Efficacy of linagliptin and teneligliptin for glycemic control in type 2 diabetic patients with chronic kidney disease: assessment by continuous glucose monitoring; a pilot study

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Abstract

Introduction Type 2 diabetes patients complicated by chronic kidney disease (CKD) require restricted use and dose adjustment of orally administered hypoglycemic agents because of renal dysfunction, and treatment is likely to be difficult. Linagliptin and teneligliptin are dipeptidyl-peptidase (DPP)-4 inhibitors that do not require dose adjustment even in type 2 diabetes patients complicated by CKD. The aim of this pilot study was to determine the efficacy of these agents for glycemic control using continuous glucose monitoring (CGM).

Materials and methods A randomized crossover study was conducted in 13 type 2 diabetes patients with CKD who maintained glycosylated hemoglobin (HbA_{1c}) levels at <9 % by diet and exercise and had estimated glomerular filtration rates (eGFRs) <60 ml/min 1.73 m². They were treated with teneligliptin at 20 mg/day or linagliptin at 5 mg/day for 6 days then switched to the other agent for another 6 days. CGM was performed before and during treatment. The primary outcome was changes in mean amplitude of glucose excursions (MAGE).

Results Mean MAGE was 83.8 ± 34.0 and 82.6 ± 32.6 [$\pm$ standard deviation (SD)] during treatment with linagliptin and teneligliptin, respectively, with no significant difference between agents. The two agents showed comparable beneficial effects on 24-h mean sensor glucose levels and area under the curve for sensor glucose levels

≥ 180 mg/dl (AUC ≥ 180), and their use was associated with comparable incidence of hypoglycemia.

Conclusions Linagliptin and teneligliptin have comparable effects on MAGE in type 2 diabetes patients with CKD and are potentially useful and safe for treatment of such patients.

Keywords Chronic kidney disease · Type 2 diabetes · Continuous glucose monitoring · DPP-4 inhibitor · Linagliptin · Teneligliptin

Introduction

Type 2 diabetes patients are at high risk of chronic kidney disease (CKD) in association with diabetic nephropathy, hypertension, obesity, and various other pathological changes related to type 2 diabetes [1]. The estimated worldwide prevalence of CKD in patients with type 2 diabetes ranges from 25 to 40 % [2–4]. Furthermore, the risk of cardiovascular-related death in patients with CKD is 10–30 times higher than in the general population [5], and this risk is reported to be even higher when CKD is complicated by type 2 diabetes [6]. However, in type 2 diabetes patients with CKD, the use of orally administered hypoglycemic agents is limited, and the dose of these agents needs to be adjusted due to the prolonged half-life of these agents in the presence of renal dysfunction [7, 8]. The risk of serious hypoglycemia in such patients is also high because of diminished renal gluconeogenesis and decreased insulin clearance [9, 10]. These problems often make treatment difficult.

Dipeptidyl-peptidase (DPP)-4 inhibitors are orally administered hypoglycemic agents with a potent hypoglycemic effect that not only reduce fluctuations in blood

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glucose level but also the risk of hypoglycemia [11]. Among the different DPP-4 inhibitors available in the market today, linagliptin and teneligliptin, which do not require dose adjustment even for patients with renal dysfunction [12–15], are considered to be effective and safe for type 2 diabetes patients with CKD. However, there is little information on the efficacy and safety of these agents in type 2 diabetes patients with CKD. Therefore, our pilot study was designed to determine the effectiveness and safety of linagliptin and teneligliptin on glycemic control in a group of type 2 diabetes patients with CKD. For this purpose, we compared and analyzed the effects of these agents by using continuous glucose monitoring (CGM).

