Title:

Dipeptidyl peptidase-4 inhibitors Mitigates Glycemic Variability in Metformin based Multiple Daily injected Type 2 Diabetes, a Prospective Randomized Controlled Trial

Fukumi Yoshikawa [1], [‡], Hiroshi Uchino [1], [*], Tomoko Nagashima [1], [‡], Shuki Usui [1], Masahiko Miyagi [1], Yasuyo Ando [1] Naoki Kumashiro [1] and Takahisa Hirose [1]

1) Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Toho University Graduate School of Medicine, Tokyo, Japan

‡These authors contributed equally to this work.

Running title:

Metformin/DPP-4 Inhibitor ameliorates GV

*Corresponding author:

Hiroshi Uchino MD PhD

Division of Diabetes, Metabolism and Endocrinology

Department of Internal Medicine

Toho University Graduate School of Medicine

6-11-1 Omori-nishi, Ota-ku

Tokyo, 143-8541 Japan

Phone: +81-3-3762-4151

Fax: +81-3-3765-6488

Email: h.uchino@med.toho-u.ac.jp

Conflicts of interest

Masahiko Miyagi, Hiroshi Uchino declare that they have no conflict of interest.

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Abstract

To cope the high glycemic variability (GV) is crucial in the management of multiple daily insulin (MDI) in diabetes. We compared the effect of low dose metformin 750mg/d adding vildagliptin 100mg/d (DPP4+LMET) or the high dose metformin 1500mg/d (HMET), in type 2 diabetes (T2D) with MDI, evaluating GV by continuous glucose monitoring (CGM). Single center, open-label, 12 weeks - 2 period crossover 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 performed after each 12 weeks treatment periods. There was no significant difference in HbA1c, body weight changes, total daily dose of insulin. DPP4+LMET compared to the HMET, significantly reduced the calculated GV value, mean (7.15±1.3 vs 7.82±1.6, p<0.05), 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). The GV metrics with hypoglycemia and nocturnal hypoglycemia were not significantly different.

DPP4+LMET decreased GV associated with hyperglycemia. Adding DPP4 inhibitor to the lower dose of metformin is an alternative approach to the stable GV in MDI.

Key Words: glycemic variability, continuous glucose monitoring, dipeptidyl Peptidase-4

inhibitor, metformin

Introduction

Multiple daily injection of insulin is the last resort in the context of the diabetes treatment strategy, both in type 1 and 2 diabetes. However, several criticism has been emerged as, increasing body weight, high glycemic variability 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 risk of increased body weight and insulin dosages. Several previous study of randomized clinical trials with meta-analyses and trial sequential analyses has been shown that combination therapy of insulin and metformin were associated with a significant reduction in HbA1c, weight gain, and insulin dose, all-cause mortality, compared to insulin alone (3, 4).

There is considerable clinical implication that supports the negative impact on GV in 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 subjects. 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, 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 reduced HbA1c in the management of

diabetes. However, there was no evidence of lowering glucose variability by adding

metformin 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 this various synonyms, some studies have reported a connection

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 CGM based GV metrics specific to

targeting the level of hypoglycemia on the patients with multiple daily insulin injection

employed to which adding incretin drugs 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), results in improvement of glycemic control without hypoglycemia (12). Oral antidiabetics studies, which, suggested that the incretin system modulate daily glucose profiles and variability and might be an option in adjunctive treatment to metformin 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 Toho University in Tokyo, Japan. 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 to 80 years old, diagnosed type 2 diabetes mellitus using insulin for at least 1 year, and were controlled 7.0% <HbA1c ≦9.0%. Patients were treated with basal and bolus insulin therapy and metformin 750 mg/d 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, by the cause of the judgment of the physician.

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 ≧2mg/dl) , severe hepatic dysfunction (serum

alanine transaminase or aspartate transaminase≧ 100IU/L), treatment with antidiabetic

agents other than metformin, history of hypersensitivity to any of the ingredients of the

study drugs, and judged to be unsuitable for participation for medical reasons. A

complete study design and included and excluded number were available in the

appendix 1 and 2.

