Diabetes, Metabolic Syndrome and Obesity

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CLINICAL TRIAL REPORT

Effect of Imeglimin, a Novel Anti-Diabetic Agent, on Insulin Secretion and Glycemic Variability in Type 2 Diabetes Treated with DPP-4 Inhibitor: A 16-Week, Open Label, Pilot Study

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Purpose: Imeglimin is a novel oral antidiabetic agent that improves glucose tolerance. This study aimed to investigate the efficacy of combining imeglimin with dipeptidyl peptidase-4 inhibitor (DPP-4i), the most frequently prescribed first-line treatment for patients with type 2 diabetes (T2D) in Japan, to improve glycemic control.

Patients and Methods: Eleven patients with T2D treated with DPP-4i alone (6.5% ≤ hemoglobin A1C [HbA1c] < 10%) received 1000 mg imeglimin twice daily for 16 weeks. A meal tolerance test (MTT) was conducted on seven of these patients to assess parameters associated with islet function or insulin tolerance, such as homeostasis model assessment (HOMA)-β-cell function (HOMA-β), HOMA-insulin resistance (HOMA-IR), C-peptide immunoreactivity (CPR) index, and glucagon kinetics. Continuous glucose monitoring was conducted to evaluate parameters for glycemic variability.

Results: Sixteen weeks after imeglimin administration, the HbA1c level improved from 7.5%±1.3% to 6.5%±0.5% ($p < 0.05$), the casual blood glucose level significantly improved from 168.2±55.4 to 127.8±20.0 mg/dL ($p=0.027$), time in range increased from 65.0%±0.34% to 90.0%±0.08% ($p < 0.05$), and time above range reduced from 34.0%±0.034% to 9.0%±0.08% ($p < 0.05$). During MTT, we observed significantly reduced area under the curve (AUC)0–180 glucose, increased AUC0-180 CPR/AUC0-180 glucose, CPR index, and HOMA-β ($p<0.05$). HOMA-IR and glucagon kinetics did not change with the addition of imeglimin.

Conclusion: The addition of imeglimin to DPP-4i significantly improved glycemic control and glycemic variability, based on increased glucose-induced insulin secretion, indicating its potential as a therapeutic option for patients with T2D.

Keywords: imeglimin, DPP-4 inhibitor, time in range, glycemic variability, continuous glucose monitoring, meal tolerance test

Introduction

To maintain optimal glycemic conditions, it is crucial to select appropriate antidiabetic agents. In Japan, dipeptidyl peptidase-4 inhibitors (DPP-4i) are the most commonly prescribed first-line treatment for patients with T2D owing to their high efficacy, tolerability, and low incidence of hypoglycemia and weight gain.[1,2] Moreover, the efficacy of DPP-4is in modifying glycemic variability by enhancing insulin secretion has been reported,[1] and DPP-4is also exhibit high performance when combined with other agents.[3] Therefore, DPP-4 inhibitors are anticipated to remain a widely used treatment option for patients with type 2 diabetes in the future. Generally, if the therapeutic goal cannot be achieved, it is recommended to initiate combination therapy with drugs that have different mechanisms of action at an early stage. Furthermore, it has been suggested that diabetes prognosis can be improved by early intervention to address decreased

Received: 28 September 2024
Accepted: 31 December 2024
Published: 9 January 2025

insulin secretion and increased insulin resistance.[3] However, if inadequate glycemic control is observed in patients treated with DPP-4i, no guidelines have been established regarding a second-line option.

Imeglimin is the first drug in a class of tetrahydrotriazine-containing antidiabetic agents called "glimins", and its glucose-lowering mechanism is distinct from that of existing antidiabetic agents.[4] Imeglimin enhances insulin action and protects pancreatic β-cells[5,6] by improving mitochondrial function through an increase in nicotinamide phosphoribosyl transferase gene expression[7] and inhibition of the respiratory chain complex.[8] In clinical settings, clinical trials (phases 1 and 2) have shown favorable safety and tolerability among patients.[4,9] Furthermore, the Trial for Imeglimin Efficacy and Safety (TIMES; Phase 3) showed that imeglimin alone or in combination with other treatments significantly reduced hemoglobin A1c (HbA1c) level.[10–12] Notably, some recent studies have shown that imeglimin may improve the response of β-cells to glucose, increasing insulin secretion in response to glucose, thus improving prandial glucose elevation[13] and time in range (TIR).[14] In addition, considerable improvements in glycemic control have been reported when imeglimin was combined with other drugs;[10] however, to the best of our knowledge, no study has evaluated the efficacy using meal tolerance test (MTT) and continuous glucose monitoring (CGM) limited to combination therapy of DPP-4is and imeglimin. In this clinical trial, we aimed to confirm the effect of imeglimin as an adjunct to DPP-4i on glucose profile using MTT and CGM for the first time.

