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The Effect of DPP4 Inhibitor on Glycemic Variability in Patients with Type 2 Diabetes treated with twice-daily Premixed Human Insulin*

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Abstract

Objective. To evaluate the effect of adding DPP4 inhibitor (DPP4-i) on glycemic variability (GV) in patients with type 2 diabetes mellitus (T2DM) treated with premixed human insulin (MHI).

Methodology. We conducted a prospective study in patients with T2DM on twice-daily MHI with or without metformin therapy. Blinded continuous glucose monitoring was performed at baseline and following 6 weeks of Vildagliptin therapy.

Results. Twelve patients with mean (SD) age of 55.8 (13.1) years and duration of disease of 14.0 (6.6) years were recruited. The addition of Vildagliptin significantly reduced GV indices (mmol/L): SD from 2.73 (IQR 2.12-3.66) to 2.11 (1.76-2.55), *p*=0.015; mean amplitude of glycemic excursions (MAGE) 6.94(2.61) to 5.72 (1.87), *p*=0.018 and CV 34.05 (8.76) to 28.19 (5.36), *p*=0.010. In addition, % time in range (3.9-10 mmol/l) improved from 61.17 (20.50) to 79.67 (15.33)%, *p*=0.001; % time above range reduced from 32.92 (23.99) to 18.50 (15.62)%, *p*=0.016; with reduction in AUC for hyperglycemia from 1.24 (1.31) to 0.47 (0.71) mmol/day, *p*=0.015. Hypoglycemic events were infrequent and the reduction in time below range and AUC for hypoglycemia did not reach statistical significance.

Conclusion. The addition of DPP4-I to commonly prescribed twice-daily MHI in patients with T2DM improves GV and warrants further exploration.

Key words: glycemic variability, dipeptidyl peptidase 4 inhibitors, premixed human insulin, continuous glucose monitoring, type 2 diabetes mellitus

INTRODUCTION

Glycemic variability (GV) has become an emerging target for optimal glycemic control in patients with diabetes independent of HbA1c.[1-3] Recent studies have highlighted the association of GV to hypoglycemia and its associated adverse consequences.[4-6] In addition, there are increasing data in the literature supporting association of GV to microvascular and macrovascular diabetic complications although definitive evidence on hard clinical outcomes remains limited.[1,6-9] Nonetheless, with the advent of continuous glucose monitoring (CGM), the focus of glycemic management in diabetes has moved beyond HbA1c to include reduction of GV and hypoglycemic events.

Type 2 diabetes mellitus (T2DM) is a progressive disease and many patients will require insulin therapy in order to achieve glycemic control. In Asia, premixed insulin, often in combination with metformin, is commonly used for the treatment of T2DM.[10,11] While more convenient for the patients, premixed insulin with a fixed ratio of prandial and intermediate insulin is less flexible and may be associated with more hypoglycemic risk and greater GV. In addition, in resource-limited countries and public institutions, premixed human insulin is still commonly prescribed. Premixed human insulin may further increase the GV compared to premixed insulin analogues due to its less physiological pharmacokinetic profile.[12,13] Hence, a strategy to reduce GV in patients on premixed human insulin is highly desired.

Incretin-based therapies especially the dipeptidyl peptidase 4 inhibitors (DPP4-i) have been increasingly used for the treatment of T2DM. Few studies have shown DPP4-i to be effective in reducing GV in patients treated

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with metformin.[14-17] Studies on the effect of DPP4-i on GV in patients with T2DM treated with insulin are very limited. We, therefore, undertook this study to evaluate the effect of Vildagliptin on GV in patients with T2DM treated with premixed human insulin.