Study design

We conducted this investigator-initiated, single-center, randomized, open-label,

exploratory pilot study with 12weeks - 2 period cross over design.   Consisting of a

screening period (-12 to 0 week).   We will apply analysis of variance (ANOVA): repeated

measures, within-between interaction, setting an alpha level of 0.05, and approximately

10 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, 10 did not meet the inclusion criteria 20

participate in the trial. Then 20 eligible patients were randomly assigned to HMET (n =

8) or DPP4/LMET (n = 12). The subjects were informed that participation was voluntary,

it would not influence their clinical care, and they could stop using the HMET or

DPP4/LMET 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 group which increased metformin to 1500 mg/d or DPP4+LMET group add vildagliptin 100 mg/d to current treatment. After 12 weeks treatment, at the second period, 13-24 weeks, HMET group ordered to receive vildagliptin 100 mg/d and metformin 750 mg/d and DPP4+LMET group changed to receive metformin 1500mg/d.

Continuous glucose monitoring (CGM) examination, we used Medtronic diabetes CGMs iPro2 (Medtronic, Northridge, CA, USA), performed on 5 consecutive days on after each 12 weeks treatment period.   Registered data from CGMs Digital recorder and the blood glucose meter were downloaded using CARELINK PRO software (Medtronic, Northridge, CA, USA).

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 ten

hours or more on 12 and 24 weeks, measurements were HbA1c, glycated albumin (GA), fasting plasma glucose (FBG), 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, Easy GV © (available free for non-commercial use at WWW.easygv.co.uk). The Easy GV © 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 ©).

Lability Index (LI):

Represents as lability values during past 4weeks.

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.

Glycemic risk assessment diabetes equation (GRADE):

Represents as the risk attributable to hypoglycemia and hyperglycemia.

Mean of daily differences (MODD):

It indicates amount of the difference between values on different days but at the same

time.

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.

M-Value:

Represents to quantify post prandial blood glucose variation.

Mean absolute glucose (MAG):

It calculates the sum of the differences between successive glucose values divided by the total time measured in hours.

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

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) was 0.48 ± 0.22 U/kg, basal insulin percentage of TDD (%Basal) was 37.6 ± 11.6% . The HbA1c level and TDD of insulin was significantly higher at DPP4+LMET group. All other parameters were not different, between two groups.

After 12 weeks treatment, the difference between two groups (we analyzed as HMET treated group, N=20, and DPP4+LMET treated group, N=20) were shown in Table 2 . There were no differences in physical findings and TDD, basal insulin percentage of TDD, blood and urine parameter between two groups.

Physical findings

As a result, baseline BW, BMI and other anthropometrics were comparable with both groups (BW: HMET 70.7±20.6 kg; p=0.48, DPP4+ LMET 71.2±16.3 kg; p=0.48, BMI:

HMET 25.8 ±4.5 kg/m2; p=0.48, LMET+DPP4 27.2±4.2 kg/m2; p=0.25). Regardless of

treatment assignment, BW, BMI, abdominal circumference and blood pressures were

also comparable in both 12-weeks treatment period.

Insulin Dose

Total daily dose of insulin (TDD) (U/Kg) was not different between baseline and post-12

weeks treatment within both groups (HMET 0.55±0.26; p=0.14, DPP4+LMET 0.49±0.22;

p=0.48). Furthermore, basal / bolus ratio and basal insulin percentage of TDD were

similar between Pre- and Post-treatment in both groups (%Basal: HMET 37.8±14.8;

p=0.44, DPP4+LMET 38.4 ±14.4; p=0.41).

Glycemic control

The HbA1c level was significantly decreased in both groups compared to the pre-

treatment (HMET, 7.57±0.80 to 7.12±0.76; p=0.01, DPP4+LMET, 7.57±0.80 to

6.86±0.62; p<0.01), and were not different between two groups at post 12 weeks

treatment period (p=0.12). Fasting plasma glucose were similar in both groups at the

baseline (HMET 155.0±49.1 mg/dl vs. DPP4+LMET 138.7±34.6 mg/dl; p=0.12), and

furthermore, in post 12 weeks treatment period between two groups (p=0.12).

