Influence of switching from dulaglutide to oral semaglutide on glycaemic control and clinical parameters in Japanese patients with well-controlled type 2 diabetes: a retrospective, observational study

KENTARO WATANABE, MINAMI KOSUDA, AKIKO NAGASAWA, KAORI NAKAYAMA, TARO SAIGUSA, HISAMITSU ISHIHARA

Abstract

Aims: This study sought to evaluate retrospectively how switching from dulaglutide to oral semaglutide affected glycaemic control and clinical parameters in patients with well-controlled type 2 diabetes (T2DM).

Methods: The study included 18 patients with well-controlled T2DM (mean HbA_{1c} 6.99%) who were taking dulaglutide. HbA_{1c} levels and clinical parameters were measured at baseline and two, four and six months later. Changes in these parameters during the study period were assessed retrospectively.

Results: HbA_{1c} levels at two months from baseline were significantly higher than at baseline (7.43 ± 0.72 vs. 6.99 ± 0.39%, p = 0.003), whereas no significant change was observed at four or six months from baseline. Subjects with improved glycaemic control at six months from baseline (n = 5) had significantly lower gamma-glutamyl transferase levels at baseline compared to those who did not show improvement (n = 13) (13.8 ± 3.0 vs. 47.9 ± 53.6 IU/L, p = 0.026). Notably, high-density lipoprotein cholesterol levels at six months were significantly higher than at baseline (p = 0.006).

Conclusion: Glycaemic control worsened temporarily after switching from dulaglutide to oral semaglutide, but no significant difference was observed between baseline and six months later.

Br J Diabetes 2025;25(2):78-83
https://doi.org/10.15277/bjd.2025.492

Key words: dulaglutide, oral semaglutide, switching, dulaglutide supply insufficiency, high-density lipoprotein cholesterol, gamma-glutamyl transferase

Division of Diabetes and Metabolic Diseases, Department of Internal Medicine, Nihon University School of Medicine, Japan

Address for correspondence: Dr Kentaro Watanabe
Division of Diabetes and Metabolic Diseases, Department of Internal Medicine, Nihon University School of Medicine, 30-1 Oyaguchikami-cho, Itabashi-ku, Tokyo, 173-8610, Japan
E-mail: watanabe.kentaro@nihon-u.ac.jp

Background

The beneficial effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on body weight are used to achieve cosmetic weight loss.[1] The off-label use of GLP-1RAs for cosmetic weight loss has been promoted by social media and celebrity influence, with the internet search volume for GLP-1RAs increasing rapidly over the last five years.[2] As a result, global demand for the off-label use of GLP-1RAs has had a negative impact on their supply for appropriate medical use, resulting in a GLP-1RAs shortage by 2023.[3] In Japan, once-weekly GLP-1RAs supplies were insufficient in 2023. Physicians, including the authors, generally believed that patients with well-controlled T2DM who were taking GLP-1RAs should continue their treatment to the greatest extent possible. As a result of increased demand, patients with T2DM had no choice but to switch from once-weekly GLP-1RAs to oral semaglutide, which remained in sufficient supply in 2023. This decision was made without regard for the clinical factors of patients, particularly improving their glycaemic control. The effect on glycaemic control and clinical parameters of switching between GLP-1RAs in patients with well-controlled type 2 diabetes is unknown. This study sought to assess retrospectively the effect of switching from dulaglutide to oral semaglutide on glycaemic control and clinical parameters in patients with well-controlled T2DM.

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Methods

Study subjects

The study included 18 patients with well-controlled T2DM (11 men and seven women, mean age 59.8 ± 11.7 years) who were taking hypoglycaemic agents that included dulaglutide. All subjects were ambulatory and received care at the Division of Diabetes and Metabolic Diseases, Department of Internal Medicine, Nihon University School of Medicine. These subjects had to switch from dulaglutide to oral semaglutide since there was a shortage of dulaglutide between May 1 and September 31, 2023.

Informed consent and ethical regulations

This study was designed following the principles of the Declaration of Helsinki. This was a retrospective, observational

study that utilized a clinical database. The study protocol was authorised by the ethics committee of Nihon University School of Medicine (No.RK-231114-10). The protocol for this study is available on the Ethics Committee website, and we provided subjects with the option to opt out of the study. The requirement for written informed consent was waived due to the retrospective approach of the ethics committee.

