

# Real-world Efficacy and Safety of Dulaglutide in Korean Patients with Type 2 Diabetes Mellitus: A Retrospective Study in a Tertiary Referral Center

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## Research article

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# Abstract

**Background:** This study was conducted to evaluate the efficacy and safety of once-weekly dulaglutide therapy as add-on to oral antidiabetic drugs (OADs) and basal insulin in Korean patients with type 2 diabetes mellitus (T2DM) in the real-world clinical practice.

**Methods:** We retrospectively reviewed the medical records of 112 patients who received dulaglutide in a tertiary referral center. The primary efficacy endpoint was a change in glycated hemoglobin (HbA1c) between baseline and 6 months. The secondary endpoints were the percentage of patients achieving HbA1c <7.0% or  $\leq$ 6.5% and the change of body weight at 6 months.

**Results:** At baseline, the mean HbA1c was 8.7 % (8.8% in the add-on to OAD and 8.5% in the add-on to insulin group). The mean adjusted HbA1c at 6 months decreased by  $-1.13\%$  in the overall patients ( $p < 0.001$ ), and by  $-1.36$  and  $-0.74\%$  in the add-on to OAD and add-on to insulin group, respectively. A significant reduction of  $-2.9$  kg in body weight was observed in the overall patients at 6 months ( $p < 0.001$ ). Approximately 34.8% and 23.2% of patients achieved HbA1c <7.0% and  $\leq$ 6.5%, respectively. Higher baseline HbA1c and no previous insulin therapy were associated with good response to dulaglutide on multivariate analysis. In subgroup analysis to evaluate the long-term efficacy of dulaglutide ( $n=82$ ), the mean adjusted HbA1c decreased by  $-0.86\%$  from baseline to 12 months ( $p < 0.001$ ). Mild gastrointestinal issues (23.2%) were the most frequently observed adverse events.

**Conclusions:** Dulaglutide is an effective and durable treatment option as add-on to OAD and basal insulin therapy in Korean patients with T2DM.

## Background

Type 2 diabetes mellitus (T2DM) is emerging as a prevalent disease worldwide and has affected 14.4% of adults aged 30 or older in Korea [1]. A wide range of glucose-lowering agents has been developed to achieve glycemic target goals in T2DM, which is a chronic, progressive, metabolic disorder. The American Diabetes Association and the European Association for the Study of Diabetes recommends metformin as the first-line therapy for T2DM [2, 3]. When additional antidiabetic therapies are required to achieve the glycemic target, an individualized, patient-based approach, with due consideration to the presence of atherosclerotic cardiovascular disease and chronic kidney disease, body weight, hypoglycemia, and cost-effectiveness, is suggested. The glucagon-like peptide-1 (GLP-1) receptor agonist (RA) is preferred as the second-line therapeutic agent in patients who need adjuvant antidiabetic therapy. Moreover, GLP-1 RAs are preferred injectable therapy to insulin in patients with inadequate glycemic control with oral antidiabetic drugs (OADs).

The GLP-1 is an incretin hormone, which increases glucose load-based insulin secretion and decreases glucagon secretion, and thereby slows gastric emptying and reduces appetite [4]. The GLP-1 RAs have demonstrated glucose-lowering efficacy with a low risk of hypoglycemia as well as marked body weight reduction in several randomized controlled trials (RCTs) [5–7]. In addition, treatment with GLP-1 RA has

showed a significant reduction of major cardiovascular disease risk and mortality, and improved renal outcomes [8].

Dulaglutide is a long-acting human GLP-1 RA that has been approved for the treatment of T2DM, and is administered weekly. Since its introduction, the usage of dulaglutide has continuously increased in Korea. The initiation of dulaglutide therapy can be considered in various clinical settings; however, given the concerns associated with insurance coverage, dulaglutide is generally used in combination therapy with OAD or basal insulin. Several recent real-world studies have shown consistent glucose-lowering efficacy with body weight reduction in patients with T2DM treated with dulaglutide when compared with the results from previous RCTs [9, 10]. Similar findings from Korean patients with T2DM were reported in two studies that evaluated the glycemic efficacy of dulaglutide for 6 months [11, 12]. However, there are limited data on the long-term efficacy and safety of dulaglutide in the real-world clinical scenario. Furthermore, little is known about the differences in glucose-lowering efficacy of dulaglutide according to the background glucose-lowering regimen.

Therefore, we aimed to evaluate the efficacy and safety of dulaglutide as add-on to OAD and basal insulin in a real-world clinical setting in Korean patients with T2DM.

## Methods

### Study population

We retrospectively reviewed the medical records of patients with T2DM who started dulaglutide therapy in Chonnam National University Hwasun Hospital between January 2017 and August 2019. This study included patients with T2DM who received dulaglutide for more than 6 months. We excluded patients who had been previously treated with other types of GLP-1 RA, those who had self-reported low adherence, and received high-dose steroid therapy and chemotherapy during dulaglutide therapy for the analysis. We further excluded the patients who experienced significant changes in treatment regimens, such as the addition of insulin or change in OAD class at the initiation of dulaglutide or during the treatment. A total of 112 patients were included in the final analysis. The patients were divided into two groups according to the background glucose-lowering therapy: the add-on to OAD group (i.e., dulaglutide in combination with OADs) and the add-on to insulin group (i.e., dulaglutide in combination with basal insulin). The add-on to OAD group was further subdivided into two groups based on the history of insulin therapy prior to the initiation of dulaglutide. Meanwhile, the add-on to insulin group was further subdivided into two groups by the history of bolus insulin therapy prior to the initiation of dulaglutide therapy.

