Diabetology International (2022) 13:124–131
https://doi.org/10.1007/s13340-021-00513-6

ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitor improves glycemic variability in multiple daily insulin-treated type 2 diabetes: a prospective randomized-controlled trial

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Received: 2 January 2021 / Accepted: 12 May 2021 / Published online: 5 June 2021

Abstract

Aims To improve glycemic variability (GV) is crucial in the management of multiple daily insulin (MDI) treatment in diabetes. To evaluate the GV improvement in MDI treated type 2 diabetes (T2D) with low-dose metformin 750 mg/day (LMET), which was popular in the clinical practice in Japan, we compared the effect of adding vildagliptin 100 mg/day (LMET + DPP4i treatment) or increased metformin dose to 1500 mg/day (HMET treatment), in the setting of continuous glucose monitoring (CGM) analysis.

Materials and methods Single-center, open-label, 12 weeks—two period cross-over design. Twenty T2D with inadequately controlled (7.0% < HbA1c ≤ 9.0%) with MDI + LMET were enrolled. Primary endpoints were GV and hypoglycemia derived from CGM indices, performed after each 12 week treatment periods.

Results There was no significant difference in both LMET + DPP4i treatment and HMET treatment, in terms of HbA1c, body weight changes, and total daily dose of insulin to achieve the targeted glycemia. LMET + DPP4i treatment compared to HMET treatment, significantly reduced the calculated GV value, mean (7.15 ± 1.30 vs 7.82 ± 1.60, $p = 0.04$), standard deviation (1.78 ± 0.55 vs 2.27 ± 1.11, $p = 0.03$), continuous overlapping net glycemic action (6.44 ± 1.28 vs 7.12 ± 1.69, $p < 0.05$), J-Index (26.7 ± 11.0 vs 34.9 ± 19.8, $p < 0.05$), high blood glucose index (3.01 ± 1.96 vs 6.73 ± 4.85, $p = 0.02$), and mean amplitude of glycemic excursions (4.53 ± 1.35 vs 5.50 ± 2.34, $p = 0.03$).

Conclusion The GV metrics regarding daily and nocturnal hypoglycemia were not significantly different between LMET + DPP4i treatment and HMET treatment. LMET + DPP4i treatment decreased GV associated with hyperglycemia. Adding DPP-4-inhibitor to the lower dose of metformin is an alternative approach to the stable GV in MDI compared to additional high-dose metformin. National Clinical Trial registration in Japan, number is JPRN-UMIN000024663.

Keywords Glycemic variability · Insulin · Metformin

Introduction

Multiple daily injection of insulin is a last resort in the context of diabetes treatment strategy, both in type 1 and 2 diabetes. However, several criticism has been emerged as, increasing body weight, high glycemic variability (GV), and consequently hypoglycemia. In the current consensus guidelines stated in American Diabetes Association [1] and the European Association for the Study of Diabetes [2] recommends that continuing metformin might be an alternative option when insulin is initiated to minimize the risk of increased body weight and insulin dosages. Several previous studies of randomized clinical trials with meta-analyses and trial sequential analyses have been shown that combination

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therapy of insulin and metformin was associated with significant reduction in HbA1c, weight gain, and insulin dose and all-cause mortality, compared to the insulin alone [3, 4].

There is considerable clinical implication that negative impact on GV might have any effect on the development of diabetes complications. Recent publications from "Beyond A1c Writing Group" [5] warranted that HbA1c has limited accuracy to elucidate the pattern of glycemic excursions following vulnerability of the individual subject. According to the members of decision-making for the "Type 1 Diabetes Outcomes Program", has been elucidated an alternative approach imperative to assess the therapies for type 1 DM, beyond HbA1c [6]. In recent years, high GV has been proposed as an additional risk factor for complications of diabetes independent of hyperglycemia [7]. Thus, lowering glycemic variability is quite important as well as reduce HbA1c in the management of diabetes. However, there was no evidence of lowering glucose variability by adding oral hypoglycemic agents on multiple daily insulin therapy.

