level of 0.05% and a power of over 80% [38, 39]. Considering a potential 20% dropout rate, a sample size of 58 individuals was needed. Second, the change in the oxidative stress marker, d-ROMs, was evaluated, aiming to detect a nominal treatment difference of 16.0 U.CARR with an SD of 39.7. To achieve 80% power at a significance level of 0.05% and assuming a 20% withdrawal rate, 48 randomized patients were required [23, 40]. Taking both calculations into account, a total of 58 cases would be required.

Statistical analysis

The normally distributed continuous data were expressed as mean and SD, while the non-normally distributed continuous data were expressed as median (interquartile range). Categorical data were expressed as numbers and percentages. Differences in continuous variables between the semaglutide and DPP-4 inhibitor groups at baseline and after treatment were evaluated using the independent samples *t*-test or Mann–Whitney *U* test, as appropriate. For comparing categorical variables, the chi-squared test was used. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 22 for Windows (IBM Corp., Armonk, NY, USA).

Results

Patient sample and characteristics

Figure 2 illustrates the patient inclusion process. Initially, 60 patients were screened, with one declining to participate and one not meeting the inclusion criteria. Of the remaining 58 patients, 30 were randomly assigned to the semaglutide group and 28 to the DPP-4 inhibitor group. Six patients in the semaglutide group were excluded due to gastrointestinal side effects ($n=3$), moving house ($n=1$), interruption of hospital visits ($n=1$), and dementia ($n=1$). One patient in the DPP-4 inhibitor group declined to participate. Ultimately, 24 patients

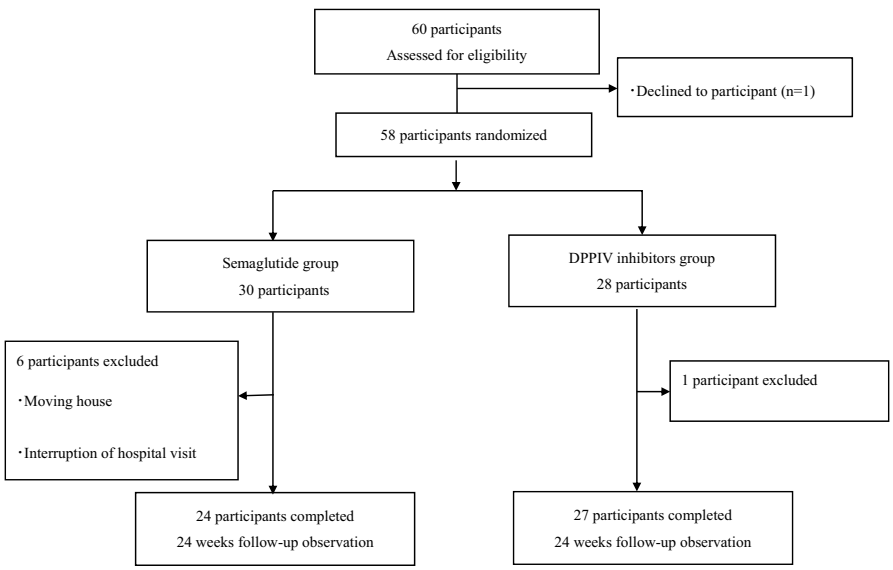


Fig. 2 Participant flow during the trial. A total of 58 participants were enrolled, with 30 assigned to switch to oral semaglutide and 28 to continue their current DPP-4 inhibitors. Finally, 24 and 27 participants in the respective groups completed the 24-week study

in the semaglutide group and 27 in the DPP-4 inhibitor group were included for analysis (Fig. 2). Table 1 summarizes the baseline clinical characteristics. The mean age, diabetes duration, and HbA1c values of the semaglutide and DPP-4 inhibitor groups were 65.6 ± 11.1 and 66.7 ± 9.9 years, 13.7 ± 6.0 and 14.4 ± 8.9 years, and 7.6% ± 0.4% and 7.6% ± 0.4%, respectively. The clinical and biochemical characteristics at baseline did not significantly differ between the two groups except for thiazolidine use.