Of the 112 patients, 82 patients who continued the dulaglutide therapy for at least 12 months were analyzed for long-term durable efficacy of dulaglutide. Briefly, four patients who were lost to follow-up and nine patients who did not undergo regular glycated hemoglobin (HbA1c) measurements after 6 months were excluded. Additionally, 17 patients were excluded from the analysis as they had

discontinued dulaglutide therapy after 6 months due to inadequate glycemic control (n = 9), adverse events (n = 3), or patients' request (n = 5).

## **Efficacy and safety assessment**

For the evaluation of clinical characteristics, we collected data on age, sex, body weight, body mass index (BMI), duration of diabetes, total daily insulin dose, and comorbidities including hypertension, dyslipidemia, and cardiovascular diseases. The HbA1c measurements were conducted at baseline, and repeated after 3 months ( $\pm$  4 weeks) and 6 months ( $\pm$  4 weeks) following dulaglutide initiation. We further collected data on the levels of fasting plasma glucose (FPG), total cholesterol, triglyceride, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, liver enzymes, serum creatinine, and estimated glomerular filtration rate.

The primary efficacy endpoint was a change in HbA1c between baseline and 6 months. The secondary efficacy endpoints were the percentage of patients who achieved a glycemic target of HbA1c  $<$  7.0% or  $\leq$  6.5% at 6 months as well as the change in body weight between baseline and 6 months. Additionally, we investigated the clinical characteristics of patients who achieved a good response to dulaglutide, which was defined as a decrease in HbA1c of more than 1.0% after 6 months of dulaglutide therapy. We further examined the long-term efficacy of the therapy in patients who continued dulaglutide therapy for at least 12 months by analyzing the change in HbA1c between baseline and 12 months.

The self-reported adverse events including hypoglycemia, gastrointestinal problems, and injection-related reactions were collected from a review of the medical records.

## **Statistical analysis**

Continuous variables were expressed as the mean  $\pm$  standard deviation and categorical variables were expressed as the number (%). The chi-square test was used for the comparison of categorical variables. The paired *t*-test was used to compare the changes in HbA1c and body weight between baseline and 6 months in each treatment group. Intergroup comparisons were undertaken with the analysis of covariance after adjusting for the baseline levels. The changes in each parameter were expressed as the adjusted least square (LS) means and standard error. Univariate and multivariate logistic regression analyses were conducted to evaluate the predictive factors for the therapeutic response to dulaglutide. Risk was reported as odds ratios and 95% confidence intervals (CIs). For the analysis of 12-month efficacy of dulaglutide, repeated-measures one-way analysis of variance was used to assess the change in HbA1c values between baseline and 12 months. All statistical analyses were performed using SPSS software version 25.0 for Windows (IBM Corp., Armonk, NY, USA). *P*-values  $<$  0.05 were considered to indicate statistical significance.

## **Results**

### **Baseline characteristics of the study population**

The baseline characteristics of the study participants are presented in Table 1. The mean age was 59.7 years and 35.7% of them was female. The mean body weight was 77.9 kg and BMI was 27.7 kg/m<sup>2</sup>. The mean duration of diabetes was 12.2 years in the entire study cohort, and was significantly longer in the add-on to insulin group than in the add-on to OAD group ( $p = 0.015$ ). Before the initiation of dulaglutide therapy, the majority of patients had received metformin. Approximately 46.4% of the patients were treated with insulin before the initiation of dulaglutide therapy, and the mean total daily insulin dose was 44.7 IU. At the initiation of dulaglutide therapy, approximately 20.9 IU of insulin switched to dulaglutide in the add-on to OAD group. The mean total daily insulin dose was 51.8 IU in the add-on to insulin group. Six patients titrated their insulin doses ( $> 10\%$  of the baseline) at the initiation of dulaglutide.