Materials and Methods

Study Design and Population

As a data sharing statement required for publication, no additional data beyond what is presented in this paper will be shared. This single-center, prospective, nonrandomized, single-arm, open-label trial study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000049203), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors, approved by the Medical Ethics committee of Toho University Omori Medical Center (Approval number: #M22089 August 29, 2022), and conducted in accordance with the tenets of the Declaration of Helsinki and current legal regulations in Japan. Written informed consent was obtained from all eligible participants prior to their enrollment in the study. A total of 323 patients with T2D who visited our section between February 1, 2022, and April 30, 2023, were screened for eligibility. The inclusion criteria were as follows: the presence of T2D, aged 20–80 years, controlled HbA1c level ≥ 6.5% (47 mmol/mol) but < 10% (86 mmol/mol), and a history of DPP-4i monotherapy for >3 months. Exclusion criteria: diagnosis of type 1 diabetes or secondary forms of diabetes, incomplete remission of metabolic disorder, acute coronary syndrome, stroke, or severe infection, presence of comorbidities of renal disorder (eGFR<45 mL/min/1.73 m^2) or hepatic disorder (serum alanine transaminase or aspartate transaminase ≥100 IU/L), hypersensitivity to any of the components of the drugs used in the present study, and exclusion as a result of medical reasons. Eligible patients were prescribed 1000 mg imeglimin twice daily in addition to DPP-4i for 16±2 weeks. The prescription of Imeglimin is prescribed within the Japanese National Health Insurance and is not provided by any specific organization. Medication adherence was verified through interviews conducted during the 6±2 and 16±2 week visits. The initiation date of imeglimin was indicated as the start date of this study. After enrollment, all participants were prohibited from changing the dose of concomitant drugs (antidiabetic, anti-hypertension, and lipid-lowering agents). MTT and CGM were conducted before and 16 weeks after the initiation of imeglimin treatment in addition to DPP-4i. In addition to CGM, participants' height, body weight, and waist circumference were measured. Blood samples were collected on the day of examination. Biochemical parameters were measured at the central laboratory of our hospital, and the HbA1c level was measured using liquid chromatography (TOSHO HLC-723G9; Tosoh, Tokyo, Japan). Tests that could not be conducted in our hospital laboratory were outsourced to an external laboratory, SRL Inc, Tokyo, Japan, where glucagon levels were measured using sandwich ELISA.

Meal Tolerance Test

A standard MTT was performed at baseline and 16 weeks after the initiation of imeglimin administration. The patients visited the hospital at 09:00 am after a 12-h fast. Patients ingested a calorie-controlled meal. The test meals

used were home-delivered medical meals (#NS0B015, Nissin Healthcare Food Service, Tokyo, Japan). The total energy content of the test meal, which contained 65.4 g of carbohydrates, 18.5 g of protein, and 15.5 g of lipids was approximately 460 kcal. All patients consumed the meal within 15 min. Blood samples were collected at 0, 30, 60, 120, and 180 min before and after the consumption of the test meal to measure the following parameters: plasma glucose, glucagon, insulin, and C-peptide immunoreactivity (CPR) concentrations. Patients maintained their regular medication regimen.

Continuous Glucose Monitoring

To evaluate glucose variability, all participants wore the FreeStyle Libre Pro® monitor (Abbott Diabetes Care, Tokyo, Japan) at baseline and 16 weeks after the initiation of imeglimin administration. The participants removed the monitor themselves and sent it to our hospital at the end of the 14-day measurement period. Glucose data were downloaded from the sensor, and the required software was used for analysis (CareLink, Abbott Diabetes Care). Through CGM, we obtained data on daily glucose level, TIR (defined as percentage of glucose between 70 and 180 mg/dL), time in tight range (TITR) (defined as percentage of glucose between 70 and 140 mg/dL), time below range (TBR) (defined as percentage of glucose < 70 mg/dL), and time above range (TAR) (defined as percentage of glucose > 180 mg/dL).[15]

Study Outcomes

The primary outcome of this study was the comparison of HbA1c level at baseline and at the end of study. The secondary outcomes included the comparison of the following parameters at baseline and 16 weeks after the initiation of imeglimin administration: (a) MTT parameters: glucose level, CPR, and their area under the curve (AUC); (b) CGM parameters: TIR, TTIR, TBR, and TAR.

Statistical Analysis

To our knowledge, only a few studies have evaluated the magnitude of improvement in HbA1c level with imeglimin and DPP-4i administration. To address this concern, the sample size calculation in this study was based on the magnitude of improvement in HbA1c level in the previous study.[9] In the previous study, the magnitude of improvement in HbA1c level with the addition of imeglimin from baseline (DPP-4i alone) was −0.92% and the standard deviation was 0.11%. The required sample size for this study was determined to be seven participants. This number was calculated to achieve a 5% significance level and 80% statistical power. Therefore, we planned to enroll 15 participants after accounting for potential dropouts. The 15 participants were enrolled from October 13, 2022 to March 17, 2023. The AUC was calculated using the trapezoidal method. To adjust for hyperglycemia-induced insulin secretion, insulin secretion relative to increased glucose level was mainly used in a previous study;[4] however, in the present study, we could not obtain data on insulin concentration in some patients due to hemolysis, except for the data at 0 min. Therefore, we used CPR relative to increased glucose level, indicated as AUC0-180 CPR/AUC0-180 glucose. Data analysis was conducted using Statcel (OMS, Saitama, Japan). Values at baseline and 16 weeks after the initiation of imeglimin administration were compared using a paired *t*-test or Wilcoxon signed-rank test. All data are presented as mean ± standard deviation. Statistical significance was set at $p < 0.05$.