Effects of semaglutide and DPP-4 inhibitors on oxidative stress and glycemic parameters

Table 2 and Table S1 summarizes the clinical and biochemical characteristics of our patients. Switching to oral semaglutide for 24 weeks significantly decreased d-ROMs from 348.5 ± 73.1 to 305.0 ± 52.4 U.CARR ($p = 0.022$), FPG from 144.6 ± 27.0 to 129.6 ± 23.9 mg/dL ($p = 0.047$), and HbA1c values from 7.6 ± 0.4 to 7.1% ± 0.6% ($p = 0.003$), whereas 24 weeks of continuous treatment with DPP-4 inhibitors did not affect these parameters. There were significant differences in changes in d-ROMs (− 43.5 ± 46.1 *vs.* − 5.4 ± 49.9 U.CARR, $p = 0.007$), FPG levels (− 15.0 ± 22.4 *vs.* 2.7 ± 36.8 mg/dL, $p = 0.047$), and HbA1c values (− 0.5% ± 0.5% *vs.* 0.0% ± 0.5%, $p = 0.001$) between the semaglutide and DPP-4 inhibitor groups. The semaglutide group had a higher rate of achieving HbA1c values below 7.0% compared to the DPP-4 inhibitor group (50.0% *vs.* 14.8%, $p = 0.007$).

Figure 3 illustrates the 24-h blood glucose profiles as assessed by the CGM. Switching to oral semaglutide for 24 weeks significantly improved MAGE from 105.4 ± 26.9 to 88.1 ± 26.3 mg/dL ($p = 0.029$), TAR from 28.3 ± 15.4% to 17.8% ± 17.6% ($p = 0.033$), and TIR from 70.6 ± 14.5% to 81.0% ± 17.2% ($p = 0.028$). In addition, semaglutide therapy modestly, but not significantly, improved MGL from 157.1 ± 21.8 to 143,1 ± 26.4 mg/dL ($p = 0.051$), SD from 40.1 ± 6.9 to 35.8 ± 10.1 mg/dL ($p = 0.091$) and MODD from 34.0 ± 7.8 to 30.2 ± 9.6 mg/dL ($p = 0.140$). In contrast, 24 weeks of continuous treatment with DPP-4 inhibitors did not improve MAGE, TAR, and TIR. Switching to oral semaglutide therapy demonstrated significantly better outcomes than continuous DPP-4 inhibitor therapy in terms of changes in various glycemic parameters, such as MGL (− 14.0 ± 21.4 *vs.* 2.3 ± 18.9 mg/dL, $p = 0.006$), SD (− 4.3 ± 8.2 *vs.* 1.8 ± 7.6 mg/dL, $p = 0.007$), MAGE (− 17.3 ± 4.3 *vs.* 5.6 ± 22.2 mg/dL, $p = 0.001$), MODD (− 3.8 ± 6.3 *vs.* 1.6 ± 7.6 mg/dL, $p = 0.008$), TAR (− 10.5% ± 15.8% *vs.* 1.4% ± 15.2%, $p = 0.009$), TIR (10.4% ± 15.4% *vs.* − 1.5% ± 15.1%, $p = 0.008$).

Table 3 presents the correlations between changes in d-ROMs and changes in BW and glycemic parameters in the semaglutide group. Univariate analysis revealed that the change in d-ROMs was significantly correlated with the change in MODD ($r = 0.485$, $p = 0.016$) and tended to be associated with the change in SD ($r = 0.374$, $p = 0.072$).

Effects of semaglutide and DPP-4 inhibitors on BW, blood pressure, serum lipids, liver, and renal function

During the study periods, there was no significant decrease in BW in either group. However, there was a significant difference in the changes in BW between the two groups. BW loss was significantly larger in the semaglutide group than in the DPP-4 inhibitor group (− 2.3 ± 1.8 *vs.* − 0.4 ± 1.3 kg, $p < 0.001$). Blood pressure, serum lipids, and liver and renal function did not change significantly in either group during the study periods, and there were no significant differences in the changes in these parameters between the two groups.

Effects of semaglutide and DPP-4 inhibitors on DTSQ scores

Table 4 summarizes self-reported patient treatment satisfaction evaluated by the DTSQ scores at baseline and 24 weeks after treatment. DTSQ scores were assessed for 40 participants. There was no significant difference in the change in overall DTSQ score between the semaglutide and DPP-4 inhibitor groups at 24 weeks. Among the subscale scores, the change in "perceived frequency of hypoglycemia" from baseline was significantly lower in the DPP-4 inhibitors group (0.8 ± 1.1 *vs.* − 0.4 ± 1.9, $p = 0.020$), and the "current treatment" score tended to be higher in the semaglutide group than in the DPP-4 inhibitor group (0.5 ± 0.9 *vs.* − 0.1 ± 1.0, $p = 0.060$).

Safety

As shown in Fig. 2 and Table S2, three participants in the semaglutide group discontinued treatment due to gastrointestinal side effects, while no adverse events were observed in the DPP-4 inhibitor group. There were no cases of severe hypoglycemia in either group throughout the study.