Glucose variability and hypoglycemia by CGM data

Glucose fluctuation parameters provided from CGM data are shown in Figure 1.

Mean GV (mmol/L) was significantly different between HMET and DPP4+LMET (7.82±1.60 vs. 7.15±1.30; p=0.04). And, between two groups, DPP4+LMET 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), MAGE (5.50±2.34 vs. 4.53±1.35; p=0.03). Moreover, it 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/night) shown in Figure 2 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 group, in this context, there was not significantly difference between two groups (381.0±830.4 vs. 109.9±293.5; p=0.08). Including the consecutive and protracted hypoglycemia, low BG Index (LBGI), glycemic risk assessment diabetes equation (GRADE) - %Hypo and average daily risk range (ADDR) has implicated as the magnitude of hypoglycemia. 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 DPP4 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 DPP4 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 DPP4-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 has 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 DDP-4, and therefore improving pancreatic α- and β-cell sensitivity to glucose, leading to suppress glucagon release as a consequence to reduce GV (18). DDP-4 inhibitors thus complement to the effect of metformin that decreases hepatic glucose production without improving insulin secretion (19). Insofar as using DPP4 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 DPP4 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 DPP4+ LMET 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.

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 24h-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 DPP4+LMET and HMET with CGM derived GV metrics specific to the low glucose value: LBGI, GRADE-%Hypo and ADRR. Despite having favorable result in the range of hyperglycemia with DPP4+LMET group, there was no significant difference in neither hypoglycemic parameters between two groups. 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 counties, the dose of metformin adjunct to the insulin therapy was lower with basal dose of ～750 mg/day versus 1 to 1.5 g/day (26, 27). In a long-term study on the effect of DPP4 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 postmeal 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-DPP4 group. Underlying this cross-over study, targeting to evaluate the metabolic difference between two groups, might not feasible to compare the effect in 12 weeks study period.   Although there was no difference in TDD at the end of 12 weeks study period, between HMET group and LMET+DPP4 group accompanied by marginally higher TDD at the baseline in LMET+DPP4 group, indicates that reduced TDD in LMET+DPP4 might have some

potentials to reduce the TDD with adding the DPP4 inhibitor compared to increase the dose of metformin.

Treatment adverse events

The risk of other severe and non-severe adverse events were not significantly different between DPP4+LMET and HMET groups during the study periods. Increased the dose of metformin has been shown to elevate the rate of gastrointestinal disturbances (29, 30). We therefore attempt the study to include participant already taking low dose metformin 750mg/day to minimize the adverse effect of having increased metformin in the period of the higher dose 1500mg/day in Japan (31).

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. Secondary, analyses of patient relevant outcomes were based on very sparse data and the possibility of insufficient significant results. Thirds, 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, HBGI, these variables are, at best, invalidated surrogate markers of a potentially reduced risk of microvascular and macrovascular complications (32, 33).

Conclusion

Addition to multiple insulin injection, DPP4 inhibitor with low dose metformin compared to substantial high dose metformin monotherapy, decreased glycemic variability especially in hyperglycemic excursion in type 2 diabetes.

Acknowledgments

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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Tanabe-Mitsubishi.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance

with the ethical standards of the Ethics Committee of the Toho University Omori Medical

Center Hospital and with the 1964 Helsinki Declaration and its later amendments.

Informed consent was obtained from all individual participants included in the study.

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.

Contribution Statement

The authors contributed to the present work as follows: FY, HU, TN, and TH contributed

to data curation, formal analysis and methodology, SU and MM to the acquisition of data

or analysis and YA and NK to the interpretation of data and investigations. FY and HU

drafted the original and revised manuscripts and all authors approved the final approval

of the version to be published.