Patients and methods

Patients

Patients had type 2 diabetes and were admitted to the hospital between October 2012 and March 2013, maintained glycosylated hemoglobin (HbA_{1c}) levels at <9 % through diet and exercise alone, and had an estimated glomerular filtration rate (eGFR) of <60 ml/min 1.73 m² (GFR category G3a–G5) for >3 months [16]. Diabetic complications were evaluated as follows: diabetic retinopathy was diagnosed according to the results of fundoscopic examination performed by expert ophthalmologists; diabetic nephropathy was classified as stage 2 (≤ 30 urinary albumin ≤ 299 mg/g creatinine), stage 3 (urinary albumin ≥ 300 mg/g creatinine or urinary protein ≥ 0.5 g/g creatinine and eGFR ≥ 30 ml/min/1.73 m²), stage 4 (eGFR <30 ml/min/1.73 m², regardless of albuminuria/proteinuria status), and stage 5 (any status on continued dialysis therapy). Diabetic neuropathy was diagnosed by the presence of two or more clinical symptoms (bilateral spontaneous pain, hypoesthesia or paraesthesia of the legs), absence of Achilles tendon reflexes, and decreased vibration sensations using a C128 tuning fork. Patients who had already been diagnosed with coronary heart disease, cerebrovascular disease, or arteriosclerosis obliterans were considered to have macrovascular complications at the time of enrollment. Exclusion criteria were type 1 diabetes patients, those receiving other types of orally administered hypoglycemic agents or insulin, those with serious infections, those with acute kidney diseases, and those with hepatic dysfunction identified by abnormal transaminase levels that were at least three times higher than the upper limit of the reference range. Before this study was conducted, all patients received written or verbal explanation about the study and then provided informed consent. The protocol was carried out in accordance with the ethical principles stated in the Declaration of Helsinki revised in

2000 and approved by suitably constituted Ethics Committee of Nakama Municipal Hospital.

Study protocol

This pilot study was randomized and crossover in design, and patients were allocated by a random number table to group A or B (Fig. 1). In group A, teneligliptin was first administered orally at 20 mg/day for 6 days from hospital day 5 and then switched to linagliptin at 5 mg/day on hospital day 11 and administered for 6 days. In group B, linagliptin was first administered orally at 5 mg/day for 6 days from hospital day 5 and then switched to teneligliptin at 20 mg/day on hospital day 11 and administered for 6 days.

Measurements were made three times using a CGM system (CGMS System Gold; Medtronic Inc., Fridley, MN, USA) in the following manner: the sensor was placed on the patients in the morning of hospital day 2 and removed in the morning of hospital day 5 for the first measurement; in the morning of hospital day 7 and removed on hospital day 11 for the second measurement; and in the morning of hospital day 13 and removed in the morning of hospital day 17 for the third measurement. To ensure stability of CGM data, those obtained on hospital days 4, 10, and 16 were used for analysis. For hemodialysis patients, we used CGM data obtained on the day of hemodialysis for analysis. Although interstitial glucose concentrations measured using the CGM are, strictly speaking, not blood glucose levels, they were reported to correlate well with venous glucose concentrations [17]. Hereinafter, measurements obtained by the CGM are referred to as sensor glucose levels.

Meals during hospitalization were designed to provide 1577 ± 124 kcal (28.2 ± 1.8 kcal/standard body weight), which was kept constant until the end of this study. Moreover, exercise therapy was not performed during the study period, and patients were instructed to keep in-hospital activity levels to walking level. No changes were made to the drugs used for treating hypertension and dyslipidemia.

Biochemical and clinical measurements

The following parameters were computed from CGM measurements: 24-h mean sensor glucose levels, mean nocturnal sensor glucose levels (from 12:00 a.m. to 7:00 a.m.), and mean diurnal sensor glucose levels (from 7:00 a.m. to 12:00 a.m.); standard deviation (SD) of sensor glucose levels; mean amplitude of glycemic excursions (MAGE); maximum 24-h sensor glucose levels and maximum sensor glucose levels after each meal; minimum 24-h sensor glucose levels; 24-h area under the curve for sensor

Fig. 1 Randomized crossover study: participants allocated to either group A or group B. Patients were treated with either teneligliptin 20 mg/day or linagliptin 5 mg/day. Continuous glucose monitoring (CGM) was applied three times (first: days 2–5; second: days 7–11; third: days 13–17)

glucose levels ≥ 180 mg/dl ($AUC \geq 180$); 24-h area over the curve for sensor glucose levels < 70 mg/dl ($AOC < 70$). With regard to other parameters, HbA_{1c} and glycated albumin (GA) levels were measured on admission. Serum C-peptide levels were measured before and 6 min after venous injection of 1 mg of glucagon.