Discussion

To the best of our knowledge, this is the first clinical study comparing the effects of oral semaglutide and DPP-4 inhibitors on oxidative stress and glucose variability measured by CGM. The present study demonstrated that switching to oral semaglutide therapy for 24 weeks was more effective than continuous DPP-4 inhibitor therapy in reducing d-ROMs, an oxidative stress marker, and improving glucose variability in patients with T2DM.

In this study, we evaluated oxidative stress levels by measuring d-ROMs. The d-ROMs is a comprehensive evaluation of oxidative stress in the body by measuring the levels of hydroperoxides, which are metabolic

Table 1 Clinical characteristics of subject at baseline

	Semaglutide group (n = 24)	DPPI inhibitors group (n = 27)	p value
Age (years)	65.6 ± 11.1	66.7 ± 9.9	0.714
Sex, male, n (%)	13 (54.2)	15 (55.6)	0.921
Body weight (kg)	67.9 ± 12.7	65.1 ± 12.0	0.420
Body mass index (kg/m^2)	26.2 ± 3.0	25.0 ± 3.4	0.193
Duration of diabetes (years)	13.7 ± 6.0	14.4 ± 8.9	0.947
Hypertension, n (%)	13 (54.2)	15 (55.6)	0.921
Dyslipidemia, n (%)	19 (79.2)	23 (85.2)	0.718
Blood pressure (mm Hg)			
Systolic	131.5 ± 17.8	130.6 ± 14.6	0.843
Diastolic	75.1 ± 9.2	73.1 ± 11.3	0.847
HDL-C (mg/dL)	55.2 ± 12.3	56.7 ± 11.6	0.658
LDL-C (mg/dL)	94.9 ± 16.2	96.3 ± 21.0	0.789
Triglyceride (mg/dL)	117.0 (93.5–205.0)	110.0 (83.0–183.0)	0.365
AST(GOT) (IU/L)	20.5 (17.3–26.8)	19.0 (16.0–28.0)	0.545
ALT(GPT) (IU/L)	24.0 (16.0–36.8)	21.0 (15.0–36.0)	0.533
γ-GTP (IU/L)	28.0 (20.4–41.5)	29.0 (20.0–58.0)	0.947
eGFR (ml/min/1.73 m^2)	74.1 ± 21.4	69.7 ± 15.5	0.397
UACR (mg/g Cre)	22.9 (10.6–53.9)	25.0 (8.6–47.1)	0.828
FPG (mg/dL)	144.6 ± 27.0	149.0 ± 24.7	0.549
HbA1c (%)	7.6 ± 0.4	7.6 ± 0.4	0.956
Mean glucose level (mg/dL)	157.1 ± 21.8	159.4 ± 18.2	0.679
Markers of glucose variability			
SD (mg/dL)	40.1 ± 6.9	39.8 ± 8.5	0.706
MAGE (mg/dL)	105.4 ± 26.9	99.9 ± 20.8	0.411
MODD (mg/dL)	34.0 ± 7.8	34.0 ± 8.0	0.938
%CV (mg/dL)	25.9 ± 5.4	25.0 ± 4.7	0.512
Time above range (%)	28.3 ± 15.4	28.3 ± 14.1	0.995
Time in range (%)	70.6 ± 14.5	71.6 ± 14.1	0.807
Time below range (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.743
d-ROMs (U.CARR)	348.5 ± 73.1	362.1 ± 93.8	0.858
Macroangiopathy	1 (4.2)	6 (22.2)	0.103
Neuropathy	8 (33.3)	9 (33.3)	1.000
Nephropathy	12 (50.0)	10 (37.0)	0.351
Retinopathy	8 (33.3)	11 (40.7)	0.585
Antidiabetic drugs			
Sulfonylureas, n (%)	4 (16.7)	6 (22.2)	0.731
Glinides, n (%)	2 (8.3)	1 (3.7)	0.595
Thiazolidine, n (%)	6 (25.0)	1 (3.7)	0.042
α-glucosidase inhibitors, n (%)	2 (8.3)	5 (18.5)	0.425
Metformin, n (%)	21 (87.5)	21 (77.8)	0.473
SGLT2 inhibitors, n (%)	19 (79.2)	17 (63.0)	0.205
DPP4 inhibitors			
Sitagliptin (50 mg/day)	3 (12.5)	4 (14.8)	
Linagliptin (5 mg/day)	12 (50.0)	15 (55.6)	
Alogliptin (25 mg/day)	5 (27.8)	3 (11.1)	
Vildagliptin (100 mg/day)	1 (4.2)	4 (14.8)	
Anagliptin (200 mg/day)	1 (4.2)	0 (0.0)	
Teneligliptin (20 mg/day)	2 (8.3)	1 (3.7)	
Antihypertensive drugs			