Beside chronically elevated glucose, high glycemic variability is associated with increased frequency of nocturnal hypoglycemia and consequently to hypoglycemic unawareness [8]. There is still extensive debate regarding hypoglycemia as a predictive risk factor for diabetes macrovascular and cardiovascular complications. In the face of growing interest in various synonyms, some studies have reported connections between hypoglycemia and not only cardiovascular diabetes complications [9] but also all-cause mortality despite of glycemic treatment group assignment [10]. Although the potential for a causal relationship has been demonstrated in clinical studies treated with oral hypoglycemic agents, the evidence from multiple daily insulin injection studies that hypoglycemia is a major causal contributor to cardiovascular events is limited to date. We focus on the time range (i.e., nocturnal) and continuous glucose monitor (CGM)-based GV metrics specific to targeting the magnitude of hypoglycemia on the patients with multiple daily insulin injection employed to which adding incretin mimetics or metformin.

DPP-4 inhibitors act by enhancing the actions of incretin, which promotes insulin secretion and suppresses glucagon secretion depending on blood glucose levels [11], and results in improvement of glycemic control without hypoglycemia [12]. Oral antidiabetic studies suggested that the incretin system modulates daily glucose profiles and variability and might be an option in adjunctive treatment to metformin and causing glycemic control without inducing weight gain and hypoglycemia [13]. Insofar, there was no study comparing GV and the rate of hypoglycemia assessed with CGM in subject using metformin monotherapy compared to metformin plus DPP-4 inhibitors, in addition to multiple daily insulin injection type 2 diabetes. Thus, we wish to evaluate the GV, in terms of multiple CGM parameters, such as standard deviation (SD), mean amplitude of glucose excursion (MAGE), and continuous overall net glycemic action (CONGA) in patients using multiple daily insulin injection.

Materials and methods

Subject

Patients were enrolled and randomized between Feb, 2017, and Mar, 2018, given explanations of this study protocol, and provided informed consent. The study protocol was approved by the Ethical Committee of Toho University School of Medicine, Tokyo, Japan (No 91-23, 22/Jan/2016). The National Clinical Trial registration in Japan, number is JPRN-UMIN000024663 at 1/11/2016. All the subjects finished the study until 1/Jul/2018.

Included patients were 20–80 years old, diagnosed type 2 diabetes mellitus using insulin for at least 1 year, and whether glycated hemoglobin (HbA1c) within the range of $7.0\% < \text{HbA1c} \leq 9.0\%$, an indicator of dysglycemia, Patients were treated with basal and bolus insulin therapy and metformin 750 mg/day without any other antidiabetic drugs for 12 weeks before entry (run in period). During that period and until finished this study, basal and bolus insulin adjusting algorithms, and antidiabetic drugs, antihypertensive drugs, hypocholesterol drugs were not changed.

The key exclusions criteria included history of type 1 diabetes or secondary forms of diabetes, ketoacidosis, coma, myocardial infarction, unstable angina, or stroke in the past 6 months, severe infection, pre- or post-operative, or severe trauma, moderate or severe renal dysfunction (serum creatinine level ≥ 2 mg/dL), severe hepatic dysfunction (serum alanine transaminase or aspartate transaminase ≥ 100 IU/L), treatment with antidiabetic agents other than metformin, history of hypersensitivity to ingredients of the study drugs, and judged to be unsuitable for participation for medical reasons. An included and excluded number of subjects were available at the CONSORT statement (Online Appendix 1) and complete study design was shown in Online Appendix 2.

Study design

We conducted this investigator-initiated, single-center, randomized, open-label, exploratory pilot study with 12 weeks—two period cross-over design. Consisting of a screening period (− 12–0 week). We applied analysis of variance (ANOVA): repeated measures, within-between interaction, setting an alpha level of 0.05, and approximately, ten participants will provide 89% power to detect a statistical significance. Recruitment was increased ($n = 15$ in each arms) for both arms and inflated to 30 to counter 66% attrition rate. Of the 30 patients screened, ten did not meet the inclusion criteria and 20 participate in the trial. Then, 20