METHODOLOGY

Subjects and study design

This was a prospective study involving adult patients with T2DM attending diabetes clinics in 2 state hospitals in Malaysia. Patients with HbA1c of 7-10% who were treated with stable dose of twice-daily premixed human insulin (30% regular insulin, 70% Neutral Protamine Hagedorn) for at least 3 months, with or without metformin as combination therapy, were recruited. Participants who consented attended baseline visit with a diabetes nurse educator and were briefed on the use of continuous glucose monitoring (CGM) before undergoing a 7-day blinded CGM (Medtronic MiniMed, Northridge, CA) to collect baseline GV data. They were instructed to perform self-monitoring of blood glucose (SMBG) 4 times daily for CGM calibration during the 7-day period and record any symptomatic hypoglycemic episode in the SMBG diary. Baseline demographics, insulin dosage as well as HbA1c and renal function were collected. Subjects and investigators were blinded to the results of the CGM until the end of the study.

Participants returned after completion of the 7-day CGM and were then started on vildagliptin (Novartis Pharma AG, Basel, Switzerland) for 6 weeks. The dose of Vildagliptin was determined based on calculated eGFR using MDRD (Modification of Diet in Renal Disease) IDMS (isotope dilution mass spectrometry) traceable formula. Vildagliptin 50 mg twice daily was prescribed for patients with eGFR ≥50 ml/min while patients with eGFR <50 ml/min received vildagliptin 50 mg daily as per prescription information recommendation. Drug accountability was assessed by tablet count. Throughout the study period, insulin doses were kept stable but may be adjusted by the investigators in the event of recurrent or severe hypoglycemia. The participants were also given the diabetes team's contact number for adjustment of insulin should they experience more frequent hypoglycemia with initiation of vildagliptin, as per usual clinical practice.

After 6 weeks of vildagliptin therapy, participants returned for the third trial visit and a repeat 7-day CGM was performed. Changes in weight, insulin dosage and any symptomatic hypoglycemic episode occurring during the study period were recorded. Data collected from the CGM device were analyzed with EasyGV software to derive the glycemic variability parameters. Primary outcome measures for GV were changes in mean amplitude of glycemic excursions (MAGE), standard deviation of the mean glucose levels (SD) and % coefficient of variation (CV). We also examined other secondary GV measures including M value, mean absolute glucose (MAG), continuous overlapping net glycemic action (CONGA), low blood glucose index (LBGI), high blood glucose index (HBGI) and lability index (LI). In addition, we explored quality of glycemic control with addition of DPP4-i treatment by assessing the % time in range (TIR) with blood glucose in target range of 3.9-10.0 mmol/L, % time above range (TAR), % time below range (TBR) and % of time spent in clinically significant level 2 hypoglycemia (blood glucose <3.0 mmol/L regardless of symptoms). Area under the curve (AUC) above and below blood glucose target of 3.9 and 10.0 mmol/L respectively, as well as glycemic estimate, i.e. estimated HbA1c (eA1c) from CGM data were also assessed before and after vildagliptin treatment.

Sample size and statistical analysis

A prior study investigating GV variable (MAGE) from matched pairs of study subjects indicated that the difference in the response of matched pairs was normally distributed with an estimated standard deviation of 3.0.[18] Based on the true difference in the mean response of matched pairs estimated at 3.5, we needed to study a minimum of 8 pairs of subjects to be able to reject the null hypothesis that this response difference was zero with a probability of (power) 0.8. The Type I error probability associated with the test of this null hypothesis was 0.05.[19] After incorporating 30% for non-response rate, the required sample size was 12 subjects.

Data analysis was performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Continuous data were expressed as mean (standard deviation) or median (interquartile range); whereas, categorical data were reported as counts (percentages). Normality distributions were determined by Shapiro-Wilk test, a p-value of ≥0.05 considered the data distributions as normal. Means of normally distributed continuous data at baseline vs. end of study and before vs. after vildagliptin therapy were compared using paired t-test. For non-normally distributed variables, Wilcoxon Sign Rank test was used. A two-sided p-value <0.05 was considered to be statistically significant for both tests.