Table 1 (continued)

	Semaglutide group (n = 24)	DPPI inhibitors group (n = 27)	p value
ARBs or ACEs, n (%)	10 (41.7)	14 (51.9)	0.467
Calcium channel blockers, n (%)	6 (25.0)	9 (33.3)	0.514
Diuretics, n (%)	1 (4.2)	0 (0.0)	0.471
α-blockers, n (%)	1 (4.2)	0 (0.0)	0.471
β-blockers, n (%)	0 (0.0)	1 (3.7)	1.0000
Antihyperlipidemic drugs			
Statins, n (%)	16 (66.7)	21 (77.8)	0.375
Fibrates, n (%)	2 (11.1)	2 (7.4)	1.000
Ezetimibe, n (%)	0 (0.0)	2 (7.4)	0.492
DTSQ score	n = 20	n = 20	
Treatment satisfaction	24.4 ± 4.9	24.2 ± 5.2	0.926
Frequency of hyperglycemia and hypoglycemia	4.4 ± 2.0	4.2 ± 2.6	0.784

Data are expressed as mean ± standard deviation, medians (interquartile ranges), or numbers (%)

HDL-C High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *eGFR* Estimated glomerular filtration rate, *FPG* Fasting plasma glucose, *HbA1c* Hemoglobin A1c, *SD* Standard deviation, *MAGE* Mean amplitude of glycemic excursions, *MODD* Mean of daily difference of blood glucose, *%CV* Percentage coefficient of variation for glucose *d-ROMs* Diacron-reactive oxygen metabolites, 1 U.CARR (arbitrary unit) = The oxidant capacity of a 0.08 mg/dL H_2O_2 solution, *SGLT* Sodium glucose cotransporter, *DPP-4* Dipeptidyl peptidase 4, *ARB* Angiotensin II receptor blocker, *ACE* Angiotensin-converting enzyme inhibitor, *DTSQ* Diabetes treatment satisfaction questionnaire

products produced when lipids, proteins, amino acids, and nucleic acids are oxidized [41]. About 1.7-fold increase in total mortality, including CVD death for the comparison of top (≥ 368 U.CARR) versus bottom d-ROMs tertile (< 320 U.CARR) was observed in a German cohort [41]. We found here that semagulitide therapy significantly reduced d-ROMs by about 40 U.CARR, which would be clinically relevant for our patients.

We have previously shown that d-ROMs are associated with daily and day-to-day glucose variability in patients with T2DM [42]. In addition, we found that improvement by glucose-lowering therapies in daily glucose variability and day-to-day glucose variability was correlated with reduction of d-ROMs in T2DM [22]. Consistent with our previous findings, Rizzo et al. reported that DPP-4 inhibitors improve glucose variability assessed by CGM, thereby reducing oxidative stress in patients with T2DM [43]. Dulaglutide, a once-weekly injectable GLP-1RA, has also been shown to improve glucose variability [44] and reduce oxidative stress in patients with T2DM [28]. Moreover, a Phase III clinical trial of oral semaglutide demonstrated significant improvement in self-monitored postprandial glucose levels compared to placebo at 26 weeks [38, 45]. These observations suggest that incretin-based therapies, such as injectable GLP-1RAs, DPP-4 inhibitors, and oral semaglutide, could improve glucose variability in patients with T2DM. However, to date, no clinical studies have investigated the effects of oral semaglutide on oxidative stress and glucose variability evaluated by CGM simultaneously, nor have reports compared the differences in changes between oral semaglutide and DPP-4 inhibitors. Our present findings for the first time showed that switching to oral semaglutide from DPP-4 inhibitors significantly reduces d-ROMs, an oxidative stress marker, and improves glucose variability in patients with T2DM. Therefore, the present study indicates that compared to DPP-4 inhibitors, oral semaglutide may more efficiently reduce oxidative stress generation in patients with T2DM, partly through its effect on reducing glucose variability. In the present study, semaglutide therapy decreased percentage coefficient of variation (%CV) of glucose by *ca.* 1%. It has been reported that a 1% decrease in CV, an index of glycemic variability independent of MGL, is associated with 0.19 unit/year increase in thickened-lesion grey-scale median of carotid arteries, which may correspond to approximately 1.4% risk reduction in CVD [46], thereby having some clinical impact in our patients. However, in this study, there was a significant difference of changes in SD between the semaglutide and DPP-4 inhibitors groups, but the difference in CV changes was only marginally significant ($p < 0.1$). Switching to semaglutide therapy had a tendency to decrease MGL, while continuous treatment with DPP-4 inhibitors to increase it. Therefore, MGL-lowering effect of semaglutide but not DPP-4 inhibitors may account for the difference. In any case, given that SD or CV was not statistically significantly changed by switching therapy to semaglutide, at this time, no definite conclusion about a causal relationship between semaglutide administration and glucose variability itself can be drawn.

