ORIGINAL RESEARCH

Immediate Impact of Switching from Dipeptidyl Peptidase 4 (DPP4) Inhibitors to Low-Dose (0.3 mg) Liraglutide on Glucose Profiles: A Retrospective Observational Study

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ABSTRACT

Introduction: As treatment agents for diabetes, liraglutide is a long-acting glucagon-like peptide 1 receptor agonist, and dipeptidyl peptidase 4 (DPP4) inhibitors are widely used because of their safety and tolerability. Regular treatment with liraglutide has been reported to significantly reduce blood glucose levels, but the impact of low-dose (0.3 mg) liraglutide on blood glucose levels immediately after treatment switching from a DPP4 inhibitor remains unknown.

Methods: We conducted a single-arm, retrospective, observational study in 55 inpatients with type 2 diabetes (T2D) to investigate the changes (Δ) in their blood glucose levels at six time points (6-point) from the day before (day −1) to the day after (day 1) by switching the antidiabetic treatment from a DPP4 inhibitor to liraglutide 0.3 mg (low-dose liraglutide) once daily. We also attempted to identify factors associated with the blood glucose-lowering effects of liraglutide.

Results: The median values of the changes in fasting, preprandial, and postprandial blood glucose levels and the fluctuations in the blood glucose levels expressed as the standard deviation of the 6-point blood glucose levels were significantly lower on day 1 than on day −1 ($P < 0.05$, $P < 0.0001$, $P < 0.0001$, $P < 0.01$, respectively); there were no cases of severe hypoglycemia. The Δ blood glucose levels were not associated with the baseline serum hemoglobin A1c values or with any markers of the insulin secreting capacity. There were no associations between the previously used blood glucose-lowering drug and the Δ blood glucose levels.

Conclusion: Switching from a DPP4 inhibitor to low-dose (0.3 mg) liraglutide once daily significantly reduced the blood glucose levels and excursions of the blood glucose levels even from the very day after the treatment switch, with no serious adverse events.

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Keywords: Liraglutide; Glucagon-like peptide 1 receptor agonist; Type 2 diabetes

Key Summary Points

Why carry out this study?

Liraglutide is a long-acting glucagon-like peptide-1 receptor agonist that is administered once daily in the treatment of type 2 diabetes.

Regular doses of liraglutide have been reported to significantly reduce blood glucose levels in long-term studies, but the glucose-lowering effects of low-dose (0.3 mg) liraglutide the day after switching from a dipeptidyl peptidase 4 (DPP4) inhibitor remained unknown.

What was learned from the study?

Switching from a DPP4 inhibitor to low-dose liraglutide once daily significantly reduced the blood glucose levels and excursions of blood glucose by the day after the switch without causing any serious adverse events.

The low-dose liraglutide once daily as a substitute for a DPP4 inhibitor among patients with type 2 diabetes effectively reduced blood glucose irrespective of baseline serum hemoglobin A1c (HbA1c) values, parameters of insulin secreting capacity, and the drugs used previously.

These findings suggest switching from a DPP4 inhibitor to low-dose liraglutide is effective and safe for glycemic control of patients with type 2 diabetes.

INTRODUCTION

The American Diabetes Association (ADA) guideline for diabetes has set a target serum hemoglobin A1c (HbA1c) value of below 7% (52 mmol/mol) [1] based on past reports of a decrease in the incidence of microvascular complications with intensive glucose-lowering therapy during the early stages of type 2 diabetes (T2D) [2, 3]. Fasting hyperglycemia contributes more to HbA1c elevations than postprandial hyperglycemia levels [4], but an association between the 2-h blood glucose level in the oral 75-g glucose tolerance test and the risk of death from cardiovascular disease (CVD) has been suggested [5, 6]. Thus, it is necessary to manage both the fasting and postprandial blood glucose levels in patients with T2D, as early in the course of the disease as possible.

The Standards of Medical Care in Diabetes 2023 published by the ADA recommend starting treatment early with a glucagon-like peptide 1 receptor agonist (GLP-1 RA) such as liraglutide, dulaglutide, or semaglutide in patients with established arteriosclerotic cardiovascular disease (ASCVD), indicators of high ASCVD risk, or chronic kidney disease (CKD), independent of their baseline HbA1c, individualized target HbA1c, or metformin use [7]. GLP-1 RAs are also recommended for patients who are not at an elevated risk for the development of such diseases, as effective regimens with minimized risks of hypoglycemia and weight gain [7]. More than 70% of patients with T2D are treated with dipeptidyl peptidase 4 (DPP4) inhibitors or GLP-1 RAs, and DPP4 inhibitors are the most frequently prescribed oral glucose-lowering agents in Japan, where the major pathogenetic mechanism underlying the development of T2D is impaired β-cell function [8, 9].

Liraglutide is a glucagon-like peptide 1 (GLP-1) analogue that shows 97% amino acid sequence identity with naïve human GLP-1 [10, 11]. In the LEAD trials, liraglutide effectively reduced both fasting and postprandial blood glucose and HbA1c levels, with a low risk of hypoglycemia and weight gain [12, 13]. Significant reduction in the risk of CVD and CKD development with liraglutide has also been observed in and LEADER trials [14, 15]. The starting dosage of liraglutide in Japan is 0.3 mg once daily, and the dose can be increased by 0.3 mg/week to a maximum of 1.8 mg/day [16]. In the past study involving patients who had inadequate glycemic control with metformin, adding liraglutide 1.2 mg/day or 1.8 mg/day resulted in greater reduction of HbA1c compared to sitagliptin 100 mg/day [17]. When DPP4 inhibitor fails to achieve reduction in blood glucose levels, switching to GLP-1 RA is considered.