Characteristics of the study subjects

Clinical characteristics including sex, age, body mass index (BMI), smoking habits, systolic and diastolic blood pressure, hypertension, statin use and biochemical variables were assessed in the study participants. Each subject's oral semaglutide dosage was investigated throughout the study. Biochemical variables related to liver function tests, lipid metabolism, uric acid and HbA_{1c} levels were assessed after an overnight fast. Alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γGTP), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), uric acid (UA), serum creatinine and glycosylated haemoglobin (HbA_{1c}) were evaluated using an automatic analyzer. Renal function was defined using the estimated glomerular filtration rate (eGFR). eGFR was determined using the following formula: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).[4] Blood pressure was taken while individuals were sitting down at the outpatients department in the morning. Patients with hypertension were defined as those who were treated for hypertension or had a blood pressure greater than 140/90 mmHg measured at a hospital, following the Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension.[5]

Statistical analysis

The primary endpoint was the comparison of HbA_{1c} levels at baseline versus two, four or six months later. The secondary endpoint was to compare BMI, systolic and diastolic blood pressure, AST, ALT, γGTP, LDL and HDL cholesterol, UA and eGFR at baseline and two, four or six months later. The subjects were divided into two groups: those who showed improved glycaemic control at six months from baseline (n = 5) and those who did not improve (n = 13), and the differences in baseline characteristics of the study subjects were compared between the two groups. The comparison of primary or secondary endpoint parameters between baseline and six months later was evaluated using the Wilcoxon signed-rank test. The baseline clinical characteristics between groups that improved or did not improve their glycaemic control were compared using the Mann-Whitney U-test. Data are presented as means ± standard deviation (SD), or number (%). Statistical significance was defined as $p < 0.05$. All analyses were carried out using IBM SPSS Statistics for Windows Version 25 J (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics of study subjects

Table 1 presents the study subjects' baseline clinical characteristics. The average HbA_{1c} level before switching was 6.99 ± 0.39% (Table 1). Sodium-glucose co-transporter 2 (SGLT2) inhibitors were the most commonly used medications among the study subjects (n = 11), with three subjects receiving insulin therapy (Table 1). The lipid profile and blood pressure were well controlled; however, the average BMI met the obesity criteria (28.91 ± 6.68 kg/m^2) (Table 1).

Table 1. Baseline clinical characteristics of study subjects

Clinical characteristics	Mean ± SD, n (%)	Range
Age (years)	59.8 ± 11.7	30 – 73
Sex (men/women)	11 (61.1)/7 (38.9)	
BMI	28.91 ± 6.68	18.7 – 45.2
Blood pressure (mmHg)		
Systolic	126.5 ± 13.3	103 – 147
Diastolic	73.6 ± 12.4	59 – 89
Smoking habit		
None	9 (50.0)	
Recent	4 (22.2)	
Current	5 (27.8)	
Hypertension	12 (66.7)	
Statin use	13 (72.2)	
AST (IU/L)	23.8 ± 23.6	12 – 52
ALT (IU/L)	28.5 ± 23.6	9 – 99
γGTP (IU/L)	38.4 ± 47.7	11 – 169
HDL-C (mg/dL)	53.1 ± 14.7	38 – 82
LDL-C (mg/dL)	96.6 ± 21.5	56 – 133
Triglyceride (mg/dL)	126.6 ± 59.2	54 – 274
Uric acid (mg/dL)	5.57 ± 1.66	2.5 – 9.2
eGFR (mL/min/1.73m^2)	62.93 ± 27.25	10.4 – 119.6
HbA_{1c} (%)	6.99 ± 0.39	6.3 – 7.8
Medication of diabetes	11 (61.1)	
Metformin	8 (44.4)	
Pioglitazone	15 (83.3)	
SGLT2-inhibitors	2 (11.1)	
α-glucosidase inhibitors	3 (16.7)	
Imeglimin	4 (22.2)	
Sulfonylureas	5 (27.8)	
Insulin	3 (16.7)	

