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ORIGINAL

Comparative effects of vildagliptin and sitagliptin determined by continuous glucose monitoring in patients with type 2 diabetes mellitus

Naohide Koyanagawa[1)], Hideaki Miyoshi[1)], Kota Ono[2)], Akinobu Nakamura[1)], Kyu Yong Cho[1)], Kohei Yamamoto[1)], Yoshinari Takano[1)], Midori Dan-noura[1)] and Tatsuya Atsumi[1)]

[1)] *Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[2)] *Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan*

Abstract. The dipeptidyl peptidase-4 inhibitors vildagliptin and sitagliptin are effective in treating patients with type 2 diabetes mellitus. Patients receiving standard doses of sitagliptin plus insulin may require increased doses of sitagliptin or switching to vildagliptin to improve blood glucose control. This study compared the effects of increasing sitagliptin and switching to vildagliptin in type 2 diabetes patients receiving standard doses of sitagliptin plus insulin. This prospective, randomized, parallel-group comparison trial enrolled 33 type 2 diabetes patients receiving 50 mg sitagliptin once daily plus insulin. Seventeen patients were randomized to 50 mg vildagliptin twice daily, and 16 to 100 mg sitagliptin once daily, and evaluated by continuous glucose monitoring at baseline and after 8 weeks. The primary end-point was the change in mean amplitude of glycemic excursions (MAGE). MAGE decreased from baseline in both the vildagliptin (−13.4 ± 35.7 mg/dL) and sitagliptin (−8.4 ± 24.3 mg/dL) groups, but neither within- nor between-group changes were statistically significant. Similarly, the areas under the curve for blood glucose levels ≥180 mg/dL and <70 mg/dL tended to improve in both groups, but these differences were not statistically significant. In contrast, HbA1c was significantly reduced only in the vildagliptin group, from 7.1 ± 0.6% at baseline to 6.8 ± 0.6% at 8 weeks (p=0.006). Increasing sitagliptin dose and switching to vildagliptin had limited effects in improving MAGE in type 2 diabetic patients treated with standard doses of sitagliptin.

Key words: Vildagliptin, Sitagliptin, Mean amplitude of glycemic excursions (MAGE)

INCRETIN increases insulin secretion and decreases glucagon secretion by the pancreas to varying degrees depending on plasma glucose concentrations [1]. In addition, incretin plays an important role in avoiding hypoglycemia by suppressing insulin secretion and disinhibiting suppression of glucagon secretion under conditions of normoglycemia and hypoglycemia [1]. Compared with the sulfonylurea glimepiride, vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has been associated with reduced fluctuation of glucose levels in patients with type 2 diabetes mellitus (T2DM) on stable metformin monotherapy, as assessed by continuous glucose monitoring (CGM) [2].

The combination of a DPP-4 inhibitor, such as vildagliptin or sitagliptin, and insulin is frequently employed in clinical practice to treat patients with T2DM. These combinations have been shown to reduce both HbA1c and the incidence of hypoglycemia [3, 4]. Moreover, a study using CGM confirmed that adding 50 mg/day sitagliptin (the approved dose in Japan) to insulin significantly reduced the mean amplitude of glycemic excursions (MAGE) and the proportion of time patients are hyperglycemic without increasing hypoglycemia [5].

Several studies have analyzed the effects of DPP-4 inhibitors on MAGE in patients with T2DM not receiving insulin. These trials showed that 100 mg/day (50 mg twice daily) vildagliptin was significantly better than 50 or 100 mg/day sitagliptin in decreasing MAGE [6-8].

Patients with T2DM treated with 50 mg/day sitagliptin plus insulin may not attain their treatment target. To date, however, the optimal step-up regimen has not been determined. This open label, randomized, interventional study compared the effects of switching to the Japanese standard dose of 100 mg vildagliptin

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Correspondence to: Hideaki Miyoshi, M.D., Ph.D., Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, North 15, West 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: hmiyoshi@med.hokudai.ac.jp

and increasing to the maximal dose (100 mg/day) of sitagliptin on Japanese T2DM patients treated with insulin and 50 mg/day sitagliptin.