eligible patients were randomly assigned to HMET treatment ($n=8$) or LMET + DPP4i treatment ($n=12$). The subjects were informed that participation was voluntary, it would not influence their clinical care, and they could stop using the HMET treatment or LMET + DPP4i treatment at any time and still get the monetary compensation. The randomization was conducted independently at a central office using a computer-generated random allocation sequence table. Allocation concealment was performed by enclosing assignments in sequentially numbered, opaque, closed envelopes. At first period, 0–12 weeks, patients were randomly allocated to two groups, HMET treatment which increased metformin to 1500 mg/day or LMET + DPP4i treatment adding vildagliptin 100 mg/day to current treatment. After 12 week treatment, at the second period, 13–24 weeks, HMET treatment ordered to receive vildagliptin 100 mg/day and metformin 750 mg/day and LMET + DPP4i treatment changed to receive metformin 1500 mg/day. The dose of insulin needs to be titrated based on the self-monitored blood glucose to control the patient's preprandial blood glucose in the range of 140 mg/dL (5.6 and 7.8 mmol/L). A dose titration algorithm to increase basal insulin dose by 2 units if the mean 3 days before breakfast glucose > 140 mg/dL (7.8 mmol/L). The each bolus insulin dose was up-titrated by 2 units if the mean 3 days next meal preprandial glucose > 140 mg/dL (7.8 mmol/L) and down-titrated by 2 units if the glucose < 100 (5.6 mmol/L).

Continuous glucose monitoring (CGM) examination, we used Medtronic diabetes CGMs iPro2 (Medtronic, Northridge, CA, USA), performed on 5 consecutive days on after each 12 week treatment period. Registered data from CGMs Digital recorder and the blood glucose meter were downloaded using CARELINK PRO software (Medtronic, Northridge, CA, USA). Primary endpoint was metric of the glycemic variability (GV) and secondary was hypoglycemia; both were derived from CGM data sets.

Measurements

Patients were checked body weight, abdominal circumference, blood pressure, on 0, 12, and 24 weeks. Blood and urine sample were collected subsequently fasting for 10 h or more on 12 and 24 weeks, and measurements were HbA1c, glycated albumin (GA), fasting plasma glucose (FPG), triglyceride (TG), HDL-cholesterol, LDL-cholesterol, plasma C-peptide immunoreactivity (CPR), urinary albumin (U-Alb), and urinary creatinine (U-Cr).

Glycemic indices based on CGM

After downloading the CGM data, the following values [14] were analyzed using a computer program, glycaemic variability calculator: EasyGV (available free for non-commercial use, Oxford University Innovation, Oxford, UK). The EasyGV© is used to calculate the following measures of glycemic variability;

Metrics of glycemic variability were as follows;

Standard deviation (SD):

Represents as a grade of dispersion from average.

Average glucose value (mean).

Continuous overlapping net glycemic action (CONGA):

Represents as the difference between values at different set intervals (the default is 60 min on Easy GV©).

J-Index:

It indicates glucose variability calculated with Mean GV and SD.

Low BG Index (LBGI)/High BG Index (HBGI):

Represents as a measure of the frequency and extent of the low and high blood glucose.

Mean amplitude of glycemic excursions (MAGE):

It quantifies the glycemic peaks and nadirs encountered during a day.

Average daily risk range (ADDR):

The process of calculated is analogous to the LBGI/HBGI calculation. It contributes to the risk of hypoglycemia and hyperglycemia to the transformed point.

In addition to using CGM data, we calculated hypoglycemia as area over the curve (AOC < 70) of glucose < 70 mg/dL during the night (0:00 am–6:00 am).

All GV metrics are summarized in Online Appendix 3.

Statistical analysis

The research sample was randomly selected from the patients from out-patient clinic of volunteers who met the criteria for inclusion in the group. The trial had 90% power at a two-sided alpha level of 0.05 to detect hazard ratios consistent with an expected GV metrics difference between two groups of 20%, and the GV parameters regarding hypoglycemia with 20%, respectively. Data are shown as the mean ± standard deviation.

The paired t test was used to compare values between patients taking different drugs or pre- and post-treatment, with the level of significance set at $p < 0.05$.

