Efficacy of switching from dipeptidyl peptidase-4 inhibitors to dulaglutide in patients with type 2 diabetes

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Abstract

Background: Several reports showed that the effects of daily Glucagon-like peptidase-1 (GLP-1) receptor agonists for lowering plasma glucose and body weight are superior to those of dipeptidyl peptidase-4 (DPP-4) inhibitors, while the superiority of weekly GLP-1 receptor agonists, dulaglutide, is still unclear. The aim of this study was to evaluate the efficacy of dulaglutide therapy switching from DPP-4 inhibitors in patients with type 2 diabetes. Methods: We retrospectively evaluated the 79 Japanese patients with type 2 diabetes at the Diabetes Outpatient Clinic in Tomakomai City Hospital whose treatment was switched from DPP-4 inhibitors to dulaglutide. We investigated the change of hemoglobin A1c (HbA1c), casual plasma glucose (CPG) levels and body weight 4 weeks, 8 weeks and 12 weeks after switching from DPP-4 inhibitors to dulaglutide. In addition, we defined the group in which HbA1c was improved more than 1% as “improved group” (n = 37) and the group in which HbA1c was improved less than 1% as “non-improved group” (n = 42), and compared the patients’ background in both the groups. The subtraction of HbA1c at each weeks and baseline HbA1c was defined as ⊿HbA1c. Results: After switching to dulaglutide, HbA1c showed a significant decrease from 4 weeks later, and the effect was maintained even after 12 weeks. The “improved group” had lower estimated glomerular filtration rate (eGFR) and higher baseline HbA1c than the “non-improved group”. In the “improved group”, ⊿HbA1c showed a significant correlation with eGFR and baseline HbA1c. Conclusion: Switching from DPP-4 inhibitors to dulaglutide could improve HbA1c, especially in cases with low eGFR and high HbA1c.

Background

GLP–1 is one of incretin hormones, which is secreted from small intestines via stimulation of oral ingestion [1–3]. It binds to GLP–1 receptors in pancreatic cells and increases cyclic adenosine monophosphate, resulting in insulin secretion [4,5]. Then, GLP–1 is rapidly degraded and inactivated by DPP–4 [6]. DPP–4 inhibitors are a group of incretin-related drugs that have a hypoglycemic effect by inhibiting degradation of GLP–1 and by increasing concentration of endogenous active incretin [7]. Contrary to DPP–4 inhibitors, GLP–1 receptor agonists, which are classified into daily or weekly type, directly promote GLP–1 receptor activity. Therefore, GLP–1 receptor agonists are estimated to be potentially more effective in a decrease of plasma glucose levels than DPP–4 inhibitors. Several reports showed that the effects of daily GLP–1 receptor agonists for lowering plasma glucose and body weight are superior to those of DPP–4 inhibitors [8], while the superiority of weekly GLP–1 receptor agonists, dulaglutide, is still unclear. In the current study, we aimed to clarify the effectiveness of dulaglutide therapy switching from DPP–4 inhibitors in patients with type 2 diabetes, and subsequently to explore the predictive factors for its anti-diabetic effect.

Methods

Ethics statement

The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval was obtained from the institutional review board of Tomakomai City Hospital (approval number: 2018–6).

Study design and population

This was a single-center, single-armed, retrospective and observational study using data collected from medical records. Japanese patients with type 2 diabetes whose treatment was switched from DPP–4 inhibitors to dulaglutide at our department between April 2015 and May 2018 were registered in the present study. The patients who had a history of dulaglutide use were included. We excluded pregnant women and patients aged <18 years. First, we analyzed the patients including those whose concomitant drugs were switched or increased the dosage. Then, we also analyzed patients without those whose concomitant drugs were switched or increased the dosage.