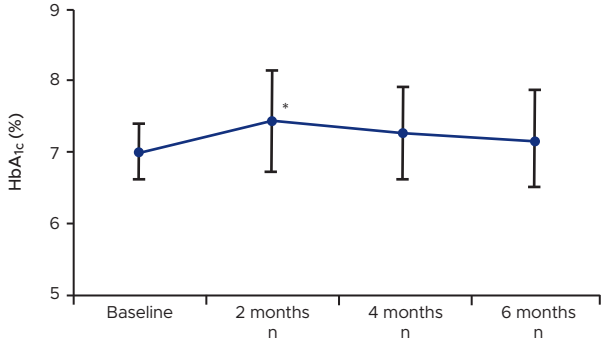
Key: SD = standard deviation; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine transaminase; γGTP = γ-glutamyl transferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol: eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated haemoglobin; SGLT2 = sodium-glucose transporter 2

At four months after baseline, one patient started receiving imeglimin at a dosage of 2,000 mg/day, while another patient had their imeglimin dosage increased from 1,000 mg/day to 2,000 mg/day. Additionally, one patient began taking pemafibrate at a dosage of 0.2 mg/day at four months after baseline.

Transition in the oral semaglutide dosage during the study period

According to the protocol for oral semaglutide dosage in public health insurance, the initial oral semaglutide dose was 3 mg/day for the first four weeks. Four weeks after baseline, the dosage was increased to 7 mg or 14 mg/day if a dosage of 3 mg/day or 7 mg /day did not achieve adequate glucose control levels,

Figure 1. Changes in HbA_{1c} during the study period.



		Baseline	2 months	4 months	6 months
		n	n	n	n
Oral semaglutide dosage	3 mg/day	15	1	1
	7 mg/day	3	16	14
	14 mg/day	0	1	3

* P < 0.05 vs. baseline. HbA_{1c} = glycosylated haemoglobin

or the dosage was maintained at 3 mg/day if adequate glycaemic control was achieved, as determined by the physician during the study period. Figure 1 shows the number of subjects who received 3, 7 or 14 mg/day of semaglutide treatment two, four and six months after the baseline. Finally, the number of subjects who received 3, 7 or 14 mg/day six months after baseline was 1, 14 and 3, respectively (Figure 1).

Primary endpoint: comparison of HbA_{1c} levels between baseline and two, four or six months from baseline

The mean HbA_{1c} level at two weeks from baseline was significantly higher compared to baseline (7.43 ± 0.72 vs. 6.99 ± 0.395%, p = 0.003) (Figure 1). Subsequently, the mean HbA_{1c} levels at four and six months after baseline (7.24 ± 0.65 and 7.16 ± 0.71%, respectively) (Figure 1) gradually declined. Finally, there were no significant differences in mean HbA_{1c} levels at baseline and six months later (Figure 1).

Association between baseline clinical characteristics and improvement in glycemic control

Five subjects demonstrated improved glycaemic control six months after baseline (Table 2). In terms of baseline clinical characteristics, the mean γGTP levels were considerably lower in subjects with improved glycaemic control than in those without improvement (13.8 ± 3.0 vs. 47.9 ± 53.6 IU/L, p = 0.026). Other clinical characteristics did not differ significantly between subjects with and without improved glycaemic control (Table 3).

Secondary endpoints

The mean BMI, LDL and HDL cholesterol levels all changed significantly during the study period (Table 3). Specifically, the mean HDL cholesterol levels gradually increased throughout the study period. HDL cholesterol levels at six months after baseline were significantly higher than at baseline (57.3 ± 14.2 vs. 53.1 ± 14.7 mg/dL, p = 0.006) (Table 3). Excluding one subject who started pemafibrate during the study period (n = 17), the change in HDL cholesterol levels showed the same trend in all subjects

Table 2. Association between baseline clinical characteristics and improvement in glycaemic control