Table 1  
Baseline characteristics of study population

	Overall ( <i>n</i> = 112)	Add-on to OAD ( <i>n</i> = 72)	Add-on to insulin ( <i>n</i> = 40)	<i>p</i> value
Age, yr	59.7 ± 11.6	58.7 ± 11.9	61.3 ± 10.9	0.259
Female sex	40 (35.7)	26 (36.1)	14 (35.0)	0.906
Height, cm	166.5 ± 8.1	166.9 ± 8.3	165.8 ± 7.8	0.513
Body weight, kg	77.9 ± 16.0	79.3 ± 17.5	75.3 ± 12.6	0.225
Body mass index, kg/m <sup>2</sup>	27.7 ± 4.2	27.9 ± 4.3	27.2 ± 4.1	0.416
Duration of diabetes, yr	12.2 ± 8.6	10.7 ± 7.9	14.9 ± 9.3	0.015
Systolic blood pressure, mmHg	129.2 ± 15.0	129.9 ± 15.7	128.1 ± 13.7	0.552
Diastolic blood pressure, mmHg	74.9 ± 10.8	76.6 ± 10.6	71.8 ± 10.7	0.024
HbA1c, %	8.7 ± 1.4	8.8 ± 1.5	8.5 ± 1.4	0.376
Fasting plasma glucose, mg/dL	180.1 ± 67.0	190.1 ± 70.6	159.9 ± 54.8	0.037
Total cholesterol, mg/dL	155.7 ± 43.3	160.0 ± 37.0	147.7 ± 52.7	0.175
Triglyceride, mg/dL	154.7 ± 92.8	150.1 ± 87.0	163.8 ± 103.9	0.486
HDL cholesterol, mg/dL	43.0 ± 9.1	42.9 ± 8.7	43.4 ± 10.0	0.807
LDL cholesterol, mg/dL	86.6 ± 30.4	89.9 ± 27.1	80.1 ± 35.4	0.128

Values are expressed as mean ± standard deviation or number (%)

Hypertension is defined as a systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or taking anti-hypertensive medication. Dyslipidemia is defined as taking lipid-lowering agents including statin, ezetimibe, fibrate, and omega-3.

OAD, oral anti-diabetic drug; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP4, Dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2.

	Overall ( <i>n</i> = 112)	Add-on to OAD ( <i>n</i> = 72)	Add-on to insulin ( <i>n</i> = 40)	<i>p</i> value
Aspartate aminotransferase, U/L	30.2 ± 18.6	32.9 ± 21.5	24.9 ± 9.5	0.034
Alanine aminotransferase, U/L	34.2 ± 26.0	38.5 ± 30.3	25.8 ± 10.9	0.012
Serum creatinine, mg/dL	1.05 ± 0.91	1.05 ± 0.76	1.06 ± 0.42	0.981
Estimated glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	81.5 ± 30.3	83.8 ± 30.0	77.2 ± 31.0	0.400
Hypertension	65 (58.0)	38 (52.8)	27 (67.5)	0.130
Dyslipidemia	82 (73.2)	51 (70.8)	31 (77.5)	0.445
Cardiovascular disease	22 (19.6)	15 (20.8)	7 (17.5)	0.671
Dulaglutide dose				0.001
0.75 mg	29 (25.9)	11 (15.3)	18 (45.0)	
1.5 mg	83 (74.1)	61 (84.7)	22 (55.0)	
Treatment before dulaglutide initiation				
Insulin therapy	52 (46.4)	12 (16.7)	40 (100.0)	< 0.001
Daily insulin dose, IU/day	44.7 ± 29.7	20.9 ± 10.1	51.8 ± 30.0	0.001
OAD				
Metformin	104 (92.9)	67 (93.1)	37 (92.5)	0.913
Sulfonylurea	66 (58.9)	47 (65.3)	19 (47.5)	0.067
DPP4 inhibitor	73 (65.2)	49 (68.1)	24 (60.0)	0.391
Thiazolidinedione	13 (11.6)	10 (13.9)	3 (7.5)	0.312

Values are expressed as mean ± standard deviation or number (%)

Hypertension is defined as a systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or taking anti-hypertensive medication. Dyslipidemia is defined as taking lipid-lowering agents including statin, ezetimibe, fibrate, and omega-3.

OAD, oral anti-diabetic drug; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP4, Dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2.

	Overall ( <i>n</i> = 112)	Add-on to OAD ( <i>n</i> = 72)	Add-on to insulin ( <i>n</i> = 40)	<i>p</i> value
SGLT2 inhibitor	9 (8.0)	7 (9.7)	2 (5.0)	0.378
Alpha-glucosidase inhibitor	2 (1.8)	1 (1.4)	1 (2.5)	0.671
Values are expressed as mean ± standard deviation or number (%)				
Hypertension is defined as a systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or taking anti-hypertensive medication. Dyslipidemia is defined as taking lipid-lowering agents including statin, ezetimibe, fibrate, and omega-3.				
OAD, oral anti-diabetic drug; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DPP4, Dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2.				

At baseline, the mean HbA1c was 8.7% in overall patients, 8.8% in the add-on to OAD group and 8.5% in the add-on to insulin group. The mean FPG concentration was higher in the add-on to OAD group than that in the add-on to insulin group (190.1 mg/dL vs. 159.9 mg/dL, *p* = 0.037). There were no significant differences in the baseline fasting lipid profile, serum creatinine, and estimated glomerular filtration rates levels between the two groups. Although the levels of aspartate aminotransferase and alanine aminotransferase were higher in the add-on to OAD group than in the add-on to insulin group (*p* = 0.034 and *p* = 0.012, respectively), both parameters were within the reference ranges. The prevalence of hypertension, cardiovascular disease, and dyslipidemia did not differ between the two groups. Approximately 74.1% of all patients received 1.5 mg dulaglutide; the add-on to OAD group was associated with higher dose of dulaglutide than add-on to insulin group (*p* = 0.001).