The effectiveness of the treatment switch from a DPP4 inhibitor to liraglutide has been

assessed in previous studies, and the results showed greater reductions in HbA1c levels, body weight, and fasting blood glucose levels [18, 19]. In all of these studies, the patients were switched from sitagliptin (100 mg/day) to liraglutide (1.2 mg/day or 1.8 mg/day), but the effectiveness of switching from a DPP4 inhibitor to low-dose (0.3 mg) liraglutide had never been investigated. We previously showed that both blood glucose levels and blood glucose excursions significantly decreased by a day after dulaglutide, a weekly GLP-1 RA, administration irrespective of prior use of DPP4 inhibitors [20].

In this study, we investigated the effectiveness and safety of switching from a DPP4 inhibitor to liraglutide 0.3 mg on fasting and postprandial blood glucose levels and glucose excursions on the day after the treatment switch. We also attempted to identify factors that were possibly associated with the effect of the treatment switch on glycemic control in patients with T2D.

METHODS

Subjects

This was a retrospective observational study of patients with T2D conducted at Yokohama City University Hospital. The inclusion criteria were patients with T2D who were at least 20 years old, who were receiving a treatment with a DPP4 inhibitor prior to the treatment switch to liraglutide (0.3 mg, administered daily by subcutaneous injection daily) for the first time, and who were hospitalized for glycemic control between May 1, 2011 and September 30, 2020.

The exclusion criteria were serious ketosis, diabetic coma, mental illness, pancreatic exocrine disorder, endocrinological disorder, liver disorder, cancer, infection, injury, and postoperative state. This study was approved by the ethics committee of Yokohama City University Hospital (B201200061). The study protocol was in compliance with the principles outlined in the 1964 Declaration of Helsinki and its later amendments.

The need for obtaining written informed consent from the subjects was waived because of the anonymized nature of the data collected from the existing medical records. The participants were informed about the study protocol and about their right to refuse participation in the study through the website of Yokohama City University Hospital.

Study Design

This study is a continuation of our previous study and follows the same protocol [20]. Blood glucose levels were measured using a glucometer (Medisafe Fit Smile, Terumo Corporation). The data were collected before and 2 h after each meal, at 07:30 ($n = 55$), 10:30 ($n = 51$–55), 11:30 ($n = 51$–55), 14:30 ($n = 51$–55), 17:30 ($n = 53$–55), and 20:30 ($n = 53$–55) for 4 days (Fig. 1).

Overnight fasting blood samples and spot urine samples were collected before the start of liraglutide administration and within 4 days of hospital admission. Twenty-four-hour urine specimens were collected for C-peptide and microalbumin measurements, and body weight and waist circumference were measured within 6 and 3 days, respectively, of hospital admission. Blood pressure and heart rate were measured daily, and the data on the day before the initiation of liraglutide administration were adopted for use in the analyses. Data were collected from electronic health records at Yokohama City University Hospital.

Administration of DPP4 inhibitors was discontinued on the day of the first injection of liraglutide. Other glucose-lowering medications, including insulin, were continued, with their doses adjusted as needed. No additional drugs were started during the 3 days before or after the initiation of liraglutide administration.

The changes in blood glucose levels at six time points (6-point blood glucose levels) from baseline to the day after the switch to liraglutide was the primary endpoint of the study. Associations between changes in the blood glucose levels and the patient characteristics and laboratory data were also examined. The estimated glomerular filtration rate (eGFR) was calculated by using the modified IDMS-MDRD formula: $194 \times$ serum creatinine $(Cre)^{-1.094} \times age^{-0.287} (\times 0.739$ for women). The plasma HbA1c was measured by
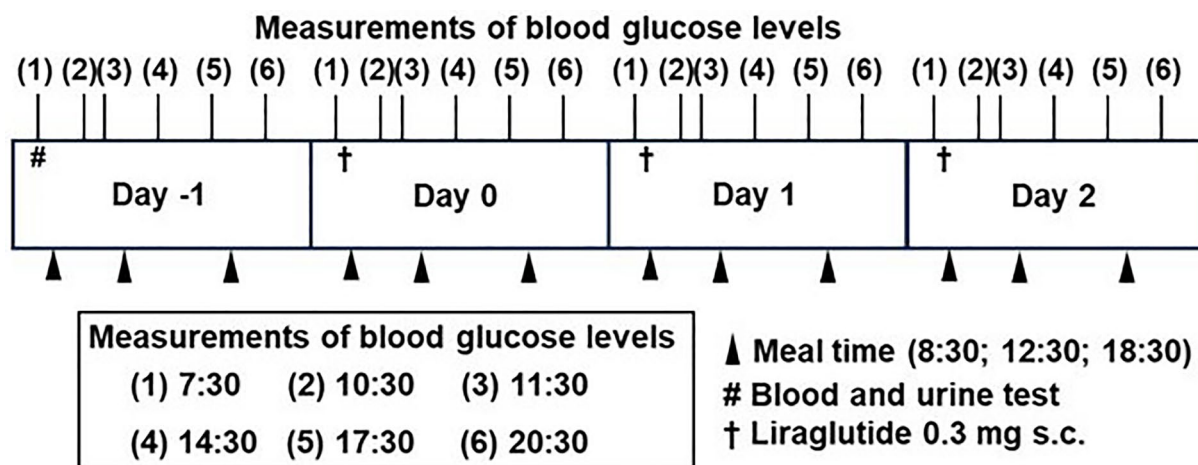
Measurements of blood glucose levels

Fig. 1 Study design. The glucose levels were measured at indicated times. The triangles represent meal times. Liraglutide was injected just before breakfast on day 0, day 1, and day 2

using high-performance liquid chromatography (HPLC). The C-peptide index (CPI) was calculated using the following formula: fasting C-peptide immunoreactivity (CPR)/fasting blood glucose × 100. The liver fibrosis 4 (FIB-4) index was calculated as follows: serum aspartate aminotransferase level (AST) (IU/L) × age/platelet $(10^9/L)$ × $\sqrt{}$ serum alanine aminotransferase level (ALT) (IU/L).