Outcomes

Changes of body weight, CPG levels and HbA1c at baseline, 4, 8, and 12 weeks after switching from DPP–4 inhibitors to dulaglutide were evaluated. The subtraction of HbA1c at each weeks and baseline HbA1c was defined as HbA1c. Patients with and without over 1% reduction of HbA1c at 12 weeks from switching were classified as “improved group” and “non-improved group”, respectively. To clarify the factors influencing the efficacy of dulaglutide therapy, the patients’ medical records were retrospectively reviewed and the following demographic, clinical, and laboratory data at baseline were verified by the authors: age, sex, disease duration, body weight, body mass index (BMI), CPG level, HbA1c, eGFR and data about concomitant medications including insulin, metformin, glinide, sulfonylurea, -glucosidase inhibitors, sodium-glucose cotransporter–2 (SGLT–2) inhibitors, and thiazolidine. In addition, safety of dulaglutide was analyzed by frequency of hypoglycemia and gastrointestinal adverse events which occurred in the observational period. Hypoglycemia was defined as signs attributable to hypoglycemia or CPG levels less than 70 mg/dL in spite of hypoglycemic symptoms. Definition of severe hypoglycemia was made by an episode requiring the assistance of another person to actively administer therapy, as determined by the investigator [9].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and were compared using t-test. Categorical variables were expressed as number and percentage. Correlation of continuous variables between two groups was assessed by Pearson’s coefficients. Probability values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP Pro software (ver. 12.0; SAS Institute Inc., Cary, NC, USA).

Results

1. Patient enrollment and baseline characteristics

A total of seventy-nine patients (42 males and 37 females) with type 2 diabetes whose treatment drugs were switched from DPP–4 inhibitors to dulaglutide were enrolled in the study. The baseline clinical and metabolic characteristics of the patients are shown in Table1. The mean age of patients was 63.3 ± 12.4 years old. The mean BMI was 26.7 ± 5.5 kg/m^2. The mean levels of HbA1c and CPG were 8.6 ± 1.1% and 197.0 ± 90.4 mg/dL, respectively. In all the patients, DPP–4 inhibitors (36 vildagliptin, 29 linagliptin, 7 alogliptin, 5 anagliptin, 1 sitagliptin or 1 omarigliptin) were changed to 0.75 mg of dulaglutide at the time of enrollment. Regarding anti-diabetic concomitant agents, metformin was administered for 58 patients, insulin for 29, glinide for 29, sulfonylurea for 26, α-glucosidase inhibitors for 22, SGLT–2 inhibitors for 16, and thiazolidine for 2. There were 22 patients who have increased the dosage of current drugs or added new drugs during the observational period.

2. Changes in body weight and CPG and HbA1c

During the observation periods, HbA1c significantly decreased at 4 weeks after switching from DPP–4 inhibitors to dulaglutide (ΔHbA1c: 0.57 ± 0.77 %, $P < 0.01$) and the effect was maintained at 12 weeks (ΔHbA1c: 0.97 ± 1.30 %, $P < 0.01$). (Figure 1). There were no statistically significant differences in body weight and CPG levels at 0, 4, 8, and 12 weeks. Even those patients who have not increased the dosage of current drugs or added new drugs showed significant improvement of ΔHbA1c from 4 weeks (ΔHbA1c: 0.62 ± 0.79 %, $P < 0.01$) to 12 weeks (ΔHbA1c: 1.10 ± 1.35 %, $P < 0.01$) after switching from DPP–4 inhibitors to dulaglutide. (Figure 2)

3. Relationship between the efficacy and clinical characteristics

To reveal the factors associated with more than 1% of HbA1c improvement after switching to dulaglutide at 12 weeks, the baseline clinical characteristics were statistically compared between the improved and non-improved groups. Of 79 patients, 37 and 42 patients were divided into the improved and non-improved groups, respectively. The levels of eGFR were statistically lower in improved group (56.4 ± 22.0 mL/min/1.73m^2) than those in “non-improved group” (72.2 ± 21.2 mL/min/1.73m^2) (t-test, $P < 0.01$). Furthermore, baseline HbA1c was higher in improved group (9.1 ± 1.1%) compared with non-improved group (8.2 ± 1.0%) (t-test, $P < 0.01$) (Table 2). In the improved group, a significant positive correlation between ΔHbA1c at 12 weeks and baseline HbA1c ($R = 0.75$, $P < 0.01$), a significant inverse correlation between ΔHbA1c at 12 weeks and eGFR ($R = -0.40$, $P < 0.05$) were observed (Figure 3). ΔHbA1c showed a significant correlation with baseline HbA1c ($R = 0.86$, $P < 0.01$) and eGFR ($R = -0.41$, $P < 0.05$) at 12 weeks even with the patients who have not increased the dosage of current drugs or added new drugs. (Figure 4)