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Figure Legends

Fig. 1 Glycemic variability (GV) based on CGM results

HMET group (Gray) and LMET+DPP4 group (purple) columns shows the result

of the CGM analysis. Standard Deviation (SD), Average Glucose Value (Mean),

Continuous overlapping net glycemic action (CONGA), Lability Index (LI), J-

Index, Low BG Index (LBGI) / High BG Index (HBGI), Glycemic risk assessment

diabetes equation (GRADE),

Mean of daily differences (MODD), Mean amplitude of glycemic excursions

(MAGE), Average daily risk range (ADDR), Mean absolute glucose (MAG). *P

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

Fig. 2 Nocturnal hypoglycemia

This Figure shows the area over the curve (AOC) of nocturnal hypoglycemia

(blood glucose < 70mg/dL, 0:00am~6:00am) based on CGM data.

Fig. 3 Summary of the GV metrics

Standard Deviation (SD): It shows a grade of dispersion from average. Average

Glucose Value (Mean) Continuous overlapping net glycemic action (CONGA): It

was the SD of the glycemic differences recorded between a specific point on

the CGM profile and a point n hours previously. Lability Index (LI): It shows

lability values during past 4weeks. J-Index: It indicates glucose variability

calculated with Mean GV and SD. Low BG Index (LBGI) / High BG Index

(HBGI): these were parameters accounted for the frequency and amplitude of

hyperglycemic and hypoglycemic events. Glycemic risk assessment diabetes

equation (GRADE): It shows the risk attributable to hypoglycemia and

hyperglycemia.

Mean of daily differences (MODD): It was calculated as the mean of the

absolute differences between glycemic gaps observed during the same time

interval on 2 consecutive days, as an expression of the "between-day" glucose

variability. Mean amplitude of glycemic excursions (MAGE): It was calculated as

the arithmetic mean of the difference between consecutive glycemic peak and

nadirs. Only considering change in glycemic values of more than 1 SD. 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. M-Value: It used to quantify post

prandial blood glucose variation. Mean absolute glucose (MAG): It was

calculated the sum of the differences between successive glucose values

divided by the total time measured in hours. *P value from the two-sided test

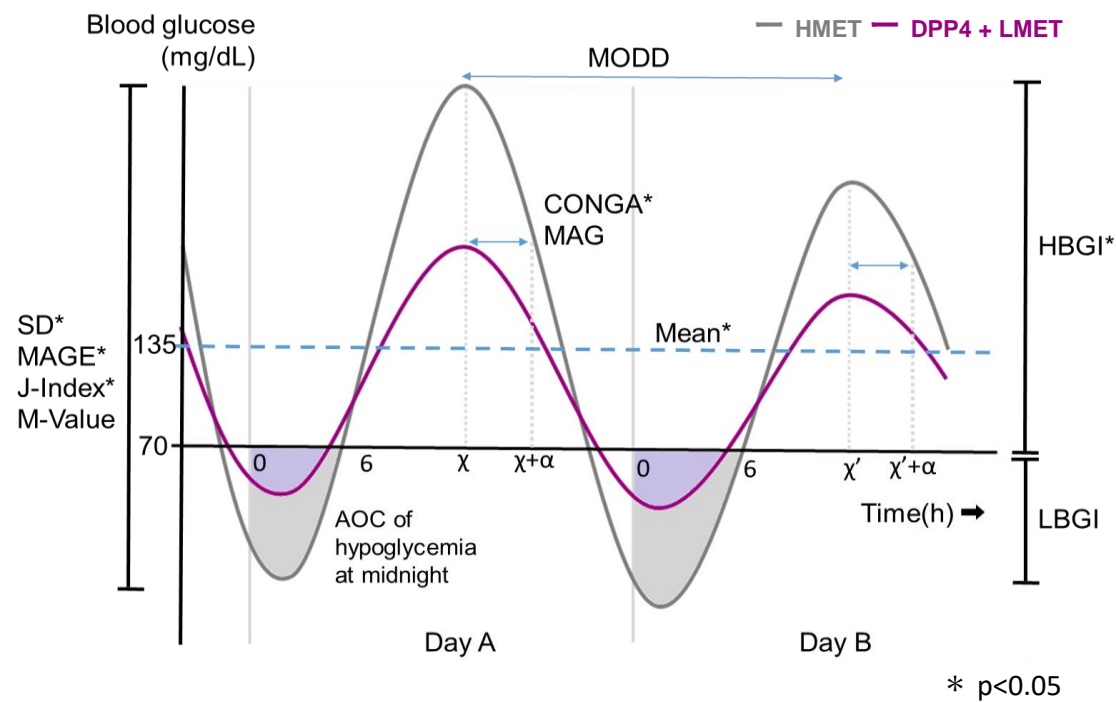with a normal 5% significance level.