Statistical Analysis

The 6-point blood glucose levels are described as the mean ± standard deviation (SD). The fasting, preprandial, and postprandial blood glucose levels, and the SD of the 6-point blood glucose levels are shown as median values (interquartile range (IQR), i.e., 25th–75th percentile). The changes (Δ) in the blood glucose levels between day −1 and day 1 were described as median values, except for the changes regarding sex, which were expressed as the mean values. The differences in blood glucose levels are statistically analyzed by the Wilcoxon signed-rank test. The correlations between the Δ blood glucose levels and continuous variables were evaluated by simple linear regression analysis. The associations of the Δ blood glucose levels and categorical variables were evaluated by the Mann–Whitney

U test. The JMP Pro version 15.0.0 software program (SAS Institute Inc., NC, USA) was used for statistical analysis. Differences were considered significant if the *P* value was < 0.05.

RESULTS

Baseline Characteristics

A total of 99 cases were screened, with 2 patients excluded because of skipping a meal for imaging and 1 patient because of use of prednisolone. A further 41 cases were excluded for the following reasons: continuation of DPP4 inhibitors, new drugs within 3 days before liraglutide administration, change of insulin type on day 0, change of liraglutide dosage on day 1, and partially missing blood glucose values from day −1 or day 1. A total of 55 patients with T2D participated in this study. The number of cases used for analysis were as follows: day −1, 55 cases; day 0, 48 cases; day 1, 55 cases; day 2, 50 cases. The baseline characteristics of the patients are shown in Table 1. The median age of the patients was 64 (53–70) years, the median body mass index (BMI) was 27.2 (24.0–31.5) kg/m^2, the median HbA1c value was 9.1% (8.3–10.3%) (76 (67–89)

Table 1 Baseline patient characteristics (including baseline oral hypoglycemic agents)

Baseline characteristics	Values ($N = 55$)
Age (years)	64 (53–70)
Sex (male/female)	32/23
BMI (kg/m^2)	27.2 (24.0–31.5)
HbA1c (%)	9.1 (8.3–10.3)
FPG (mg/dL)	157 (136–187)
eGFR (mL/min/1.73 m^2)	65.6 (48.4–83.1)
Urinary CPR (µg/day)	99.1 (65.6–135.5)
Fasting serum CPR (ng/mL)	2.3 (1.8–3.6)
Baseline oral hypoglycemic agents	
Metformin	20 (36.3%)
Thiazolidinediones	7 (12.7%)
Sulfonylureas	14 (25.5%)
α-GIs	8 (15.5%)
Glinide	11(20%)
SGLT2 inhibitor	11 (20%)
Insulin	36 (65.5%)
Total daily units of insulin	5 (0–29)
Rapid-acting insulin	28 (50.9%)
Long-acting insulin	35 (63.6%)
Premix insulin	1 (1.8%)

The data on sex are described as the actual numbers. The data on oral hypoglycemic agents are described as the actual numbers and percentages. Other data are the median values (25th–75th percentile)

BMI body mass index, *FPG* fasting plasma glucose, *CPR* C-peptide immunoreactivity, *HbA1c* serum hemoglobin A1c, *α-GIs* alpha-glucosidase inhibitors, *SGLT2* sodium glucose cotransporter 2

Table 2 DPP4 inhibitors and dosages administered before the treatment switch to liraglutide (0.3 mg)

DPP4 inhibitors	No. of cases	Dosage (/day)
Alogliptin	8	25 mg
Linagliptin	8	5 mg
Saxagliptin	1	2.5 mg
Sitagliptin	20	50 mg, 19 cases; 100 mg, 1 case
Teneligliptin	10	20 mg, 9 cases; 40 mg, 1 case
Vildagliptin	8	50 mg, 1 case; 100 mg, 7 cases

DPP4 dipeptidyl peptidase 4

teneligliptin (18.2%), linagliptin/alogliptin/vildagliptin (14.5% for all), and saxagliptin (1.8%). The insulin dose was decreased in most cases and increased by 2 and 6 units, respectively, in two cases before liraglutide administration. The dose of oral hypoglycemic drugs was not increased for 3 days before and after administering liraglutide. No cases received drugs with long half-lives.

Effect of Switching from a DPP4 Inhibitor to Low-Dose Liraglutide (0.3 mg) on Daily Blood Glucose Levels

We compared the 6-point blood glucose levels at baseline (day −1) with those on the day after the treatment switch from a DPP4 inhibitor to liraglutide 0.3 mg (day 1), to investigate the immediate effect of switching from a DPP4 inhibitor to low-dose liraglutide on the blood glucose levels (Fig. 2).

Significant reductions in both fasting and postprandial blood glucose levels were observed on day 1 compared day −1 ($P < 0.05$ for the pre-breakfast values, post-breakfast values, and post-lunch values; $P < 0.01$ for the pre-dinner values and post-dinner values; $P < 0.0001$ for the pre-lunch values) (Fig. 2). The blood glucose excursions expressed as the SD of the 6-point blood glucose levels were also significantly reduced on day 1 as compared with day −1 ($P < 0.01$) (Fig. 3).
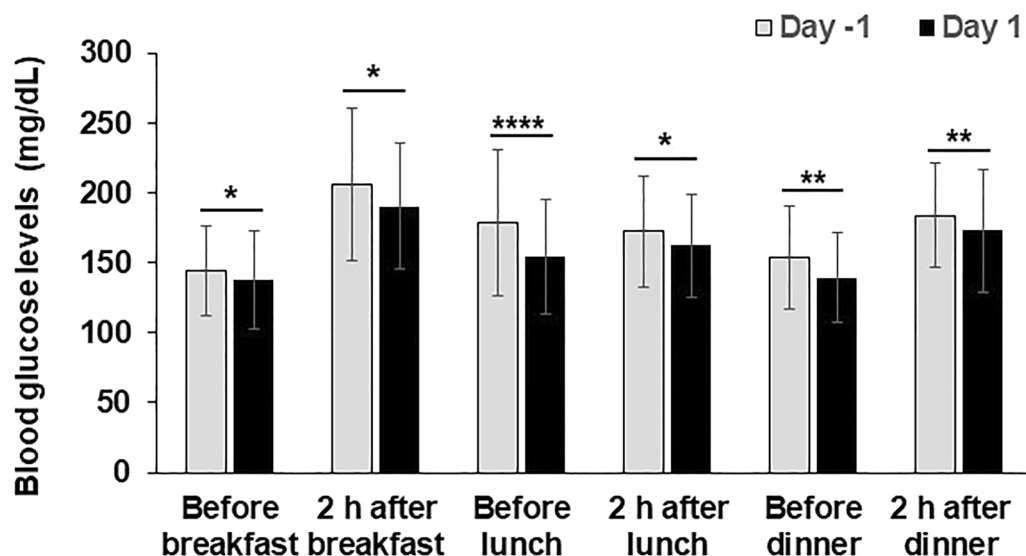
mmol/mol), and the median urinary CPR was 99.1 (65.6–135.5) µg/day. The DPP4 inhibitors used before the treatment switch to liraglutide 0.3 mg and their dosages are shown in Table 2. The most commonly administered DPP4 inhibitor was sitagliptin (36.4%), followed by

