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Dulaglutide as an Effective Replacement for Prandial Insulin in Kidney Transplant Recipients with Type 2 Diabetes Mellitus: A Retrospective Review

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Dulaglutide, a weekly injectable glucagon-like peptide-1 receptor agonist, has demonstrated effectiveness when combined with basal insulin. We examined whether the efficacy of dulaglutide is comparable to that of prandial insulin in kidney transplant (KT) recipients with type 2 diabetes mellitus (T2DM) undergoing multiple daily insulin injection (MDI) therapy. Thirty-seven patients, who switched from MDI therapy to basal insulin and dulaglutide, were retrospectively analyzed. Changes in glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) levels, body weight, and basal insulin dose were evaluated over 6 months. Dulaglutide was comparable to three injections of prandial insulin in terms of glycemic control (HbA1c 7.1% vs. 7.0%; 95% confidence interval [CI], –0.53 to 0.28; $P=0.53$). The basal insulin and dulaglutide combination resulted in a reduction in FPG levels by 9.7 mg/dL (95% CI, 2.09 to 41.54; $P=0.03$), in body weight by 4.9 kg (95% CI, 2.87 to 6.98; $P<0.001$), and in basal insulin dose by 9.52 IU (95% CI, 5.80 to 3.23; $P<0.001$). Once-weekly dulaglutide may be an effective alternative for thrice-daily prandial insulin in KT recipients with T2DM currently receiving MDI therapy.

Keywords: Diabetes mellitus, type 2; Dulaglutide; Insulin

INTRODUCTION

Multiple daily insulin injection (MDI) therapy is commonly used in type 2 diabetes mellitus (T2DM) patients who have undergone kidney transplant (KT) for diabetic end-stage renal disease (ESRD) [1]. MDI therapy is inconvenient and can induce poor compliance; thus, a weekly injectable glucagon-like peptide-1 receptor agonist (GLP-1RA), such as dulaglutide, may be suggested as a substitute for prandial insulin by decreasing the number of injections. Previous studies have demonstrated the efficacy and safety of dulaglutide in combination with basal insulin [2,3]. GLP-1RA also facilitates weight loss and reduces the risk of hypoglycemia [4-6]. However, there is limited evidence regarding the possibility of such a transition of therapy. This study examined whether dulaglutide could replace prandial insulin in KT recipients with T2DM on MDI therapy.

METHODS

Study population

Initially, 68 patients with T2DM who initiated dulaglutide treatment after KT from January 1, 2016, to December 31, 2019, at Asan Medical Center (Seoul, Korea) were reviewed. Of these patients, those who were not receiving MDI therapy ($n=6$), received KT for ESRD due to diseases other than diabetes ($n=4$), used dulaglutide for less than 6 months ($n=10$), had missing values ($n=5$), were hospitalized for other diseases

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(n=4), or had discontinued dulaglutide due to adverse events (n=2), were excluded. Finally, 37 patients who switched from prandial insulin to dulaglutide, and continued dulaglutide for more than 6 months, were included in the retrospective chart review. The patients were initiated on 0.75 mg of dulaglutide, which was increased to 1.5 mg only if adverse events were tolerable after 1 month. This study was conducted in compliance with the ethical guidelines of the Declaration of Helsinki and Korean Good Clinical Practice and was approved by the Institutional Review Board of the Asan Medical Center (2018-1050). Informed consent was waived by the board.

Measurements

Baseline data regarding age, sex, weight, height, blood pressure, duration of diabetes, insulin dose, presence of hypertension or dyslipidemia, and dulaglutide dose were collected by reviewing the electronic medical records. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters, and blood pressure was measured by an automatic manometer after a 5-minute rest. Laboratory measurements, including serum levels of glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting C-peptide, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, and liver enzymes, were conducted at baseline, 3 months (±4 weeks), and 6 months (±4 weeks) after dulaglutide treatment.

Study outcomes

The primary outcome was the change in HbA1c levels over the 6-month treatment duration. The secondary outcomes were the changes in FPG levels, body weight, and basal insulin dose between baseline and 6 months. Adverse events were reviewed from the electronic medical records.

