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Effects of Teneligliptin on HbA1c levels, Continuous Glucose Monitoring-Derived Time in Range and Glycemic Variability in Elderly Patients with T2DM (TEDDY Study)

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Background: To evaluate the effects of teneligliptin on glycosylated hemoglobin (HbA1c) levels, continuous glucose monitoring (CGM)-derived time in range, and glycemic variability in elderly type 2 diabetes mellitus patients.
Methods: This randomized, double-blinded, placebo-controlled study was conducted in eight centers in Korea (clinical trial registration number: NCT03508323). Sixty-five participants aged ≥65 years, who were treatment-naïve or had been treated with stable doses of metformin, were randomized at a 1:1 ratio to receive 20 mg of teneligliptin (n=35) or placebo (n=30) for 12 weeks. The main endpoints were the changes in HbA1c levels from baseline to week 12, CGM metrics-derived time in range, and glycemic variability.
Results: After 12 weeks, a significant reduction (by 0.84%) in HbA1c levels was observed in the teneligliptin group compared to that in the placebo group (by 0.08%), with a between-group least squares mean difference of –0.76% (95% confidence interval [CI], –1.08 to –0.44). The coefficient of variation, standard deviation, and mean amplitude of glycemic excursion significantly decreased in participants treated with teneligliptin as compared to those in the placebo group. Teneligliptin treatment significantly decreased the time spent above 180 or 250 mg/dL, respectively, without increasing the time spent below 70 mg/dL. The mean percentage of time for which glucose levels remained in the 70 to 180 mg/dL time in range (TIR70–180) at week 12 was 82.0%±16.0% in the teneligliptin group, and placebo-adjusted change in TIR70–180 from baseline was 13.3% (95% CI, 6.0 to 20.6).

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Conclusion: Teneligliptin effectively reduced HbA1c levels, time spent above the target range, and glycemic variability, without increasing hypoglycemia in our study population.

Keywords: Aged; Blood glucose self-monitoring; Diabetes mellitus, type 2; Dipeptidyl peptidase 4; Glycated hemoglobin A

INTRODUCTION

Globally, approximately 20% of people aged over 65 years have diabetes [1]. In 2018, the prevalence of diabetes among the Korean population aged over 65 was 27.6% [2]. Given the increased prevalence of diabetes in recent decades and the general increase in life span, the number of older adults with diabetes is expected to further increase [1,3,4]. However, despite the high prevalence of diabetes in elderly individuals, they have often been excluded from randomized controlled trials (RCTs) of antidiabetic treatment [5,6].

The clinical characteristics of type 2 diabetes mellitus (T2DM) in elderly people are distinct from those in younger people. Impaired glucose tolerance is associated with aging, and elderly onset diabetes is characterized by marked defects in β-cell function [7]. Postprandial hyperglycemia is a prominent feature of T2DM in elderly adults [5,7]. Age-related decrease in renal function increases the risk of hypoglycemia caused by certain antidiabetic medications [5]. A lack of awareness of hypoglycemia symptoms leads to severe hypoglycemia in elderly patients [8]. Considering these characteristics, elderly patients with T2DM usually experience greater variability in blood glucose levels at a given glycosylated hemoglobin (HbA1c) level [5,7,8]. Indeed, glycemic variability (GV) has been reported to increase with age [9,10]. Emerging evidence suggests that GV is associated with an increased risk of microvascular and macrovascular complications, hypoglycemia, and mortality [11,12].

Meanwhile, the international consensus recommendations on continuous glucose monitoring (CGM)-based glycemic targets has recently been established and among the proposed core CGM metrics, the time spent in the target glucose range (TIR) has been suggested as a useful clinical target that complements HbA1c levels in patients with diabetes [13]. In particular, the TIR has been reported in several recent studies to be associated with diabetes complications [13-17]. Therefore, in addition to lowering average glucose, increasing TIR may provide additional benefit to elderly patients with diabetes.

Dipeptidyl peptidase 4 (DPP-4) inhibitors predominantly affect postprandial plasma glucose excursion, are at low risk for causing hypoglycemia, and are well tolerated [5]. Based on their safety and efficacy profiles, DPP-4 inhibitors are widely used for the treatment of diabetes in elderly patients [18]. Moreover, a meta-analysis reported that compared to other antidiabetic medications, DPP-4 inhibitors significantly reduced GV [19]. However, to our knowledge, no study has been conducted on the effects of DPP-4 inhibitors using CGM-based glycemic targets in elderly patients.

Teneligliptin is a potent and long-acting DPP-4 inhibitor, with well-recognized clinical efficacy and safety in the management of diabetes [20,21]. The aim of this study was to evaluate the efficacy of teneligliptin in controlling HbA1c levels, GV and time spent in target glucose range, hyperglycemia, and hypoglycemia measured by CGM in elderly patients with T2DM, who were drug-naïve or on metformin alone.

METHODS

Study design and participants

This was a randomized, multicenter, double-blinded, parallel group, placebo-controlled trial, conducted in eight centers in the Republic of Korea between April 3, 2018, and December 2, 2019. Men and women aged 65 years or older with T2DM, who were treatment-naïve or had been treated with stable doses of metformin for at least 8 weeks, were screened for eligibility after obtaining their informed consent in writing. At screening, eligible patients were those with HbA1c levels of 7.0% to 9.0%, fasting plasma glucose (FPG) levels <270 mg/dL, and a body mass index between 20 and 40 kg/m^2. Patients who had taken antidiabetic agents other than metformin or insulin within 12 and 6 weeks, respectively, before screening were excluded. Patients with type 1 diabetes mellitus (T1DM), estimated glomerular filtration rate <30 mL/min/1.73 m^2, and a history of severe heart disease (myocardial infarction, unstable angina pectoris, New York Heart Association class III or IV heart failure, or arrhythmia requiring treatment within 6 months before screening) were excluded from the trial. Use of medications that could affect GV such as corticosteroid or un-

stable treatment of thyroid hormone replacement were also excluded from the trial, however none of the patients received prohibited medication during the study.