## Efficacy

At 6 months, dulaglutide therapy exhibited a significant reduction in HbA1c levels of - 1.13% (95% CI, - 1.38 to - 0.89; *p* < 0.001) in the overall patients. The mean adjusted HbA1c decreased by - 1.36% (95% CI, - 1.61 to - 1.10) in the add-on OAD group and - 0.74% (95% CI, - 1.08 to - 0.40) in the add-on to insulin group (*p* < 0.001 and *p* = 0.001, respectively). The difference in the LS mean change between the two groups was - 0.62% (95% CI, - 1.04 to - 0.19; *p* = 0.005; Fig. 1). There was a significant reduction of - 2.9 kg in the body weight in the overall patients (*p* < 0.001), and of - 3.5 kg in the add-on to OAD group (*p* < 0.001); however, a statistically significant difference was not observed in the add-on to insulin group (- 1.8 kg, *p* = 0.068).

In the add-on to OAD group, there was no significant difference in the glucose-lowering efficacy between the insulin-naïve and previous insulin therapy group (LS mean change - 1.39% and - 1.47%, respectively; between-treatment difference in HbA1c of 0.080 [95% CI, - 0.620 to 0.779]; *p* = 0.821; Table 2). Similarly, in the add-on to insulin group, the magnitude of the HbA1c reduction did not differ between the bolus insulin-naïve and previous bolus insulin therapy group (LS mean change - 0.80 and - 0.68%, respectively; between-treatment difference of - 0.217 [95% CI, - 0.930 to 0.497]; *p* = 0.542). The total daily insulin dose

decreased by - 20.7 IU in the add-on to insulin group ( $p < 0.001$ ), and by - 16.0 and - 23.5 in the bolus insulin-naïve and previous bolus insulin therapy group, respectively.

Table 2

Changes in HbA1c after 6 months of treatment with dulaglutide as add-on to OAD and add-on to insulin

Variable	Baseline	6 months	LS mean change from baseline (95% CI)	Difference in LS mean change (95% CI) <sup>a</sup>
Add-on to OAD				
Overall ( $n = 72$ )	8.8 ± 0.1	7.4 ± 0.1	-1.36 (-1.61 to -1.10) <sup>b</sup>	
Insulin-naïve ( $n = 60$ )	8.8 ± 0.2	7.4 ± 0.2	-1.39 (-1.67 to -1.10) <sup>b</sup>	0.080 (-0.620 to 0.779) <sup>c</sup>
Previous insulin therapy ( $n = 12$ )	9.0 ± 0.5	7.4 ± 0.4	-1.47 (-2.10 to -0.83) <sup>b</sup>	
Add-on to insulin				
Overall ( $n = 40$ )	8.5 ± 0.2	7.9 ± 0.2	-0.74 (-1.08 to -0.40) <sup>b</sup>	
Bolus insulin-naïve ( $n = 15$ )	8.7 ± 0.3	7.9 ± 0.4	-0.80 (-1.36 to -0.23) (0.007) <sup>b</sup>	-0.217 (-0.930 to 0.497) <sup>c</sup>
Previous bolus insulin therapy ( $n = 25$ )	8.4 ± 0.3	7.9 ± 0.3	-0.68 (-1.01 to -0.14) (0.002) <sup>b</sup>	
Values are presented as mean ± standard error.				
LS, least square; CI, confidence interval. <sup>a</sup> Difference in the LS mean change, which was calculated as insulin-naïve minus previous insulin therapy in add-on to OAD group and bolus insulin-naïve minus previous bolus insulin therapy in add-on to insulin group. <sup>b</sup> $p < 0.05$ from baseline in overall patients and each treatment subgroup, <sup>c</sup> $p < 0.05$ for the between-treatment group difference.				

The proportion of patients who achieved HbA1c < 7.0% at 6 months was 34.8% in overall patients, 41.7% in the add-on to OAD group, and 22.5% in the add-on to insulin group ( $p = 0.041$ ). Moreover, with the HbA1c ≤ 6.5% as the glycemic target, 23.2% of all patients achieved the glycemic target goal (31.9% in the add-on to OAD group and 7.5% in the add-on to insulin groups,  $p = 0.003$ ; Fig. 2).

In overall, 60 patients (53.6%) were categorized as good responders (HbA1c reduction ≥ 1.0%) after 6 months of dulaglutide therapy. Shorter duration of diabetes and higher baseline glycemic parameters (HbA1c and FPG) were associated with a good response to dulaglutide. Whereas, patients who had a history of insulin therapy showed a poor response to dulaglutide (Table 3). Logistic regression analyses were used for the identification of predictable parameters for the glucose-lowering effect of dulaglutide. Univariate regression analysis showed that shorter duration of diabetes, higher baseline HbA1c, and no previous insulin use were associated with a good response to dulaglutide at 6 months. On multivariate

analysis, higher baseline HbA1c and no previous insulin therapy remained statistically significant (**Supplementary Table 1**).