Results

Patients' Characteristics

Fifteen participants were enrolled in this study. Of these, two changed their mind and withdrew consent, and two withdrew from the study due to adverse events. Adverse events were observed in few patients; however, subjects generally showed good adherence with the treatment. Data from 4 of 11 patients who underwent MTT were unavailable because blood glucose values were missing due to an error. Finally, 11 participants completed the study, and 7 underwent MTT (Figure 1). Table 1 and Table 2 present the participants' baseline clinical characteristics.

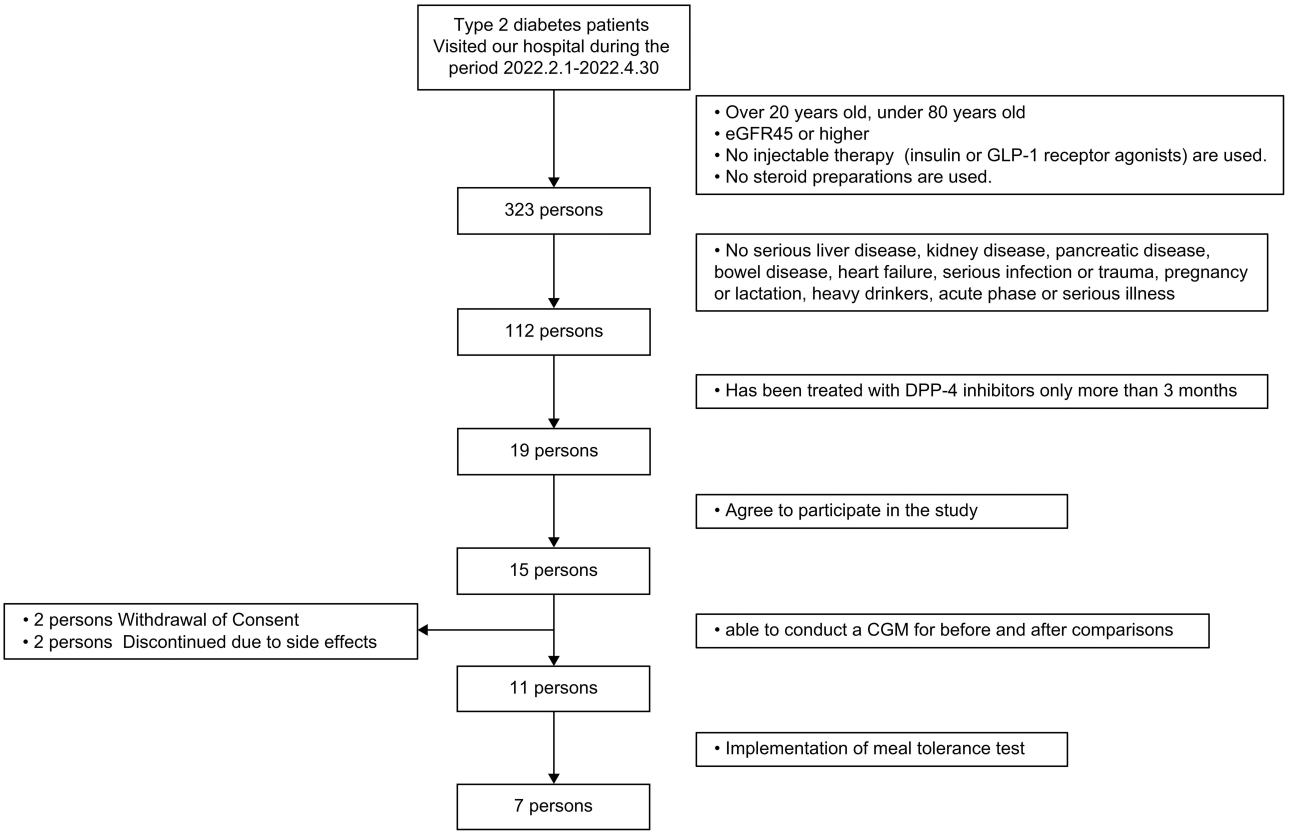

Figure 1 Flowchart of participant selection.

Glycemic Control, Anthropometric Data, and Other Parameters

After 16 weeks of treatment with imeglimin combined with DPP-4i, the HbA1c level significantly improved by −1.0% from 7.5%±1.3% to 6.5%±0.5% (p=0.032). In addition, the casual blood glucose level significantly improved from 168.2 ±55.4 to 127.8±20.0 mg/dL (p=0.027). Renal function and hepatic enzymes remained unaffected by imeglimin. Furthermore, body weight and body mass index (BMI) significantly decreased after 16 weeks of treatment with imeglimin combined with DPP-4i when compared with baseline values (Table 2).