Table 2 Comparison of clinical and biochemical parameters at baseline and 24 weeks

	Semaglutide group			DPP-4 inhibitors group			
	Baseline	24 weeks	p^1 value	Baseline	24 weeks	p^1 value	p^2 value
Body weight (kg)	67.9 ± 12.7	65.6 ± 12.8	0.353	65.1 ± 12.0	64.7 ± 12.0	0.899	< 0.001*
Systolic blood pressure(mmHg)	131.5 ± 17.8	130.5 ± 20.1	0.862	130.6 ± 14.6	131.6 ± 18.1	0.818	0.683
Diastolic blood pressure(mmHg)	74.1 ± 11.3	75.4 ± 13.3	0.728	74.7 ± 11.3	73.8 ± 15.1	0.800	0.404
HDL-C (mg/dL)	55.2 ± 12.3	58.3 ± 12.5	0.395	56.7 ± 11.6	57.3 ± 12.5	0.866	0.133
LDL-C (mg/dL)	94.9 ± 16.2	94.8 ± 23.4	0.989	96.3 ± 20.8	96.6 ± 20.2	0.924	0.623
Triglyceride (mg/dL)	117.0 (93.5–205.0)	119.0 (91.3–168.8)	0.853	110.0 (83.0–183.0)	123.0 (88.0–227.0)	0.421	0.456
AST(GOT) (U/L)	20.5 (17.3–26.8)	20.5 (17.0–28.0)	0.910	19.0 (16.0–28.0)	22.0 (17.0–26.0)	0.516	0.208
ALT(GPT) (U/L)	24.0 (16.0–36.8)	20.5 (15.0–33.8)	0.680	21.0 (15.0–36.0)	21.0 (14.0–35.0)	0.723	0.082
γ-GTP (U/L)	28.0 (20.4–41.5)	27.5 (20.3–38.5)	0.781	29.0 (20.0–58.0)	29.0 (20.0–68.0)	0.723	0.119
eGFR (ml/min/1.73 m^2)	74.2 ± 21.4	72.4 ± 18.3	0.766	69.7 ± 15.5	65.8 ± 18.8	0.413	0.623
UACR (mg/g Cre)	22.9 (10.6–53.9)	30.6 (9.4–74.3)	0.757	25.0 (8.6–47.1)	21.6 (11.8–42.7)	0.972	0.462
FPG (mg/dL)	144.6 ± 27.0	129.6 ± 23.9	0.047*	149.0 ± 24.7	151.7 ± 36.1	0.753	0.047*
HbA1c (%)	7.6 ± 0.4	7.1 ± 0.6	0.003*	7.6 ± 0.4	7.5 ± 0.6	0.921	0.001*
Mean glucose level (mg/dL)	157.1 ± 21.8	143.1 ± 26.4	0.051	159.4 ± 18.2	161.7 ± 22.7	0.690	0.006*
SD (mg/dL)	40.1 ± 6.9	35.8 ± 10.1	0.091	39.8 ± 8.5	41.7 ± 9.6	0.458	0.008*
MAGE (mg/dL)	105.4 ± 26.9	88.1 ± 26.3	0.029*	99.9 ± 20.8	105.5 ± 24.4	0.371	0.001*
MODD (mg/dL)	34.0 ± 7.8	30.2 ± 9.6	0.140	33.9 ± 8.0	35.5 ± 9.4	0.493	0.008*
%CV	25.9 ± 5.4	25.0 ± 5.6	0.572	25.0 ± 4.7	25.7 ± 4.8	0.577	0.099
Time above range (%)	28.3 ± 15.4	17.8 ± 17.6	0.033*	28.3 ± 14.1	29.7 ± 18.0	0.758	0.009*
Time in range (%)	70.6 ± 14.5	81.0 ± 17.2	0.028*	71.6 ± 14.1	70.1 ± 18.0	0.737	0.008*
Time below range (%)	0.0 (0.0–0.0)	0.0 (0.0–0.7)	0.945	0.0 (0.0–0.0)	0.0 (0.0–0.1)	0.203	0.780
d-ROMs (U.CARR)	348.5 ± 73.1	305.0 ± 52.4	0.022*	362.1 ± 93.8	356.7 ± 105.3	0.672	0.007*