The protocol was approved by the Institutional Review Board of each center and registered at ClinicalTrials.gov (NCT-03508323). This study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Randomization and masking

A CGM (iPro2; Medtronic, Northridge, CA, USA) device was provided to each eligible patient for 5 days at baseline. Participants who were on metformin before screening were instructed to continue taking it while wearing the CGM device. Participants were instructed to measure their glucose levels using a glucose meter (Barozen H; i-SENS Inc., Seoul, Korea) at least three times a day and input the values into the CGM device for calibration. The collected CGM data were considered adequate for evaluation if the device had been calibrated three or more times per day for at least 3 days of the 5-day monitoring period. All participants who had adequate baseline CGM data were randomly assigned by the investigators at a 1:1 ratio to receive either teneligliptin 20 mg or a matching placebo tablet once daily for 12 weeks. Randomization was performed according to the random sequence generated by the Interactive Web Response System (cubeIWRS; CRScube Inc., Seoul, Korea). Randomization was stratified by the previous use of metformin (metformin and drug-naïve) at screening, baseline HbA1c level (<7.5% and ≥7.5%), and standard deviation (SD) of CGM glucose levels (≤35 and >35 mg/dL). All participants, study investigators, and site staff were blinded to the treatment assignments. The matching placebo tablets were identical in appearance, taste, and smell to the 20 mg teneligliptin tablets.

Procedure

After randomization, patients were administered 20 mg of teneligliptin or the matching placebo tablet once daily for 12 weeks. Patients who had been on metformin before screening were instructed to continue taking it. Dose adjustment of metformin was not allowed during the study period. Participants were requested to monitor their blood glucose levels using a glucose meter and instructed to record these results and hypoglycemic symptoms, if any during the 12-week study period in a diary. Adherence to the study treatment was assessed by reviewing the returned and unused study drugs, and used medications at week 12.

At screening, participants were surveyed for demographic information and medical histories. Vital signs, anthropometric measurements, and blood samples for laboratory tests were collected at screening and week 12. CGM was performed for 5 days at baseline and at week 12. The participants visited the respective centers 5 days before the day of assessment for week 12 to receive the CGM devices. While wearing the CGM devices, the participants were instructed to record the exact time of study drug administration in their diaries. Height, body weight, and blood pressure were measured using standard methods. Blood samples for laboratory tests were obtained from the participants' antecubital veins after an overnight fast (>12 hours).

CGM metrics were calculated using EasyGV (by NR Hill, University of Oxford, Oxford, UK; available at www.easygv.co.uk). To determine the efficacy of teneligliptin in lowering blood glucose levels, the samples were analyzed at the central laboratory (Seoul Clinical Laboratories, Seoul, Korea) using standard validated methods. HbA1c levels were measured through an immunoturbidimetric assay using the Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland). The National Glycohemoglobin Standardization Program (NGSP)-certified method was used to determine HbA1c levels. FPG was measured using Roche Reagent Packs and an automated chemistry analyzer (Hitachi 7600-010 automatic analyzer; Hitachi Ltd., Tokyo, Japan). Plasma glucose levels were determined using the hexokinase method.

Outcomes

The main endpoints were the change in HbA1c levels and CGM metrics from baseline to week 12. The coefficient of variation (CV), SD, mean blood glucose, mean amplitude of glycemic excursion (MAGE), and time spent in the target glucose range (TIR) were included in the CGM metrics. The range for TIR was defined as 70 to 180 mg/dL (TIR70–180). Time spent above or below the target glucose range was defined as the time above range (TAR) >180 mg/dL (TAR >180) and >250 mg/dL (TAR >250) or time below range (TBR) <70 mg/dL (TBR <70) and <54 mg/dL (TBR <54); these represented the duration of hyperglycemic and hypoglycemic status, respectively. Other efficacy endpoints were the proportion of subjects who had HbA1c levels <7.0% or <6.5% at week 12, and the change in FPG levels during the 12 weeks of treatment.

Safety was assessed by monitoring adverse events (AEs), hypoglycemic events, laboratory tests, vital signs (heart rate,

blood pressure, and body temperature), and 12-lead electrocardiogram. Hypoglycemic events were identified through reported hypoglycemic symptoms and blood glucose levels of <70 mg/dL (plasma glucose measurement or finger-prick blood glucose measurement). Additionally, CGM data were evaluated separately to identify the occurrence of hypoglycemia, especially nocturnal hypoglycemia. Severe hypoglycemia was defined as an event that required immediate assistance from another individual.

Statistical analysis

The sample size required to demonstrate the superiority of teneligliptin (20 mg) over placebo was determined by assuming a mean difference of 0.49% in HbA1c levels between baseline and week 12. For calculations, we used a common SD of 0.6% and a two-sided significance level of 0.05. Assuming a 20% drop-out rate between randomization and week 12, 32 participants per treatment group (total 64) were required to provide at least 80% statistical power for comparison between the treatment groups.

Efficacy outcomes were compared in the full analysis set, consisting of participants who received at least one dose of the trial medication and for whom efficacy endpoints were measured 12 weeks after randomization. Safety analyses were performed using the data of all randomly assigned patients who took at least one dose of the trial medication. Differences in baseline characteristics between the treatment groups were analyzed using a two-sample *t*-test, Wilcoxon rank-sum test, and chi-square test. The two-sample *t*-test was used to analyze normally distributed continuous variables, while the Wilcoxon rank-sum test was used to analyze non-normally distributed continuous variables. Categorical data were analyzed using the chi-square test. To determine efficacy, an analysis of covariance (ANCOVA) with baseline values and stratification factors (at randomization) as covariates was used to compare the changes in variables from baseline to week 12 between the treatment groups. Intrasubject differences in variables between baseline and week 12 were analyzed using the last observation carried forward imputation method. The changes in variables from baseline to week 12 for each treatment group were expressed as least squares mean (LS mean) with standard error (SE). The LS mean was calculated using the ANCOVA test, with baseline values and stratification factors as covariates. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline demographics and clinical characteristics

Sixty-five of 78 patients screened were randomized, and 63 of the 65 participants completed the study (Fig. 1): 35 and 30 patients were assigned to the teneligliptin and placebo groups, respectively. There were no significant differences in baseline demographics and clinical characteristics between the treatment groups (Table 1). The mean age of participants was 70.4 years, with 50% of them being older than 70 years of age. The median duration of diabetes was 2.9 years, and 31% of the participants were drug-naïve at baseline. The mean HbA1c level was 7.5%, and the mean SD measured by CGM at baseline was 45.1 mg/dL.