4. Safety

Hypoglycemia episode was not found during the observation periods, whereas 3 patients complained of nausea after switching from DPP–4 inhibitors to dulaglutide. However, as dulaglutide therapy was continued, nausea disappeared in all the patients. No patients discontinued dulaglutide during the follow-up period due to adverse events.

Discussion

In this study, switching from DPP–4 inhibitors to dulaglutide showed a significant improvement of HbA1c. However, it didn't contribute to weight loss and a decrease of CPG. HbA1c declined especially in patients with low eGFR and high levels of baseline HbA1c.

A previous double-blind and parallel arm randomized control study compared the anti-diabetic effects of two doses of dulaglutide (1.5 mg and 0.75 mg) with DPP–4 inhibitors. In this study, the enrolled diabetes patients were naive for both dulaglutide and DPP4-inihibitors. Both dulaglutide doses significantly reduced HbA1c levels and body weight compared with DPP–4 inhibitors. However, 1.5 mg dulaglutide weight reduction effect was greater than 0.75 mg dulaglutide [10]. This can be explained that the extra-pancreatic action of 0.75 mg dulaglutide, such as reduction in appetite and delaying gastric emptying [11], may not be as strong as that of 1.5 mg dulaglutide. Only 0.75 mg dose of dulaglutide is available in Japan. Our results were consistent with the previous report about change in HbA1c, not about weight loss. The lower baseline body weight, compared with previous study, may have led to this result. Another study showed that switching from sitagliptin to liraglutide, a daily GLP–1 receptor agonist, reduced fasting plasma glucose levels, HbA1c and body weight in patients with type 2 diabetes.[8] On the other hand, a retrospective observational study revealed that 6-month adherence of weekly dulaglutide (54.2%) was better than that of daily liraglutide (44.3%) [12]. Persistency rate was also higher in dulaglutide users (71.0%) compared with liraglutide users (64.0%). Therefore, switching DPP–4 inhibitors to dulaglutide may result in better adherence than that of liraglutide.

Our study pointed out switching DPP–4 inhibitors to dulaglutide contributed to better glycemic control in type 2 diabetic patients, especially in those with renal dysfunction. Dulaglutide has been reported to show higher blood concentration in patients with impaired renal function. This suggests that high concentrations of dulaglutide may lead to better anti-diabetic effect in patients with impaired renal function. Nausea and hypoglycemia are major side effects of dulaglutide. However, it is generally considered that hypoglycemia less likely occurs because GLP–1 secretion depends on plasma glucose levels. [13] There were no patients who had symptomatic hypoglycemia in our study. It is also known that nausea improves as time goes on. [14–17]

Glycemic control is sometimes difficult in patients with renal dysfunction. As kidney function worsens, the risk of hypoglycemia and other adverse effects increases. [18–20] Therefore, in case of treatment of diabetes in patients with renal dysfunction, clinicians often face difficulty in selecting anti-diabetic agents.

This study suggests that switching from DPP–4 inhibitors to dulaglutide would be effective and safe for controlling hyperglycemia in patients with impaired renal function.

Our study was single arm study that evaluated the efficacy of switching to dulaglutide from DPP–4 inhibitors. DPP–4 inhibitor is one of the most used drugs in patients with type 2 diabetes. The result of our study suggests dulaglutide is an effective second-line therapeutic option in the patients with type 2 diabetes with poor glycemic control who are treated with DPP–4 inhibitors.

The potential limitations of our study were small sample size, short study duration and retrospective design. To resolve these issues, our findings need to be validated in a larger population over a longer period. Furthermore, in this study, the effect of non-drug therapy such as diet exercise therapy was not taken into consideration. These factors may have contributed to anti-diabetic effect. In addition, the evaluation of unconscious hypoglycemia might be insufficient with our definition of hypoglycemia.

