NOTE

Efficacy of sitagliptin on blood glucose fluctuation in Japanese type 2 diabetic patients with basal-supported oral therapy

Mitsuyoshi Takahara¹⁾, Toshihiko Shiraiwa²⁾, Hideaki Kaneto¹⁾, Naoto Katakami¹⁾, Taka-aki Matsuoka¹⁾ and Ichiro Shimomura¹⁾

¹⁾ Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

²⁾ Shiraiwa Medical Clinic, Osaka, Japan

Abstract. We retrospectively investigated the effect of adding dipeptidyl peptidase-4 (DPP-4) inhibitor and tapering sulfonylurea on blood glucose fluctuation in Asian patients with type 2 diabetes mellitus under basal-supported oral therapy (BOT). We recruited twenty-two consecutive Japanese patients with type 2 diabetes mellitus who had blood glucose fluctuation under the combination therapy of insulin glargine and glimepiride and had sitagliptin initiated with glimepiride tapered. Their hemoglobin A1c levels and mean blood glucose profiles of seven points in self-monitoring blood glucose (SMBG) were $7.4 \pm 0.6\%$ and 8.6 ± 2.0 mmol/L, respectively. Sitagliptin was initiated with the dose of 50 mg per day and titrated up to 100 mg per day when necessary. Glimepiride was withdrawn if possible. Blood glucose fluctuation was evaluated with SMBG by calculating M-value, its range (the difference of maximum and minimum blood glucose levels), and its coefficient of variation (CV). Two months after sitagliptin add-on, M-value was decreased from 19 ± 13 to 13 ± 8 ($p = 0.04$). Blood glucose range and CV were also improved from 9.6 ± 2.9 mmol/L to 7.9 ± 2.6 mmol/L ($p = 0.01$), and from $33 \pm 8\%$ to $29 \pm 8\%$ ($p < 0.01$), respectively. Hemoglobin A1c levels and mean blood glucose profiles were unchanged ($p = 0.93$ and 0.47). In conclusion, blood glucose fluctuation was significantly improved two months after adding sitagliptin and tapering glimepiride in type 2 diabetic Japanese patients who were treated by BOT with insulin glargine and glimepiride.

Keywords: Sitagliptin, Basal-supported oral therapy, Blood glucose fluctuation

BASAL-SUPPORTED ORAL THERAPY (BOT), or combination therapy of long-acting insulin analogue with oral hypoglycemic agents, especially with sulfonylurea, has been regarded as an effective option for glycemic control in type 2 diabetes mellitus [1], and is now widely used in clinical practice. However, some patients under BOT fail to achieve a strict glycemic control; although their preprandial glucose levels are low enough, there still remains uncontrolled hyperglycemia in postprandial period [2, 3]. This coexistence of sufficiently lowered glycemia and uncontrolled hyperglycemia, i.e., daily blood glucose fluctuation, is a challenging problem of existing BOT with long-acting insulin analogue plus sulfonylurea.

Recently, a new oral hypoglycemic agent, dipeptidyl peptidase-4 (DPP-4) inhibitor, has been available in clin-

ical practice [4]. The agent promotes insulin secretion similarly to sulfonylurea but its effect is in theory limited to postprandial and hyperglycemic period, which is in contrast to sulfonylurea. Its pinpoint hypoglycemic effect was therefore expected to improve blood glucose fluctuation in diabetic patients under BOT.

The aim of the current study was to investigate whether the addition of DPP-4 inhibitor and the dose reduction of sulfonylurea could improve blood glucose fluctuation in type 2 diabetic patients with BOT.

Patients and Methods

We retrospectively analyzed the data of twenty-two consecutive Japanese patients with type 2 diabetes mellitus who had blood glucose fluctuation under the combination therapy of insulin glargine, long-acting insulin analogue, and glimepiride, sulfonylurea, and thereby had sitagliptin, DPP-4 inhibitor, initiated with glimepiride tapered. Blood glucose fluctuation was defined by seven-point self-monitoring blood glucose (SMBG) on three days as follows: 1) the highest

Submitted Jun. 11, 2012; Accepted Jul. 18, 2012 as EJ12-0220
Released online in J-STAGE as advance publication Jul. 27, 2012

Correspondence to: Hideaki Kaneto, M.D., Ph.D., Department of Metabolic Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.