Glycemic Variability

The duration of CGM was 14.3±1.5 and 14.2±1.6 days at baseline and at the end of the 16-week treatment with imeglimin combined with DPP-4i, respectively. As shown in Table 3 and Figure 2, the addition of imeglimin significantly improved the mean glucose level from 166.6±56.0 to 126.4±16.2 mg/dL (p=0.03) and the glucose management indicator

Table 1 Baseline for Subjects in This Study

n=11	
Male/Female	7/4
Age(years)	70±3.67
Estimated disease duration(year)	7.0±1.65
DPP-4 inhibitor (Linagliptin/Sitagliptin/Vildagliptin/Omarigliptin)	(4/3/2/2)
Diabetic retinopathy (±)	(0/11)
Diabetic nephropathy (Stage 1/2/3/4/5)	(9/0/2/0/0)
Diabetic neuropathy (±)	(4/0)

Note: Data are presented as mean ± SD.

Table 2 Clinical Course of Weight, BMI, Blood Pressure, Blood and Urine Samples

	Base Line	6W		16W	
n=11			p value		p value
Body weight (kg)	71.3±22.9	70.5±22.6	0.06	69.5±21.2	0.025*
BMI	25.8±5.9	25.5±5.8	0.049*	25.2±5.3	0.021*
SBP (mmHg)	128.6±10.7	123.5±9.8	0.16	125.5±9.0	0.319
DBP (mmHg)	74.3±5.7	70.7±6.8	0.186	72.0±6.6	0.365
HbA1c (%)	7.5±1.3	7.0±0.7	0.026*	6.5±0.5	0.032*
Casual blood glucose (mg/dL)	168.2±55.4	129.8±21.0	0.044*	127.8±20.0	0.027*
TG (mg/dL)	142.5±113.2	133.3±105.6	0.546	124.6±95.6	0.319
LDL (mg/dL)	107.9±25.5	105.1±19.8	0.477	108.8±27.9	0.835
Cr (mg/dL)	0.9±0.1	0.8±0.1	0.625	0.9±0.1	0.856
eGFR (mL/min/1.73□)	64.7±14.1	64.7±9.7	0.988	63.1±9.6	0.518
Alb (g/dL)	4.3±0.2	4.3±0.2	0.553	4.3±0.1	0.8
T-bil (mg/dL)	0.8±0.3	0.7±0.3	0.521	0.7±0.3	0.518
UA (mg/dL)	5.1±1.0	5.4±1.0	0.221	5.6±1.1	0.098
AST (U/L)	22.6±7.6	23.3±7.5	0.761	24.0±8.8	0.612
ALT (U/L)	23.0±8.9	27.2±16.7	0.339	27.5±15.8	0.27
γ-GTP (U/L)	73.3±132.4	81.2±132.8	0.453	67.3±93.6	0.72
Urinary albumin excretion index (mg/g·Cr)	129.6±218.6	118.7±205.9	0.735	81.4±145.5	0.073

Notes: Data are presented as mean ± SD. p-values indicate differences from baseline values. *p<0.05 for differences from baseline.

Table 3 Comparison of CGM Parameters Before and After Imeglimin Initiation

	Before	After	p-value
TAR (%)	34±0.342	9±0.082	0.021*
TIR (%)	65±0.339	90±0.081	0.02*
TBR (%)	0±0.006	1±0.008	0.038*
TITR (%)	46±0.310	71±0.177	0.006*
CV (%)	25±0.034	26±0.027	0.41
Mean glucose level (mg/dL)	166.6±56.1	126.4±16.2	0.03*
Glucose management indicator (%)	7.3±0.013	6.3±0.004	0.024*

Notes: Data are presented as mean ± SD. p-values indicate differences from baseline values. *p<0.05 for differences from baseline.
Abbreviations: TBR, Time below range; TIR, Time in range; TAR, Time above range; TITR, Time in tight range.

from 7.3%±0.013% to 6.3%±0.004% (p=0.024). Similarly, the addition of imeglimin significantly increased the TIR and TTIR from 65%±0.34% to 90%±0.08% (p=0.02) and 46%±0.31% to 71%±0.18% (p=0.006), respectively, whereas it significantly decreased TAR from 34% ± 0.34% to 9% ± 0.08% (p=0.021). TBR increased by 1% after adding imeglimin; however, no participant exhibited symptoms of hypoglycemia. Figure 3 shows a curve of the mean blood glucose level trend recorded through CGM over a 24-h period for the 11 participants. After the addition of imeglimin, the overall curve shifted downward, and the amplitude of SD was modified.