Conclusion

We demonstrated that switching from DPP–4 inhibitors to dulaglutide significantly improved HbA1c, particularly in patients with low eGFR and high HbA1c. It could be a useful treatment option for poorly controlled type 2 diabetes patients with impaired renal function.

Abbreviations

GLP–1: Glucagon-like peptidase–1; DPP–4: dipeptidyl peptidase–4; HbA1c: hemoglobin A1c; CPG: casual plasma glucose; eGFR: estimated glomerular filtration rate; BMI: body mass index; SGLT–2: sodium-glucose cotransporter–2.

Declarations

Ethics approval and consent to participate

Ethics approvals were received from Tomakomai City Hospital research ethics committee. Approval identification number 2018–6.

Consent for publication

Not applicable.

Availability of data and material

Not applicable

Competing interests

All authors have declared no conflicts of interest.

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Authors' contributions

KC, MO, HN and TN conceived the study concept ant participated in the design of the study. KC performed the analyses of the study. KC, MO, HN, AU, YK, HI, TN, TH participated in the data and helped in the development of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of the participants (n = 79)

Age (years)	63.3 ± 12.4
Sex (male/female)	42 / 37
Diabetes duration (years)	16.4 ± 10.6
Body weight (kg)	70.0 ± 17.6
BMI (kg/m^2)	26.7 ± 5.5
Casual plasma glucose (mg/dL)	197.0 ± 90.4
HbA1c (%)	8.6 ± 1.1
eGFR ($mL/min/1.73m^2$)	64.8 ± 22.9
Concomitant medications	
Metformin	58 (73%)
Insulin	29 (37%)
Glinide	29 (37%)
Sulfonylurea	26 (33%)
a-glucosidase inhibitors	22 (28%)
SGLT-2 inhibitors	16 (20%)
Thiazolidine	2 (3%)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SGLT-2, sodium-glucose cotransporter-2. Continuous valuables were shown mean ± standard deviation. Categorical variables were expressed as number (percentage).

Table 2. Comparison with “improved group” and “non-improved group”

	improved group (n = 37)	non-improved group (n = 42)	*P value
Age (years)	68.1 ± 11.9	64.6 ± 12.6	0.22
Diabetes duration (years)	15.3 ± 11.9	17.5 ± 9.3	0.38
Body weight (kg)	70.0 ± 15.4	69.9 ± 19.4	0.97
Plasma glucose (mg/dL)	206.4 ± 102.9	188.7 ± 78.1	0.39
eGFR (mL/min/1.73m^2)	56.4 ± 22.0	72.2 ± 21.2	< 0.01
HbA1c (%)	9.1 ± 1.1	8.2 ± 1.0	< 0.01

eGFR, estimated glomerular filtration rate. Data was shown as mean ± standard deviation. *t-test.