Primary and secondary outcomes

The primary outcome was MAGE during treatment with teneligliptin and linagliptin. The secondary outcomes were mean, maximum, and minimum sensor glucose levels, as well as $AUC \geq 180$ during the treatments.

Statistical analysis

Data are expressed as mean $\pm$ SD values. The Wilcoxon signed-rank test was used to compare the effects of teneligliptin and those of linagliptin, as well as the effects of each agent between before and during use. A p value < 0.05 was considered to indicate a significant difference. Statistical analysis was performed using Statistical Package for Social Sciences software, version 21.0 (SPSS, Chicago, IL, USA).

Results

Table 1 shows clinical characteristics of participating patients. Of the 14 patients, one was excluded because of infection and the other 13 completed the study. The 13 patients had a mean age of 68.4 ± 13.1 years, body mass index (BMI) of 24.9 ± 4.6 kg/m², HbA_{1c} level of 6.7 ± 0.8 %, and GA level of 19.6 ± 4.4 %. Although mean eGFR was 28.2 ± 15.3 ml/min/1.73 m², two patients were on hemodialysis during the study.

Figure 2 shows variations in 24-h sensor glucose levels measured by CGM before and during treatments with linagliptin and teneligliptin, and Table 2 shows the glycemic profile. Mean MAGE during treatment with lina-

Table 1 Patient baseline characteristics

Variables	Measurements
Age (years)	68.4 ± 13.1
Sex (males/females)	10/3
Duration of type 2 diabetes (year)	13.1 ± 8.8
Body mass index (kg/m ²)	24.9 ± 4.6
Fasting plasma glucose (mg/dl)	135.0 ± 34.4
HbA_{1c} (%)	6.7 ± 0.8
Glycated albumin (%)	19.6 ± 4.4
Serum C-peptide (ng/ml)	
Glucagon-stimulated test	
At 0 min (ng/ml)	2.5 ± 2.3
At 6 min (ng/ml)	4.0 ± 2.8
Creatinine (mg/dl)	2.7 ± 2.0
eGFR (ml/min/1.73 m ²)	28.2 ± 15.3
Urinary protein (mg/day)	2327 ± 4781
CKD classification ^a	
CKD G3a- A1/A2/A3 (%)	7.7/7.7/0
CKD G3b- A1/A2/A3 (%)	7.7/7.7/7.7
CKD G4- A1/A2/A3 (%)	0/7.7/23.1
CKD G5- A1/A2/A3 (%)	0/0/30.8
Microvascular complications	
Retinopathy (%)	61.5
Nephropathy (%)	53.4
Neuropathy (%)	77.0
Macrovascular complications	
Coronary heart disease (%)	15.4
Cerebrovascular disease (%)	7.7
Arteriosclerosis obliterans (%)	7.7
Hemodialysis (%)	15.4

Data are mean $\pm$ standard deviation

HbA_{1c} glycosylated hemoglobin, eGFR estimated glomerular filtration rate, CKD chronic kidney disease

^a CKD 3a, eGFR 45–60 ml/min/1.73 m²; CKD 3b, eGFR 30–45 ml/min/1.73 m²; CKD 4, eGFR 15–30 ml/min/1.73 m²; CKD 5, eGFR < 15 ml/min/1.73 m²; A1, urinary albumin < 30 mg/g creatinine; A2, urinary albumin 30–300 mg/g creatinine; A3, urinary albumin ≥ 300 mg/g creatinine or urinary protein ≥ 0.5 g/g creatinine