The study was registered at the Malaysian National Medical Research Register (NMRR 18-2293-43523) and approved by the Malaysian Medical Research and Ethics Committee. Written informed consents were obtained from all participants. The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

RESULTS

Patient characteristics

Twelve patients (6 males) with a mean (SD) age of 55.8 (13.1) years old and mean duration of diabetes of 14.0 (6.6) years participated in the study. Their baseline demographic and clinical characteristics are presented in Table 1. They had significant microvascular and macrovascular complications and majority of them had concomitant hypertension and dyslipidemia. Mean HbA1c at baseline was 8.4 (1.0) % and mean eGFR was 62.1 (25.8) ml/min/kg/m^2. 42% of the participants had stage 3 chronic kidney disease. Two-thirds of them received metformin therapy in combination with their premixed insulin. Mean insulin dose was 0.63 u/kg/day. Treatment adherence was good with drug accountability of 98%.

Glycemic variability parameter

Table 2A summarizes the GV parameters derived from the CGM before and after DPP4-i treatment. The addition of Vildagliptin significantly reduced GV indices in our

Table 1. Demographic and clinical characteristics at baseline and end of study

	Baseline	End of study	*P* value
Age (years)	55.8 (13.1)		
Duration of diabetes (years)	14.0 (6.6)		
Duration on premixed insulin (years)	6.8 (3.6)		
Baseline HbA1c (%)	8.4 (1.0)		
Diabetes complication rate (%)			
Retinopathy	9 (75.0%)		
Nephropathy	10 (83.3%)		
Peripheral neuropathy	3 (25.0%)		
Ischemic heart disease	3 (25.0%)		
Cerebrovascular accident	1 (8.3%)		
Hypertension	11 (92.0%)		
Dyslipidemia	11 (92.0%)		
Drugs			
Metformin	8 (67.0%)		
RAAS blockade	11 (92.0%)		
Statin	11 (92.0%)		
Antiplatelet	6 (50.0%)		
Body Weight (kg)	75.1 (11.9)	73.7 (13.7)	0.54
BMI (kg/m^2)	29.4 (4.7)	28.6 (5.4)	0.42
Insulin dosage (unit/day)	47.2 (14.8)	46.5 (15.3)	0.26
Insulin dosage (unit/kg/day)	0.6 (0.2)	0.6 (0.2)	0.75
eGFR (ml/min/1.73m^2)	62.1 (25.8)	58.4 (24.3)	0.30

HbA1c: glycated hemoglobin, RAAS: renin–angiotensin–aldosterone system, BMI: body mass index, eGFR: estimated glomerular filtration rate. Data are mean (SD) and n (%) on 12 adult patients with Type 2 diabetes mellitus treated with premixed human insulin.

patients on twice-daily premixed human insulin. While the mean blood glucose was not different before or after Vildagliptin, standard deviation of the mean glucose levels (SD) and coefficient of variation (CV) were significantly reduced. Mean amplitude of glycemic excursions (MAGE), one of the most commonly used parameters to reflect GV, was reduced from 6.94 (2.6) mmol/L at baseline to 5.72 (1.9) mmol/L (p=0.018). CONGA was not different but there was a significant reduction in mean absolute glucose (MAG), M value and liability index (LI).

Glycemic control parameters

Estimated HbA1c derived from CGM data improved significantly from 7.36% to 6.60% (p=0.031). Body weight, insulin dose and renal function did not change significantly before and after Vildagliptin treatment (Table 1). There was an improvement in the time in range (TIR) at blood glucose of 3.9-10.0 mmol/L, contributed by significant reduction in time above range (TAR) as well as AUC for TAR (Table 2B). HBGI was significantly reduced. Overall hypoglycemic events were infrequent and there was no episode of severe level 3 hypoglycemia reported by the participants during the study period. There was a reduction in % time below range (TBR), AUC for TBR, as well as % of time with level 2 hypoglycemia (blood glucose below 3.0 mmol/L) with addition of Vildagliptin, but these parameters did not reach statistical significance. LBGI and GRADE also showed a non-significant reduction with Vildagliptin treatment.