Materials and Methods

Patients

This open-label, randomized, prospective, parallel-group study included patients with T2DM undergoing outpatient treatment at Hokkaido University Hospital from March 2013 to June 2014. Participants were given a detailed description of the study and were informed of possible risks and benefits of participation prior to their providing written informed consent and enrollment in the study. Patients were included if they were ≥20 years old, had HbA1c (NGSP) levels between 6.2% and 8.4%, and had received nutrition/ exercise therapy, as well as drug therapy with sitagliptin (50 mg once daily) and insulin for over 3 months. HbA1c (JDS), which was adopted at the start of the study, was later converted to NGSP. Patients were excluded if they had serious hepatic dysfunction, renal failure, or heart complications, or if they were pregnant, lactating, or had a history of hypersensitivity to the ingredients of vildagliptin. This study was approved by the Institutional Review Board of Hokkaido University Hospital, and was performed in accordance with the Declaration of Helsinki. The Clinical Trial registration No. is UMIN000010199.

Study protocol

The study protocol is illustrated in Fig. 1. Patients were randomly allocated to the vildagliptin (50 mg twice daily) or sitagliptin (100 mg once daily) group by an independent organization at the beginning of the study period. Randomization was stratified by mean age, disease duration, HbA1c concentration and total insulin dose using the minimization method with system filemaker Pro v11. Daily glucose levels were monitored with a CGM system (iPro2®, Medtronic MiniMed, Northridge, CA.) for 3 to 5 days during treatment with insulin and sitagliptin (50 mg daily). Patients were subsequently treated with 50 mg vildagliptin twice daily or 100 mg sitagliptin once daily for 8 (±4) weeks. The doses of other medications, including insulin, were maintained without change during the study period, unless there was a risk of hypoglycemia. After the treatment period, daily glucose levels were again monitored by CGM for 3 to 5 days. Fasting blood and urine samples were collected at the times of fitting the CGM system.

The primary end-point of this study was change in MAGE [9]. Secondary end-points included change of M-value, average daily blood glucose level, area under the curve (AUC) > 180 mg/dL within 3 h of each meal, AUC < 70 mg/dL over 24 h, glucose and lipid profiles, β-cell response (CPR/FPG), C-reactive protein, urinary 8-OHdG, and pentraxin 3 (PTX3).

Statistical analysis

Based on a previous study, which compared the change in MAGE between patients treated with vildagliptin and sitagliptin without insulin [8], power calculations determined that a sample size of 13 individuals per group was required to have at least 80% power to detect a between-group difference. To account for potential loss of subjects, the sample size was set at 17 patients

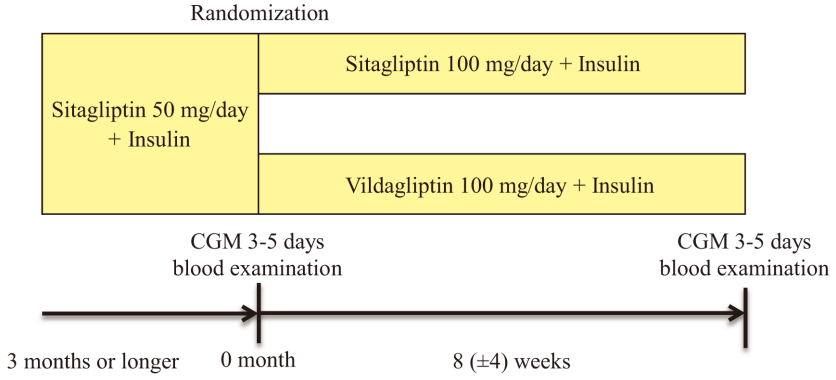

Fig. 1 Study protocol
After treatment with sitagliptin (50 mg/day) plus insulin for 3 months or longer, patients were randomly allocated to treatment with vildagliptin (50 mg twice daily) or the sitagliptin (100 mg once daily) plus insulin. All patients were evaluated by continuous glucose monitoring at baseline and after 8 (±4) weeks of treatment.

per group. Statistical analyses were performed on the full analysis set (FAS), which included all patients who were randomized, received at least one dose of study drug and had at least one MAGE value after study drug administration. Results were expressed as mean, median and range. Between-group differences in baseline characteristics were assessed by Welch's *t*-tests or Mann–Whitney U tests for continuous variables. Mean changes between baseline and the end of the study of laboratory markers in both groups were assessed by Welch's *t*-test or the Mann-Whitney U test. The Shapiro-Wilk test for normality was used to determine the appropriate statistical test for continuous variables. A p-value <0.05 was considered statistically significant. Data were analyzed using Ekuseru-Toukei 2011 (Social Survey Research Information, Tokyo, Japan).