Figures

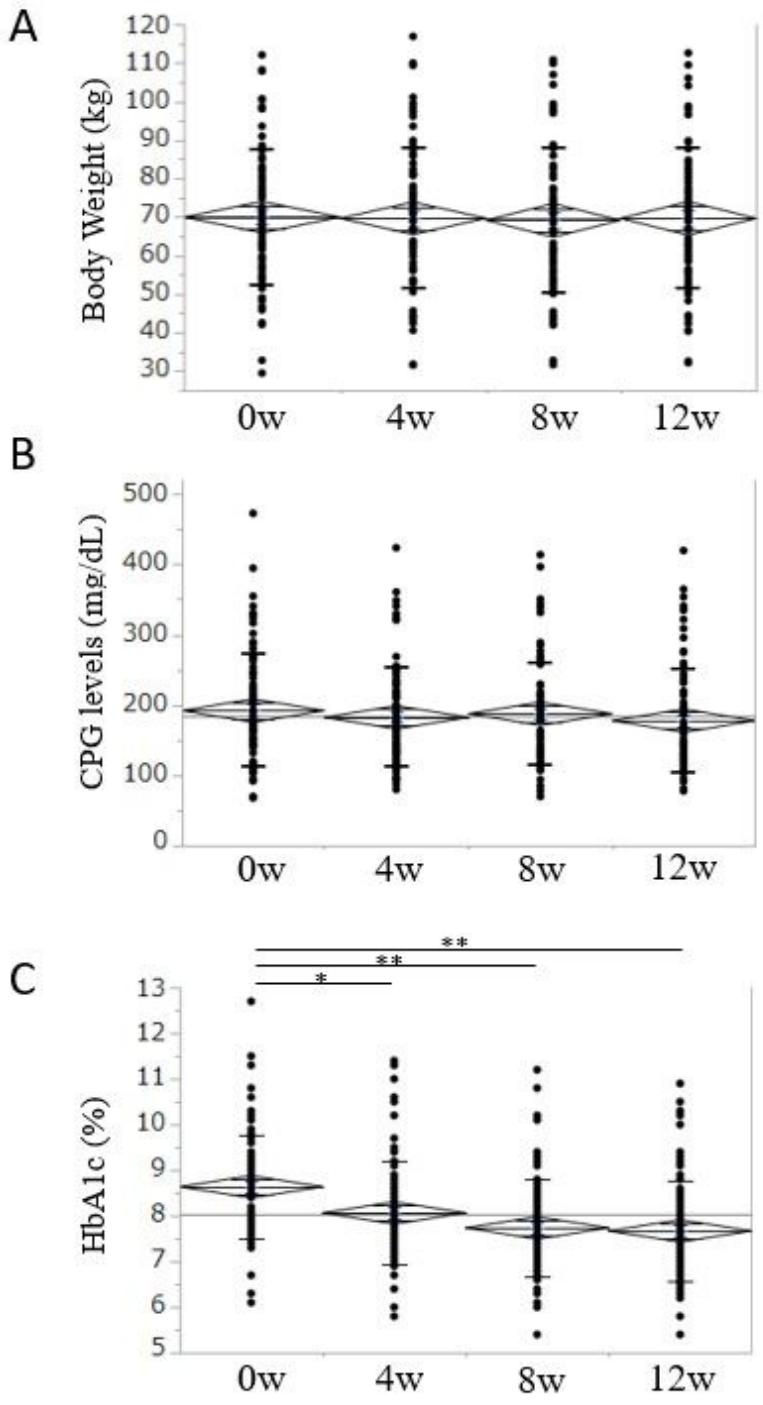

Figure 1

Body weight (A), casual plasma glucose (CPG) levels (B) and HbA1c (C) over 12 weeks after switching from DPP-4 inhibitors to dulaglutide including patients whose concomitant drugs were switched or increased the dosage. Diamond shapes show mean and its 95% confidence interval. Horizontal lines indicate standard deviation. *P < 0.005 (vs baseline, paired t-test), **P < 0.0001 (vs baseline, paired t-test).