Effects of teneligliptin on blood glucose variability

During the 5-day CGM data collection period, adequate data were obtained for 4.6 days (4.7 days in teneligliptin group, 4.6 days in placebo group) at baseline and 4.4 days (4.5 days in teneligliptin group, 4.3 days in placebo group) at week 12, representing 92.8% and 88.0% of the total CGM time, respectively. Participants treated with teneligliptin showed significant improvements in several metrics for GV as compared to those in the placebo group after 12 weeks of treatment (Table 2). The LS mean change in the MAGE, SD and CV between baseline and week 12 was −32.0 mg/dL, −12.7 mg/dL, and −5.1% in the teneligliptin group compared to −4.5 mg/dL, −0.2 mg/dL, and −0.5% in the placebo group, respectively ($P<0.001$, $P<0.001$, and $P=0.001$ vs. placebo, respectively). Teneligliptin reduced the mean blood glucose level by −19.1 mg/dL (95% confidence interval [CI], −29.7 to −8.6; $P=0.001$) compared to placebo.

Subgroup analysis in participants older than 70 years or with HbA1c level of <7.5% were performed for GV parameters (Supplementary Tables 1 and 2). With the treatment of teneligliptin, a significant reduction in MAGE and SD were observed in subjects older than 70 years compared to placebo. Additionally, the change in MAGE, SD and CV appeared significant reduction in subjects with HbA1c below 7.5% compared to those in placebo in teneligliptin group.

Effects of teneligliptin on time spent in the target glucose range

Treatment with teneligliptin resulted in a significant improvement in TIR70–180 (Table 2, Fig. 2). The mean percentage of TIR70–180 at week 12 was 82.0%±16.0% in the teneligliptin

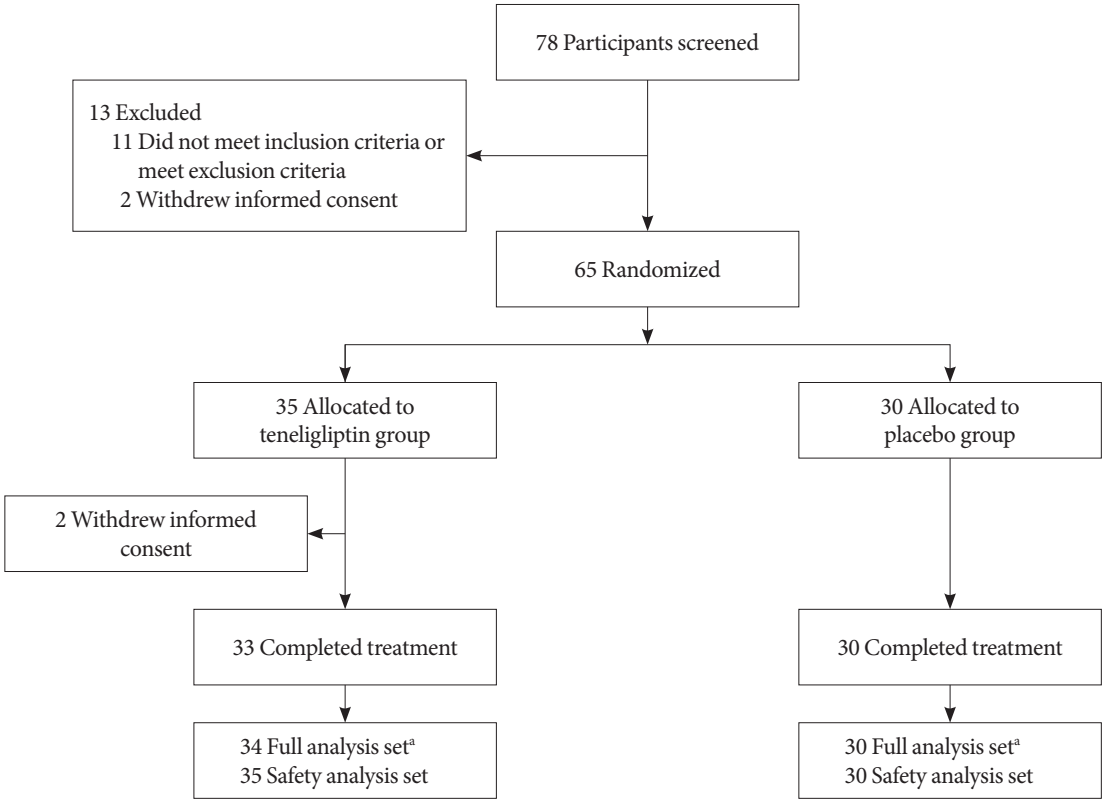

Fig. 1. Trial profile. [a]The full analysis set consisted of all participants who received at least one dose of the trial medication and for whom primary efficacy endpoints were measured at week 12 after randomization.

Table 1. Baseline characteristics of the participants

Full analysis set	Teneligliptin (n=34)	Placebo (n=30)	P value
Age, yr	70.3±4.4	70.5±3.8	0.694[a]
≥70	16 (47.1)	16 (53.3)	0.704[b]
Male sex	23 (67.7)	20 (67.7)	0.934[b]
Body mass index, kg/m^2	25.5±3.5	24.5±2.6	0.181[c]
Duration of diabetes, mo	39.7 (0.2–391.7)	30.6 (0.2–270.9)	0.845[a]
Diagnosed at ≥65 years	23 (67.7)	21 (70.0)	0.839[b]
Drug-naïve	11 (32.3)	9 (30.0)	0.839[b]
HbA1c, %	7.5±0.5	7.5±0.5	0.627[a]
<7.5	21 (61.8)	18 (60.0)	0.885[b]
Fasting glucose, mg/dL	135.9±21.3	143.0±26.5	0.237[c]

Values are presented as mean±standard deviation, number (%), or median (range).
HbA1c, glycosylated hemoglobin.
[a]Wilcoxon rank-sum test, [b]Chi-square test, [c]Two sample t-test.