Results

A total of 33 patients were randomly assigned to either vildagliptin (n=17) or sitagliptin (n=16), with 14 and 12 of these patients, respectively completing the study. The reasons for non-completion included patient discontinuation (n=2), moving from the area (n=4), and withdrawal of consent after randomization (n=1). The baseline characteristics of the randomized patients are presented in Table 1. The two groups were well balanced at baseline in mean age, disease duration, HbA1c concentration, and total insulin dose. Baseline CGM parameters including MAGE, M-value, average daily blood glucose level, AUC < 70 mg/dL, AUC > 180 mg/dL, and the baseline blood glucose control indicators glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG), were equivalent statistically in the two groups.

Insulin doses were reduced by physicians in three patients being treated with vildagliptin to avoid hypoglycemia. The mean total insulin doses in this group decreased from 30.4 ± 19.4 to 29.5 ± 19.0 U/day, whereas there was no change in the sitagliptin group. The average daily profiles of all patients in both groups are shown in Fig. 2. The CGM data suggested that vildagliptin was superior to sitagliptin, but the difference between these two groups was not statistically significant (Table 2). The change in MAGE after a mean 8.9 weeks of vildagliptin treatment was −13.4 ± 35.7 mg/dL, compared with a change after a mean 8.2 weeks of treatment with the higher dose of sitagliptin was −8.4 ± 24.3 mg/dL. Neither the change from baseline in each group nor the between group difference at the end of the study was statistically significant. Although there was no significant between group difference in reduction of HbA1c concentrations, HbA1c was significantly reduced in the vildagliptin group, from 7.1 ± 0.6% at baseline to 6.8 ± 0.6% after treatment (p=0.006). There were no significant between group differences in β-cell response, lipid parameters, C-reactive protein, and urinary 8-OHdG, although the plasma pentraxin 3 concentration was significantly lower in the vildagliptin group (p=0.04) (Table 3).

Table 1 Clinical characteristics of subjects

	Vildagliptin	Sitagliptin	*P*-value
Age (years)	65.9 ± 7.5	64.5 ± 9.8	0.92
Diabetes duration (years)	17.4 ± 9.9	15.7 ± 9.2	0.98
HbA1c (%)	7.1 ± 0.6	7.3 ± 0.4	0.38
Total insulin dose (unit)	30.4 ± 19.4	21.3 ± 13.4	0.18
MAGE (mg/dL)	101.0 (86.0-145.3)	130.3 (90.4-152.3)	0.37 §
M-value	44.6 (29.7-79.8)	83.6 (22.4-117.3)	0.26 §
AUC<70 mg/dL (mg/dL/day)	0 (0-0.9)	0 (0-0.1)	0.41 §
AUC>180 mg/dL (mg/dL/day)	2.6 (1.3-17.8)	12.4 (4.2-23.2)	0.09 §
GA (%)	17.3 ± 3.2	19.0 ± 2.3	0.16
1,5AG (μg/mL)	7.1 ± 2.9	9.2 ± 6.7	0.46
Diabetic medication (n):			
None/SU/BG/TZT/αGI	3/4/9/4/1	5/3/6/1/0	
Insulin regimen (n):			
MDI/Basal/Mix	3/5/6	3/8/1	

Data are mean ± SD. § by Mann–Whitney U tests. Abbreviations: MAGE, mean amplitude of glycemic excursions; AUC, area under the curve; GA, glycated albumin; 1,5-AG, 1,5-anhydroglucitol; SU, Sulfonylureas/glinides; BG, Biguanides; TZT, Thiazolidines; αGI, Alpha-glucosidase inhibitors; MDI, Multiple dailyinjection; Basal, Long-acting insulin; Mix, Mixed insulin.

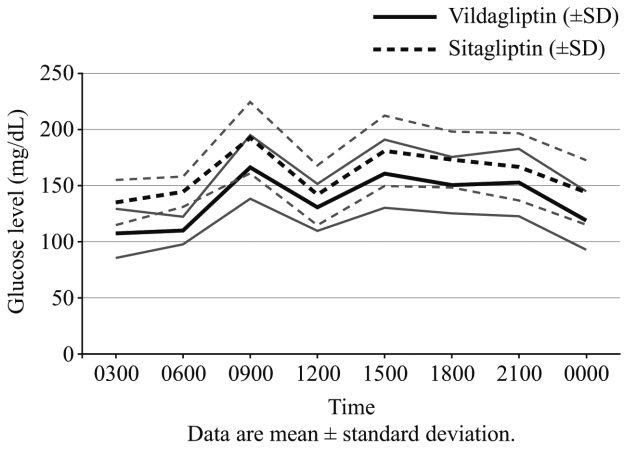

Fig. 2 Average daily glucose profiles during treatment with 100 mg/day vildagliptin or 100 mg/day sitagliptin
The solid line shows the mean of the vildagliptin group (n=14) and the light solid lines show the ± SD. The dotted line shows the mean of the sitagliptin group (n=12) and the light dotted lines show the ± SD.