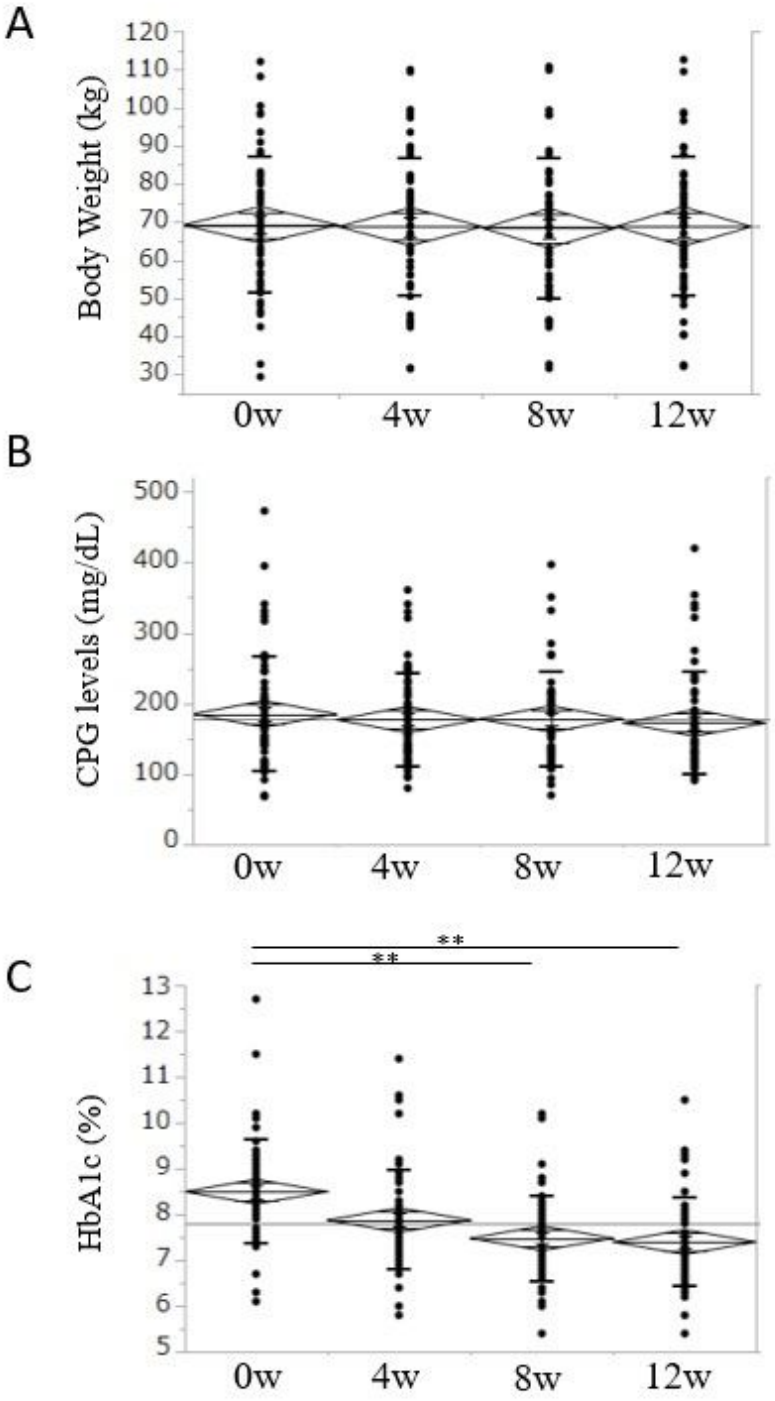

Figure 2

Body weight (A), casual plasma glucose (CPG) levels (B) and HbA1c (C) over 12 weeks after switching from DPP-4 inhibitors to dulaglutide in patients without whose concomitant drugs were switched or increased the dosage. Diamond shapes show mean and its 95% confidence interval. Horizontal lines indicate standard deviation. *P < 0.005 (vs baseline, paired t-test), **P < 0.0001 (vs baseline, paired t-test).