Result

A total of the 30 patients were randomized and 20 patients (Male 10, Female 10) completed. Baseline demographics and clinical characteristics of total and two groups patients are shown in Table 1, mean age was 57.1 ± 11.1 years, and mean duration, since diagnosis was 13.0 ± 9.9 years, body weight was 71.0 ± 17.6 kg, mean body mass index (BMI) was 26.6 ± 4.5 kg/m^2, mean HbA1c was 7.57 ± 0.8%. Before enrollment in this study, total daily dose of insulin (TDD)

Table 1 Characteristics of the study subjects at baseline and post-12 week treatment period

	Baseline	Post 12 week treatment		
		HMET	LMET + DPP-4	HMET vs DPP-4 + LMET
				p value
No. of treatment subjects	20	20	20	
Body weight (kg)	71.0 ± 17.6	70.8 ± 17.2	70.7 ± 33.6	0.49
BMI (kg/m^2)	26.6 ± 4.5	26.6 ± 4.5	26.7 ± 9.15	0.48
Abdominal circumference (cm)	91.4 ± 11.2	93.9 ± 13.6	91.3 ± 26.9	0.31
SBP (mmHg)	132.6 ± 19.3	127.2 ± 14.2	129.5 ± 21.9	0.29
DBP (mmHg)	79.1 ± 13.7	75.1 ± 10.9	77.1 ± 16.4	0.26
Total daily dose of insulin (unit/kg)	0.48 ± 0.22	0.55 ± 0.26	0.49 ± 0.44	0.22
Basal insulin dose/TDD (%)	37.6 ± 11.6	37.8 ± 12.3	38.4 ± 28.9	0.45
HbA1c (%)	7.57 ± 0.8	7.12 ± 0.8	6.86 ± 1.2	0.12
GA (%)	18.5 ± 2.80	16.8 ± 3.4	16.9 ± 6.0	0.49
Fasting plasma glucose (mg/dL)	164.8 ± 72.2	155.0 ± 49.1	138.7 ± 69.1	0.12
HDL-cholesterol (mg/dL)	57.4 ± 17.7	57.5 ± 17.8	56.2 ± 34.5	0.41
LDL-cholesterol (mg/dL)	110.9 ± 39.7	111.0 ± 37.0	105.5 ± 68.2	0.31
Triglyceride (mg/dL)	144.7 ± 75.0	168.5 ± 161.4	145.9 ± 193.8	0.30
Urine creatinine (mg/g cre)	86.9 ± 145.7	95.5 ± 218.8	75.8 ± 365.4	0.39
Plasma C-peptide (ng/mL)	1.89 ± 1.08	1.73 ± 1.15	1.70 ± 2.00	0.47

The data are mean ± SD. Mean changes from the baseline to week 12 are shown with ± SD. The within group *p* values were calculated using the Wilcoxon signed-rank test; *p* values < 0.05 are indicated as significant

was 0.48 ± 0.22 U/kg, and basal insulin percentage of TDD (%Basal) was 37.6 ± 11.6%.

After 12 week treatment, the difference between two treatments (we analyzed as HMET treatment, $N = 20$, and LMET + DPP4i treatment, $N = 20$) is shown in Table 1. There were no differences in physical findings and TDD, basal insulin percentage of TDD, blood, and urine parameters between two groups.

Physical findings

As a result, BW, BMI, and other anthropometrics were comparable between both treatments at the end of this study. Furthermore, the difference between those data, at the baseline and post-12 week treatment were also comparable between two treatments. Regardless of treatment assignment, BW, BMI, abdominal circumference, and blood pressures were also comparable in both 12-week treatment period.

Insulin dose

Total daily dose of insulin (TDD) (U/Kg) was not different between baseline and post-12 week treatment within both groups (HMET treatment 0.55 ± 0.26; $p = 0.14$, LMET + DPP4i treatment 0.49 ± 0.22; $p = 0.48$). The change of TDD (U/Kg) was also comparable (HMET treatment, 0.06 ± 0.09 vs LMET + DPP4i treatment, 0.03 ± 0.28; $p = 0.23$). Furthermore, basal/bolus ratio and basal insulin percentage of TDD were similar between pre- and post-treatment in both groups (%Basal: HMET treatment 37.8 ± 14.8; $p = 0.44$, LMET + DPP4i treatment 38.4 ± 14.4; $p = 0.41$).