Fig. 2 Blood glucose levels at day −1 (the baseline) and day 1 (on the day after the first liraglutide (0.3 mg) administration switching from a DPP4 inhibitor). *$P < 0.05$ vs. day −1, **$P < 0.01$ vs. day −1, ***$P < 0.001$ vs. day −1, ****$P < 0.0001$ vs. day −1. All data shown are the means ± SD. *DPP4* dipeptidyl peptidase 4, *SD* standard deviation

On the basis of these results, low-dose liraglutide (0.3 mg) once daily did not worsen but improved the blood glucose levels and daily blood glucose fluctuations in patients with insufficiently controlled T2D who were previously receiving treatment with a DPP4 inhibitor. Reductions in the fasting, preprandial, and postprandial blood glucose levels and in the SD of the 6-point blood glucose levels were also observed on day 2 after the switch to liraglutide (day 2) ($P < 0.0001$ for the pre- and post-prandial blood glucose levels; $P < 0.001$ for the fasting blood glucose levels and SD) (Fig. 4). The adverse events observed from day 0 to day 2 were mild nausea (4 cases, 7.2%), mild appetite loss (3 cases, 5.5%), diarrhea (2 cases, 3.6%), and dizziness (1 case, 1.8%). There were no cases of hypoglycemia.

Factors Associated with Blood Glucose-Lowering Effect of Liraglutide (0.3 mg) on Day 1 After Treatment Switch from a DPP4 Inhibitor

As shown in Tables 3 and 4, we attempted to identify factors that were associated with the Δ blood glucose levels between day −1 and day 1
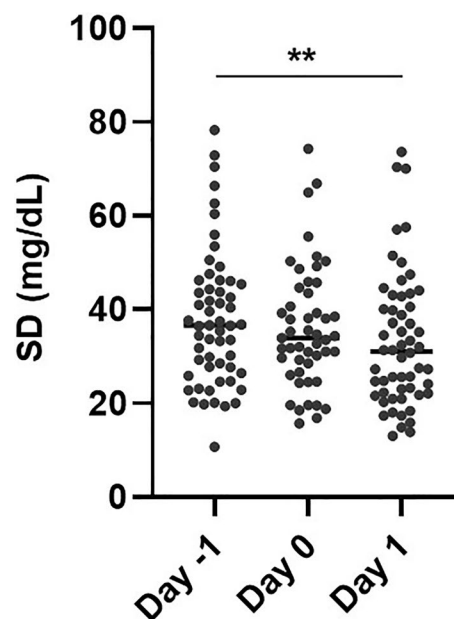

Fig. 3 Changes in the standard deviation of the 6-point blood glucose levels, from day −1 (the baseline) to day 1 (the day after the initiation of liraglutide (0.3 mg). Day 0 is the day the DPP4 inhibitor was discontinued and the administration of liraglutide (0.3 mg) was initiated. **$P < 0.01$ vs. day −1. All data shown are the median values ± IQR. *DPP4* dipeptidyl peptidase 4, *SD* standard deviation of the 6-point blood glucose levels

in the patients who were switched from a DPP4 inhibitor to liraglutide 0.3 mg/day. There were no significant associations of the age and sex with the glucose-lowering effect of liraglutide following the treatment switch. There were 27 patients (49.1%) who were over 65 years old and 8 patients (14.5%) who were over 75 years old. Improvements in the Δ blood glucose values were also observed in this elderly patient group, except for the Δ fasting blood glucose level (FBS), which was – 8 mg/dL in the over 75-years age group. However, there were no significant differences in the Δ blood glucose values, including the ΔFBS values, between the elderly and younger patient group. Although BMI was not correlated with the changes in the blood glucose levels following liraglutide administration, the non-obese group showed a higher ΔSD in the 6-point blood glucose values ($P < 0.01$). The baseline HbA1c values were not associated with the changes in the blood glucose values either. The baseline glycated albumin (GA) was positively associated ΔFBS and Δ mean value of 6-point blood glucose levels ($P < 0.05$ for both). None of the markers of the insulin secretory capacity (fasting CPR, urinary CPR, and CPI) correlated with the changes in the blood glucose levels. There were no correlations between the Δ blood glucose values and the duration of diabetes. Evaluation of the influence of diabetic complications revealed that the group with cerebrovascular disease had a greater Δ mean 6-point blood glucose value ($P < 0.05$). There were 38 cases of diabetic peripheral neuropathy, 23 cases of diabetic nephropathy, and 17 cases of autonomic neuropathy; however, only a few of the subjects had ischemic heart disease, cerebrovascular disease, and peripheral arterial disease ($n = 7$, 3, and 3, respectively). FIB-4 index was negatively correlated with Δ post-breakfast blood glucose levels ($P < 0.05$). Other factors that were found to be associated with the Δ blood glucose levels were the red blood cell (RBC) count, serum sodium (Na), serum phosphorus (P), heart rate, and a family history of diabetes (Tables 3 and 4).