Table 2 Parameters of glucose variability in the two groups at baseline and after 8 weeks

	100 mg vildagliptin		100 mg sitagliptin		*P*-value
	Base line	After 8 weeks	Base line	After 8 weeks	
MAGE (mg/dL)	101 (86-145.3)	91.3 (72.4-135.2)	130.3 (90.4-152.3)	114.1 (81.9-134.9)	0.43 §
Average blood glucose level (mg/dL)	141.3 ± 29.3	133.1 ± 30.1	154.6 ± 29.1	159.0 ± 26.4	0.32
M-value	44.6 (29.7-79.8)	26.4 (15.3-52.5)	83.6 (22.4-117.3)	64.2 (20.2-114.9)	0.61 §
AUC<70 mg/dL (mg/dL/day)	0 (0-0.9)	0 (0-0.72)	0 (0-0.1)	0 (0-0.1)	0.23 §
AUC>180 mg/dL (mg/dL/day)	2.6 (1.3-17.8)	1.9 (0.5-8.2)	12.4 (4.2-23.2)	12.0 (1.1-13.9)	0.76 §

Data are mean ± SD or median (range). § by Mann–Whitney U tests. Abbreviations: MAGE, mean amplitude of glycemic excursions; AUC, area under the curve; GA, glycated albumin; 1,5-AG, 1,5-anhydroglucitol.

Table 3 Laboratory markers in the two groups at baseline and after 8 weeks

	100 mg vildagliptin		100 mg sitagliptin		*P*-value
	Baseline	After 8 weeks	Baseline	After 8 weeks	
HbA1c (%)	7.1 ± 0.6	6.8 ± 0.6 *	7.3 ± 0.4	7.2 ± 0.4	0.15
GA (%)	17.3 ± 3.2	17.3 ± 3.3	18.9 ± 2.3	18.6 ± 2.0	0.72
1,5AG (μg/mL)	7.1 ± 2.9	8.4 ± 4.3	9.2 ± 6.7	9.7 ± 6.8	0.37
CPR/FPG ($\times 10^{-2}$)	0.87 ± 0.50	1.08 ± 0.40	0.90 ± 0.60	0.89 ± 0.55	0.13
LDL-C (mg/dL)	86.9 ± 23.6	87.0 ± 23.5	100.8 ± 14.1	99.5 ± 20.8	0.88
HDL-C (mg/dL)	57.1 ± 16.7	58.0 ± 17.5	53.8 ± 15.0	54.0 ± 13.7	0.92
TG (mg/dL)	135 (77-186)	115 (66-140)	93 (61-135)	81 (61-145)	0.26 §
FFA (μEq/L)	518.4 ± 213.2	453.3 ± 210.1	482.3 ± 232.4	428.3 ± 124.3	0.68
C-reactive protein (mg/dL)	435 (309-1,210)	457 (306-789)	512 (323-1,830)	612 (431-2,580)	0.68 §
PTX3 (ng/mL)	1.74 (1.66-1.9)	1.52 (1.3-1.86)	1.68 (1.36-2.3)	1.57 (1.18-2.4)	0.04 †§
Urinary 8-OHdG (ng/mL)	9.9 (9.2-11.5)	9.9 (7.4-11.3)	11.3 (0-17.4)	10.6 (6.8-18.9)	0.66 §

Data are mean ± SD. *P*-value: mean changes between baseline and the end of the study (Welch's *t*-test or Mann-Whitney U test).
* $P < 0.05$ between baseline and the end of the study (paired-sample *t*-tests). † $P < 0.05$ between groups (Mann–Whitney U test).
§ by Mann–Whitney U tests. PTX3, pentraxin 3.