E-mail: kaneto@endmet.med.osaka-u.ac.jp

blood glucose level was ≥ 10.0 mmol/L (180 mg/dL) whereas the lowest blood glucose level was below 5.0 mmol/L (90 mg/dL) and therefore the range exceeded 5.0 mmol/L (90 mg/dL), or 2) the equivalent range (i.e., > 5.0 mmol/L) existed between the minimum and maximum blood glucose levels, where the minimum glucose level achieved the target recommended by the Japan Diabetes Society (i.e., < 7.2 mmol/L) [5]. Their hypoglycemic medications administered were only insulin glargine and glimepiride and no other anti-diabetic medication was combined.

After the affirmation of their daily glucose fluctuation, sitagliptin, DPP-4 inhibitor, was initiated with a dose of 50 mg per day and titrated up to 100 mg per day when necessary. Glimepiride was reduced in dose by half or more at the same time of sitagliptin initiation. In some patients, the medication was further tapered, and sometimes withdrawn thereafter, which was judged by their daily blood glucose profiles. The dosage of insulin glargine was also adjusted if necessary, to escape undesirable hyperglycemia and hypoglycemia.

Glycemic control at baseline and two months after sitagliptin-combined therapy was evaluated with blood glucose profiles obtained from SMBG, as well as hemoglobin A1c levels. To assess blood glucose fluctuation, M-value [6], glucose range (the difference between the maximum and minimum glucose levels), and coefficient of variation (CV) (standard deviation of glucose levels divided by their average values) were calculated. Hemoglobin A1c values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values in accordance with the official equation [7]. Hypoglycemia was defined as blood glucose levels less than 4.4 mmol/L. We also determined severe hypoglycemia as < 3.1 mmol/L [8].

We performed the current study in accordance with the declaration of Helsinki, and it was approved by the local ethics committee. Informed consent was obtained from every participant in the current study. Data are given as means and standard deviations for continuous variables or as percentages for dichotomous variables. A *p* value less than 0.05 was considered to be significant. Statistical analyses were performed using IBM SPSS Statistics Version 19 (SPSS Inc.).

Results

Table 1 shows baseline characteristics of the study population. Thirteen patients (59%) were male and

Table 1 Clinical characteristics of the study population

Age (year)	64 $\pm$ 8
Sex: male / female	13 (59%) / 9 (41%)
Body mass index (kg/m ²)	24.8 $\pm$ 3.5
Diabetic duration (year)	11 $\pm$ 5
Hemoglobin A1c (%)	7.4 $\pm$ 0.6
Mean blood glucose (mmol/L)	8.6 $\pm$ 2.0
Maximum blood glucose (mmol/L)	14.2 $\pm$ 3.2
Minimum blood glucose (mmol/L)	4.7 $\pm$ 1.2
Hypertension	12 (55%)
Dyslipidemia	14 (64%)

Data are means $\pm$ standard deviations or *n* (%). Mean, maximum, and minimum blood glucose were obtained from seven-point daily blood glucose profiles on three days.

nine (41%) were female. They were 64 $\pm$ 8 years old, and their baseline hemoglobin A1c levels were 7.4 $\pm$ 0.6%, under BOT with 13 $\pm$ 7 units per day of insulin glargine and 0.7 $\pm$ 0.3 mg per day of glimepiride. Their minimum and maximum blood glucose levels at baseline were 4.7 $\pm$ 1.2 mmol/L (84 $\pm$ 21 mg/dL) and 14.2 $\pm$ 3.2 mmol/L (256 $\pm$ 58 mg/dL), respectively. The minimum blood glucose levels were observed before breakfast in four patients (18%), two hours after breakfast in two patients (9%), before lunch in nine patients (41%), two hours after lunch in one patient (5%), before supper in four patients (18%), and at bedtime in two patients (9%). The maximum blood glucose levels were observed two hours after breakfast in three patients (14%), two hours after lunch in ten patients (45%), two hours after supper in seven patients (32%), and at bedtime in two patients (9%). Their average blood glucose profiles at baseline were as follows: 6.7 $\pm$ 0.9 mmol/L before breakfast, 9.1 $\pm$ 3.5 mmol/L two hours after breakfast, 6.3 $\pm$ 1.8 mmol/L before lunch, 11.5 $\pm$ 2.8 mmol/L two hours after lunch, 7.5 $\pm$ 3.0 mmol/L before supper, 10.7 $\pm$ 2.6 mmol/L two hours after supper, and 9.1 $\pm$ 2.3 mmol/L at bedtime. Twenty patients (91%) had their minimum glucose levels less than 6.1 mmol/L, whereas the prevalence of fasting (pre-breakfast) glucose levels < 6.1 mmol/L was only 32% (*n* = 7).