Clinical characteristics	Glycaemic control: Improved (n = 5)	Glycaemic control: Not improved (n = 13)	P value
Age (years)	58.8 ± 11.1	60.2 ± 12.3	0.703
Sex (men/women)	2 (40.0)/3 (60.0)	9 (69.2)/4 (30.8)	0.326
BMI	27.03 ± 4.96	29.76 ± 7.39	0.743
Blood pressure (mmHg)			
Systolic	129.6 ± 13.2	125.3 ± 13.7	0.646
Diastolic	80.2 ± 7.3	67.6 ± 20.7	0.160
Smoking habit			
None	0 (0.0)	4 (30.8)	0.142
Recent	1 (20.0)	4 (30.8)	0.142
Current	4 (80.0)	5 (38.5)	0.142
Hypertension	4 (80.0)	8 (61.5)	0.615
Statin use	3 (60.0)	10 (76.9)	0.583
AST (IU/L)	18.0 ± 7.1	26.1 ± 10.6	0.075
ALT (IU/L)	16.0 ± 6.4	33.3 ± 26.2	0.059
γGTP (IU/L)	13.8 ± 3.0	47.9 ± 53.6	0.026
HDL-C (mg/dL)	58.6 ± 20.1	51.0 ± 12.4	0.633
LDL-C (mg/dL)	93.6 ± 15.1	97.8 ± 23.9	0.775
Triglyceride (mg/dL)	115.2 ± 52.5	130.9 ± 63.0	0.703
Uric acid (mg/dL)	5.65 ± 21.7	5.54 ±1.58	0.549
eGFR (mL/min/1.73m²)	51.58 ± 26.35	67.30 ± 27.32	0.387
HbA_{1c} (%)	7.14 ± 0.28	6.94 ± 0.12	0.246

Mean ± SD, n (%)

Key: SD = standard deviation; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine transaminase; γGTP = γ-glutamyl transferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol: eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated haemoglobin

Table 3. The change of parameters in secondary endpoints during the study period

Parameters	Study period: Baseline	2 months	4 months	6 months
BMI	28.91 ± 6.68	28.49 ± 6.21*	28.54 ± 6.25*	28.90 ± 6.08
Blood pressure (mmHg)				
Systolic	126.5 ± 13.3	121.3 ± 12.4	123.6 ± 9.6	127.9 ± 14.8
Diastolic	73.6 ± 12.4	75.1 ± 10.9	75.8 ± 10.0	75.4 ± 11.2
AST (IU/L)	23.8 ± 23.6	23.8 ± 13.3	26.3 ± 17.2	23.6 ± 11.3
ALT (IU/L)	28.5 ± 23.6	29.3 ± 29.0	29.8 ± 30.3	26.0 ± 23.1
γGTP (IU/L)	38.4 ± 47.7	31.2 ± 25.5	30.8 ± 33.4	30.8 ± 33.7
HDL-C (mg/dL)	53.1 ± 14.7	53.8 ± 13.8	56.6 ± 16.3	57.3 ± 14.2**
LDL-C (mg/dL)	96.6 ± 21.5	108.8 ± 25.9**	99.8 ± 20.7	100.7 ± 21.8
Triglyceride (mg/dL)	126.6 ± 59.2	143.2 ± 65.2	109.4 ± 44.6	130.7 ± 64.9
Uric acid (mg/dL)	5.57 ± 1.66	5.67 ± 1.45	5.48 ± 1.43	5.58 ± 1.72
eGFR (mL/min/1.73m²)	62.93 ± 27.25	61.33 ± 24.21	62.28 ± 22.44	62.00 ± 22.26

Mean ± SD, n (%) * P < 0.05, ** P < 0.01 vs. baseline.

Key: SD = standard deviation; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine transaminase; γGTP = γ-glutamyl transferase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol: eGFR = estimated glomerular filtration rate

(58.0 ± 14.3 vs. 53.8 ± 14.7 mmol/L, p = 0.010). There were no significant changes during the study period in systolic and diastolic blood pressure, triglycerides, UA, eGFR, AST, ALT or γGTP levels (Table 3).

Adverse effects

No significant adverse effects, such as gastrointestinal and hypoglycaemic episodes, were reported in the clinical records of the study subjects during the study period.

Discussion

The current study found that there were no significant differences in glycaemic control or clinical parameters between baseline and six months after switching from dulaglutide to oral semaglutide in Japanese patients with well-controlled T2DM. Oral semaglutide had the same glycaemic control effect as dulaglutide. The investigation of the effect on clinical characteristics, including glycaemic control, of switching from GLP-1 RA injections to GLP-1 RA tablets in patients with appropriate management of T2DM was the study's standout feature. To our knowledge, no studies have examined the impact of switching from dulaglutide to oral semaglutide on glycaemic control and clinical parameters in patients with well-controlled T2DM.