Meal Tolerance Test

Table 4 presents the MTT results. The addition of imeglimin to DPP-4i significantly reduced the glucose level at each point during the test (Figure 4) and the AUC0-180 glucose. No significant difference in CPR was observed across the time points; however, the ratio of CPR to glucose, represented as AUC0-180 CPR/AUC0-180 glucose, showed a significant increase. Furthermore, the CPR index and homeostasis model assessment of β-cell function (HOMA-β) level, which are indices of insulin secretion, also significantly increased. Conversely, no changes were observed in

https://doi.org/10.2147/DMSO.S495930

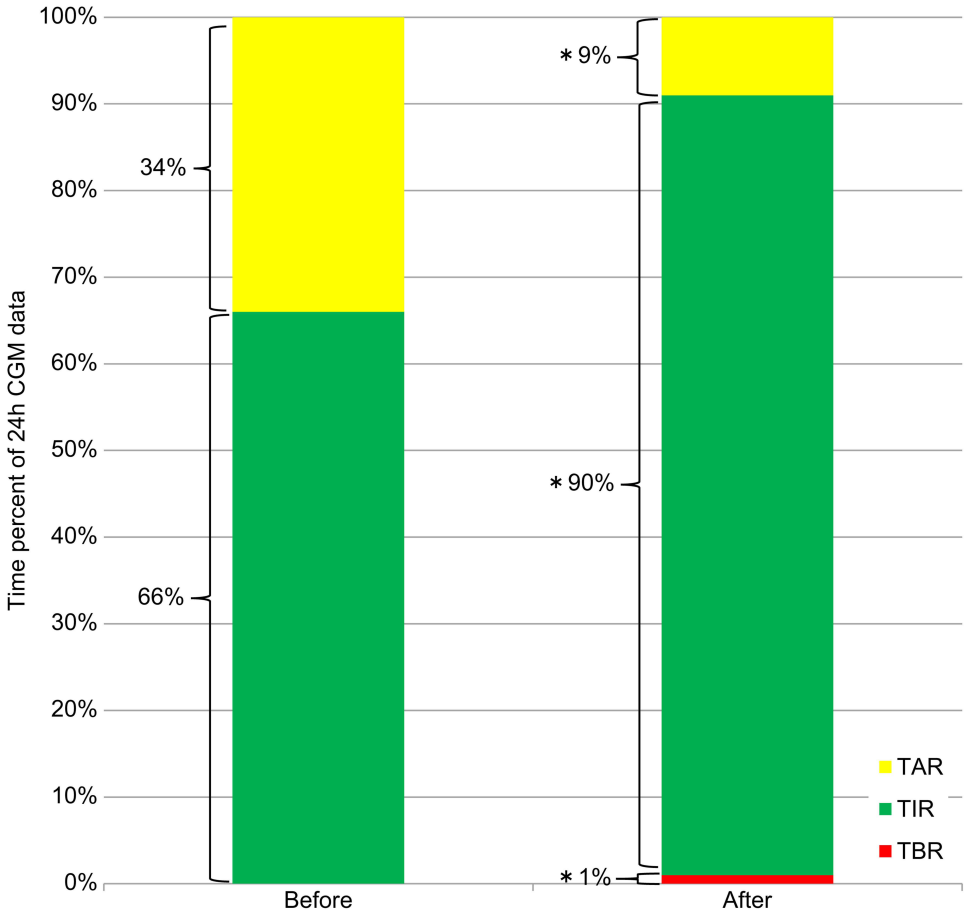

Figure 2 Changes in indices derived from CGM before and after adding imeglimin. The colored bars indicate the average number of hours spent per day: <70 mg/dL (time below range; TBR: red), 70–180 mg/dL (time in range; TIR: green), and >180 mg/dL (time above range; TAR: yellow). *p<0.05 for differences from baseline.

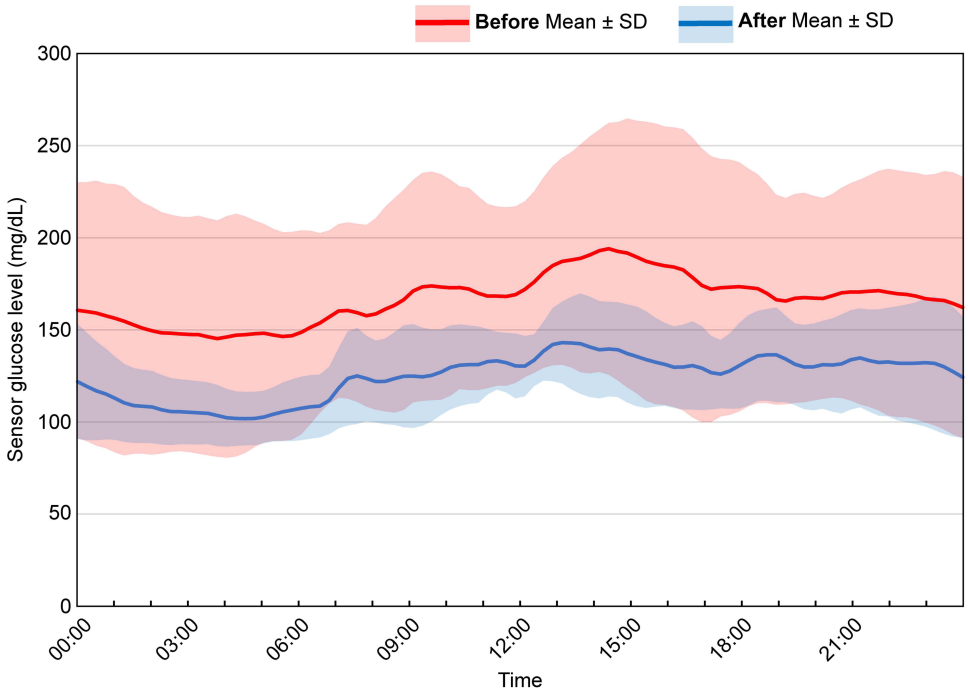

Figure 3 Curves for the comparison of mean blood glucose level trends recorded through CGM before and after adding imeglimin. The curves were based on changes in blood glucose levels over a 24-h period in 11 participants. The red and blue lines indicate the curves of mean glucose ± SD before and after adding imeglimin, respectively.