Two months after sitagliptin add-on, twenty patients (91%) had sitagliptin titrated to 100 mg per day, whereas the rest two (9%) kept the dosage of 50 mg per day. On the other hand, glimepiride was finally tapered to 0.5 mg per day in five patients (23%), and was withdrawn in the rest seventeen (77%). Five patients (23%) had the dosage of insulin glargine increased, whereas

Table 2 Glycemic control before and two month after sitagliptin initiation

	Baseline	After 2 months	<i>p</i> value
Hemoglobin A1c (%)	7.4 ± 0.6	7.4 ± 0.6	0.93
Mean blood glucose (mmol/L)	8.6 ± 2.0	8.4 ± 1.3	0.47
M-value	19 ± 13	13 ± 8	0.04
Blood glucose range (mmol/L)	9.6 ± 2.9	7.9 ± 2.6	0.01
CV of blood glucose (%)	33 ± 8	29 ± 8	< 0.01

Data are means and standard deviations. Mean blood glucose, blood glucose range (the difference between the maximum and minimum glucose levels), coefficient of variation (CV), and M-value were calculated from seven-point daily blood glucose profiles on three days.

the rest seventeen (77%) had the dosage unchanged or reduced. The average dosage of insulin glargine as a whole was 14 ± 7 units per day, with no statistical difference from that at baseline ($p = 0.21$). The average blood glucose profiles were: 7.0 ± 1.2 mmol/L before breakfast ($+0.4 \pm 1.3$ mmol/L from baseline), 9.1 ± 2.5 mmol/L two hours after breakfast (-0.05 ± 2.8 mmol/L from baseline), 6.4 ± 1.1 mmol/L before lunch ($+0.1 \pm 1.5$ mmol/L from baseline), 10.3 ± 2.2 mmol/L two hours after lunch (-1.2 ± 2.9 mmol/L from baseline), 7.2 ± 1.6 mmol/L before supper (-0.3 ± 2.5 mmol/L from baseline), 10.4 ± 2.0 mmol/L two hours after supper (-0.3 ± 2.5 mmol/L from baseline), and 8.8 ± 2.3 mmol/L at bedtime (-0.2 ± 3.1 mmol/L from baseline), respectively (all $p > 0.05$ vs. baseline).

Table 2 shows the change of their glycemic control two months after the initiation of sitagliptin. Although mean blood glucose levels as well as hemoglobin A1c levels remained unchanged, M-value, glucose range, and CV were significantly reduced for two months ($p = 0.04$, 0.01 , and < 0.01 , respectively), indicating significant improvement of blood glucose fluctuation. Incidence of hypoglycemia (< 4.4 mmol/L) was reduced from 0.44 to 0.26 per person per day, but there was no statistical significance ($p = 0.10$). On the other hand, incidence of severe hypoglycemia (< 3.1 mmol/L) was significantly reduced from 0.07 to 0 per person per day ($p = 0.04$). We also performed these analyses in the seventeen patients whose insulin dosage was unchanged or reduced, excluding the five with insulin dosage increased. As a result, glucose range and CV were here again significantly decreased from 9.1 ± 2.3 mmol/L to 7.6 ± 2.6 mmol/L ($p = 0.04$), and from $33 \pm 8\%$ to $28 \pm 9\%$ ($p < 0.01$), respectively. M-value was also decreased from 17 ± 11 to 12 ± 6 , but it did not

reach statistical significance ($p = 0.08$). Hemoglobin A1c and mean glucose levels were unchanged ($p = 0.96$ and 0.83). Incidence of hypoglycemia (< 4.4 mmol/L) and severe hypoglycemia (< 3.1 mmol/L) were both significantly reduced, from 0.54 to 0.22 per person per day ($p = 0.02$) and from 0.10 to 0 per person per day ($p = 0.04$).