We also analyzed the data to determine the associations between the previously used antidiabetic agents and the changes in the blood glucose levels observed between day –1 and
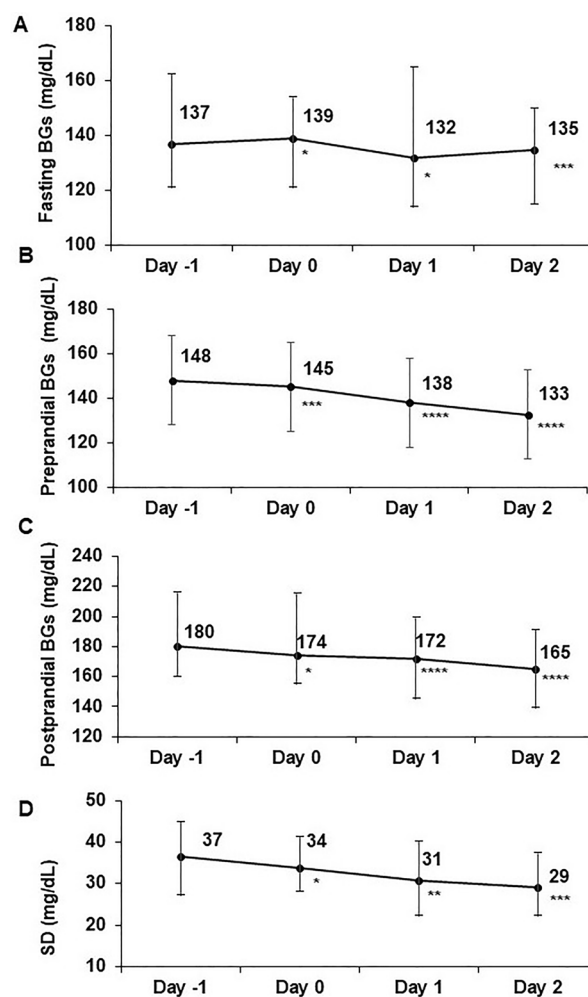

Fig. 4 Temporal trends in parameters of blood glucose levels. **A** Fasting blood glucose levels, **B** preprandial blood glucose levels, **C** postprandial blood glucose levels, **D** standard deviation of the 6-point blood glucose levels. Day 0 indicates the day of first administration of liraglutide 0.3 mg and the day the DPP4 inhibitor was discontinued. *SD* standard deviation. *$P < 0.05$ vs. day −1, **$P < 0.01$ vs. day −1, ***$P < 0.001$ vs. day −1, ****$P < 0.0001$ vs. day −1. All data shown are the median values ± IQR. *BGs* blood glucose levels, *DPP4* dipeptidyl peptidase 4, *SD* standard deviation

day 1 in the patients who were switched from a DPP4 inhibitor to liraglutide 0.3 mg/day, but the results revealed no correlations between the previously used glucose-lowering drugs and the changes in the blood glucose levels following the treatment switch (Table 5). Thus, there were no significant associations between the Δ blood

Table 3 Correlations between the changes in the blood glucose levels and the patient characteristics and laboratory data

Variable	Δ fasting blood glucose level (mg/dL)		Δ 2-h post-breakfast blood glucose level (mg/dL)		Δ mean value of 6-point blood glucose levels (mg/dL)		Δ standard deviation of 6-point blood glucose levels (mg/dL)	
	r	P value	r	P value	r	p value	r	P value
Age	− 0.042	0.760	0.092	0.504	0.076	0.583	0.197	0.150
BMI	− 0.104	0.448	− 0.162	0.228	− 0.180	0.189	− 0.187	0.171
Waist circumference	− 0.068	0.640	− 0.113	0.434	− 0.128	0.377	− 0.237	0.098
Duration of diabetes	0.197	0.186	0.058	0.700	0.137	0.358	− 0.094	0.530
Systolic BP	0.083	0.550	0.046	0.741	0.033	0.811	− 0.109	0.434
Diastolic BP	− 0.108	0.437	− 0.182	0.188	− 0.254	0.063	− 0.288	0.035*
Heart rate	0.105	0.455	− 0.160	0.253	− 0.100	0.474	− 0.286	0.038*
HbA1c	0.244	0.073	− 0.120	0.384	0.066	0.630	0.056	0.686
eGFR	0.112	0.416	0.078	0.569	0.112	0.417	0.155	0.260
Urinary CPR	− 0.064	0.644	− 0.101	0.467	− 0.149	0.283	− 0.045	0.745
Fasting CPR	− 0.116	0.399	− 0.005	0.972	− 0.122	0.373	− 0.068	0.623
WBC	− 0.070	0.610	− 0.120	0.384	− 0.172	0.210	− 0.208	0.128
RBC	0.242	0.075	− 0.046	0.741	− 0.089	0.519	− 0.267	0.049*
Hb	0.021	0.882	0.081	0.557	− 0.024	0.864	− 0.022	0.874
Plt	0.209	0.126	0.222	0.104	0.253	0.062	0.032	0.818
TP	0.049	0.721	− 0.116	0.340	− 0.136	0.322	− 0.187	0.171
Alb	0.025	0.855	− 0.105	0.445	0.002	0.991	− 0.083	0.547
AST	0.017	0.904	− 0.020	0.885	0.027	0.844	− 0.024	0.860
ALT	0.070	0.611	− 0.001	0.991	0.036	0.792	− 0.044	0.747
γ-GTP	− 0.068	0.623	− 0.001	0.997	0.119	0.386	0.087	0.527
FIB-4 index	− 0.118	0.392	− 0.337	0.012*	− 0.151	0.271	0.074	0.592
ALP	− 0.066	0.640	0.006	0.967	− 0.004	0.975	0.039	0.782
LDH	− 0.028	0.841	− 0.028	0.839	− 0.082	0.552	− 0.044	0.748
ChE	− 0.038	0.817	− 0.027	0.870	− 0.035	0.832	− 0.005	0.975
AMY	0.139	0.347	0.039	0.791	− 0.046	0.756	− 0.179	0.223
BUN	− 0.080	0.563	− 0.140	0.309	− 0.113	0.412	− 0.091	0.507
Cre	− 0.011	0.939	− 0.137	0.318	− 0.163	0.236	− 0.248	0.068
UA	− 0.088	0.526	− 0.089	0.521	− 0.118	0.396	− 0.202	0.144
Na	− 0.210	0.124	− 0.177	0.174	− 0.186	0.174	− 0.308	0.022*