Fig. 2 Twenty-four-hour mean sensor glucose levels before treatment and after 6 days of treatment with linagliptin/teneligliptin in 13 patients. Values are mean

Table 2 Effects of each treatment on various parameters computed from continuous glucose monitoring

	Baseline	Linagliptin	Teneligliptin	<i>p</i> value ^a
MAGE (mg/dl)	101.3 ± 35.4	83.8 ± 34.0**	82.6 ± 32.6	0.807
Change in MAGE (%)	—	−18.1 ± 15.8	−15.0 ± 26.4	0.650
SD of 24-h sensor glucose levels (mg/dl)	35.7 ± 13.1	29.1 ± 12.3**	28.5 ± 12.9*	0.807
24-h mean sensor glucose levels (mg/dl)	167.9 ± 31.4	148.8 ± 26.8**	151.4 ± 29.9**	0.753
0–7 h mean sensor glucose levels (mg/dl)	136.9 ± 29.8	126.2 ± 31.3**	127.4 ± 29.1	0.675
7–24 h mean sensor glucose levels (mg/dl)	180.1 ± 34.9	158.8 ± 30.1**	161.8 ± 32.5*	0.463
Maximum sensor glucose levels (mg/dl)	250.7 ± 54.5	222.4 ± 46.1**	223.4 ± 48.3	0.807
Postprandial peak sensor glucose levels				
Breakfast (mg/dl)	230.9 ± 49.6	184.8 ± 37.0**	190.9 ± 38.5**	0.432
Lunch (mg/dl)	220.9 ± 46.0	194.9 ± 38.8**	205.5 ± 49.1	0.552
Dinner (mg/dl)	233.5 ± 54.7	216.0 ± 48.7*	207.0 ± 36.8*	0.363
Minimum sensor glucose levels (mg/dl)	113.5 ± 22.1	93.8 ± 21.3**	105.3 ± 27.2	0.152
24-h AUC-180 (mg/dl/day)	14.8 ± 18.5	6.6 ± 9.5**	7.6 ± 12.9*	0.859
24-h AOC-70 (mg/dl/min)	0.0 ± 0.0	0.4 ± 1.4	12.3 ± 44.4	0.655

Data are mean ± standard deviation

MAGE mean amplitude of glycemic excursions, AUC-180 area under the curve for glucose >180 mg/dl, AOC-70 area over the curve for glucose <70 mg/dl

* $P < 0.05$, vs before treatment by Wilcoxon test, ** $p < 0.01$, vs before treatment Wilcoxon test

^a Comparison between values measured under treatment with linagliptin and teneligliptin

gliptin (83.8 ± 34.0) was not significantly different from that during treatment with teneligliptin (82.6 ± 32.6 , $p = 0.807$, Fig. 3). There was also no significant difference in SD of sensor glucose levels between linagliptin and teneligliptin. Furthermore, the effects of both agents were comparable on any of the mean sensor glucose levels obtained during the 24-h, nocturnal (0–7 h), and diurnal (7–24 h) periods. In addition, there were no significant differences between the two agents in terms of maximum

and minimum sensor glucose levels, AUC ≥ 180 , and AOC <70. In one patient, sensor glucose levels measured by CGM decreased to <70 mg/dl during treatment with both agents, but no subjective symptoms of hypoglycemia were observed, so the incidence of hypoglycemia was equal between the two agents.

Next, we defined the effect of each treatment. First, there was no significant difference in the rate of change in MAGE during treatment with each agent ($p = 0.650$).