DISCUSSION

Traditionally, patients with T2DM initiated on or intensified to twice-daily premixed insulin often have their oral anti-diabetes medication further simplified. Metformin therapy is usually maintained while other oral anti-diabetes agents including DPP4-i are typically discontinued.[20] Blood glucose control is then achieved by titration of insulin dosage or further intensification to basal-bolus insulin regimen. While these strategies may lower blood glucose and improve HbA1c, they are associated with increased risk of hypoglycemia and weight gain. The effect on GV may also be heterogeneous.

Premixed human insulin is commonly used for treatment of patients with T2DM, either at initiation of insulin therapy or during intensification from basal insulin.[10,21] While simpler, more convenient, and acceptable to patients due to reduced injection burden, it is less flexible and may be associated with higher glucose fluctuations. In addition, in

Table 2. Indices of glycemic variability and glycemic control parameters before and after vildagliptin therapy

	Before Vildagliptin	After Vildagliptin	*P* value
2A. GV parameters (mmol/L)			
Mean blood glucose	8.81 (2.43)	8.17 (1.63)	0.325
SD	2.73 (2.12 - 3.66)	2.11 (1.76 - 2.55)*	0.015[a]
% CV	34.05 (8.76)	28.19 (5.36)**	0.010
MAGE	6.94 (2.61)	5.72 (1.87)*	0.018
MAG	1.34 (1.16 - 1.82)	1.12 (0.89 - 1.39)**	0.002[a]
CONGA	8.13 (2.39)	7.58 (1.46)	0.400
M Value	9.18 (5.45 - 17.05)	3.56 (2.55 - 7.12)*	0.023[a]
LI	2.44 (1.43 - 4.48)	1.54 (0.92 - 2.31)[a, **]	0.002[a]
2B. Glycemic control parameters			
Estimated HbA1c (eA1c)	7.36 (1.51)	6.60 (0.92)*	0.031
% time in range	61.17 (20.50)	79.67 (15.33)**	0.001
% time above range	32.92 (23.99)	18.50 (15.62)*	0.016
% time below range	5.92 (9.74)	1.84 (2.58)	0.183
% time below 3.0 mmol/L	1.50 (2.88)	0.25 (0.62)	0.187
LBGI (mmol/L)	3.50 (3.38)	1.66 (1.28)	0.077
HBGI (mmol/L)	7.29 (4.60 - 12.67)	4.86 (2.99 - 7.42)*	0.034[a]
AUC above 10.0 mmol/day	1.24 (1.31)	0.47 (0.71)*	0.015
AUC below 3.9 mmol/day	0.03 (0.54)	0.01 (0.02)	0.163

MAGE: mean amplitude of glycemic excursions, MAG: mean absolute glucose, CONGA: continuous overlapping net glycemic action, LI: liability index, HbA1c: glycated hemoglobin, LBGI: low blood glucose index, HBGI: high blood glucose index, AUC: area under the curve.
Data are mean (SD) or median (interquartile range) on 12 adult patients with Type 2 diabetes mellitus treated with premixed human insulin.
* P<0.05 vs. before vildagliptin; ** P≤0.01 vs. before vildagliptin

resource-limited countries, premixed human insulin is still widely used. Compared to premixed insulin analogues, premixed human insulin is associated with a higher risk of hypoglycemia as well as higher postprandial glucose excursion.[13,22] Hence, a strategy to reduce GV in patients treated with premixed human insulin is highly desirable. Newer anti-diabetic drugs including the incretin-based therapy have been shown to reduce GV in addition to their glucose lowering effect.[23,24] Since its introduction more than a decade ago, DPP4-i has been widely used for glycemic management of patients with T2DM. Hence, we undertake the current study to examine if the addition of DPP4-i will improve GV in patients with T2DM treated with premixed human insulin.

The addition of a DPP4-i to an insulin regimen has been reported to have moderate efficacy in a meta-analysis,[25] reducing HbA1c around 0.5% without increasing the risk of hypoglycemia or weight gain. DPP4-i effect on GV has been less well-studied. A systematic review and meta-analysis performed by Lee et al., to evaluate the effect of DPP4-I compared to other oral anti-diabetes drugs on GV in patients with T2DM included 304 patients in 7 studies and found a significant reduction of MAGE for patients treated with DPP4-i compared to sulfonylurea.[26] All patients in the studies were drug-naive or on metformin monotherapy.