Table 3  
Clinical characteristics between the good responder and the poor responders in overall patients

	Good responders ( <i>n</i> = 60)	Poor responders ( <i>n</i> = 52)	<i>p</i> value
Age, yr	58.9 ± 11.4	60.5 ± 11.9	0.478
Female sex	22 (36.7)	18 (34.6)	0.821
Body weight, kg	78.6 ± 17.5	77.0 ± 14.2	0.590
Body mass index, kg/m <sup>2</sup>	27.8 ± 4.3	27.5 ± 4.2	0.768
Duration of diabetes, yr	10.2 ± 8.0	14.6 ± 8.7	0.008
Hypertension	39 (65.0)	26 (50.0)	0.109
Dyslipidemia	40 (66.7)	42 (80.8)	0.093
Cardiovascular disease	12 (20.0)	10 (19.2)	0.919
Baseline HbA1c, %	9.3 ± 1.3	8.0 ± 1.3	< 0.001
Baseline fasting plasma glucose, mg/dL	194.4 ± 65.2	163.1 ± 65.7	0.022
Previous insulin therapy before dulaglutide initiation	20 (33.3)	32 (61.5)	0.003
Total daily insulin dose before dulaglutide initiation (IU)	41.7 ± 36.2	46.6 ± 25.3	0.567
Values are presented as mean ± standard deviation or number (%).			

In a subgroup analysis to evaluate the long-term efficacy of dulaglutide therapy (*n* = 82), the mean adjusted HbA1c decreased by - 0.86% (95% CI, - 0.35 to - 1.38) from baseline to 12 months (*p* < 0.001). The HbA1c level showed a maximum decrease of - 1.19% (95% CI, - 0.72 to - 1.67) at 3 months (*p* < 0.001), which was maintained for more than 12 months during dulaglutide therapy (Fig. 3).

## Safety profiles

Adverse events were reported in 44 patients (39.3%) during the 6 months of dulaglutide therapy. The most common adverse events were gastrointestinal problems, including nausea, vomiting, dyspepsia, and abdominal pain (23.2%). Hypoglycemia was observed in 15 patients (13.4%), which was associated with the use of sulfonylurea (*n* = 7) and basal insulin (*n* = 8) as background therapy. Severe hypoglycemia was not reported in the study population during the dulaglutide therapy. Four patients (3.6%) had injection-site reactions that were self-limited.

## Discussion

In this analysis of real-world clinical data, we demonstrated that dulaglutide significantly improved the glycemic control in Korean patients with T2DM. The glucose-lowering efficacy of dulaglutide was observed either in adding to OAD or adding to basal insulin, and the effect was sustained over a 12-month period. Moreover, dulaglutide induced significant reduction in body weight. Our findings are similar to those of previous RCTs and real-world clinical studies in patients with T2DM who received dulaglutide treatment.

In the present study, dulaglutide exhibited a significant reduction in HbA1c of  $-1.13\%$  at 6 months, which was consistent with the results from clinical trials [13–15], and similar or slightly greater than that from real-world clinical studies conducted in Western countries [16–18]. This may be associated with the pharmacokinetic and pharmacodynamic differences of GLP-1 RA in Caucasian and Asians, wherein Asian patients have higher postprandial glucose and postprandial excursion related to impaired  $\beta$ -cell function [19, 20]. We further analyzed the efficacy of dulaglutide separately as add-on to OAD or basal insulin because these two regimens are generally accepted in clinical practice. The glucose-lowering efficacy of dulaglutide therapy was observed in both groups. However, the magnitude of HbA1c reduction was greater in the add-on to OAD than in the add-on to insulin group ( $-1.36\%$  vs  $-0.74\%$ ). Comparable glycemic efficacy of dulaglutide was reported in previous RCTs with dulaglutide in combination with OADs. The HbA1c-lowering effect of dulaglutide 1.5 mg was  $-1.42\%$  at 26 weeks with metformin in the Assessment of Weekly Administration of LY2189265 in Diabetes-6 (AWARD-6) trial and  $-1.40\%$  with sulfonylurea in the AWARD-8 trial [13, 21].

The observed glucose-lowering efficacy of dulaglutide as add-on to insulin ( $-0.74\%$ ) was lower than those previously reported in the AWARD-9 trial [22]. In the AWARD-9 trial, the mean HbA1c changes from baseline was  $-1.44\%$  at 28 weeks in T2DM patients after adding to insulin glargine, and 66.7% of the patients achieved a target goal of HbA1c  $<7.0\%$ . Meanwhile, a real-world study in Korean patients revealed a  $-0.97\%$  mean change in HbA1c at 6 months after dulaglutide therapy as add-on to basal insulin [11]. These two studies similarly showed a decrease of  $-11.7$  IU in the total daily insulin dose, whereas our study showed a decrease of  $-20.7$  IU at 6 months. This disparity may be attributed to several differences in the study population between the studies as well as real-world factors. In our study, a considerable proportion (62.5%) of patients switched the treatment regimen from basal-bolus to basal insulin + dulaglutide in the add-on to insulin group in contrast to the abovementioned studies, and dulaglutide add-on decreased approximately 23.5 IU of insulin. Furthermore, as the insulin dose was self-titrated for the individual patient during dulaglutide treatment, there is a possibility that a marked glucose reduction or hypoglycemia might have led to a subsequently inadequate insulin dose, and the patient's low adherence may have affected the glycemic control.