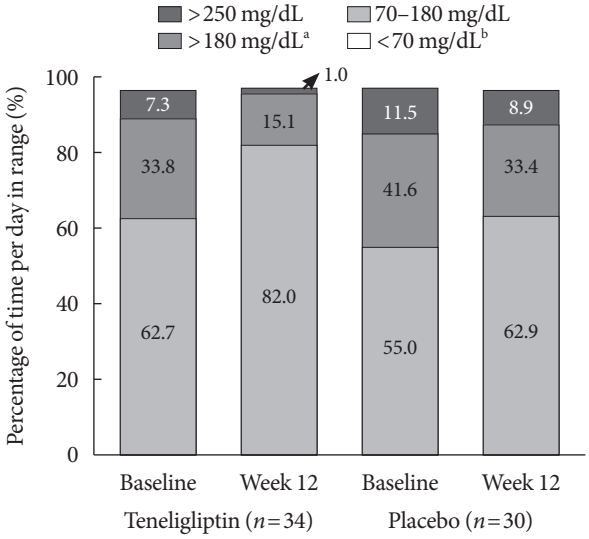

Fig. 2. Percentage of time spent in glycemic ranges of <70, 70–180, >180, and >250 mg/dL among participants monitored with continuous glucose monitoring. Data are presented as mean. [a]Includes percentage of values >250 mg/dL, [b]Includes percentage of values <54 mg/dL. The percentage of values <70 mg/dL was less than 0.3%.

group and 62.9%±23.9% in the placebo group. The placebo-adjusted changes from baseline to week 12 in the percentage of

Table 2. Changes in the CGM variables from baseline to week 12

Parameter	Teneligliptin (n=34)	Placebo (n=30)	Between-group difference (95% CI)	P value
Valid CGM data, day				
Baseline	4.7±0.9	4.6±1.0		0.954[a]
Week 12	4.5±1.1	4.3±1.0		0.707[a]
Mean glucose, mg/dL				
Baseline[a]	169.1±26.6	180.2±34.6		
Change from baseline[b]	–25.9±4.0	–6.8±4.2	–19.1(–29.7 to –8.6)	0.001[c]
CV, %				
Baseline[a]	26.1±6.7	25.9±4.9		
Change from baseline[b]	–5.1±1.1	–0.5±1.2	–4.6 (–7.3 to –1.9)	0.001[c]
SD, mg/dL				
Baseline[a]	44.1±13.1	46.3±10.9		
Change from baseline[b]	–12.7±1.8	–0.2±1.9	–12.5 (–17.6 to –7.4)	<0.001[c]
MAGE, mg/dL				
Baseline[a]	107.3±34.1	111.0±25.8		
Change from baseline[b]	–32.0±4.9	–4.5±5.1	–27.5 (–39.4 to –15.5)	<0.001[c]
TIR70–180 mg/dL, %				
Baseline[a]	62.7±20.9	55.0±22.7		
Change from baseline[b]	19.9±2.8	6.6±2.9	13.3 (6.0 to 20.6)	0.001[c]
TAR>250 mg/dL, %				
Baseline[a]	7.3±8.5	11.5±14.2		
Change from baseline[b]	–6.7±1.5	–1.0±1.5	–5.7 (–9.5 to –1.9)	0.004[c]
TAR>180 mg/dL, %				
Baseline[a]	33.8±20.0	41.6±22.7		
Change from baseline[b]	–19.5±2.6	–7.0±2.7	–12.4 (–19.2 to –5.6)	0.001[c]
TBR<70 mg/dL, %				
Baseline[a]	0.2±0.9	0.2±0.6		
Change from baseline[b]	–0.1±0.2	0.2±0.3	–0.3 (–0.9 to 0.4)	0.383[c]
TBR<54 mg/dL, %				
Baseline[a]	0.1±0.3	0.0±0.1		
Change from baseline[b]	–0.1±0.4	0.2±1.3	–0.3 (–0.8 to 0.2)	0.199[c]

Values are presented as mean±standard deviation or least-squares mean±standard error.
CGM, continuous glucose monitoring; CI, confidence interval; CV, coefficient of variation; SD, standard deviation; MAGE, mean amplitude of glycemic excursion; TIR, time in target glucose range; TAR, time above target glucose range; TBR, time below target glucose range.
[a]Wilcoxon rank-sum test, [b]Least-squares mean±standard error, [c]Analysis of covariance (ANCOVA) with baseline values and stratification factors (at randomization) as covariates.

TIR70-180 was 13.3%±3.6% (95% CI, 6.0 to 20.6; P=0.001) in the teneligliptin group, indicating that glucose levels stayed 3.2 hours more per day in the target range (70 to 180 mg/dL) with teneligliptin than with placebo. After 12 weeks of treatment, the blood glucose levels of participants who received teneligliptin stayed lesser at >180 mg/dL than those of participants who received placebo. The placebo-adjusted difference from baseline to week 12 in the percentage of TAR >180 was –12.4%±3.4% (95% CI, –19.2 to –5.6; P=0.001), which was estimated to be 3.4 hours less per day in the teneligliptin group.