Table 4 Meal Tolerance Test (n=7) Results Before and 16 weeks After Imeglimin Initiation

		Before	After	p-value
Glucose (mg/dL)	0 min	152.3±68.0	117.5±14.1	0.028*
	30 min	198.3±64.8	153.0±15.6	0.018*
	60 min	232.9±54.9	191.0±16.8	0.018*
	120 min	231.1±58.9	184.5±38.9	0.028*
	180 min	209.9±67.5	147.5±28.2	0.018*
CPR (ng/mL)	0 min	2.14±1.27	2.08±1.27	0.81
	30 min	3.14±1.67	3.05±1.32	0.678
	60 min	4.01±1.92	4.42±2.12	0.081
	120 min	5.47±2.37	6.39±2.21	0.205
	180 min	6.05±2.55	5.98±1.97	0.926
Glucagon (pg/mL)	0 min	44.7±29.4	54.9±26.1	0.128
	30 min	78.5±45.0	66.7±25.4	0.398
	60 min	65.3±59.3	55.9±32.8	0.735
	120 min	45.5±39.3	34.5±18.8	0.237
	180 min	39.4±21.3	47.4±32.2	0.612
IRI (μU/mL)	0 min	7.45±6.28	10.51±9.29	0.398
$AUC_{0\text{-}180}$Glucose		38875.7±1049.6	29,434.3 ±3549.8	0.018*
$AUC_{0\text{-}180}$CPR		816.43±328.61	884.19±305.01	0.237
$AUC_{0\text{-}180}$Glucagon		9873.4±7256.0	8827.1±4285.2	0.398
$AUC_{0\text{-}180}$CPR/$AUC_{0\text{-}180}$Glucose		0.088±0.053	0.094±0.041	0.018*
CPR index		1.48±0.92	1.69±1.00	0.017*
HOMA-β		34.0±26.8	72.4±58.8	0.045*
HOMA-IR		3.57±5.27	3.10±3.20	0.5

Notes: Data are presented as mean ± SD. p-values indicate differences in the results between before and after adding imeglimin, as evaluated using Wilcoxon signed-rank test. CPR, C-peptide; CPR index is calculated as C-peptide/Glucose×100; HOMA-β is calculated as IRI×360/(Glucose-63); HOMA-IR is calculated as Glucose×IRI/405. *p<0.05 for differences from baseline.

glucagon and homeostasis model assessment of insulin resistance (HOMA-IR) levels, which are indices of insulin sensitivity.

Adverse Events

Adverse events were observed in 9 of the 13 participants who received at least a dose of imeglimin. These events were mainly gastrointestinal disorders, including abdominal discomfort (n=6), loss of appetite (n=2), constipation (n=2), nausea (n=1), and diarrhea (n=1). These symptoms improved spontaneously in seven patients, who then continued imeglimin treatment. However, one participant with severe nausea and another with a transient loss-of-consciousness seizure had to discontinue the study, although the causal relationship was unclear.

Discussion

In the present prospective clinical trial, we evaluated, for the first time, the effect of imeglimin as an adjunct to DPP-4i on glycemic control and variability in Japanese patients with T2D using CGM and MTT and found that the HbA1c level decreased significantly 16 weeks after the initiation of imeglimin administration. Furthermore, CGM revealed that the TIR and TITR significantly increased, whereas TAR significantly decreased. We also observed improvements in glucose tolerance during MTT.

Regarding the HbA1c-lowering effect of imeglimin in Japanese patients, a Phase 2 trial has shown a significant reduction of −0.51% in HbA1c level after 24 weeks of administering 1000 mg imeglimin alone twice daily.[11] Furthermore, the phase 3 trial of TIMES 2 showed a reduction of −0.46% in HbA1c level after 52 weeks of administering imeglimin alone.[9] In the present study, a significant reduction of −1.0% in HbA1c level was observed after 16 weeks of administering imeglimin in combination with DPP-4i. Patients in the present trial exhibited a greater reduction in HbA1c