Table 3 continued

Variable	Δ fasting blood glucose level (mg/dL)		Δ 2-h post-breakfast blood glucose level (mg/dL)		Δ mean value of 6-point blood glucose levels (mg/dL)		Δ standard deviation of 6-point blood glucose levels (mg/dL)	
	r	P value	r	P value	r	p value	r	P value
K	0.009	0.947	0.003	0.981	−0.001	0.992	0.096	0.487
Cl	−0.102	0.459	0.049	0.723	−0.021	0.881	−0.210	0.124
Ca	0.058	0.683	−0.056	0.692	−0.010	0.944	−0.050	0.724
P	−0.393	0.006**	−0.241	0.099	0.007	0.960	−0.107	0.469
Mg	−0.127	0.448	−0.034	0.454	−0.125	0.454	−0.310	0.058
Ferritin	0.110	0.476	−0.080	0.604	0.072	0.643	0.225	0.141
T-Bil	0.277	0.054	0.095	0.272	0.160	0.272	0.051	0.726
CRP	0.057	0.681	−0.042	0.760	0.032	0.814	−0.098	0.478
T-Chol	0.014	0.475	0.083	0.573	0.095	0.514	0.103	0.482
TG	−0.151	0.270	0.059	0.670	−0.111	0.420	0.038	0.786
HDL-C	0.017	0.901	0.140	0.308	0.160	0.242	0.126	0.361
LDL-C	0.167	0.223	0.013	0.924	0.100	0.470	0.013	0.923
TSH	0.152	0.354	−0.184	0.261	0.032	0.845	−0.124	0.543
FT4	−0.003	0.982	0.093	0.575	−0.014	0.934	0.159	0.333
GA	0.403	0.015*	0.199	0.246	0.331	0.049*	0.321	0.056
CPI	−0.165	0.227	0.009	0.950	−0.130	0.344	−0.118	0.391
Urinary microalbumin	0.023	0.870	−0.155	0.264	−0.081	0.561	−0.010	0.945

Δ Change from the baseline, calculated as the value on day −1 minus the value on day 1; *r* correlation coefficient

ALT alanine aminotransferase, *Alb* albumin, *AMY* amylase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *BMI* body mass index, *BP* blood pressure, *BUN* blood urea nitrogen, *Ca* calcium, *ChE* cholinesterase, *Cl* chloride, *CPI* C-peptide index, *CPR* C-peptide immunoreactivity, *Cre* serum creatinine, *CRP* c-reactive protein, *FT4* free T4, *GA* glycated albumin, *Hb* hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *K* potassium, *LDH* lactate dehydrogenase, *LDL-C* low density lipoprotein cholesterol, *Mg* magnesium, *Na* sodium, *P* phosphorus, *Plt* platelet, *T-Bil* total bilirubin, *T-Chol* total cholesterol, *TG* triglycerides, *TP* total protein, *TSH* thyroid-stimulating hormone, *UA* uric acid, *WBC* white blood cell count, *RBC* red blood cell count, *γ-GTP* γ-glutamyl transpeptidase, *HbA1c* serum hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *FIB-4* liver fibrosis 4

*$P < 0.05$, **$P < 0.01$

glucose levels following treatment switch to liraglutide and the antidiabetic drugs taken previously by the patients.

DISCUSSION

In this observational study, we investigated the immediate glucose-lowering effect and safety of switching from a DPP4 inhibitor to once-daily

Table 4 Differential changes in blood glucose levels according to the patient characteristics/diabetic complications

	Fasting blood glucose levels (mg/dL)			2-h post-breakfast blood glucose levels (mg/dL)			mean value of 6-point blood glucose levels (mg/dL)			SD of 6-point blood glucose levels (mg/dL)		
	Δ		P value	Δ		P value	Δ		P value	Δ		P value
	+	−		+	−		+	−		+	−	
Sex[†]	10.7	1.1	0.550	13.6	19.0	0.912	13.0	14.8	0.676	3.0	7.4	0.403
Age over 65 years	2.0	11.0	0.439	14.0	14.5	0.490	16.5	9.3	0.506	6.0	2.0	0.192
Age over 75 years	− 8.0	9.0	0.189	14.0	14.0	0.685	15.2	9.3	0.474	10.3	4.5	0.163
Smoking history	2.0	14.5	0.156	12.0	16.0	0.668	12.3	11.5	0.600	4.5	5.4	0.680
Drinking history	5.0	5.5	0.897	15.0	13.0	0.568	14.7	9.3	0.472	5.2	4.8	0.591
Family history of diabetes	5.0	8.0	0.764	9.0	20.5	0.041*	5.5	21.3	0.180	5.1	5.0	0.870
Obesity	5.0	6.0	0.957	6.0	30.0	0.083	7.3	22.9	0.106	1.0	13.3	0.009**
Hyperlipidemia	7.0	2.0	0.659	13.0	17.5	1.000	12.3	9.5	0.765	5.1	5.0	0.896
Hypertension	3.0	13.0	0.123	10.5	34.0	0.350	7.3	22.7	0.171	4.2	5.4	0.5552
Ischemic cardiac disease	0.0	7.0	0.781	13.0	14.5	0.677	9.3	13.0	0.830	6.0	4.8	0.677
Cerebrovascular disease	0.0	6.0	1.000	27.0	13.5	0.308	41.7	9.3	0.030*	6.0	4.8	1.000
Peripheral arterial disease	− 15.0	5.0	0.239	17.0	15.0	0.709	5.5	13.8	0.356	5.5	4.5	0.875
Diabetic retinopathy	0.0	12.0	0.232	13.0	12.0	0.808	20.0	9.2	0.808	1.0	5.1	0.707
Diabetic nephropathy	3.0	6.0	0.798	9.0	17.5	0.707	16.5	9.3	0.986	3.0	5.4	0.149
Diabetic peripheral neuropathy	2.0	15.0	0.117	7.5	35.5	0.054	7.4	18.8	0.089	4.2	9.9	0.283
Diabetic autonomic neuropathy	5.0	7.0	0.967	15.0	17.5	0.350	9.3	14.9	0.842	6.6	4.8	0.592