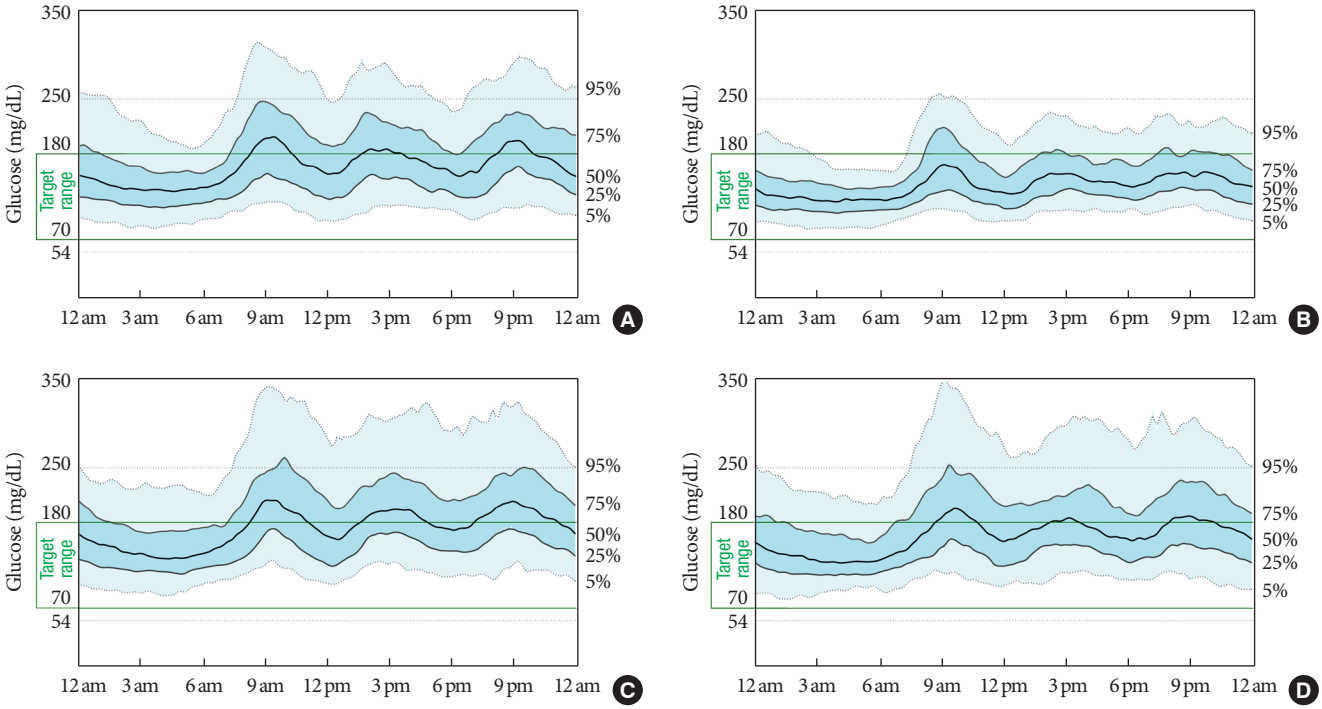

Fig. 3. Ambulatory glucose profiles at baseline and week 12. (A) Teneligliptin group at baseline. (B) Teneligliptin group at week 12. (C) Placebo group at baseline. (D) Placebo group at week 12. Median (50%) and other percentiles are shown for a single day in each treatment group.

Additionally, TAR >250 decreased in the teneligliptin group by –5.7%±1.9% (95% CI, –9.5 to –1.9; P=0.004) compared to that in the placebo group, which was significant. In contrast, there were no significant changes in the percentage of time spent below glucose levels of 70 or 54 mg/dL between the teneligliptin and placebo groups after 12 weeks of treatment. Even after teneligliptin use for 12 weeks, the TBR <70 was very low (0.2%) (Table 2); moreover, most of the patients who reached the target HbA1c level had a low TBR rate (Supplementary Table 3). Additional analysis of TIR, TBR, and TAR was performed in subgroups older than 70 years or with HbA1c level of <7.5%. The subgroups' results were similar to that of all participants (Supplementary Tables 1 and 2).

CGM tracings of the mean 24 hours glucose excursions revealed that the inter-quartile range of individual glucose levels was within the target range of 70 to 180 mg/dL during most time windows in the teneligliptin group, whereas no change was observed in the placebo group after 12 weeks of treatment. Postprandial glucose excursion decreased in the teneligliptin group compared to that in the placebo group (Fig. 3).

Effects of teneligliptin on HbA1c and fasting glucose levels

After 12 weeks of treatment, a significant reduction (by 0.84%) in HbA1c levels from baseline was observed in the teneligliptin group compared to that in the placebo group (by 0.08%), with a between-group LS mean difference of –0.76% (95% CI, –1.08 to –0.44; P<0.001) (Fig. 4A, B). Additionally, the LS mean change in the FPG levels from baseline was significantly greater in the teneligliptin group than in the placebo group (–14.1 mg/dL; 95% CI, –24.5 to –3.7; P=0.009) (Fig. 4C). The proportion of participants who reached HbA1c levels <7% or <6.5% was greater in the teneligliptin group than in the placebo group (P=0.001 and P=0.002, respectively) (Fig. 4D). At week 12, 26 of the 34 participants (76.5%) in the teneligliptin group achieved the HbA1c target of less than 7.0%, as compared to nine out of 30 participants (30.0%) in the placebo group. Similarly, 47.1% of the participants treated with teneligliptin achieved the HbA1c target of <6.5%, whereas only 6.7% of participants in the placebo group reached this level. There was no difference in HbA1c changes irrespective of whether teneligliptin was used as a monotherapy (by 0.87%) or an add-on to metformin (by 0.81%) (Supplementary Table 4).