Fig 1
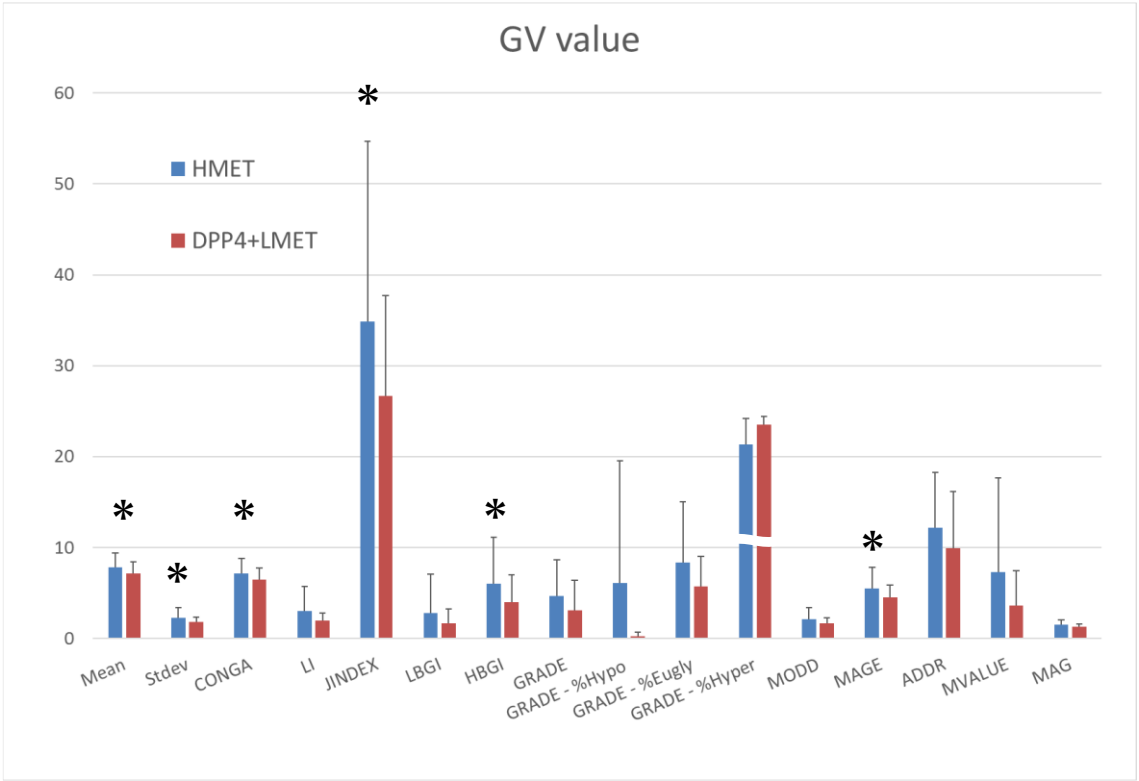
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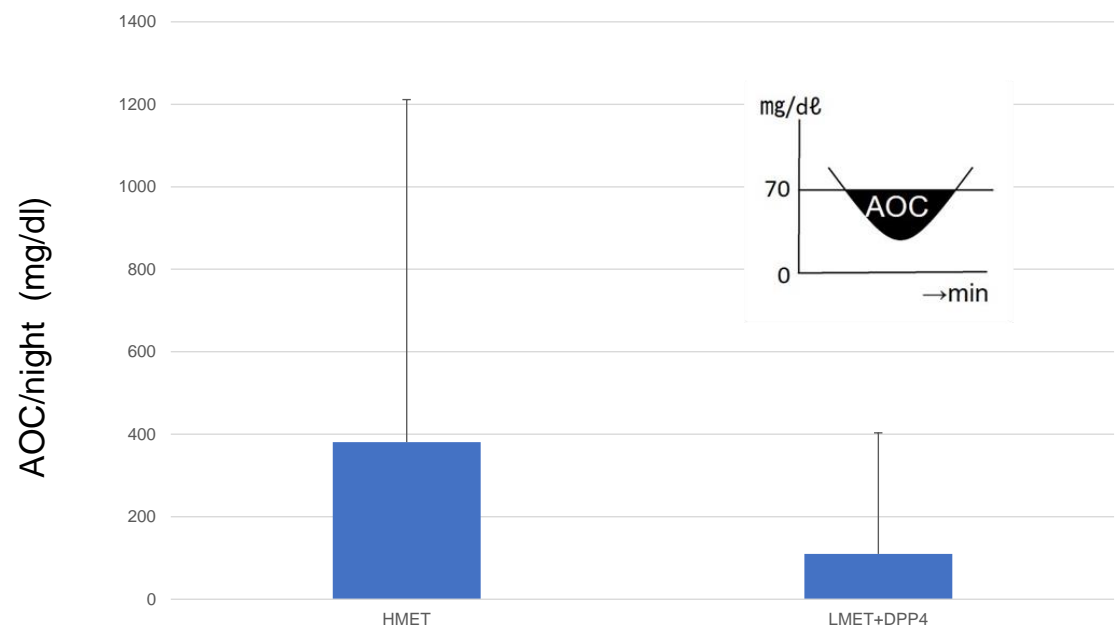
Fig 3.