Glycemic control

The HbA1c level was significantly lowered in both groups compared to the pre-treatment (HMET treatment, 7.57 ± 0.80 to 7.12 ± 0.76; $p = 0.01$, LMET + DPP4i treatment, 7.57 ± 0.80 to 6.86 ± 0.62; $p < 0.01$), and were not different between two groups at post-12 week treatment period ($p = 0.12$). FPG were also comparable between both treatments at post-12 week treatment period.

Glucose variability and hypoglycemia by CGM data

Glucose fluctuation parameters provided from CGM data are shown in Table 2.

Mean GV (mmol/L) was significantly different between HMET treatment and LMET + DPP4i treatment (7.82 ± 1.60 vs 7.15 ± 1.30; $p = 0.04$). And, between two groups, LMET + DPP4i treatment was significantly reduced parameters relatively with glycemic variability, SD (2.27 ± 1.11 vs 1.78 ± 0.55; $p = 0.03$), CONGA (7.12 ± 1.69 vs 6.44 ± 1.28; $p = 0.046$), J-Index (34.9 ± 19.8 vs 26.7 ± 11.0; $p = 0.04$), and MAGE (5.50 ± 2.34 vs 4.53 ± 1.35; $p = 0.03$). Moreover, it

Table 2 Glycemic variability (GV) based on CGM results

	HMET treatment	LMET + DPP4i treatment	*p* value
Mean	7.65 ± 1.82	6.94 ± 1.11	0.03
Stdev	2.50 ± 1.18	1.83 ± 0.60	0.02
CONGA	6.94 ± 1.94	6.22 ± 1.06	0.03
J-Index	35.88 ± 23.35	25.70 ± 10.18	0.02
LBGI	3.38 ± 4.80	2.14 ± 1.67	0.17
HBGI	6.56 ± 5.90	3.84 ± 2.78	0.02
MAGE	6.13 ± 2.35	4.75 ± 1.42	0.03
ADDR	12.40 ± 6.55	9.65 ± 6.22	0.07

Standard deviation (SD), average glucose value (mean), continuous overlapping net glycemic action (CONGA), J-Index, low BG Index (LBGI)/high BG Index (HBGI), mean amplitude of glycemic excursions (MAGE), and average daily risk range (ADDR)

*p value from the two-sided test with a normal 5% significance level

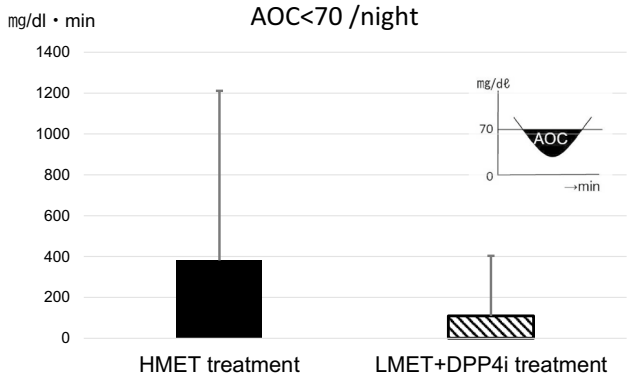

Fig. 1 Nocturnal hypoglycemia. This figure shows the area over the curve (AOC < 70) of nocturnal hypoglycemia (blood glucose < 70 mg/dL, 0:00 am–6:00 am) based on CGM data

revealed that HBGI represents high blood glucose, which the risk of hyperglycemia was significantly different between two groups (5.50 ± 2.34 vs 4.53 ± 1.35; $p = 0.03$).

The AOC of glucose < 70 mg/dL at midnight (AOC < 70/night) shown in Fig. 1 were more likely to report the risk of hypoglycemia consequently to reduce the QOL and overall survival in diabetes with patient with insulin therapy. It tended to be higher in HMET treatment, and in this context, there was not significantly difference between two groups (381.0 ± 830.4 vs 109.9 ± 293.5; $p = 0.08$). Underlying this process, all of these spectrums were similar between two treatment groups.