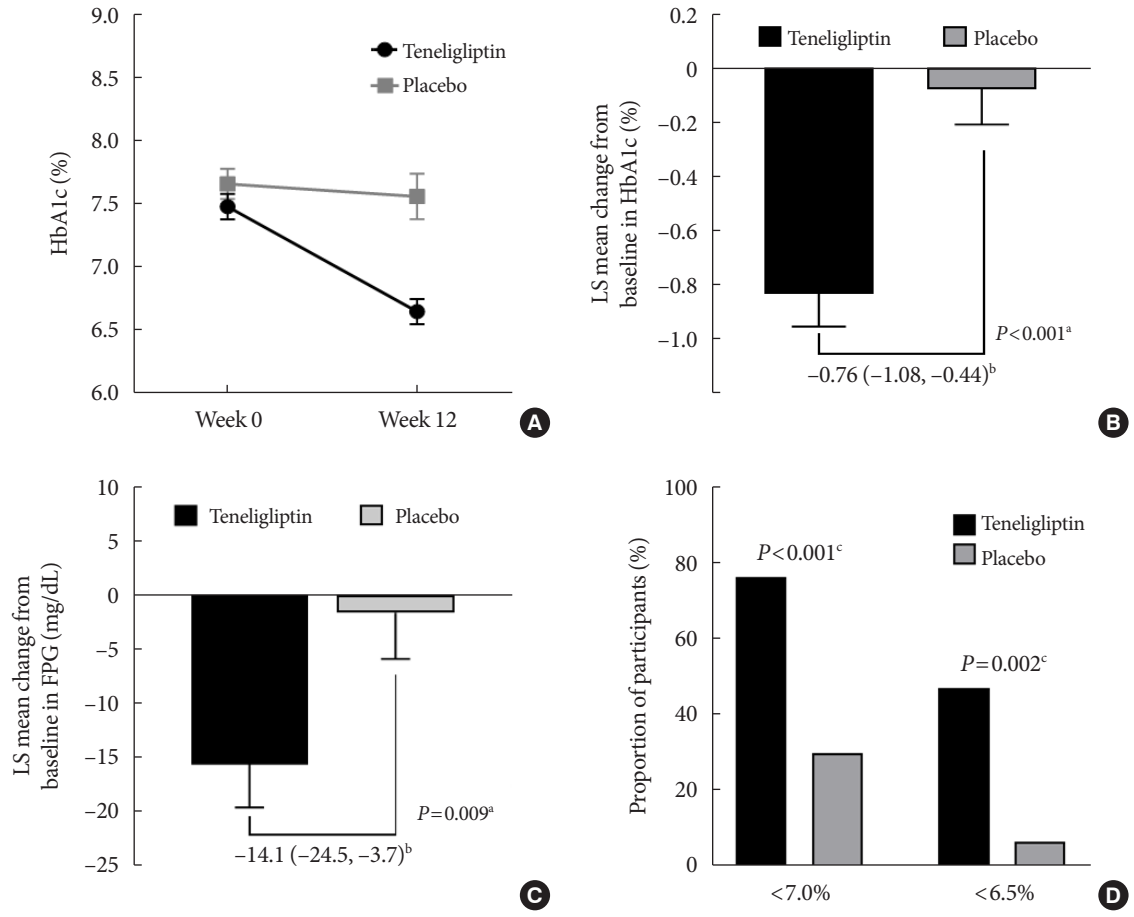

Fig. 4. (A) Glycosylated hemoglobin (HbA1c) level over time (mean±standard error [SE]). (B) Least squares mean (LS mean) change from baseline in the HbA1c level at week 12. (C) LS mean change from baseline in fasting plasma glucose (FPG) at week 12. (D) Proportion of participants achieving the target HbA1c. The error bars show the mean±SE. [a]By analysis of covariance (ANCOVA) with baseline values and stratification factors (at randomization) as covariates, [b]LS mean difference (95% confidence interval), [c]By chi-square test with baseline values and stratification factors (at randomization) as covariates.

Adverse events

During the 12 weeks of treatment, five and 10 treatment-emergent AEs (adverse events) were reported by five patients (14.3%) in the teneligliptin group and seven patients (23.3%) in the placebo group (P=0.349), respectively (Supplementary Table 5). Most AEs were mild in intensity. Hypoglycemia was reported by one participant in each group, and it was mild in severity. No severe hypoglycemic episodes were reported. One serious AE (chronic pancreatitis) was reported in one participant in the teneligliptin group. It was moderate in severity, and the participant fully recovered. This case was not considered to be related to the study treatment; the investigator considered that the patient had chronic pancreatitis as his underlying disease, and the event was caused by the participant's excessive drinking.

DISCUSSION

Diabetes management in elderly patients poses a greater challenge. However, management strategies are often based on evidence collected from studies that were conducted in younger patient populations [5,22]. This is because elderly patients are usually underrepresented in clinical trials; therefore, data on the effectiveness of treatment in this population are insufficient [5,23]. Our Tenelia Elderly Diabetes stuDY (TEDDY) involved patients with diabetes who were aged above 65 years, with 50% of the participants above 70 years of age. We provided evidence of the efficacy and safety of teneligliptin in older patients with T2DM. Treatment with teneligliptin was effective in reducing HbA1c levels in elderly patients, and significantly improved GV

and time spent in the target glucose range as shown by CGM.

In our study, the treatment with teneligliptin has been shown to improve GV. CGM metrics representing GV such as MAGE, CV, and SD [24], decreased in participants treated with teneligliptin compared to the placebo group. Particularly, treatment with teneligliptin significantly decreased TAR >180 and >250 without increasing TBR <70 and <54, thereby resulting in increased TIR70–180. It would have contributed to reducing glycemic excursion by decreasing exposure to postprandial hyperglycemia and increasing exposure to the target blood glucose range.

A comparison of the relationship between TIR70–180 and HbA1c levels, as found in our study, with those found in other studies revealed that teneligliptin considerably improved GV. In a study by Vigersky and McMahon [25] encompassing 18 RCTs and involving over 2,500 individuals with T1DM and T2DM, HbA1c levels of 7.5% and 6.7% strongly corresponded to a TIR70–180 of approximately 60% and 70%, respectively [13]. In our study, an HbA1c level of approximately 7.5% (in both groups at baseline and in the placebo group at week 12) corresponded to a TIR70–180 of approximately 60%, which is consistent with the findings of Vigersky and McMahon [25]. However, after 12 weeks of treatment, HbA1c levels of 6.7% in the teneligliptin group corresponded to a TIR70–180 of 82.0%, which was higher than that observed in the study conducted by Vigersky and McMahon [25]. A study by Beck et al. [26], involving four RCTs that included 545 patients with T1DM, showed a relationship between a change in TIR70–180 and a change in HbA1c levels. These relationships were different based on the baseline HbA1c level. For subjects with a baseline HbA1c level between 7.0% and 7.9%, a decrease in HbA1c level of 1% was associated with a 12.0% increase in TIR70–180. In our study, in subjects with a baseline HbA1c level of 7.5%, HbA1c levels decreased by 0.83% after 12 weeks of treatment with teneligliptin, while the TIR70–180 increased by 19.3% without increasing CGM hypoglycemia. These findings indicate that the blood glucose levels of participants who received teneligliptin stayed longer within the target range at the same HbA1c level, implying that they may have less GV at the same average blood glucose level. The low CV values (21.6%) in the teneligliptin group after treatment further support this inference [27]. GV activates oxidative stress and worsens cellular and vascular damage [28,29]. Teneligliptin demonstrated antioxidative properties and endothelial protective effects in several non-clinical and clinical studies [30,31]. The findings of our study might support these characteristics of teneligliptin.