Data shown are the median values, unless otherwise indicated. + Data of patients with factors or male. − Data of patients without factors or female. Δ Change

SD standard deviation

*$P < 0.05$, **$P < 0.01$

[†]Data shown are the mean values

low-dose (0.3 mg) liraglutide in patients with T2D by comparing their blood glucose levels between day −1 (the day before the treatment switch from a DPP4 inhibitor to liraglutide) and day 1 (the day after the treatment switch to liraglutide). This result is consistent with our prior study of switching to dulaglutide [20]. We also attempted to identify factors associated with the changes in the blood glucose levels following the treatment switch.

Only a few trials investigating switching from DPP4 inhibitors to GLP-1RAs had been reported. Wysham et al. [21] showed that switching from sitagliptin 100 mg/day to exenatide 2 mg/week reduced HbA1c by 0.3% over 26 weeks [21]. Pratley et al. [18] reported that switching from sitagliptin 100 mg/day to liraglutide 1.2 mg/day or 1.8 mg/day improved HbA1c by 0.2% or 0.5%, respectively, over 26 weeks. Bailey et al. [19] demonstrated that switching from sitagliptin to liraglutide 1.8 mg in patients treated

Table 5 Influence of the previously used classes of glucose-lowering drugs on the changes in the blood glucose levels observed following treatment switch from a DPP4 inhibitor to liraglutide 0.3 mg

	Fasting blood glucose level (mg/dL)			2-h post-breakfast blood glucose level (mg/dL)			Mean value of 6-point blood glucose levels (mg/dL)			SD of 6-point blood glucose levels (mg/dL)		
	Δ		P value	Δ		P value	Δ		P value	Δ		P value
	+	−		+	−		+	−		+	−	
Metformin	11.5	2.0	0.328	15.5	13.0	0.853	9.8	13.8	0.655	5.3	4.6	0.953
Thiazolidinediones	3.5	9.0	0.882	− 13.0	15.0	0.190	6.7	12.3	0.388	1.2	5.4	0.164
Sulfonylureas	− 3.0	9.0	0.275	26.5	13.0	0.427	19.3	9.3	0.714	5.1	4.6	0.318
α-GIs	− 9.0	8.0	0.177	4.0	16.0	0.312	1.5	13.1	0.587	0.2	5.4	0.261
Glinide	8.5	5.0	0.593	11.0	15.0	0.541	14.4	9.2	0.534	5.7	4.6	0.670
SGLT2 inhibitor	7.5	5.0	0.623	1.5	15.0	0.608	8.3	15.2	0.407	0.5	5.5	0.119
Insulin												
Rapid-acting insulin	12.5	1.0	0.103	13.5	15.0	0.377	12.2	12.3	0.979	5.1	4.6	0.938
Long-acting insulin	13.0	3.5	0.312	9.0	16.0	0.219	15.2	10.8	0.833	5.2	4.8	0.980
Premix insulin	13.0	0.5	0.062	14.0	14.0	0.390	9.2	13.0	0.674	5.1	5.1	0.751

Data shown are the median values. + Data of patients with factors, − data of patients without factors. Δ, change from the baseline, calculated as the value on day −1 minus the value on day 1

α-GIs alpha-glucosidase inhibitors, *DPP4* dipeptidyl peptidase 4, *SGLT2* sodium glucose cotransporter 2, *SD* standard deviation

with metformin and sitagliptin 100 mg achieved greater reduction in HbA1c than patients who continued sitagliptin (− 1.14% vs. − 0.54%).

However, there have been no previous trials of treatment switch to low-dose liraglutide, and this is the first study to show the glucose-lowering effect of liraglutide 0.3 mg once daily even on day 1 after the treatment switch from a DPP4 inhibitor to low-dose liraglutide. Switching from sitagliptin to liraglutide increased overall treatment satisfaction, likely due to improvements in both glycemic and weight control, while the treatment flexibility and the convenience score remained unchanged in the previous study [18]. Immediate improvement of blood glucose levels in this study might improve treatment satisfaction, which leads to treatment continuation, better glycemic control, and prevention of long-term diabetic complications. The more pronounced glucose-lowering effects of GLP-1 RAs than those of DPP4 inhibitors in previous studies are probably attributable to the more powerful stimulation of GLP-1 receptors by GLP-1 RAs, which circulate systemically at sustained concentrations to provide long durations of activity, whereas DPP4 inhibitors cause a twofold increase in the endogenous GLP-1 concentrations after meals, but no changes in the total GLP-1 levels [10, 22, 23]. On the basis of their mechanisms of action, the systemic circulation of low-dose (0.3 mg) liraglutide in the present study was probably sufficient to exert a more pronounced blood glucose-lowering effect than the postprandial increase of the GLP-1 concentration after meals observed following DPP4 inhibitor administration.