We observed a durable effect of dulaglutide over 12 months in the subgroup analysis. The observed reduction of HbA1c from baseline to 12 months was  $-0.86\%$ . HbA1c levels reached nadir at 3 months after dulaglutide initiation, and tended to increase until 12 months; however, HbA1c levels from 3 to 12

months were not statistically significant. This trend was consistent with the result from the AWARD trials and real-world studies [9, 23–25]. Several studies have evaluated the 12-month glucose-lowering efficacy of dulaglutide in the real-world scenario, and showed reductions in HbA1c of – 0.9 to – 1.0% that were comparable to our data [26, 27]. To the best of our knowledge, this is the first study to report the 12-month efficacy of dulaglutide in Korean patients with T2DM.

We analyzed the clinical predictive factors for a good response to dulaglutide. Higher glycemic parameters at baseline and no previous insulin therapy were significantly associated with a good dulaglutide response on multivariate regression analysis. A previous pilot study reported that low BMI and old age were linked to a good response to dulaglutide in Japanese patients with T2DM [28]. A real-world study in Korean patients demonstrated that a higher baseline HbA1c was the only predictable factor for a good response to dulaglutide [12].

Besides the HbA1c change, a significant improvement in body weight (– 2.9 kg) was observed at 6 months after dulaglutide initiation in overall population. The efficacy of weight reduction in our study is similar to the previous real-world data reported from Western countries, which reported – 2.7 to – 2.9 kg weight reduction at 6 months [16, 29]. Meanwhile, real-world data from Korea showed a weight reduction of – 2.1 kg during 6-month dulaglutide therapy in combination with various glucose-lowering treatments [12], and – 2.0 kg at 6 months with dulaglutide as an adjuvant to basal insulin therapy [11]. These differences may be attributed to the considerable reduction in insulin doses during dulaglutide therapy that leads to a synergic effect on weight loss, as shown in the present study. In addition, several combinations of OADs and selection bias may influence the body weight. In our study, if patients who stopped dulaglutide earlier due to complaints of no weight change, or took medications that conferred a possibility to gain weight, such as high-dose steroids, were excluded from the analysis.

In the present study, the incidence of gastrointestinal side effects, including mainly nausea, vomiting, and dyspepsia, was similar or slightly higher than those reported in previous RCTs and real-world data [25, 30–32]. Self-reported hypoglycemia occurred more frequently in our study (13.4%) than in previous studies and meta-analyses [13, 33, 34], and all of them received sulfonylurea and/or basal insulin. Similar to previous studies, all reported cases of hypoglycemia were mild, and no severe hypoglycemia was documented in this study. In this study cohort, 3.6% of patients had an injection-site reaction; however, the incidence was gradually decreased with repeated injections. Our data supported the safety profiles of dulaglutide in a clinical management plan that comprised various glucose-lowering regimens.

There are several limitations of the present study due to its retrospective design. The total cohort sample was small, in particular, for the analysis of glucose-lowering efficacy with regard to the background treatment regimens. Moreover, several parameters, including FPG, lipid profiles, blood pressure, and insulin sensitivity or resistance, were unavailable for an evaluation of the changes after dulaglutide therapy. Furthermore, safety profiles were not collected systematically; therefore, the self-report system might have resulted in over- and under-estimation of adverse events. Nevertheless, this study provided

meaningful data on the real-world efficacy of dulaglutide in combination with various background glucose-lowering regimen and its long-term efficacy over 12 months.

## Conclusions

Our findings prove the real-world efficacy and safety profiles of dulaglutide as add-on to OAD and basal insulin therapy in Korean patients with T2DM. A beneficial effect of body weight reduction was also observed. Dulaglutide therapy could be considered in real-world practice, either as add-on to OAD or basal insulin therapy in Korean T2DM patients with inadequate glycemic control and/or need for weight reduction.

## Abbreviations

AWARD: Assessment of Weekly Administration of LY2189265 in Diabetes; BMI: Body mass index; CI: Confidence interval; FPG: Fasting plasma glucose; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Glycated hemoglobin; LS: Least square; OAD: Oral antidiabetic drug; RCT: Randomized controlled trial; T2DM: Type 2 diabetes mellitus

## Declarations

## Authors' contributions

All authors were responsible for drafting the article and revising it critically for important intellectual content. ARH designed the study. ARH and JHY conducted the study and collected the data. ARH and JHY conducted the data analysis. All authors (JHY, ARH, WC, JYP, HKK, and H-CK) interpreted the data, drafted and revised the manuscript and approved the final version of the manuscript for publication.

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## Availability of data and materials

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

## Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review board of Chonnam National University Hwasun Hospital (IRB No.: CNUHH-2019-085).