Fig. 3 Mean amplitude of glycemic excursions (MAGE) before treatment and after 6 days treatment with linagliptin/teneeligliptin. Values are mean $\pm$ standard deviation. ** $P < 0.01$, vs before treatment by Wilcoxon test

Compared with the respective pretreatment value, treatment with linagliptin significantly reduced MAGE (Fig. 3), SD, 24-h mean sensor glucose levels, maximum and minimum sensor glucose levels, and $AUC \geq 180$. Furthermore, treatment with linagliptin also significantly reduced the 24-h, nocturnal and diurnal mean sensor glucose levels and maximum postprandial sensor glucose levels after morning, midday, and evening meals. On the other hand, compared with the respective pretreatment value, MAGE of teneeligliptin tended to be lower than that before treatment. However, there was no significant difference between the two groups ($p = 0.05$). Treatment with teneeligliptin significantly reduced the SD, 24-h mean sensor glucose levels, $AUC \geq 180$, mean diurnal sensor glucose levels, and maximum postprandial sensor glucose levels after morning and evening meals but had no effect on mean nocturnal sensor glucose levels. Although one patient developed pneumonia during treatment with linagliptin and withdrew from the study, no apparent association was found between pneumonia and the agent. In the other 13 patients who completed the study, no adverse events were noted during treatment with either drug.

Discussion

Our pilot study demonstrated that MAGE computed from CGM was comparable between linagliptin and teneeligliptin in patients with type 2 diabetes complicated by CKD.

Moreover, the effects of these two agents on mean and maximum sensor glucose levels and $AUC \geq 180$ were also comparable. Furthermore, both agents achieved comparable levels of minimum sensor glucose and $AOC < 70$ and did not worsen the incidence of hypoglycemia relative to before treatment. Both agents were also safe, and their use was not associated with serious side effects.

With regard to the efficacy of the two agents, linagliptin induced significant reductions in 24-h mean sensor glucose levels, SD, MAGE, maximum and minimum sensor glucose levels, and $AUC \geq 180$ compared with pretreatment values. On the other hand, teneeligliptin significantly reduced the 24-h mean sensor glucose levels and $AUC \geq 180$ and tended to reduce SD, MAGE, and maximum and minimum sensor glucose levels, albeit insignificantly. However, because SD, MAGE, and maximum and minimum sensor glucose levels during treatment with teneeligliptin were almost comparable with those during treatment with linagliptin, it was concluded that the two agents have similar effects and that the minor differences between the two were probably due to the relatively small sample number.

Reanalysis of data of the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation study showed that low eGFR and albuminuria are independent risk factors for cardiovascular events and death in type 2 diabetes patients [18]. Moreover, the United Kingdom Prospective Diabetes Study 64 also demonstrated that the risk of cardiovascular events increases with progression of nephropathy [19]. In Japan, the incidence of cardiovascular events is even higher in patients with the combination of CKD and type 2 diabetes [20]. Moreover, a large retrospective cohort revealed the higher incidence of hypoglycemia in CKD patients and the close association between hypoglycemia and mortality [21]. Thus, in type 2 diabetes patients complicated by CKD, good glycemic control without increasing the risk of hypoglycemia is assumed to be important.

Monnier et al. [22] reported that spikes in blood glucose level, such as postprandial hyperglycemia, rather than mean sensor glucose levels measured by CGM, are associated with oxidative stress. Furthermore, the same group recommended the use of glucose-lowering therapy that reduces MAGE and spikes in blood glucose levels to lower mortality from cardiovascular events [23]. Recently, Rizzo et al. [24] reported that DPP-4 inhibitors protect against not only MAGE but also oxidative stress and rise in levels of various inflammatory markers. Other studies examined differences in the effects of DPP-4 inhibitors on MAGE. They demonstrated that vildagliptin reduces MAGE to levels far greater than those by sitagliptin [24, 25]. However, there is no information regarding differences between linagliptin and teneeligliptin when using CGM.