We attempted to identify the predictors of a favorable response to low-dose (0.3 mg) liraglutide in the present study. No correlation of age with reductions in the blood glucose levels was observed. Patients over 65 years old and those over 75 years old showed reductions in the blood

glucose levels, except that the Δ mean FBS level was − 8 mg/dL in the latter group of patients; there were no episodes of hypoglycemia. Therefore, low-dose liraglutide was concluded to be an effective and safe treatment for obtaining satisfactory glycemic control in elderly patients with T2D. A history of obesity (BMI ≥ 25 kg/m^2) was associated with smaller reductions in the SD of the 6-point blood glucose levels, whereas BMI was not associated with the effectiveness of liraglutide after the treatment switch from DPP4 inhibitors to liraglutide in our study. A meta-analysis of the LEAD trials reported that BMI values of up to 45 exerted no influence on the reduction in the HbA1c levels provided by liraglutide [24]. The relationship between BMI values and the glucose-lowering effects of liraglutide in lean Japanese subjects remained unknown.

Although higher baseline GA was associated with greater reduction in FBS and 6-point blood glucose levels, baseline HbA1c was not correlated to Δ blood glucose levels. The results concerning the relationships between baseline HbA1c levels and the effectiveness of liraglutide from past real-world retrospective studies are conflicting. Two studies reported that higher baseline HbA1c values were associated with greater reductions in the HbA1c [25, 26], whereas another study claimed that a higher baseline HbA1c value was predictive of a worse HbA1c response [27]. The associations between baseline glycemic control and the Δ blood glucose values are difficult to interpret, because the results from previous studies are conflicting. Lower FIB-4 index was related to higher Δ post-breakfast blood glucose levels. Other markers such as procollagen III peptide, 7S domain of collagen type IV, and hyaluronic acid to evaluate hepatic steatosis and fibrosis should be analyzed in a future study.

In our study, the patients with a history of cerebrovascular disease showed greater reductions of the mean 6-point blood glucose values. Patients without diabetic complications may have a shorter history of diabetes than patients with diabetic complications, but the results concerning diabetic complications in our study are hard to interpret, because there are no published reports on the relationships of diabetic complications or diabetes duration to the effectiveness of low-dose liraglutide.

We observed no associations between the changes in the blood glucose levels and the previously used antidiabetic agents, including insulin, in the present study. Although we did not analyze the association between the number of glucose-lowering agents previously used and changes in the blood glucose levels, 91.5% of our study subjects were receiving more than two glucose-lowering agents prior to the treatment switch from a DPP4 inhibitor to low-dose liraglutide; this finding may suggest that low-dose liraglutide is effective, irrespective of the number or types of glucose-lowering agents previously taken by the patient. Although insulin doses were reduced in most of the cases and the doses of oral drugs were not increased in this study, it might be possible that drug dosage adjustment influenced the changes in blood glucose levels.

Combination treatment consisting of insulin degludec and liraglutide (IDegLira) in a fixed ratio has been found not only to reduce the treatment burden but also reduce the risk of hypoglycemia and weight gain compared with insulin therapy alone [28]. The starting dosage of IDegLira is 10 or 16 doses depending on whether the patient is insulin-naïve or already on insulin therapy, and dose adjustment twice a week in two-dose steps is recommended on the basis of the patient's fasting blood glucose levels [29]. The starting dosage of IDegLira might be 10 doses, containing 10 units of degludec and only 0.36 mg of liraglutide [29] for patients who are insulin-naïve or on insulin therapy with relatively low fasting blood glucose levels [29]. The effectiveness of the liraglutide component is a matter of concern, but the results of our study showing that low-dose (0.3 mg) liraglutide administration once daily as a substitute for a DPP4 inhibitor effectively reduced the blood glucose levels and their fluctuations irrespective of the drugs used previously might help in selecting an effective regimen for such patients with ineffectively controlled blood glucose levels.

Our study had several limitations. First, because the subjects were inpatients, the improvements observed in the blood glucose levels may have been affected by the frequent checking of the blood glucose levels, diet and exercise therapy, and dose adjustment of both the oral glucose-lowering drugs and insulin. Second, because no

washout period was established, the blood glucose levels on day 0 could have been influenced by the effects of the previously administered DPP4 inhibitor. However, the influence of the previously administered DPP4 inhibitor could be considered to have been minimal, because the improvement in the blood glucose levels observed on day 1 was sustained until day 2, when the blood concentration of the DPP4 inhibitor would have decreased significantly, since the terminal half-life is approximately 12.4 h for sitagliptin, 24 h for teneligliptin, 12.4–21.4 h for alogliptin, 2 to 3 h for vildagliptin, and 2.5 h for saxagliptin [30, 31]. Although the terminal half-life of linagliptin 5 mg/day is 131 h, its accumulation half-life is only 11.4 h [32], so that its glucose-lowering effect is unlikely to have persisted until day 1. In addition, it was impossible to establish any causal associations between the reductions in blood glucose levels and the treatment switch to liraglutide, because of the exploratory nature of our study. A prospective study with strict inclusion criteria, a washout period, and dose adjustment protocol for both oral antidiabetic drugs and insulin will be required to establish causality between the improvements in the blood glucose levels following treatment switch from a DPP4 inhibitor to low-dose (0.3 mg) liraglutide.

CONCLUSIONS

In patients with diabetes, following treatment switch from DPP4 inhibitor therapy to low-dose (0.3 mg) liraglutide treatment once daily, the fasting, preprandial, and postprandial blood glucose levels, as well as the blood glucose level excursions, decreased significantly even on day 1 after the treatment switch. The glucose-lowering effects were sustained until 2 days after the initiation of low-dose liraglutide administration, and there were no serious adverse events or hypoglycemia.

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Declarations

compliance with the principles outlined in the 1964 Declaration of Helsinki and its later amendments. Written informed consent from the subjects was not required because of the anonymized nature of the data collected from the existing medical records. We informed the participants about the objectives, method, research period and types of data collected in this study, and of their right to refuse participation in the study via a notice put up on the website of Yokohama City University Hospital.

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