To investigate whether there was inter-individual difference in improved blood glucose fluctuation, we further analyzed the association of baseline characteristics with the change of blood glucose fluctuations. The change of blood glucose fluctuation was assessed by the change of M-value, glucose range, and CV from baseline. As a result, the change of M-value from baseline was significantly associated with baseline M-value (correlation coefficient $r = -0.798$, $p < 0.01$) and baseline glucose range ($r = -0.745$, $p < 0.01$), suggesting that the patients with greater blood glucose fluctuation at baseline obtained greater improvement of blood glucose fluctuation. Sex, age, body mass index, diabetic duration, baseline glargine dosage, baseline glimepiride dosage, and baseline hemoglobin A1c levels were not associated with the change of M-value ($p = 0.28$, 0.27 , 0.67 , 0.63 , 0.15 , 0.22 , and 0.12 , respectively). Similar findings were observed when the change of glucose range was instead used. The change of glucose range had significant associations with baseline M-value ($r = -0.622$, $p < 0.01$) and baseline range ($r = -0.608$, $p < 0.01$), but not with other baseline characteristics. On the other hand, the change of CV was significantly correlated with baseline CV ($r = -0.430$, $p = 0.046$), but not with baseline M-value or glucose range ($p = 0.63$ and 0.30). The change of CV was not associated with other baseline characteristics. Baseline CV was not associated with the change of M-value or glu-

cose range ($p = 0.14$ and 0.32).

Discussion

The current retrospective single-arm study demonstrated significant improvement of blood glucose fluctuation after initiating sitagliptin and tapering glimepiride in type 2 diabetic patients with BOT. The major weakness of the current study was its study design and future prospective randomized controlled trials are needed to validate the current findings. Nonetheless, we believe that the current report is indicative in clinical practice, because little has been known about the change of blood glucose fluctuation in these clinical settings.

Some clinical trials already demonstrated the glucose-lowering effect of DPP-4 inhibitors in patients with insulin therapy [8-12]. However, they compared the addition of DPP-4 inhibitors to insulin therapy with the addition of placebo or no addition. In these clinical trials, they reported that DPP-4 inhibitors significantly improved hemoglobin A1c and fasting and post-meal glucose levels compared with placebo or no addition to insulin therapy. On the other hand, the reduction of hypoglycemia was not consistently observed among these trials. However, one must note that none of the trials compared DPP-4 inhibitors with sulfonylureas in patients with insulin therapy, and therefore it has remained unclear whether DPP-4 inhibitors lead to decreased hypoglycemia compared with sulfonylureas in insulin-treated patients.

In type 2 diabetic patients without insulin therapy, DPP-4 inhibitors had no advantage over sulfonylureas in reduction of hemoglobin A1c levels, as a recent meta-analysis revealed [13]. On the other hand, it was reported that DPP-4 inhibitors led fewer episodes of hypoglycemia than sulfonylureas [13]. Only a few reports compared postprandial glucose levels or glucose fluctuation between DPP-4 inhibitors and sulfonylureas, and some reports showed that postprandial glucose levels had little difference whereas fasting glucose levels under DPP-4 inhibitors were higher than those under sulfonylureas [14]. These previous findings suggested that DPP-4 inhibitors could be expected to lessen glucose fluctuation compared to sulfonylureas.