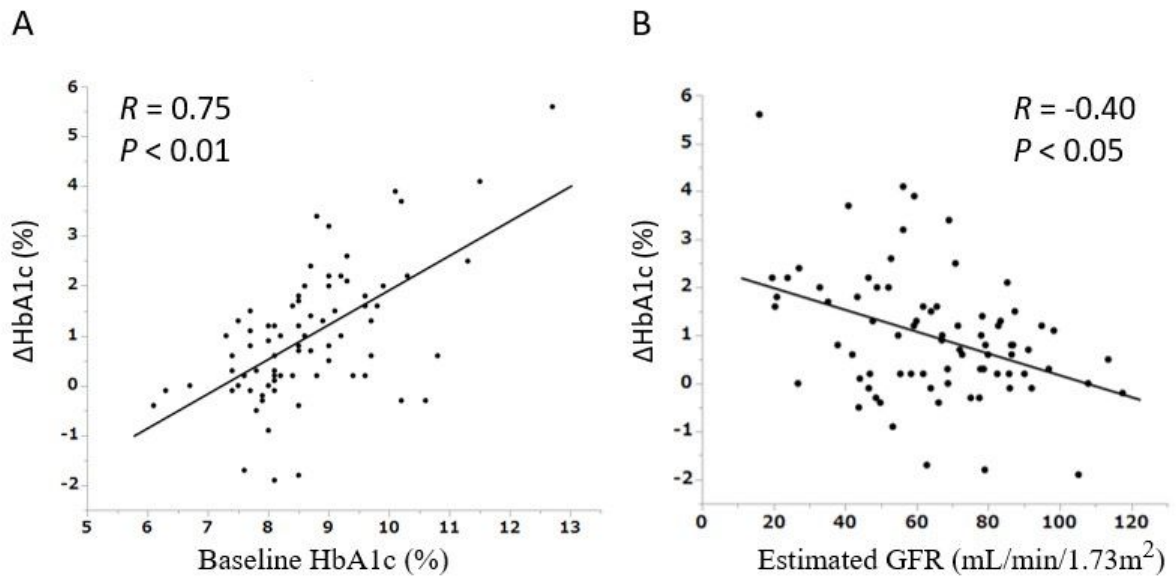

Figure 3

Correlation between ΔHbA1c at 12 weeks and baseline HbA1c (A) or estimated glomerular filtration rate (GFR) (B) after switching to dulaglutide from dipeptidyl peptidase-4 inhibitors including patients with whose concomitant drugs were switched or increased the dosage. Dots show individual results. Continuous lines were generated by regression analysis.

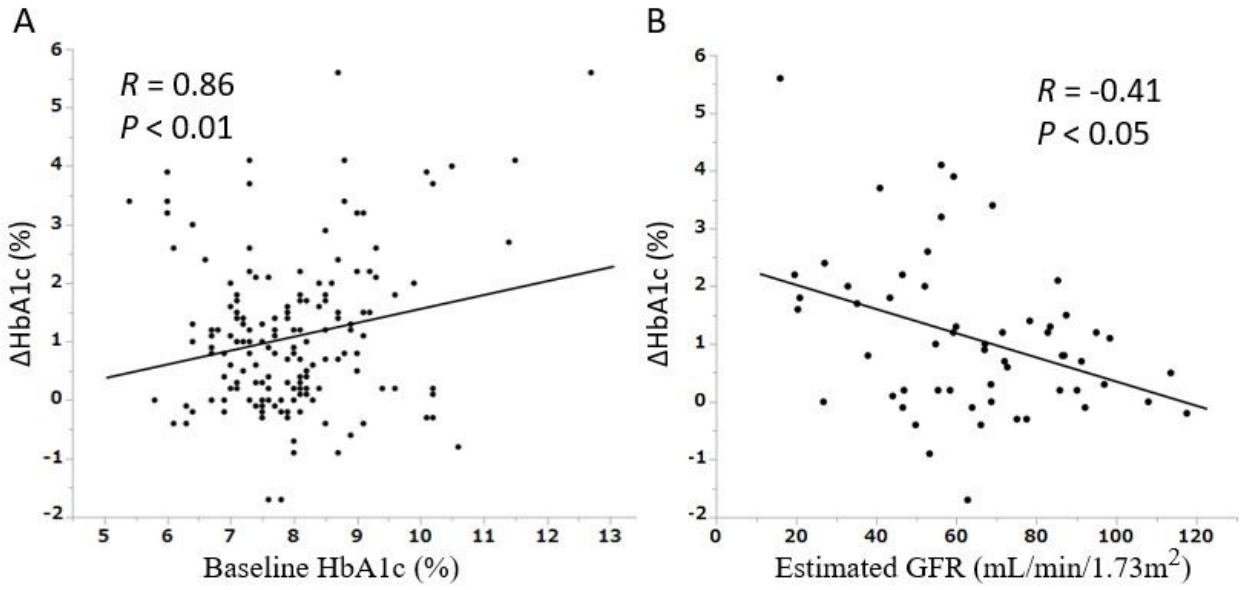

Figure 4

Correlation between HbA1c at 12 weeks and baseline HbA1c (A) or estimated glomerular filtration rate (GFR) (B) after switching to dulaglutide from dipeptidyl peptidase-4 inhibitors in patients without whose concomitant drugs were switched or increased the dosage. Dots show individual results. Continuous lines were generated by regression analysis.