Table 1

	baseline			
	Total	HMET	DPP4+LMET	HMET *vs* DPP4+LMET
				p value
No. of Patients	20	8	12	
Age (yrs)	57.1±11.1	54.5±11.4	58.8±11.0	0.20
Duration of Diabetes (yrs)	13.0±9.9	10.5±11.0	14.6±9.3	0.19
Body Weight(kg)	71.0±17.6	70.7±20.6	71.2±16.3	0.48
BMI(kg/m^2)	26.6±4.5	25.8±5.2	27.2±4.2	0.25
abdominal circumference(cm)	91.4±11.2	88.1±10.4	93.5±11.6	0.17
SBP (mmHg)	132.6±19.3	128.1±17.0	135.6±19.2	0.20
DBP (mmHg)	79.1±13.7	76.0±9.2	81.4±16.3	0.21
Total Daily Dose of insulin (unit/kg)	0.48±0.22	0.38±0.13	0.55±0.25	0.04
Basal insulin dose / TDD (%)	37.6±11.6	40.3±12.4	35.8±11.3	0.20
HbA1c(%)	7.57±0.8	7.18±0.7	7.83±0.8	0.04
GA (%)	18.5±2.80	17.2±3.1	19.3±2.3	0.05
fasting plasma glucose (mg/dL)	164.8±72.2	152.6±52.3	172.8±84.1	0.28
HDL-cholestrol (mg/dL)	57.4±17.7	60.4±22.7	55.3±14.2	0.27
LDL-cholestrol (mg/dL)	110.9±39.7	94.4±27.0	121.9±43.9	0.07
triglyceride (mg/dL)	144.7±75.0	116.9±59.6	163.3±80.7	0.09
urine creatinine (mg/g・cre)	86.9±145.7	67.2±105.6	99.4±170.1	0.33
plasma C-peptide (ng/mL)	1.89±1.08	1.82±1.18	1.94±1.07	0.41

Table 2

	baseline	post 12 weeks treatment		
		HMET	LMET+DPP4	HMET vs DPP4+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-cholestrol (mg/dL)	57.4±17.7	57.5±17.8	56.2±34.5	0.41
LDL-cholestrol (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