Both linagliptin and teneligliptin are DPP-4 inhibitors, with merits of once-daily oral administration and no need for dose adjustment even in patients with renal dysfunction. Thus, both agents are assumed to be extremely easy to use for type 2 diabetes patients complicated by CKD. A study [26] that compared the efficacy of linagliptin between three groups of patients with normal renal function ($90 \text{ ml/min } 1.73 \text{ m}^2 > \text{eGFR}$), mild renal dysfunction ($60 \text{ ml/min } 1.73 \text{ m}^2 < \text{eGFR} < 90 \text{ ml/min } 1.73 \text{ m}^2$), and moderate renal dysfunction ($30 \text{ ml/min } 1.73 \text{ m}^2 < \text{eGFR} < 60 \text{ ml/min } 1.73 \text{ m}^2$) reported no significant differences in the extent of changes in HbA_{1c} levels after 24 weeks of treatment among the three groups and in the incidence of hypoglycemia during treatment with linagliptin alone, which was $<1 \%$, among groups. In addition, in a study on the use of teneligliptin at 20 mg in type 2 diabetes patients on hemodialysis [14], teneligliptin significantly reduced HbA_{1c} levels by 0.57 %, GA levels by 3.1 %, and casual blood glucose levels by 50.5 mg/dl after 28 weeks of treatment. However, there are no comparative data on the effects of the two agents on glycemic profile.

Our pilot study performed in type 2 diabetes patients complicated by CKD hospitalized to maintain stable food intake and exercise is the first that directly compares the effects of the two agents on the glycemic profile measured by CGM while minimizing the effects of other factors. The study has certain limitations, however. First, the sample size was small, though this is a common feature of pilot studies. As mentioned earlier, we cannot rule out that the small sample size might have contributed to the lack of statistically significant differences in SD, MAGE, and maximum and minimum sensor glucose levels between the two treatment agents. Second, it was based on a crossover design that investigated the effects of 6-day treatment with both agents on CGM-based data. Because no washout period was included between the switch from one agent to another, the possible impact of carryover effects cannot be ruled out. No such period was included in the study design for fear of potential deterioration of sensor glucose levels and in order to shorten hospital stay. Third, the dose of teneligliptin can be increased from 20 to 40 mg per day, and such dose increase was reported to improve HbA_{1c} and fasting plasma glucose (FPG) [27]. Thus, teneligliptin dose escalation could likely produce a better overall improvement rather than its limited effect on MAGE at 20 mg/day. Results of this study, however, suggest comparable effects for 5 mg/day linagliptin and 20 mg/day teneligliptin on CGM-based MAGE. Further studies of larger sample size, longer observation period, and dose titration using 40 mg/day teneligliptin are warranted to confirm our results.

In type 2 diabetes patients complicated by CKD, the effects of treatment with linagliptin and teneligliptin on CGM-based MAGE were comparable. Because both agents

significantly reduced the 24-h mean sensor glucose levels and $\text{AUC} \geq 180$ but did not increase the incidence of hypoglycemia, we conclude that they have comparable efficacy and safety in type 2 diabetes patients complicated by CKD.

Compliance with ethical standards

Conflict of interest Y. Tanaka, has received consulting fees, speaking fees and/or honoraria from Mitsubishi-Tanabe Pharma, Daiichi-Sankyo, Eli Lilly Japan, and has received research grants from Mitsubishi-Tanabe Pharma and Daiichi-Sankyo. Y. Okada has received speaking fees from Daiichi-Sankyo, Eli Lilly Japan, and Mitsubishi-Tanabe Pharma. All other authors declare no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki Declaration of 1964 and later revision. Informed consent was obtained from all patients before included in the study.