BOT is an effective option for glycemic control in patients with type 2 diabetes mellitus [1]. However, it has been pointed out that the therapy can mainly control fasting glucose levels but cannot necessarily correct blood glucose fluctuation, especially when sulfo-

nylurea is combined with long acting insulin analogue. Numerous studies have demonstrated that blood glucose fluctuation is an independent risk factor for vascular endothelial dysfunction, atherosclerosis, cardiovascular diseases and mortality [15-20]. Correcting blood glucose fluctuation is now a challenging problem in BOT, and it is of great clinical interest whether the glucose fluctuation can be corrected by DPP-4 inhibitors.

The current study demonstrated that blood glucose fluctuation assessed by M-value, glucose range, and CV was significantly improved after initiating sitagliptin and tapering glimepiride in BOT. In addition, incidence of severe hypoglycemia (< 3.1 mmol/L) was significantly reduced whereas mean blood glucose levels as well as hemoglobin A1c levels were unchanged. In the current study, five patients had their dosage of insulin glargine increased, although the average dosage as a whole was not significantly increased. As was mentioned above, glucose-lowering effect of DPP-4 inhibitors was not superior but rather was sometimes inferior to that of sulfonylureas [13]. It would be of no surprise that some patients had their insulin dosage increased after the initiation of sitagliptin with reduction or withdrawal of glimepiride. When we performed analyses after excluding these five patients with their insulin dosage increased, the significant improvement of glucose fluctuation assessed by glucose range and CV, but not by M-value, was still observed. In this limited population, both incidence of hypoglycemia (< 4.4 mmol/L) and of severe hypoglycemia (< 3.1 mmol/L) were significantly decreased, with hemoglobin A1c and mean glucose levels unchanged. Sitagliptin ameliorates incretin effect by inhibiting DPP-4 activity and enhances insulin secretion in postprandial period [4]. Furthermore, its insulinotropic action is in theory limited to postprandial and hyperglycemic period, which could prevent unnecessary hypoglycemia. In addition, recent studies have demonstrated its favorable effects on glucagon secretion [21] and therefore they might also modify glucose fluctuation [22]. Taken together, it would be reasonable to observe improved blood glucose fluctuation under sitagliptin-combined BOT, although no data were available about insulin or glucagon secretion in the study population. Future studies will be needed to clarify these points.

In the current study, significant improvement was not observed when average blood glucose levels at seven points of SMBG were simply assessed. This finding was in contrast to the significant improvement

of the indices of glucose fluctuation. This discrepancy might come from the fact that not a few patients experienced lower glucose levels after meal than those before meal. Indeed, these reduced glucose levels after meal were found in 17% of the observed pairs of pre- and post-prandial glucose profiles. Fourteen patients (64%) experienced such profiles at least one time, and three patients (14%) experienced the minimum glucose levels after meal (two after breakfast and one after lunch). Consequently, a series of postprandial glucose levels were not always composed of elevated glucose levels, whereas reduced glucose levels were not necessarily observed in preprandial periods. Simple calculation of average glucose levels in pre- and post-prandial periods had a risk of underestimation of glucose fluctuation. In contrast, the indices of glucose fluctuation used in the current study (i.e., M-value, glucose range, CV) could be free from these limitations. We believe that by using these indices, we could adequately evaluate the glucose fluctuation of the study population.

Subsequent analyses showed that the change of blood glucose fluctuation, but not any other baseline characteristic, was associated with its baseline value. The patients with greater blood glucose fluctuation were likely to have greater improvement of it. In the analyses, the statistical significance of the association was not consistently observed among the three indices of glucose fluctuation (i.e., M-value, glucose range, and CV). However, these indices do not necessarily reflect the same aspects of glucose fluctuation but rather have distinctive characteristics. For instance, M-value is an index reflecting deviation from 6.7 mmol/L of glucose levels [6], whereas glucose range specializes in the difference of the two points (maximum and minimum). On the other hand, CV corrects glucose variation on the basis of its average value. It would be no surprise if different indices of glucose fluctuation provided different analytic results. Given their distinctive characteristics, their comprehensive interpretation would be valid in practice.