Discussion

DPP-4 inhibitors differ in metabolism, excretion, and potency, affecting their recommended standard daily doses, ranging from 5 mg/day saxagliptin or linagliptin to 200 mg/day anagliptin [10]. All of these agents show similar efficacy in inhibiting DPP-4 activity and lowering HbA1c levels, and in their safety profiles [10, 11]. The standard doses in clinical practice for Japanese patients with T2DM have been set at 100 mg/day (50 mg twice daily) for vildagliptin and 50 mg/day for sitagliptin. A meta-analysis evaluating placebo-controlled clinical trials investigating the efficacy and safety of DPP-4 inhibitors found that 100 mg/day vildagliptin and 100 mg/day sitagliptin (each once daily) had comparable efficacy in western patients with T2DM [10, 12]. A randomized parallel-group study using CGM and comparing 100 mg/day vildagliptin and 100 mg/day sitagliptin in 90 patients with T2DM found significant improvements in MAGE, oxidative stress, and systemic inflammation in the vildagliptin group [6, 7]. Similarly, a comparison of 100 mg/day vildagliptin with 50 mg/day sitagliptin in Japanese T2DM patients found that mean 24 h blood glucose, MAGE, highest blood glucose level after supper, and hyperglycemia after breakfast were significantly lower in the vildagliptin group [8].

To our knowledge, this is the first randomized parallel-group study evaluating T2DM subjects treated with insulin plus 50 mg/day sitagliptin for more than 3 months and monitoring their daily glycemic profile using CGM. The primary outcome of this study, MAGE, was comparable in patients switched to 100 mg/day vildagliptin and those increased to 100 mg/day sitagliptin. This result was different from previous trials using CGM. Discrepancies may have been due to differences in the severity of T2DM, in that insulin therapy is usually administered in patients with advanced diabetes. The patients enrolled in previous studies were not treated with insulin, and their diabetes duration was 4.5 to 8.6 years [6-8]. In contrast, patients in this study were being treated with insulin, and their mean disease duration was 16.6 years. The discrepancies among studies may also have been due to dietary restrictions during CGM monitoring, in that the previous studies were performed on hospitalized patients and those receiving test meals, whereas our study included outpatients in clinical practice.

In this trial, HbA1c was significantly decreased after switching from 50 mg/day sitagliptin to 100 mg/day vildagliptin. The reason for this reduction may have been due to the relative effects of sitagliptin and vildagliptin on DPP-4 activity over 24 h. A single 50-mg dose of sitagliptin was shown to suppress >80% of DPP-4 activity for almost 14 h, whereas 50 mg of vildagliptin twice daily inhibited >80% of DPP-4 activity throughout the 24 h period [7, 8]. As the costs of both dosages in Japan are similar, it may be benefit patients to switch from 50 mg/day sitagliptin to 100 mg/day vildagliptin.

Hypoglycemia is a major limiting factor to good glycemic control with insulin [13]. The addition of vildagliptin or sitagliptin to insulin treatment has been reported to reduce HbA1c without weight gain or an increase in hypoglycemia [3, 14]. Those studies, however, did not monitor patients with a CGM system and confirmed hypoglycemia was defined as patient symptoms suggestive of low blood glucose. Moreover, the addition of vildagliptin to insulin in T2DM patients receiving insulin can reduce the dose of insulin [3, 15]. CGM is required to determine the effect of agents on hypoglycemia, because patients using insulin experience many unrecognized hypoglycemic episodes [16, 17]. In the present study, hypoglycemia, defined as AUC < 70 mg/dL on CGM, tended to decrease in both groups, but not significantly.

MAGE reduction in T2DM is associated with reductions in oxidative stress. MAGE and IL-6 showed greater reductions following treatment with 50 mg of vildagliptin twice daily than 100 mg of sitagliptin once daily [7]. Although no significant between-group difference in MAGE was observed in this study, the concentration of PTX3 was significantly lower in the vildagliptin group. PTX3, an inflammatory marker protein of the pentraxin family, to which CRP also belongs, is produced by vascular endothelial and vascular smooth muscle cells and is therefore considered a more sensitive marker of local inflammation in the blood vessels than CRP, which is produced in the liver [18]. Treatment with acarbose and subsequent improvement in postprandial glucose control resulted in a significant improvement in PTX3 levels [19]. Although improvements in PTX3 may reflect a reduction of local inflammation in blood vessels *via* the direct or indirect action of vildagliptin, the mechanism cannot be assumed at present and requires further studies.

The major limitations of this study were the small sample size and the short duration of treatment, as well as differences in treatment periods. In addition, the

present study was performed in standard clinical practice and did not use test meals during the 3- to 5-day CGM periods.