The need for informed consent was waived due to the retrospective nature of the study.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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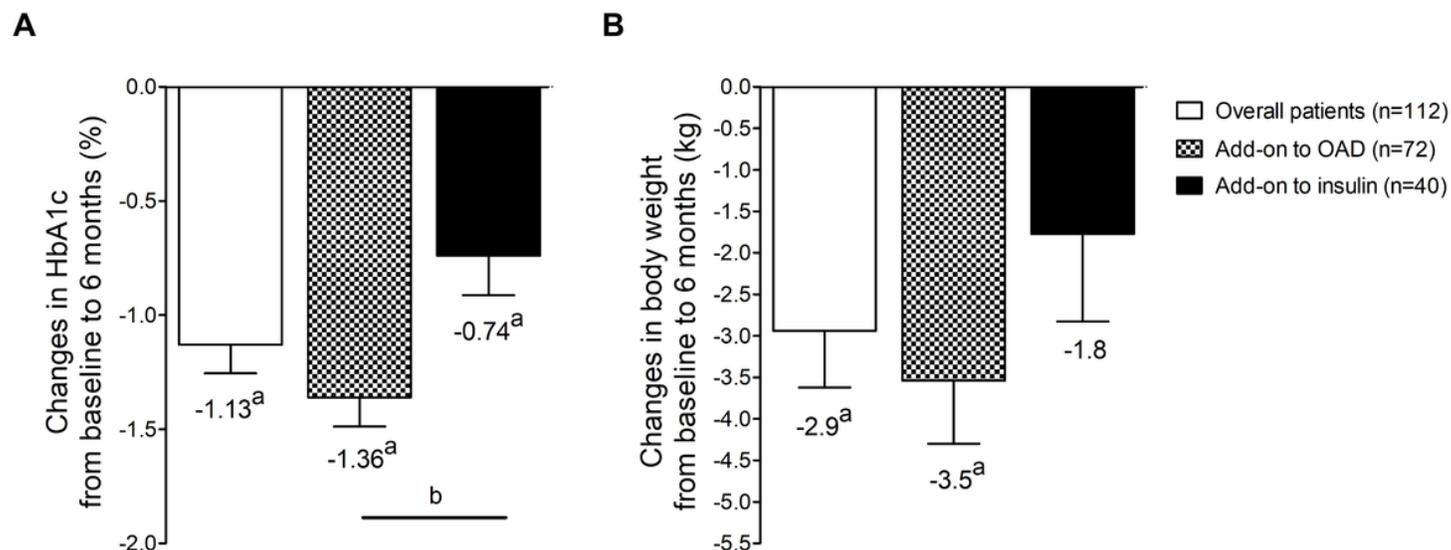
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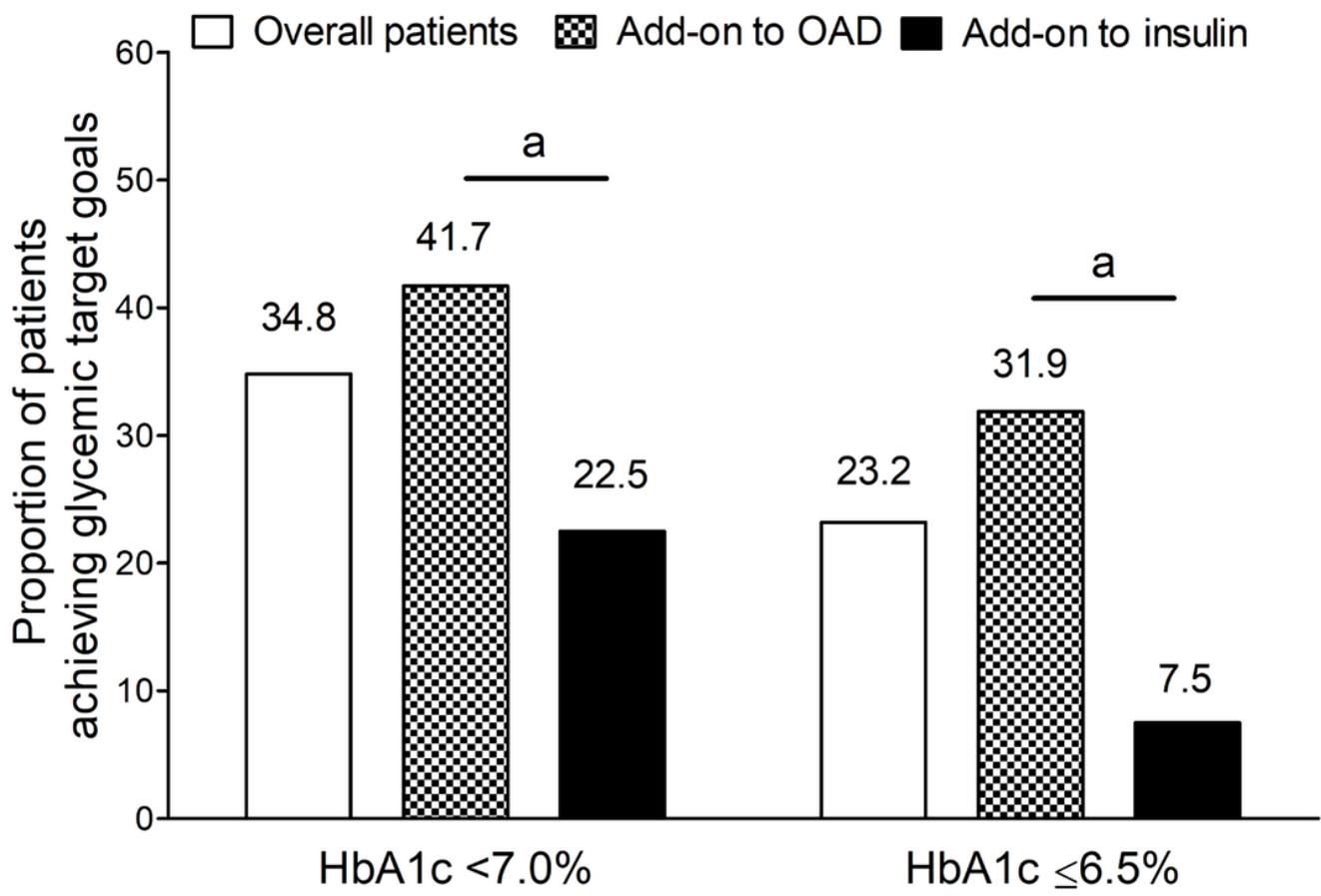
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## Figures