The current study found that oral semaglutide at a dose of 7 mg/day or higher may have a similar effect on the improvement of glycaemic control as a once-weekly subcutaneous dulaglutide 0.75 mg injection in Japanese patients with T2DM; most subjects at six months from baseline received a 7 mg/day dosage of semaglutide. In other words, at least 7 mg/day of oral semaglutide is required to achieve glycaemic control before transitioning from a once-week dulaglutide injection to once-daily oral semaglutide treatment. The PIONEER 10 trial, an open-label, randomised trial in Japanese patients with T2DM, found that the HbA_{1c} between subjects receiving oral semaglutide 7 mg/day did not differ significantly compared with that of once-weekly subcutaneous dulaglutide 0.75 mg at 26 and 52 weeks from baseline.[6] Furthermore, regarding the change in HbA_{1c} in subjects with HbA_{1c} levels below 7.5%, the average difference between oral semaglutide and dulaglutide at 26 weeks from baseline was 0.1%.[6] Hence, the PIONEER 10 trial found that using oral semaglutide 7 mg/day achieves the same management power of glycaemic control as once-weekly dulaglutide 0.75 mg after switching from dulaglutide to oral semaglutide in Japanese patients with well-controlled T2DM. Conversely, the average HbA_{1c} level two months after baseline was significantly higher than that at baseline.

The primary reason for these findings is the initial dose of oral semaglutide. The initial dose of oral semaglutide for the first four weeks is recommended to be 3 mg/day under Japanese public health insurance, regardless of whether the subjects have previously received GLP-1RA injection therapy. Indeed, in PIONEER 10, the mean HbA_{1c} level in subjects receiving dulaglutide was significantly improved compared to those receiving oral semaglutide 0.3 mg/day at 26 weeks from baseline (−1.5% and −1.1%, respectively, p < 0.001).[6] Additionally, the study found beneficial information suggesting that the plasma γGTP level at baseline in this study may be closely linked to the influence on worsening glucose metabolism after switching from dulaglutide to oral semaglutide during the study period. Plasma γGTP levels are linked to glucose metabolism and increased risk of impaired glucose tolerance,[7] type 2 diabetes,[8] and insulin resistance.[9] Glycaemic control gradually worsens in correlation with the elevation of plasma γGTP levels.[10] Furthermore, visceral fat accumulation[11] and non-alcoholic fatty liver disease (NAFLD) / metabolic dysfunction linked to steatohepatitis (MASLD) in T2DM are also related to plasma γGTP levels.[12,13]

The present study showed that LDL cholesterol levels were temporarily elevated but then returned to a prior level after six months from baseline, while HDL cholesterol levels increased significantly at six months from baseline. Similar results were found in a study on pemafibrate,[14] which increased serum LPL activity.[15] The change of plasma lipoprotein lipase (LPL) levels or activity from baseline may play an important role in lipoprotein metabolism when transitioning from dulaglutide to semaglutide. LPL produces small very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) from VLDL via LPL-mediated hydrolysis. IDLs are lipolyzed into LDL, and some are captured by hepatic remnant receptors.[15] Plasma adiponectin levels may have played a key role in HDL cholesterol elevation in the present study. Adiponectin induces plasma HDL cholesterol levels via elevation of LPL activity.[16] Indeed, low plasma adiponectin levels significantly reduce LPL activity independent of systematic inflammation and insulin resistance in patients with and without T2DM.[17] It has been reported that both dulaglutide and semaglutide increase plasma adiponectin levels.[18] However, the difference in their effects on plasma adiponectin elevation remains uncertain because no study has previously reported any difference in effect between dulaglutide and oral semaglutide on plasma adiponectin levels. An increase in HDL cholesterol can help prevent cardiovascular disease. Specifically, an increase in HDL cholesterol level of 1 mg/dL reduced the relative risk of coronary events by 2%-3%.[19]

The current study indicated the valuable information that a once-weekly GLP-1RA injection can be switched to once-daily oral semaglutide treatment in patients with well-controlled T2DM, depending on patient preference. It has been reported that satisfaction with the treatment of diabetes, as measured by the diabetic treatment burden questionnaire (DTBQ) score, gradually decreased with the treatment regimen of oral hypoglycaemic agents administered once daily and injections (administered once weekly, once daily, and twice a day or more) in patients with T2DM.[20] Japanese patients with T2DM who receive injection treatment are dissatisfied with their treatment due to the high medical costs.[21] Furthermore, in the US, oral semaglutide 14 mg/day is a more cost-effective treatment than GLP-1 RA injections in patients with well-controlled T2DM (HbA_{1c} less than 7.0%).[22] Switching from injectable to oral GLP-1RA therapy in well-controlled T2DM patients may have a minor impact on quality of life (QOL), even if HbA_{1c} is slightly elevated.