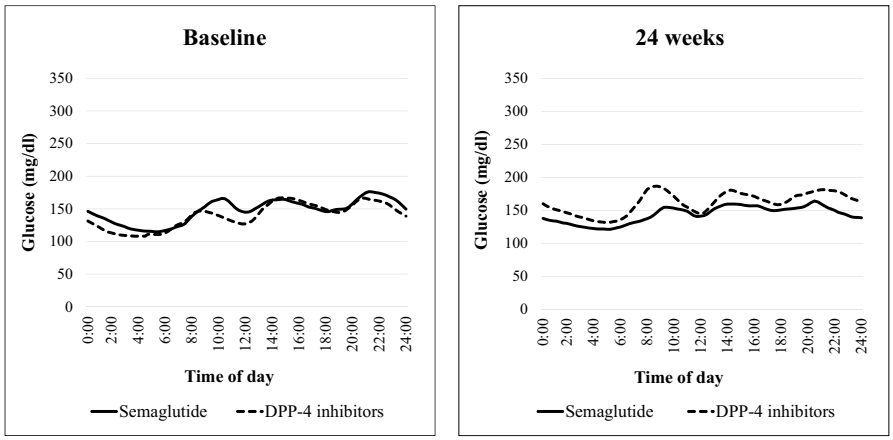
Data are expressed as mean ± standard deviation, medians (interquartile ranges), or numbers (%)

$p.^1$ value for the intragroup comparison (pre- vs post-treatment values in Semaglutide or DPP-4 inhibitors group, *:$p < 0.05$)

$p.^2$ value for the intergroup comparison (Semaglutide vs DPP-4 inhibitors group in the changes from pre- to post-treatment, *:$p < 0.05$)

HDL-C High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *eGFR* Estimated glomerular filtration rate, *FPG* Fasting plasma glucose, *HbA1c* Hemoglobin A1c, *SD* Standard deviation, *MAGE* Mean amplitude of glycemic excursions, *MODD* Mean of daily difference of blood glucose, *%CV* Percentage coefficient of variation for glucose, *d-ROMs* Diacron-reactive oxygen metabolites

To prevent the development and progression of vascular complications in diabetes, controlling HbA1c values is crucial [13], with a recommended glycemic target of < 7% [32]. The present study demonstrated that switching to oral semaglutide from DPP-4 inhibitors enabled more participants to achieve HbA1c values below 7%. This finding is consistent with the results of PIONEER 3 and Furusawa et al., which showed higher rates of achieving HbA1c levels < 7% with oral semaglutide compared to DPP-4 inhibitors [26, 27]. A meta-analysis by Kim et al. revealed that the HbA1c-lowering effects of injectable GLP-1RAs were more pronounced in Asians and in patients with a body mass index (BMI) of < 30 kg/m^2 [47]. Compared to Caucasians, Asian patients with T2DM, including Japanese individuals, typically exhibit lower β-cell function and more insulin resistance for a given BMI [48]. GLP-1RAs have been reported to enhance glucose-stimulated insulin secretion and improve insulin resistance in patients with T2DM via BW loss-dependent and -independent mechanisms [49]. Therefore, although several studies have reported that GLP-1 may be more useful in patients with preserved insulin secretory capacity [50, 51] and that insulin secretory capacity was not evaluated in the present study, more insulin-secreting and BW-reducing property of GLP-1RAs than DPP-4 inhibitors could partly explain the reason why rate of patients who achieved HbA1c values below 7% was higher in the semaglutide group than in the DPP-4 inhibitors group. In our study, the degree of reduction in HbA1c values from baseline was relatively smaller



a b

Fig. 3 Glucose level over 24 h during treatment with oral semaglutide versus dipeptidyl peptidase 4 inhibitors. Continuous glucose monitoring (CGM) data at baseline **a** and after 24 weeks of intervention **b**

Table 3 Correlations between the changes in d-ROMs and the changes in body weight and glucose metabolism

	Δd-ROMs	
	r	p
ΔWeight (kg)	0.323	0.124
ΔFPG (mg/dL)	0.085	0.694
ΔHbA1c (%)	− 0.052	0.811
ΔMean glucose level (mg/dL)	0.271	0.201
ΔSD (mg/dL)	0.374	0.072
ΔMAGE (mg/dL)	0.279	0.187
ΔMODD (mg/dL)	0.485	0.016
Δ%CV	0.330	0.116
ΔTime above range (%)	0.319	0.129
ΔTime in range (%)	− 0.327	0.118
ΔTime below range (%)	0.138	0.520