In conclusion, daily blood glucose variability was not further improved by increasing the dose of sitagliptin or switching to vildagliptin in T2DM patients being treated with insulin and sitagliptin.

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Author Contributions

N.K. contributed to the data analysis and wrote the manuscript. H.M. designed and performed the research and wrote the manuscript. K.O. contributed to the statistical analysis. A.N., Cho. KY., K.Y., and Y.T. contributed to patient enrollment. H.M., A.N., M.D., and T.A. contributed to discussions and reviewed and edited the manuscript.

Disclosures

H.M. has received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Dainippon Pharma Co., Eli Lilly, Kissei, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma and Sanofi; and has received research funding from Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo, Eli Lilly, Mitsubishi Tanabe Pharma Co., MSD, Novo Nordisk Pharma, Sanofi, Takeda Pharmaceutical Co., Ono Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., and Taisho Toyama Pharmaceutical Co., Ltd.

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N.K. and M.D. declare no conflicts of interest.

References

1. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, et al. (1993) Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36: 741-744.
2. He YL, Foteinos G, Neelakantham S, Mattapalli D, Kulmatycki K, et al. (2013) Differential effects of vildagliptin and glimepiride on glucose fluctuations in patients with type 2 diabetes mellitus assessed using continuous glucose monitoring. *Diabetes Obes Metab* 15: 1111-1119.
3. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, et al. (2007) Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia* 50: 1148-1155.
4. Mathieu C, Shankar RR, Lorber D, Umpierrez G, Wu F, et al. (2015) A randomized clinical trial to evaluate the efficacy and safety of co-administration of sitagliptin with intensively titrated iusulin glargin. *Diabetes Ther* 6: 127-142.
5. Mori Y, Taniguchi Y, Miyazaki S, Yokoyama J, Utsunomiya K (2013) Effects of add-on treatment with sitagliptin on narrowing the range of glucose fluctuateons in Japanese type 2 diabetes patients receiving insulin therapy. *Diabetes Technol Ther* 15: 237-240.
6. Marfella R, Barbieri M, Grella R, Rizzo MR, Nicoletti GF, et al. (2010) Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations. *J Diabetes Complications* 24: 79-83.
7. Rizzo MR, Barbieri M, Marfella R, Paolisso G (2012) Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. *Diabetes Care* 35: 2076-2082.
8. Sakamoto M, Nishimura R, Irako T, Tsujino D, Ando K, et al. (2012) Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): crossover pilot study (J-VICTORIA study). *Cardiovasc Diabetol* 11: 92.
9. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, et al. (1970) Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 19: 644-655.
10. Jose T, Inzucchi SE (2012) Cardiovascular effects of the DPP-4 inhibitors. *Diab VascDis Res* 9: 109-116.
11. Esposito K, Cozzolino D, Bellastella G, Maiorino MI, Chiodini P, et al. (2011) Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7 % in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 13: 594-603.

12. Fakhoury WK, Lereun C, Wright D (2010) A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. *Pharmacology* 86: 44-57.
13. Hepburn DA, Macleod KM, Pell AC, Scougal IJ, Frier BM (1993) Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes trend with insulin. *Diabet Med* 10: 231-237.
14. Sato S, Saisho Y, Kou K, Meguro S, Tanaka M, et al. (2015) Efficacy and safety of sitagliptin added to insulin in Japanese patients with type 2 diabetes: the EDIT randomized trial. *PLoS One* 10: e0121988.
15. Ito D, Inoue K, Kaneko K, Yanagisawa M, Sumita T, et al. (2015) The efficacy of vildagliptin concomitant with insulin therapy in type 2 diabetic subjects. *J Clin Med Res* 7: 303-307.
16. Ahmet A, Dagenais S, Barrowman NJ, Collins CJ, Lawson ML (2011) Prevalence of nocturnal hypoglycemia in pediatric type 1 diabetes: a pilot study using continuous glucose monitoring. *J Pediatr* 159: 297-302.
17. Chico A, Vidal-Rios P, Subira M, Novials A (2003) The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 26: 1153-1157.
18. Bonacina F, Baragetti A, Catapano AL, Norata GD (2013) Long pentraxin 3: experimental and clinical relevance in cardiovascular diseases. *Mediators Inflamm* 2013:725102.
19. Uzui H, Nakano A, Mitsuke Y, Geshi T, Sakata J, et al. (2011) Acarbose treatments improve arterial stiffness in patients with type 2 diabetes mellitus. *J Diabetes Investig* 2: 148-153.