Discussion

We evaluate two additional oral antidiabetic strategy with MDI, low-dose metformin with DPP-4-inhibitor and high-dose metformin alone in forced insulin titration algorism, with dynamics of GV amplitude and compared ability to avoid hypoglycemia and labile GV metrics. Our data demonstrated that a DPP-4-inhibitor, add-on to the low-dose metformin with MDI therapy compared to the HMET, allowed us to significantly reduce mean GV, standard deviation of GV, continuous overlapping net glycemic action, J-Index, high blood glucose index, and mean amplitude of glycemic excursions, irrelevant to total daily insulin dose and A1c. These parameters were mainly representative of the GV amplitude in high glucose components.

Glycemic variability in the treatment with metformin and DPP-4-inhibitor

Management of glucose profile, prevention of hyperglycemic exposure, and a risk of hypoglycemia are highly related to GV which had been greatest interest and crucial role of both in the physiology and pathophysiology of diabetes [15]. Subsequent studies focused on the variability of blood glucose fluctuations as an independent risk factor for complications of type 2 diabetes [16] and also to the brain cognitive function and quality of life [17]. Although various types of oral hypoglycemic drugs have been well characterized to improve A1c and fasting blood glucose, the GV has not been studied precisely.

DDP-4 inhibitors increase circulating levels of the bioactive, intact glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) by inhibition of the GLP-1/GIP degrading DPP-4, and therefore improving pancreatic α- and β-cell sensitivity to glucose, leading to suppress glucagon release as a consequence to reduce GV [18]. DPP-4 inhibitors thus complement to the effect of metformin that decreases hepatic glucose production without improving insulin secretion [19]. Insofar as using DPP-4-inhibitor to obese glucose tolerant, glycemic variability showed no significant differences in the AUC, MAGE, SD of glucose, CV of glucose, and MBG compared to the placebo [20]. To assess the effects of adding DPP-4-inhibitor compared to high-dose metformin, excessively advanced stage in type 2 diabetes require MDI, evaluate the impact of emergent adverse events in MDI. Our study shows treatment with LMET + DPP4i places a high value on preventing the potential consequences of hyperglycemia and a similar value on the possible side effects of hypoglycemia compared to the HMET treatment.

Avoiding hypoglycemia

Although reducing hyperglycemia and targeting HbA1c under 7.0% (55 mmol/L) accompanied by decreased risk of micro- and macrovascular complications [21], the risk of hypoglycemia increases with forced strengthen the treatment. In insulin-treated type 2 diabetes with

cardiovascular disease, hypoglycemic events with a continuous glucose monitoring glucose concentration < 56 mg/dL (3.1 mmol/L) were associated with a 30-fold increased frequency of 24 h-Holter electrocardiogram detected of ventricular tachycardia [22]. Underlying this process, hypoglycemia has been implicated as the primary barrier to tighten blood glucose [23]. To address these criticisms, we compared the risk of hypoglycemia between LMET + DPP4i treatment and HMET treatment with CGM-derived GV metrics specific to the low glucose value: LBGI and ADRR. Despite having favorable result in the range of hyperglycemia with LMET + DPP4i treatment, there was no significant difference in neither hypoglycemic parameters between two treatments. These results indicates that the rate and time points in hypoglycemia during the MDI in T2D with several oral agents, irrelevant to the oral drug properties. Although several studies have reported that low GV associated with decreased the rate of hypoglycemia [24], lower GV accompanied with reduced higher blood glucose component were not vast majority of hypoglycemia. To combat the life-threating hypoglycemia in MDI using several types of oral agents is warranted to facilitate further improvements in MDI.