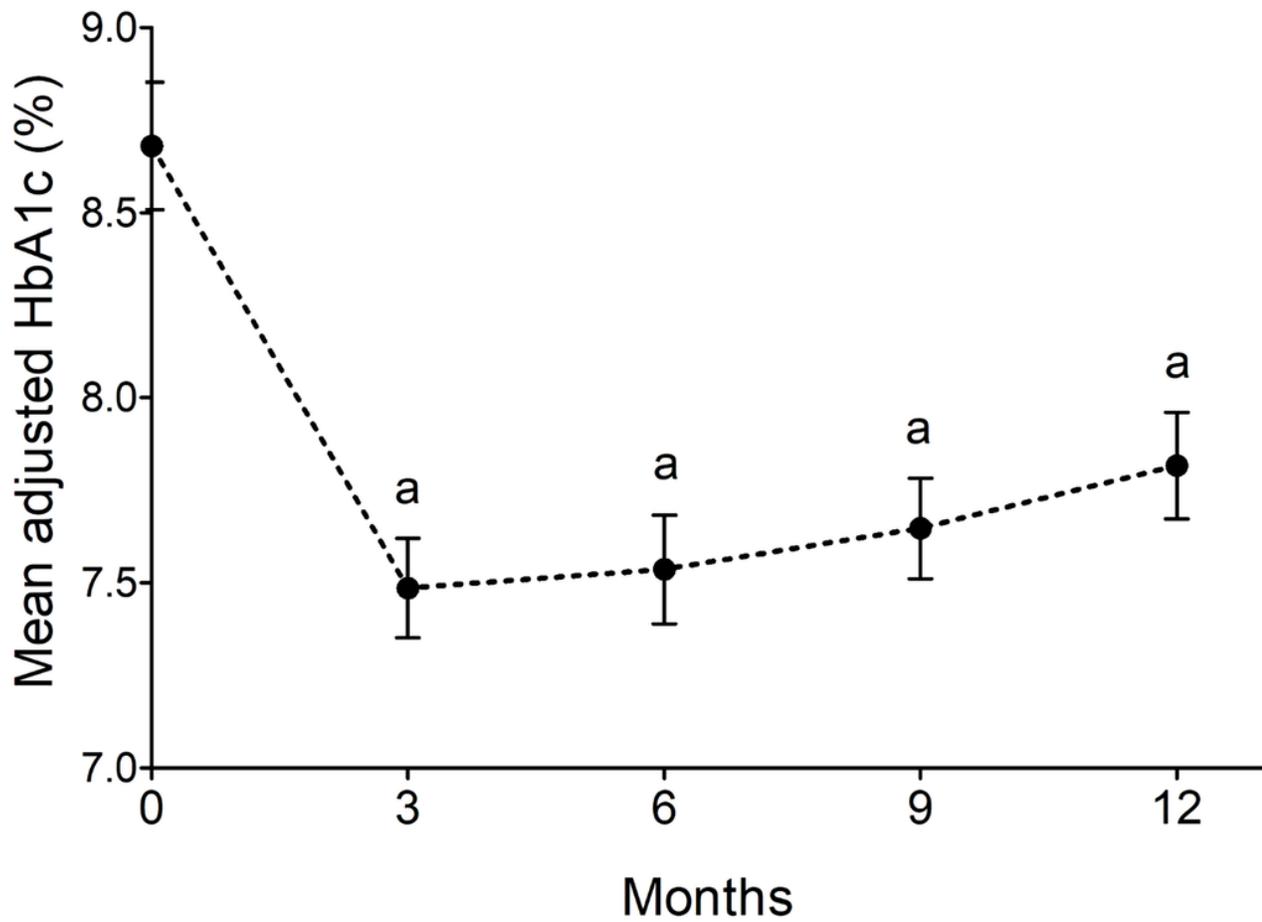
**Figure 1**

Changes in (A) HbA1c and (B) body weight after 6 months of treatment with dulaglutide. OAD, oral anti-diabetic drug. ap < 0.05 vs. baseline. bp < 0.05 between add-on to OAD group and add-on to insulin group.



**Figure 2**

Proportion of patients who achieved glycemic target goals of HbA1c <7.0% or ≤6.5%. ap < 0.05 between add-on to OAD and add-on to insulin group.



**Figure 3**

Mean adjusted HbA1c over 12 months during dulaglutide therapy in subgroup analysis (n=82).  $p < 0.05$  vs. baseline.

## Supplementary Files

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- [SupplementaryTable1.docx](#)