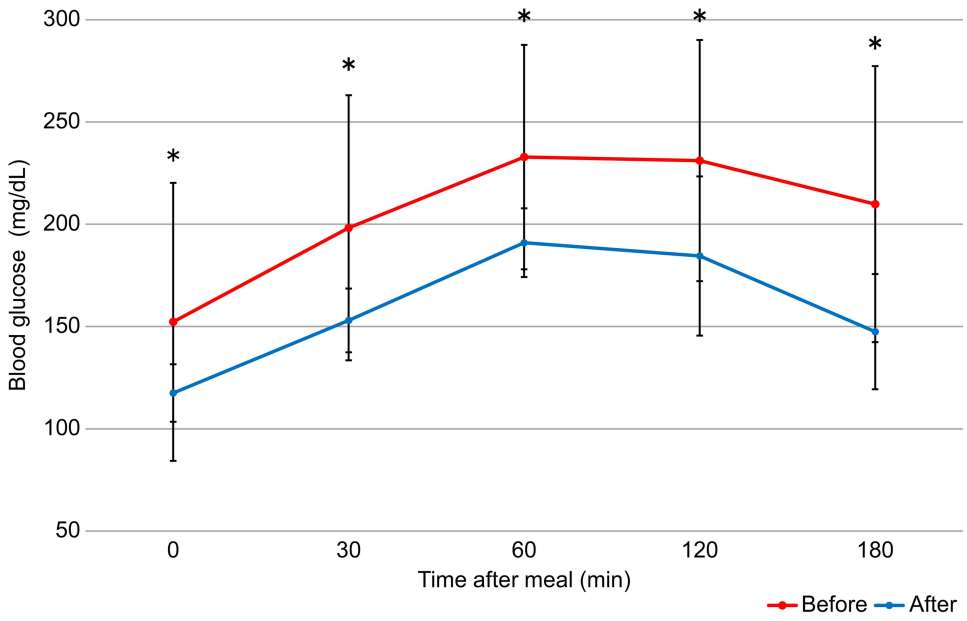

Figure 4 Glucose levels during the meal tolerance test. The red and blue lines indicate the glucose level before and after adding imeglimin, respectively. *p<0.05 for differences from baseline.

level regardless of the shorter treatment period than those in previous trials. This finding is consistent with that of previous studies on imeglimin combination therapy. In a phase 2 study on Caucasians, the HbA1c level decreased by −0.72% after 12 weeks of administering imeglimin in combination with sitagliptin.[16] Furthermore, TIMES 2, which compared the efficacy of imeglimin in combination with different antidiabetic agents, showed the greatest reduction in HbA1c level (−0.92%) with imeglimin combined with DPP-4i.[9] These findings highlight the high efficacy of imeglimin combined with DPP-4i. Recent studies have shown that imeglimin increases glucagon-like peptide 1 (GLP-1) concentration, and the good compatibility of both agents might be due to the synergistic action on the circulating concentration of insulin and GLP-1 through different mechanisms.[17] Furthermore, in the present study, the TIR and TAR significantly improved by 25% and −25%, respectively. Oda et al reported that the addition of imeglimin significantly increased the TIR and reduced the TAR in Japanese patients with T2D receiving heterogeneous treatment.[14] Regarding the modification effects of imeglimin on glycemic profile, the results of the present study are consistent with those of Oda et al.

Conversely, the improvement rate of TIR and TAR in our patients was 25%, which is significantly better than that reported by Oda et al, whose study involved patients with heterogeneous background treatments, such as insulin and polypharmacy.[14] In contrast, our study was limited to cases treated with the combination of DPP-4i and imeglimin, which may have contributed to the differences in the results. These contrasting results may support the concept that the glucose-lowering effects of imeglimin amplified synergically to achieve greater efficacy when combined with other agents.[9]

TIR has recently been reported to be strongly associated with cardiovascular diseases or diabetic complications.[18,19] Similarly, this study revealed a significant increase in TITR, indicating that their hyperglycemia was controlled in the strict range of <140 mg/dL. Postprandial blood glucose level has been suggested as a risk factor for mortality, independent of fasting blood glucose level.[20] The significant increase in TIR and TITR, along with the decrease in TAR, observed with combination therapy using imeglimin and DPP-4 inhibitors, suggests that this therapeutic approach may improve the prognosis for participants in this study. However, in the present study, TBR increased by 1% after adding imeglimin. In general, Freestyle Libre Pro has been reported to produce lower glucose values when compared to the actual measured values, with this discrepancy being more pronounced during periods of low blood glucose, such as late at night or early in the morning.[15] In this study, most of the blood glucose levels below 70 mg/dL recorded on the CGM occurred late at night, and it is possible that these lower values were mistakenly recorded as hypoglycemic when clinical hypoglycemia was not actually present. On the contrary, many studies have reported that imeglimin is less likely to cause hypoglycemia, but the TIMES 2 trial showed a slight increase in hypoglycemia occurrence with imeglimin and

an increase in the incidence rate with combination therapy.[9] Taken together, these observations support the possibility that the risk of hypoglycemia might increase when imeglimin is used in combination with other agents. However, the risk of hypoglycemia with imeglimin treatment is poorly understood, and further research with imeglimin versus placebo should be conducted. None of the participants in this study showed symptoms of hypoglycemia, and we believe that no clinically significant hypoglycemia was observed.