Δ is the changes from pre- to post-treatment, *d-ROMs* Diacron-reactive oxygen metabolites, *FPG* Fasting plasma glucose, *HbA1c* Hemoglobin A1c, *SD* Standard Deviation, *MAGE* Mean amplitude of glycemic excursions, *MODD* Mean of daily difference of blood glucose, *%CV* Percentage coefficient of variation for glucose

compared to that observed in the PIONEER trials [8, 26, 37, 44]. The difference in HbA1c-lowering effects of oral semaglutide between our study and previous trials [8, 26, 37, 44] may be partly due to the fact that our patients were already receiving treatment with DPP-4 inhibitors and had lower baseline HbA1c values than those in the PIONEER trials. Nevertheless, further clinical research is necessary to investigate whether the glucose-lowering effects of oral semaglutide differ between Asians and Caucasians.

In this study, total DTSQ scores were similar between the semaglutide and DPP-4 inhibitor groups, which is consistent with the findings of PIONEER 7 [52]. However, the DTSQ score for "current treatment" tended to increase in the semaglutide group compared to the DPP-4 inhibitor group, whereas the score for "hypoglycemia" was significantly higher in the semaglutide group than in the DPP-4 inhibitor group. Therefore, future large-scale clinical studies are necessary to confirm these findings. Patients with T2DM should be instructed to take oral semaglutide upon waking up, which may be impractical for some individuals. However, because treatment satisfaction in terms of "convenience" and "flexibility" was comparable between the oral semaglutide and DPP-4 inhibitor groups, this may support the clinical utility of oral semaglutide for T2DM treatment.

DPP-4 inhibitors have a neutral effect on BW, whereas injectable GLP-1RAs have been shown to reduce BW [53]. Our study demonstrated that switching to oral semaglutide was more effective than continuous therapy with DPP-4 inhibitors in reducing BW over 24 weeks. GLP-1RAs reduce BW through various mechanisms; they not only slow gastric emptying but also suppress appetite by promoting satiety and inhibiting hunger via the central nervous system [54, 55]. These mechanisms may contribute to the increased risk of adverse gastrointestinal side effects. A subanalysis of PIONEER 9 and 10 indicated that gastrointestinal symptoms tended to increase with age [56], with all affected patients being over 70 years old and having diabetic neuropathy. In our study, three participants in the semaglutide group discontinued treatment because of gastrointestinal side effects. Identifying patients more susceptible to these effects of oral semaglutide could help improve drug tolerability.

In this study, pioglitazone was used more frequently in the semaglutide group. Pioglitazone has been reported to reduce oxidative stress [57] and cause

Table 4 Effect of semaglutide and DPP-4 inhibitors on DTSQs

	Semaglutide group (n = 20)			DPP-4 inhibitors group (n = 20)			
	Baseline	24 weeks	p^1 value	Baseline	24 weeks	p^1 value	p^2 value
DTSQs							
Treatment satisfaction	24.4 ± 4.9	26.0 ± 6.5	0.157	24.2 ± 5.2	25.6 ± 5.8	0.428	0.355
Frequency of hyperglycemia and hypoglycemia	4.4 ± 2.0	4.7 ± 2.8	0.372	4.2 ± 2.6	4.0 ± 2.5	0.852	0.512
Subscale score							
1.Current treatment	4.4 ± 1.2	4.9 ± 1.1	0.192	4.8 ± 1.1	4.7 ± 1.0	0.841	0.060
2.Hyperglycemia	3.4 ± 1.6	3.0 ± 2.0	0.512	2.5 ± 1.5	2.7 ± 1.8	0.659	0.398
3.Hypoglycemia	1.0 ± 1.3	1.7 ± 1.6	0.121	1.7 ± 1.5	1.3 ± 1.4	0.461	0.020
4.Convenience	4.1 ± 1.0	4.4 ± 1.3	0.277	3.9 ± 1.2	4.4 ± 1.1	0.183	0.862
5.Flexbility	4.0 ± 1.0	4.2 ± 1.4	0.314	4.0 ± 1.2	4.3 ± 1.2	0.369	0.904
6.Understanding	3.9 ± 0.9	4.1 ± 1.2	0.620	4.0 ± 1.1	4.2 ± 1.2	0.583	0.947
7.Recommend	4.0 ± 0.9	4.0 ± 1.7	0.383	3.7 ± 1.5	3.9 ± 1.2	0.904	0.799
8.Continue	4.1 ± 1.1	4.5 ± 1.4	0.127	3.9 ± 1.0	4.3 ± 1.2	0.383	0.529