Statistical analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables as percentages. The baseline characteristics were compared using Student's t-tests and chi-square tests for continuous and categorical variables, respectively. To compare the changes in HbA1c, FPG, body weight, and basal insulin dose between baseline and 6 months, paired t-test was performed. SPSS software version 23.0 for Windows (IBM Co., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Baseline characteristics

The baseline characteristics of the patients are presented in Table 1. The mean age was 54.8±8.5 years, and 48.6% of patients were male. The mean total insulin dose was 44.5±17.2 IU/day; the basal dose was 24.76±12.1 IU/day, and the prandial dose was 20.5±8.4 IU/day. The mean HbA1c level was 7.0%±0.9%, and the mean BMI was 25.7±3.4 kg/m^2. Seventeen (45.9%) and 20 (54.1%) patients were administered 0.75 and 1.5 mg of dulaglutide, respectively.

Efficacy of dulaglutide as a replacement of prandial insulin

Fig. 1 shows the efficacy of dulaglutide. HbA1c levels were not significantly different between baseline and 6 months (HbA1c 7.00% vs. 7.12%; P=0.53). FPG levels, body weight, and basal insulin dose all significantly decreased after 6 months. FPG levels significantly decreased from 145.43 to 123.62 mg/dL (–21.81 mg/dL; P=0.03). The mean body weight (72.11 kg) was reduced to 67.18 kg (P<0.001). The basal insulin dose was also decreased by 9.52 units from 24.76 to 15.24 units (P<0.001). The trough level of tacrolimus and dose of corticosteroid did not change significantly over the 6-month period (Supplementary Table 1).

Adverse events

Adverse events were reported in 17 (45.9%) and 11 patients (29.7%) after 3 and 6 months of dulaglutide treatment, respectively (Supplementary Table 2). Gastrointestinal symptoms were the most frequently reported adverse event during both time points (14 [37.8%] vs. 8 [21.6%]), with nausea being the most common symptom (7 [18.9%] vs. 4 [10.8%]). Hypoglycemia was reported in only three patients during the 6-month follow-up, and severe hypoglycemia requiring hospitalization was not documented.

DISCUSSION

This study showed that dulaglutide may be used as a substitute for prandial insulin in patients with T2DM without insulin deficiency on MDI therapy after KT. The patients were started on MDI therapy for strict blood glucose control after KT due to administration of high dose immunosuppressants, not absolute insulin deficiency. After transitioning from MDI therapy to basal insulin plus dulaglutide, FPG levels, body weight, and

Table 1. Baseline characteristics of the study participants

Characteristic	Total (n=37)
Male sex	18 (48.6)
Age, yr	54.8±8.5
T2DM duration, yr	17.8±8.4
Duration after KT, mo	10.6±7.5
Total daily insulin dose, IU	44.5±17.4
Basal	24.8±12.1
Bolus	20.5±8.4
Weight, kg	72.1±11.6
Height, cm	167.3±7.8
BMI, kg/m^2	25.7±3.4
SBP, mm Hg	130.4±17.8
DBP, mm Hg	72.3±11.1
HbA1c, %	7.0±0.9
FPG, mg/dL	145.4±42.9
C-peptide, ng/mL	2.1±0.3
Total cholesterol, mg/dL	171.2±43.3
Triglycerides, mg/dL	127.3±54.2
HDL-C, mg/dL	50.7±11.5
LDL-C, mg/dL	106.7±34.2
Creatinine, mg/dL	1.1±0.3
eGFR, mL/min/1.73 m^2	71.7±18.5
AST, IU/L	20.7±6.5
ALT, IU/L	17.9±8.3
Dulaglutide dose	
0.75 mg	17 (45.9)
1.5 mg	20 (54.1)
Hypertension	18 (48.6)
Dyslipidemia	18 (48.6)
Use of oral anti-diabetic drugs	
Metformin	34 (91.9)
Sulfonylurea	19 (51.4)
Presence of retinopathy	
NPDR	3 (8.1)
PDR	26 (70.3)
Not specified	8 (21.6)

Values are presented as number (%) or mean±standard deviation.
T2DM, type 2 diabetes mellitus; KT, kidney transplant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

insulin dose were significantly reduced. Decrease in insulin dose and the weight-reducing effect of dulaglutide both seem to have contributed to the reduction of body weight. HbA1c levels were maintained even after replacing prandial insulin with dulaglutide; therefore, the change in medication was shown not to affect glycemic control.