In this study, 31% of participants were drug-naïve patients with diabetes and the remaining subjects were patients who had been on metformin monotherapy. Most of our participants were elderly onset diabetic patients and the median duration of diabetes was 2.9 years. Thus, the median baseline HbA1c for the participants in our study was 7.4% (range, 7.0% to 8.9%), which was lower than the values in other clinical trials with DPP4 inhibitors [32]. It is noteworthy that glucose variability was greatly improved in those patients with relatively low HbA1c, moreover, similar result was appeared during subgroup analysis with the patients of HbA1c below 7.5 %. In addition to improving GV and TIR70–180, teneligliptin lowered the HbA1c by 0.76% (placebo-subtracted HbA1c) over the 12-week treatment period, with 76% and 47% of patients attaining HbA1c levels <7% and <6.5%, respectively, without increasing CGM derived hypoglycemia. Based on the meta-analysis, DPP4 inhibitor as a class reduced HbA1c by approximately 0.5% to 0.7% [33]. The observed efficacy of teneligliptin in our study was as much as those observed in middle-aged patients treated with other DPP4 inhibitors [32,34]. A higher baseline HbA1c is suggested as a predictor of a greater HbA1c reduction with a DPP-4 inhibitor [35]. If the participants had a higher baseline HbA1c level, the effect of teneligliptin on HbA1c reduction would have been greater than that observed in our study.

In 2019, the international consensus recommendations on CGM-based glycemic targets were established to provide guidance for clinicians, researchers, and diabetic patients using CGM data in clinical care and research [13]. In this report, TIR, TBR, and TAR were presented as key CGM measurements and glycemic targets, with the following recommended values for adults with T1DM and T2DM: >70% of TIR70–180, <4% of TBR <70, <1% of TBR <54, <25% of TAR >180, and <5% of TAR >250. In our study, all three metrics measured at week 12 in patients treated with teneligliptin met these targets. Particularly, hypoglycemic exposure was very low, with 0.2% of TBR <70, which satisfies the stricter goal that is set for older or high-risk individuals (<1% of TBR <70) [13].

There were a few limitations to this study. First, the sample size of this study was primarily calculated to detect an estimated difference in HbA1c levels but not in CGM metrics. Nevertheless, the efficacy results from the CGM analysis are reliable because the sample size meets the minimum number of participants required to provide meaningful results on CGM metrics, as compared to the sample size of other studies with DPP-

4 inhibitors [19,36,37]. For an accurate and meaningful interpretation of CGM, it is important to ensure that adequate glucose data are available for evaluation. In our study, the data used for analysis covered 88% of the data obtained for 5 days when the CGM device was worn, which was lower than the set criteria of 70% data that should be obtained for 14 days as recommended by the international consensus group on clinical care [13]. Nevertheless, the CGM data collection periods in our study were more extensive than those in previous studies on antidiabetic drugs, as CGM was conducted continuously between 24 and 72 hours [19,36,37].

In summary, teneligliptin (20 mg/day) effectively improved not only HbA1c levels but also GV and TIR without increasing TBR in elderly patients with T2DM. There were no significant differences in AEs and hypoglycemic episodes between the teneligliptin and placebo groups. The results of this TEDDY study suggest that treatment with teneligliptin is effective and safe in improving HbA1c levels, TIR, and GV; thus, it could be a good therapeutic choice for elderly patients with T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0016.

CONFLICTS OF INTEREST

Bok Jin Hyun and Ji Eun Cha are employees of Handok Inc. The other authors declare that they have no competing interests.

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Supplementary Table 1. Changes in the continuous glucose monitoring variables from baseline to week 12 in patients aged ≥70 years

Parameter	Teneligliptin (n=16)	Placebo (n=16)	Between-group difference (95% CI)	P value[c]
Mean glucose, mg/dL				
Baseline[a]	175.1±21.6	179.1±28.2		
Change from baseline[b]	−30.0±5.2	−9.2±4.4	−20.9 (−33.6 to −8.2)	0.002
CV, %				
Baseline[a]	27.3±8.1	25.7±5.1		
Change from baseline[b]	−3.2±1.6	−1.3±1.4	−1.8 (−5.6 to 2.0)	0.332
SD, mg/dL				
Baseline[a]	47.2±13.7	45.9±11.0		
Change from baseline[b]	−13.3±2.5	−4.8±2.4	−8.4 (−15.3 to −1.6)	0.018
MAGE, mg/dL				
Baseline[a]	114.6±35.7	111.7±27.6		
Change from baseline[b]	−29.2±7.3	−10.7±6.3	−18.5 (−35.6 to −1.4)	0.035
TIR70–180 mg/dL, %				
Baseline[a]	57.4±17.9	54.9±22.5		
Change from baseline[b]	23.7±4.1	9.2±3.5	14.6 (4.7 to 24.4)	0.005
TAR>250 mg/dL, %				
Baseline[a]	8.4±7.3	10.2±10.3		
Change from baseline[b]	−7.8±1.6	−2.9±1.3	−4.9 (−8.6 to −1.1)	0.013
TAR>180 mg/dL, %				
Baseline[a]	38.9±17.6	41.8±22.1		
Change from baseline[b]	−23.9±3.6	−9.6±3.1	−14.4 (−23.3 to −5.5)	0.003
TBR<70 mg/dL, %				
Baseline[a]	0.3±1.1	0.3±0.8		
Change from baseline[b]	−0.3±0.5	0.3±0.4	−0.6 (−1.7 to 0.6)	0.305
TBR<54 mg/dL, %				
Baseline[a]	0.1±0.1	0.1±0.1		
Change from baseline[b]	−0.1±0.4	0.5±0.3	−0.6 (−1.6 to 0.3)	0.165