It has been reported that Japanese subjects with well-controlled T2DM (mean HbA_{1c} 6.5%) who switched from once-weekly semaglutide 0.5mg injection to oral semaglutide 3 to 7 mg showed a significant increase of 0.2% in HbA_{1c} (to 6.7%) at two months after switching, but no significant change in treatment satisfaction was observed.[23] In a prospective and comparative study, the total Japanese-specific diabetes therapy-related quality of life (DTR-QOL) score was higher in subjects receiving oral semaglutide 7 and 14 mg/day than in subjects receiving dulaglutide 0.75 mg after 52 weeks of treatment.[24]

There were some potential limitations to our study. First, this was a retrospective, observational study rather than a prospective study. Hence, various factors such as medication adherence, the frequency of visiting the hospital and education of diabetes by dietitians and diabetes specialist nurse/educators, may have influenced the results of our study. In this study, almost all subjects visited our outpatient department every one to two months prior to switching. However, after switching to oral semaglutide, most patients had to return approximately one month later for dose escalation from 3 mg to 7 mg daily. Therefore, it is likely that some subjects had shorter visit intervals after switching compared to before switching. Short interval visits improve glycaemic control in patients with diabetes.[25] The discontinuation of dulaglutide by physicians or poor medication adherence may have produced an effect like a washout in some subjects. We confirmed that none of the subjects had discontinued the dulaglutide treatment before switching. However, poor medication adherence may have occurred in some cases. Unfortunately, we could not evaluate whether medication adherence affected glucose metabolism before and after switching. Education in diabetes self-management contributes to improved glycaemic control, particularly with the effects that are most prominent in the early phase following intervention.[26] Among the 18 subjects, one patient received diabetes education from both dietitians and diabetes specialist nurses every two months during the study period. This patient's HbA_{1c} levels remained below 7.0% throughout the study period, except for two months following the switch. However, this patient did not achieve a reduction in HbA_{1c} at the end of the study period compared to before switching, and the frequency of consultations did not change. Thus, the contribution of diabetes education to glycaemic control appears to have had a limited effect in this study population. A well thought out prospective study design with an evaluation of quality of life (QOL) and the adverse effects of switching from dulaglutide to oral semaglutide, as well as a randomised controlled trial comparing switching dulaglutide to oral semaglutide therapy with the control group, are required to evaluate the current study results. Second, the study's sample size was small. Third, an observation period longer than six months after switching is required to assess the long-term effects of switching. Finally, visceral fat and NAFLD/MASLD, which affect glycaemic and lipid metabolism as well as hepatic enzyme levels, were not assessed using imaging such as abdominal ultrasound or computed tomography.

Key messages

- There have been no reports on the effects of switching from injectable to oral glucagon-like peptide-1 receptor agonists on glucose metabolism and other metabolic parameters
- This retrospective study evaluated how switching from dulaglutide 0.75 mg/week to oral semaglutide daily affects glycaemic control and clinical parameters in patients with well controlled type 2 diabetes
- Glycaemic control temporarily worsened after switching from dulaglutide to oral semaglutide. However, no significant differences were observed between baseline and six months after the switch
- At least 7 mg/day of oral semaglutide appears to be required to maintain glycaemic control when transitioning from once-weekly dulaglutide injections to once-daily semaglutide therapy

Conclusion

Glycaemic control deteriorated temporarily after switching from dulaglutide to oral semaglutide, but there was no significant difference between baseline and six months in patients with well-controlled T2DM. Furthermore, γGTP can indicate changes in glycaemic control when switching from dulaglutide to oral semaglutide. The current study is useful for patients with well-controlled T2DM who are considering switching from injection to oral GLP-1RA therapy. A significant increase in HDL cholesterol from baseline over six months may contribute to a reduction in cardiovascular risk.

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.
Funding This work was not supported by any grant or funding source.
Author contributions KW designed the study, conducted the data analysis and interpretation, and drafted the manuscript. MK, AN, KN and TY collected the data. HI supervised the study. All authors contributed to the review and revision of the manuscript, approved the final version for publication, and serve as guarantors of this work. All authors have read and agreed to the published version of the manuscript.
Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

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