Metabolic effects

Metformin is a cost-effective insulin-sparing oral glucose-lowering agent, and was positively recognized as an adjunctive drugs to insulin therapy [25]. In most of the Asian countries, lower BMI compared to the North American and European countries, the dose of metformin adjunct to the insulin therapy was lower with basal dose of ~ 750 mg/day versus 1–1.5 g/day [26, 27]. In a long-term study on the effect of DPP-4-inhibitor (sitagliptin) as add-on to metformin in subjects with inadequate glycemic control without insulin treatment, sitagliptin (100 mg once daily) was added to metformin alone (> 1.5 g daily) for 24 weeks showed significant reduction in A1C, fasting plasma glucose, and 2-h post-meal glucose [28].

Insofar as increasing the dose of metformin in HMET, body weight, body mass index, abdominal circumference, TDD, basal insulin percentage of TDD, A1c, GA, fasting plasma glucose, and lipid parameter were not different compared to LMET + DPP4i treatment. Underlying this crossover study, targeting to evaluate the metabolic difference between two groups, might not be feasible to compare the effect in 12 weeks study period. Although there was no difference in TDD at the end of 12 week study period, marginally higher TDD at the baseline in LMET + DPP4i treatment, indicates that reduced TDD in LMET + DPP4i treatment might have some potentials, compared to increase the dose of metformin.

Treatment adverse events

The risks of other severe and non-severe adverse events were not significantly different between LMET + DPP4i treatment and HMET treatment during the study periods. Increased dose of metformin has been shown to elevate the rate of gastrointestinal disturbances [29, 30]. We therefore attempted to include participant already taking low-dose metformin 750 mg/day to minimize the adverse effect of having increased metformin in the period of the higher dose 1500 mg/day in Japan [27].

Limitation

The weakness of our results were, first, duration of intervention in the trial was relatively short, and we were unable to explore whether these metabolic effects disappear, persist, or became more pronounced with time. Second, analyses of patient relevant outcomes were based on very sparse data and the possibility of insufficient significant results. Third, although in patients with type 2 diabetes on multiple daily injection, our results seems to support the combination of low-dose metformin and DPP-4 inhibitor compared to the combination of high-dose metformin on metrics in glycemic variability, standard deviation, J-Index, MAGE, and HBGI, these variables are, at best, invalidated surrogate markers of a potentially reduced risk of microvascular and macrovascular complications [31, 32].

Conclusion

Addition to multiple insulin injection, DPP-4-inhibitor with low-dose metformin compared to substantial high-dose metformin monotherapy, decreased glycemic variability especially in hyperglycemic excursion in type 2 diabetes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13340-021-00513-6.

Acknowledgements The authors are especially grateful to the VMAT investigators. All authors made significant contributions to study design, analysis, and interpretation of data, as well as preparing and reviewing the manuscript.

Funding No funding or sponsorship was received for this study. The article processing charges were funded by the authors.

Data availability The datasets generated during and/or analyzed during the current study are available in the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), number UMIN000024663.

Declarations

Conflict of interest The authors have no other relevant affiliations or financial involvement with any organizations or entities with a financial interest in or financial conflict with the subject or materials discussed in the manuscript apart from those disclosed. This study was not supported by any pertinent commercial company. Fukumi Yoshikawa, Hiroshi Uchino, Tomoko Nagashima, Shuki Usui, Masahiko Miyagi, Yasuyo Ando, and Naoki Kumashiro declare that they have no conflict of interest. Takahisa Hirose has received research support from Takeda Pharmaceutical Company Limited, Ono Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Company, Limited, Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Taisho Pharmaceutical Co., Ltd. Astellas Pharma Inc. Takahisa Hirose has received advisory panel and research support from Nippon Boehringer Ingelheim Co., Ltd., AstraZeneca K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., and speaker honoraria from, Sanofi K.K. Eli Lilly Japan K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Company Limited, MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Mitsubishi Tanabe Pharma Corporation, Kowa Company, Limited, and Kissei Pharmaceutical Co., Ltd.

Ethical approval All procedures performed in the study involving human participants were in accordance with the Ethical Committee of Toho University School of Medicine, Tokyo, Japan (No 91-23, 22/Jan/2016) and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Previous presentation Some of the findings from this study were presented at the 77th Scientific Sessions of American Diabetes Association, June 9–13, 2017, San Diego, California.

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