Values are presented as mean±standard deviation or least squares mean±standard error.
CI, confidence interval; CV, coefficient of variation; SD, standard deviation; MAGE, mean amplitude of glycemic excursion; TIR, time in target glucose range; TAR, time above target glucose range; TBR, time below target glucose range.
[a]Wilcoxon rank-sum test, [b]Least squares mean±standard error, [c]Analysis of covariance (ANCOVA) with baseline values and stratification factors (at randomization) as covariates.

Supplementary Table 2. Changes in the continuous glucose monitoring variables from baseline to week 12 in patients with glycosylated hemoglobin <7.5%

Parameter	Teneligliptin (n=21)	Placebo (n=18)	Between-group difference (95% CI)	P value[c]
Mean glucose, mg/dL				
Baseline[a]	160.2±19.7	167.0±18.9		
Change from baseline[b]	−21.5±5.1	−2.7±5.4	−18.9 (−33.2 to −4.6)	0.011
CV, %				
Baseline[a]	26.9±6.7	26.3±5.1		
Change from baseline[b]	−5.5±1.3	−0.9±1.4	−4.7 (−8.1 to −1.2)	0.009
SD, mg/dL				
Baseline[a]	43.1±11.9	43.8±9.0		
Change from baseline[b]	−12.7±2.5	−0.6±2.7	−12.1 (−19.3 to −4.9)	0.002
MAGE, mg/dL				
Baseline[a]	107.7±31.1	108.8±25.5		
Change from baseline[b]	−34.2±6.5	−7.4±7.1	−26.8 (−44.1 to −9.6)	0.003
TIR70–180 mg/dL, %				
Baseline[a]	69.6±15.4	64.1±16.0		
Change from baseline[b]	18.4±3.5	5.3±3.7	13.1 (3.3 to 22.9)	0.010
TAR>250 mg/dL, %				
Baseline[a]	5.0±5.2	6.0±4.6		
Change from baseline[b]	−4.4±1.9	1.5±2.0	−5.9 (−11.1 to −0.6)	0.031
TAR>180 mg/dL, %				
Baseline[a]	26.8±14.2	32.9±15.4		
Change from baseline[b]	−16.6±3.3	−5.4±3.4	−11.2 (−20.3 to −2.1)	0.018
TBR<70 mg/dL, %				
Baseline[a]	0.4±1.1	0.1±0.3		
Change from baseline[b]	−0.1±0.2	−0.1±0.2	−0.0 (−0.7 to 0.6)	0.870
TBR<54 mg/dL, %				
Baseline[a]	0.1±0.4	0.0±0.1		
Change from baseline[b]	−0.1±0.1	0.0±0.1	−0.1 (−0.5 to 0.2)	0.373

Values are presented as mean±standard deviation or least squares mean±standard error.
CI, confidence interval; CV, coefficient of variation; SD, standard deviation; MAGE, mean amplitude of glycemic excursion; TIR, time in target glucose range; TAR, time above target glucose range; TBR, time below target glucose range.
[a]Wilcoxon rank-sum test, [b]Least squares mean±standard error, [c]Analysis of covariance (ANCOVA) with baseline values and stratification factors (at randomization) as covariates.

Supplementary Table 3. Hypoglycemia detected by continuous glucose monitoring in patients achieving predefined level of HbA1c at week 12

Variable	Teneligliptin (n=34)	Placebo (n=30)	P value
HbA1c <7% and TBR <1%	24 (75.00)	8 (26.67)	<0.001
HbA1c <6.5% and TBR <1%	15 (46.88)	2 (6.67)	0.001

Values are presented as number (%).
HbA1c, glycosylated hemoglobin; TBR, time below target glucose range.

Supplementary Table 4. Changes in efficacy variables by treatment subgroup at week 12

Variable	Teneligliptin		Placebo	
	Teneligliptin (*n*=11)	Teneligliptin+metformin (*n*=23)	Placebo (*n*=9)	Placebo+metformin (*n*=21)
HbA1c, %				
Baseline	7.66±0.74	7.42±0.53	7.92±0.72	7.56±0.62
Change at week 12[a]	–0.87±0.19	–0.81±0.15	–0.05±0.22	–0.08±0.15
FPG, mg/dL				
Baseline	144.3±18.8	131.8±21.7	145.7±22.5	141.9±28.5
Change at week 12[a]	–18.9±6.3	–13.7±4.9	1.5±7.1	–2.5±4.9

Values are presented as mean±standard deviation or least-squares mean±standard error.
HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose.
[a]Least-squares mean±standard error.

Supplementary Table 5. Summary of adverse events

	Teneligliptin (n=35)	Placebo (n=30)
Number of participants with TEAE	5 (14.3)	7 (23.3)
Serious AEs	1 (2.9)	0
Discontinuations because of AEs	0	0
Reported AEs		
Hypoglycemia	1 (2.9)	2 (6.7)
Blood creatinine increased	0	1 (2.9)
Blood urea increased	0	1 (2.9)
Electrocardiogram QT prolonged	1 (2.9)	0
Constipation	1 (2.9)	0
Pancreatitis chronic	1 (2.9)	0
Conjunctivitis	1 (2.9)	0
Cystitis	0	1 (2.9)
Blister	0	1 (2.9)
Pruritus	0	1 (2.9)
Cataract	0	1 (2.9)
Glucosuria	0	1 (2.9)
Myalgia	0	1 (2.9)

Values are presented as number (%).
TEAE, treatment-emergent adverse events; AE, adverse event.