In a previous prospective study, 25 patients with T2DM receiving MDI therapy were randomized to either continue MDI therapy or to shift to basal insulin plus liraglutide for 24 weeks. The group receiving basal insulin plus liraglutide showed significant reductions in HbA1c levels, body weight, and daily insulin dose by 0.6%, 2.5 kg, and 17.4 units, respectively. On the other hand, the group on continued MDI therapy showed no difference in HbA1c levels or daily insulin dose, with a significant increase in body weight [7]. In our study, the transition from MDI therapy to basal insulin and dulaglutide resulted in significant reductions in FPG, body weight, and insulin dose without changes in HbA1c. It is important to note that while the previous study was completed in a prospective setting for restricted patients receiving a daily GLP-1RA liraglutide, the current study retrospectively analyzed the efficacy of weekly GLP-1RA dulaglutide in a real-world practice setting [7].

While the risks of hypoglycemia and weight gain are inevitable with insulin, they can be reduced with GLP-1RA. In this study, replacing prandial insulin with dulaglutide decreased weight, with only three hypoglycemic events reported. Similar results were observed in previous studies comparing the addition of either prandial insulin or GLP-1RA to basal insulin. The GetGoal Duo-2 trial showed that adding daily lixisenatide was superior to adding prandial insulin in terms of weight loss and hypoglycemia [8]. Likewise, adding weekly albiglutide to basal insulin resulted in significant weight reduction and a low hypoglycemia risk compared with adding prandial insulin [9].

Replacing prandial insulin with a GLP-1RA was associated with better patient satisfaction. In a study of 26 patients, a significantly higher satisfaction score was seen in the group that shifted from MDI therapy to lixisenatide and basal insulin compared to the group that continued MDI therapy [10]. Another study showed that the self-reported patient satisfaction score of the patients receiving liraglutide plus basal insulin significantly improved compared with the MDI group [7]. Thus, switching thrice-daily prandial insulin to once-weekly dulaglutide may be expected to improve patient satisfaction by decreasing the injection frequency.