References

1. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis.* 2012;60:850–86.
2. Koro CE, Lee BH, Bowlin SJ. Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. *Clin Ther.* 2009;31:2608–17.
3. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, Trevisan R, Vedovato M, Gruden G, Cavalot F, Cignarelli M, Laviola L, Morano S, Nicolucci A, Pugliese G, Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. *J Hypertens.* 2011;29:1802–9.
4. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2002;346:1145–51.
5. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation.* 2003;108:2154–69.
6. Bakris G, Ritz E. The message for World Kidney Day 2009: hypertension and kidney disease: a marriage that should be prevented. *J Clin Hypertens (Greenwich).* 2009;11:144–7.
7. Rigalleau V, Beauvieux MC, Gonzalez C, Raffaitin C, Lasseur C, Combe C, Chauveau P, De la Faille R, Rigothier C, Barthe N, Gin H. Estimation of renal function in patients with diabetes. *Diabetes Metab.* 2011;37:359–66.
8. Bonnet F, Gauthier E, Gin H, Hadjadj S, Halimi JM, Hanne-douche T, Rigalleau V, Romand D, Roussel R, Zaoui P. Expert consensus on management of diabetic patients with impairment of renal function. *Diabetes Metab.* 2011;37:S1–25.
9. Slinin Y, Ishani A, Rector T, Fitzgerald P, MacDonald R, Tacklind J, Rutks I, Wilt TJ. Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and

- CKD: a systematic review for a KDOQI clinical practice guideline. *Am J Kidney Dis.* 2012;60:747–69.
10. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35:1364–79.
 11. Deacon CF. Dipeptidyl peptidase-4 inhibitors in treating type 2 diabetes: a comparative review. *Diabetes Obes Metab.* 2011;13:7–18.
 12. Graefe-Mody U, Friedrich C, Port A, Ring A, Retlich S, Heise T, Halabi A, Woerle HJ. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin (*). *Diabetes Obes Metab.* 2011;13:939–46.
 13. Friedrich C, Emser A, Woerle HJ, Graefe-Mody U. Renal impairment has no clinically relevant effect on the long-term exposure of linagliptin in patients with type 2 diabetes. *Am J Ther.* 2013;20:618–21.
 14. Otsuki H, Kosaka T, Nakamura K, Shimomura F, Kuwahara Y, Tsukamoto T. Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes. *Int Urol Nephrol.* 2014;46:427–32.
 15. Nakamaru Y, Hayashi Y, Ikegawa R, Kinoshita S, Perez Madera B, Gunput D, Kawaguchi A, Davies M, Mair S, Yamazaki H, Kume T, Suzuki M. Metabolism and disposition of the dipeptidyl peptidase IV inhibitor teneligliptin in humans. *Xenobiotica.* 2014;44:242–53.
 16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3(1):1–150.
 17. Boyne MS, Silver DM, Kaplan J, Saudek K. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes.* 2003;52:2790–4.
 18. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, Macmahon S, Chalmers J, Advance Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol.* 2009;20:1813–21.
 19. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS GROUP. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63:225–31.
 20. Nakajima K, Matsuo S, Okuyama C, Hatta T, Tsukamoto K, Nishimura S, Yamashina A, Kusuoka H, Nishimura T. Cardiac event risk in Japanese patients estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. *Circ J.* 2012;76:168–75.
 21. Moen MF, Zhan M, Hsu VD, Walker LD, Einhorn LM, Seliger SL, Fink JC. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol.* 2009;4:1121–7.
 22. Monnier L, Mas E, Ginnet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA.* 2006;295:1681–7.
 23. Monnier L, Colette C, Owens DR. Integrating glycaemic variability in the glycaemic disorders of type 2 diabetes: a move towards a unified glucose tetrad concept. *Diabetes Metab Res Rev.* 2009;25:393–402.
 24. Rizzo MR, Barbieri M, Marfella R, Paolisso G. 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.* 2012;35:2076–82.
 25. Sakamoto M, Nishimura R, Irako T, Tsujino D, Ando K, Utsunomiya K. Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring (CGM): cross-over pilot study (J-VICTORIA study). *Cardiovasc Diabetol.* 2012;11:92–8.
 26. Groop PH, Del Prato S, Taskinen MR, Owens DR, Gong Y, Crowe S, Patel S, von Eynatten M, Woerle HJ. Linagliptin treatment in patients with type 2 diabetes with and without mild-to-moderate renal impairment. *Diabetes Obes Metab.* 2014;16:560–8.
 27. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig.* 2013;27:576–84.