Data are expressed as mean ± standard deviation

$p.^1$ value for the intragroup comparison (pre- vs post-treatment values in Semaglutide or DPP-4 inhibitors group)

$p.^2$ value for the intergroup comparison (Semaglutide vs DPP-4 inhibitors in the changes from pre- to post-treatment)

DTSQs Diabetes treatment satisfaction questionnaire

weight gain [58]. However, it is unlikely that pioglitazone could affect the present results for the following reasons; (1) no significant difference was observed in overall baseline d-ROMs values with or without pioglitazone use (342.6 ± 68.4 vs. 357.8 ± 86.8 U.CARR, p = 0.661) and (2) there were also no significant differences in the effects of semagulitide on d-ROMs or BW between pioglitazone use and non-use group (− 23.2 ± 49.9 vs. − 50.3 ± 44.2 U.CARR, p = 0.271 and − 2.5 ± 1.8 vs. − 2.3 ± 1.8 kg, p = 0.776).

The present study has several limitations. First, the open-label design of the randomized controlled trial may have influenced the findings. Additionally, the process of switching from conventional to novel drugs may have evoked positive psychological reactions, potentially biasing outcomes in favor of the oral semaglutide group. Second, the study period was relatively short (24 weeks); therefore, the long-term effects of oral semaglutide and DPP-4 inhibitors on oxidative stress and glucose variability in patients with T2DM remain to be elucidated. Third, the study only included Japanese patients, limiting the generalizability of the results to other populations. Fourth, Iwamoto et al. [59] reported a dose of oral semaglutide is limited to 3 mg in 20% of total participants after 6 months, but sufficiently reduced HbA1c in actual clinical practice, as the same level as the present result. However, it remains unclear whether the data using 7 mg oral semaglutide in the present study were able to be applied to the use of 3 mg semaglutide.

Conclusions

Switching to oral semaglutide from DPP-4 inhibitors improved oxidative stress and glucose metabolism, including glucose variability, in patients with T2DM. These results indicate that oral semaglutide may be a more effective therapeutic option than DPP-4 inhibitors in patients with T2DM for improving glucose variability, which is one of the risk factors for vascular complications in diabetes.

Abbreviations

DPP-4	Dipeptidyl peptidase 4
CGM	Continuous glucose monitoring
T2DM	Type 2 diabetes mellitus
d-ROMs	Diacron-reactive oxygen metabolites
DTSQ	Diabetes Treatment Satisfaction Questionnaire
CVD	Cardiovascular disease
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
BW	Body weight
FPG	Fasting plasma glucose
SD	Standard deviation
MGL	Mean glucose level
MAGE	Mean amplitude of glycemic excursions
MODD	Mean of daily difference of blood glucose
TAR	Time above range
TIR	Time in range
BMI	Body mass index
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
eGFR	Estimated glomerular filtration rate

%CV Percentage coefficient of variation for glucose

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01691-y.

Additional file1 (DOCX 23 KB)

Additional file2 (DOCX 17 KB)

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Author contributions
MO contributed to study design, data acquisition, and data analysis and wrote the manuscript. HY, HS, YM, TF, and SY reviewed and edited the manuscript for intellectual content. MO and SY drafted the manuscript. MO, HY, HS, TF, YK, TO, MI, NT, SI, MT, YM, TF, and SY interpreted data and critically revised and wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the present study are not publicly available because data sharing was not included in the consent form but are available from the corresponding author upon reasonable request. Data are located in controlled access data storage.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Showa University and adhered to the principles of the Declaration of Helsinki and current legal regulations in Japan. After thoroughly explaining the study protocol, written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
MO has received lecture fees from Eli Lilly Japan K.K. HS has received lecture fees from Astellas Pharma Inc., Novartis Pharmaceuticals Co., Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., MSD K.K., and Sanofi K.K. as well as received research funds from Novo Nordisk Pharma Ltd., Mitsubishi Tanabe Pharma Co., Nippon Boehringer Ingelheim Co., YL Biologics Ltd., and Sanofi K.K. YM holds an endowed chair funded by Ono Pharmaceutical Co., Ltd. and Nippon Boehringer Ingelheim Co., Ltd. SY has received lecture fees from Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., Sanofi K.K., and Novo Nordisk Pharma, Japan.

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