This study consisted of patients receiving MDI therapy after

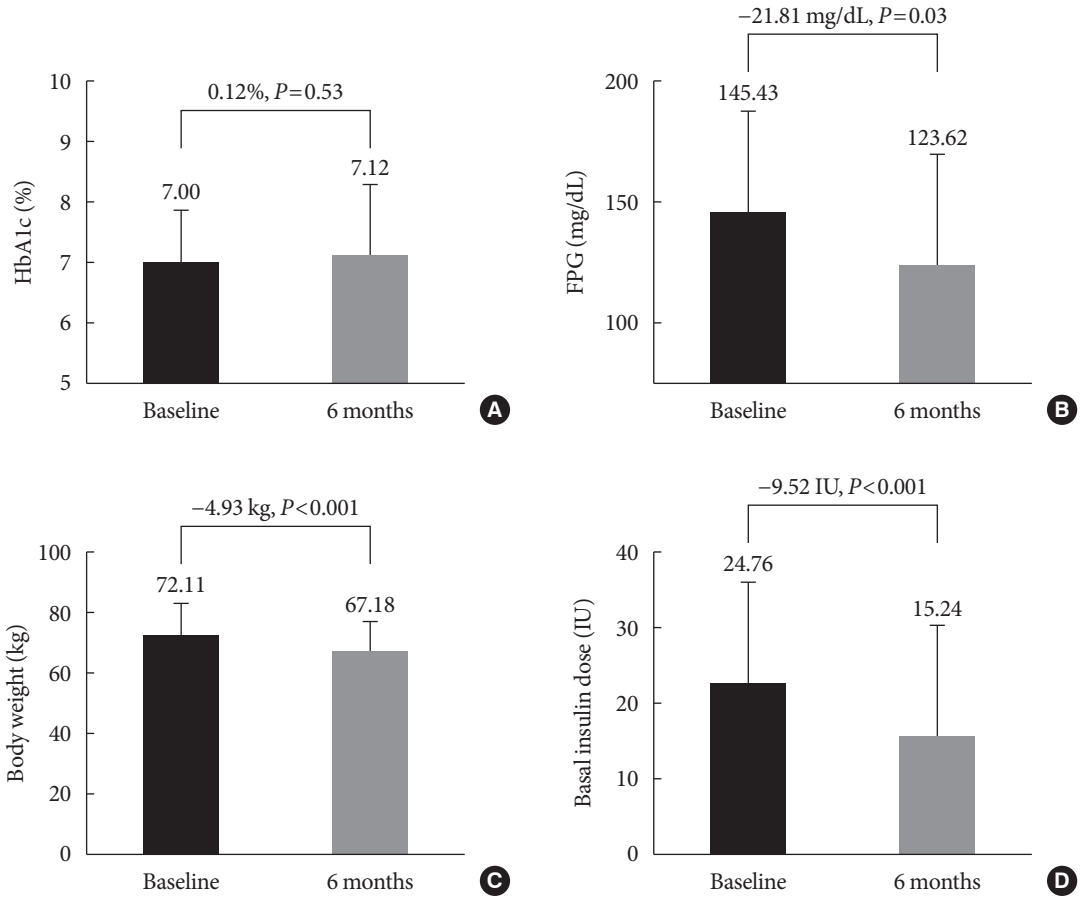

Fig. 1. Measures of therapeutic efficacy of dulaglutide over 6 months. (A) Glycosylated hemoglobin (HbA1c), (B) fasting plasma glucose (FPG), (C) body weight, and (D) basal insulin dose. IU, international unit.

KT. In a previous study on solid organ transplant recipients with diabetes, dulaglutide exhibited positive results for reducing body weight and insulin dose [11]. Furthermore, GLP-1RA decreased insulin dose and hypoglycemia risk in KT recipients [12]. Our results are consistent with these studies and support the use of dulaglutide for glycemic control in KT recipients.

The adverse events indicated in this study were similar to those reported in previous studies on GLP-1RAs [13]. Although gastrointestinal problems were reported by 14 patients at the 3-month follow-up, all 14 patients continued dulaglutide for another 3 months, and six patients showed improvement in symptoms with sustained use of dulaglutide.

This study has several limitations. First, it was a small, retrospective study, and the follow-up period was relatively short to evaluate the long-term effects of dulaglutide. Second, metformin and sulfonylurea were used along with dulaglutide in some patients, which may have influenced the efficacy of dulaglutide. Third, postprandial plasma glucose levels were not measured; thus, dulaglutide's efficacy in lowering postprandial glucose could only be predicted by HbA1c levels. Lastly, this study only included KT recipients with relatively good glycemic control and no insulin deficiency, thus, results may not be applicable to all KT recipients. Therefore, when considering a shift in therapy, the patient's insulin secretion ability should be evaluated. Despite these limitations, our study is the first to evaluate the transition from prandial insulin to a weekly GLP-1RA in a real-world setting. Further prospective studies targeting a larger population of patients receiving MDI therapy for various reasons will be necessary to validate the efficacy of this method.

In conclusion, combination therapy with dulaglutide and basal insulin is comparable to MDI therapy in terms of glycemic control. Replacement of prandial insulin with a weekly GLP-1RA may be effective for KT recipients with T2DM under stable glycemic control with MDI therapy.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0180.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: H.S.K., W.J.L.
Acquisition, analysis, or interpretation of data: H.S.K., J.L., C.H.J., J.Y.P., W.J.L.
Drafting the work or revising: H.S.K., J.L., W.J.L.
Final approval of the manuscript: H.S.K., J.L., C.H.J., J.Y.P., W.J.L.

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