The present study also showed significant improvements in postprandial glucose level during MTT and in the HOMA-β level and CPR index, which are associated with β-cell functions. Notably, some previous studies that conducted glucose tolerance tests and/or MTTs on animal models or in clinical settings have shown significant improvements in glucose tolerance,[4,8,21,22] which is consistent with the findings of the present study. These studies also showed that the increase in glucose-induced insulin secretion resulted in improved postprandial glucose level. For potential mechanisms, a recent study showed that imeglimin enhanced the early phase of glucose-induced insulin release through the transient receptor potential melastatin 2 pathways.[5] The results of the present study, including improvements in AUC0-180 CPR/AUC0-180 glucose, CPR index, and HOMA-β, partially support those of previous studies. In contrast to the results on insulin, the glucagon level during MTT did not change. In a recent study on mice, imeglimin demonstrated a protective effect on β-cells by promoting cell proliferation and inhibiting apoptosis; however, such an effect was exerted on α-cells.[6] These results may be indirectly supported by those of the present study. However, such findings have been reported by only a few studies; therefore, further research is necessary. Imeglimin not only induced insulin secretion, but also improved insulin sensitivity in the liver and skeletal muscles of a rodent model.[6] In contrast to the findings of previous studies, the HOMA-IR level did not change in the present study, which was expected, owing to the small number of patients and relatively short study duration. However, consistent with the results of the present study, those of previous clinical studies did not indicate changes in the HOMA-IR level irrespective of the Japanese or Caucasian population.[10,11,16,22] Therefore, the discrepancy in these results might be due to differences in animal species. Furthermore, a discordance in the efficacy of imeglimin in improving insulin sensitivity based on the presence or absence of obesity has been reported in rodents.[8,21] A recent meta-analysis also showed that the glucose-lowering effect of imeglimin might be attenuated with a high BMI.[23] Therefore, there is a possibility that imeglimin exerts a different effect based on BMI or body consumption; however, further research on this point is warranted.

Notably, most previous clinical studies concluded that the efficacy of imeglimin on body weight and BMI was neutral;[10,11,16,22] however, the participants of the present study exhibited significantly reduced body weight and BMI. The reason for the inconsistency in the effect of imeglimin on body weight loss is unclear; however, it might be due to the small sample size. Furthermore, since our study did not include a placebo arm, it is possible that the participants' motivation was influenced by their participation in the study or by wearing the CGM, which cannot be ruled out. Meanwhile, the phase 2 trial, or TIMES 1, showed that the rate of all adverse events was approximately 5%, with gastrointestinal disorders accounting for 2–3%,[10,11] which was lower than the rate reported in the present study. This finding may be due to the higher mean age of the participants in the present study than those in previous studies. Considering this, only four participants were diagnosed with diabetic neuropathy at baseline, but there might have been more participants who had undiagnosed neuropathy and gastrointestinal complications due to a lack of investigation or failure of patients to report of symptoms associated with gastrointestinal disorders. Consequently, it was considered that incident rate of gastrointestinal disorders might be higher than that in previous studies. Furthermore, the TIMES 2 trial showed that the incidence of adverse events was 10–37%, with imeglimin combined with metformin accounting for the highest incidence. Therefore, the incidence of gastrointestinal disorders might increase when imeglimin is used in combination with other agents. However, little is known about this; therefore, further research with a large number of participants should be conducted to gain further insights.

This study has some limitations. First, we recruited patients who attended a single university hospital in Japan. Furthermore, these patients had a relatively higher BMI than the general population; therefore, our results may not be applicable to all patients with T2D. Second, this study was conducted with a small number of patients and within a short observation period, with no placebo. Third, we did not examine the effects of imeglimin on incretin, and the mechanisms underlying the glucose-lowering effect of imeglimin could not be directly assessed in this study. However, this study

revealed that the addition of imeglimin improved glycemic control and postprandial hyperglycemia by enhancing glucose-induced insulin secretion despite the short 3-month duration.

Conclusion

The addition of imeglimin to DPP-4i significantly improved glycemic control through the modification of glycemic variability based on the stimulation of glucose-induced insulin secretion, indicating its potential as a therapeutic option for Japanese patients with T2D treated with DPP-4is.

Medical Writing, Editorial, and Other Assistance

Technical assistance with the statistical analyses of this article was provided by Hirokazu Yamada of EviPRO Co., Ltd., Tokyo, Japan. Editorial assistance for this article was provided by Editage (www.editage.com).

Abbreviations

AUC, area under the curve; BMI, body mass index; CGM, continuous glucose monitoring; CPR, C-peptide immunoreactivity; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1C; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-β-cell function; MTT, meal tolerance test; TAR, time above range; TBR, time below range; TIR, time in range; TITR, time in tight range; TIMES, Trial for Imeglimin Efficacy and Safety; T2D, type 2 diabetes.

Acknowledgments

We thank all participants of the study. Sumitomo Pharma is engaged in the manufacturing and sale of imeglimin in Japan.

Author Contributions

All authors significantly contributed to the work reported, whether it is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; approved the final version to be published; agreed to the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding or sponsorship was received for this study or publication of this article.

Disclosure

T. Hirose received research funds from Nippon Boehringer Ingelheim Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Pharma Co., Ltd. and received lecture fees from Sanofi K.K., Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Kowa, Abbot, MSD K.K., Sumitomo Pharma Co., Ltd. Yoshikawa received lecture fees from Novo Nordisk Pharma Ltd. None of the funding agencies had any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors report no other conflicts of interest in this work.

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