A recent *in vivo* study revealed that one- and two-

months glycemic control by DPP-4 inhibition improved nitric oxide release and reduced inflammation in rats, accompanying corrected postprandial hyperglycemia [23]. Although endothelial function and atherosclerosis were not evaluated in the current study, it is possible that BOT with DPP-4 inhibitor provides some favorable effect on them in human patients. Future large prospective studies will be needed to validate the efficacy of BOT with DPP-4 inhibitor not only on blood glucose fluctuation but also on endothelial function and atherosclerosis in human diabetic patients.

The current study had some limitations. First, we evaluated glucose fluctuation on the basis of the data of SMBG in daily life. We did not use test meal or prescribed diet. Therefore their glucose levels could be also influenced by what they ate during the observed period. However, we collected data of SMBG on three days but not on one specific day, which could lessen the influence to some extent. In addition, by using the data of daily life instead of load test, our data could rather successfully reflect “real world” in clinical practice.

Another limitation was the study design, as was mentioned above. Since the current study was retrospective and single-arm, future prospective controlled trials are needed to validate the current findings.

In conclusion, blood glucose fluctuation was significantly improved two months after adding sitagliptin and tapering glimepiride in type 2 diabetic Japanese patients who were treated by BOT with insulin glargine and glimepiride. Future prospective controlled trials are needed to validate the current findings.

Acknowledgements

Mitsuyoshi Takahara is a Research Fellow of the Japan Society for the Promotion of Science.

Appendix

There is no conflict of interest concerning this manuscript.

References

1. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, et al. (2008) Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet* 371: 1073-1084.
2. Fritsche A, Schweitzer MA and Haring HU (2003) Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A

- randomized, controlled trial. *Ann Intern Med* 138: 952-959.
3. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, et al. (2007) Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 357: 1716-1730.
 4. Drucker DJ and Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368: 1696-1705.
 5. The Japan Diabetes Society (2010) Evidence-based Practice Guideline for the Treatment of Diabetes in Japan. Nankodo Co., Ltd., Tokyo.
 6. Schlichtkrull J, Munck O and Jersild M (1965) The M-Valve, an Index of Blood-Sugar Control in Diabetics. *Acta Med Scand* 177: 95-102.
 7. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, et al. (2012) International clinical harmonization of glycated hemoglobin in Japan : From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 3: 39-40.
 8. 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.
 9. Vilsboll T, Rosenstock J, Yki-Jarvinen H, Cefalu WT, Chen Y, et al. (2010) Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 12: 167-177.
 10. Arnolds S, Dellweg S, Clair J, Dain MP, Nauck MA, et al. (2010) Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. *Diabetes Care* 33: 1509-1515.
 11. Fonseca V, Baron M, Shao Q and Dejager S (2008) Sustained efficacy and reduced hypoglycemia during one year of treatment with vildagliptin added to insulin in patients with type 2 diabetes mellitus. *Horm Metab Res* 40: 427-430.
 12. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, et al. (2009) Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. *Diabetes Obes Metab* 11: 1145-1152.
 13. Karagiannis T, Paschos P, Paletas K, Matthews DR and Tsapas A (2012) Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ* 344: e1369.
 14. Chung HS and Lee MK (2011) Efficacy of sitagliptin when added to ongoing therapy in Korean subjects with type 2 diabetes mellitus. *Diabetes Metab J* 35: 411-417.
 15. Monnier L, Mas E, Ginet C, Michel F, Villon L, et al. (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295: 1681-1687.
 16. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, et al. (2008) Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 57: 1349-1354.
 17. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, et al. (2000) Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 23: 1830-1834.
 18. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, et al. (1996) Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39: 1577-1583.
 19. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, et al. (1999) Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 22: 920-924.
 20. No Authors Listed (1999) Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 354: 617-621.
 21. Balas B, Baig MR, Watson C, Dunning BE, Ligueros-Saylan M, et al. (2007) The dipeptidyl peptidase IV inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. *J Clin Endocrinol Metab* 92: 1249-1255.
 22. Shah P, Vella A, Basu A, Basu R, Schwenk WF, et al. (2000) Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85: 4053-4059.
 23. Mason RP, Jacob RF, Kubant R, Walter MF, Bellamine A, et al. (2011) Effect of enhanced glycemic control with saxagliptin on endothelial nitric oxide release and CD40 levels in obese rats. *J Atheroscler Thromb* 18: 774-783.