Comparatively, data regarding the effect of DPP4-i on GV in insulin-treated patients with T2DM are very limited. Nomoto et al., found dapagliflozin was not superior to DPP4-i in reducing GV in 29 patients with T2DM treated with insulin.[27] Li et al.,[18] examined the effect of vildagliptin in Chinese patients with uncontrolled T2DM treated with either basal or premixed insulin analogues with or without metformin and found significant improvement of GV in the group with vildagliptin added on. There was a significant reduction in MAGE and mean blood glucose but no improvement in SD nor AUC >10 mmol/L in the vildagliptin-treated group compared to placebo. Apart from the difference in the insulin regimen used (around 35% basal, and the remaining premixed insulin analogues), the CGM was performed in-hospital with controlled mealtime and meal composition.

In contrast, all our patients were on human premixed insulin with or without metformin and the CGM was performed in real-life outpatient home setting. Our study showed that while mean blood glucose was the same, the addition of vildagliptin significantly improved various GV parameters including a reduction in MAGE, SD, CV, MAG, M value and LI. Vildagliptin also significantly improved estimated HbA1c (eA1c) and time in range. There was a significant reduction in % time above range and AUC for blood glucose >10.0 mmol/L. This has been attributed to enhanced insulin release from pancreatic beta cells as well as suppression of glucagon secretion during hyperglycemia.[23,27] Furthermore, the reduction in hyperglycemia was achieved without increasing the AUC of hypoglycemia, due to its glucose-dependent insulinotropic effect. In fact, in our cohort of patients with long-standing diabetes with multiple co-morbidities and reduced renal function, the addition of vildagliptin reduced the % of time below range and AUC for blood glucose <3.9 mmol/L as well as % below clinically-significant level 2 hypoglycemia with blood glucose of <3.0 mmol/L. However, as overall hypoglycemic events were infrequent, these parameters did not reach statistical significance.

This study is limited by the lack of a control group. However, we tried to minimize confounding factors by keeping intervention to a minimum. We recruited patients who were on stable doses of insulin for at least 3 months and the insulin dose was not adjusted during the study, except for hypoglycemia. Baseline CGM results were kept blinded until the end of the study, study visits were primarily for insertion and removal of the CGM sensor and interaction with the diabetes nurse was solely for the use of CGM and for hypoglycemia management. In addition, the study period was kept short to reduce changes in lifestyle and other confounding variables. Indeed, we observed no significant changes in insulin dosage or body weight for the study period. Our vildagliptin treatment duration of 6 weeks was relatively short. Although pharmacokinetic study had shown that vildagliptin and its metabolite reached a steady state after 14 days of dosing,[28] we cannot be sure that a complete therapeutic effect had been achieved.

Our study strengths include the participation of insulin-treated high-risk patients with long duration of diabetes and multiple co-morbidities, in whom reduction of GV and hypoglycemic risk are of particular clinical relevance. Strategies to reduce GV in this group of patients are limited in the literature. In addition, compared to other studies which performed CGM for 3 days only (14-18), some under inpatient setting with standardized mealtime and composition, we examined GV via 7-day CGM under real-world ambulatory setting without interfering with the patients' usual lifestyle. Thus, we believe our results are applicable clinically and better reflect the effect of DPP4-i on GV in the real-world setting.

CONCLUSION

Our study examined an important treatment strategy in real-world setting for a vast number of patients receiving premixed human insulin where addition of DPP4-i inhibitor has not been considered a standard practice.[20] Our study added to the scarce literature that DPP4-i improved GV in patients with T2DM treated with twice-daily premixed human insulin. We suggest that its role and long-term benefits in this group of patients more vulnerable to hypoglycemia and diabetic complications should be further explored.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflicts of interest.

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