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【 ORIGINAL ARTICLE 】

The Assessment of the Efficacy of Dipeptidyl Peptidase-4 Inhibitors in Patients with Glucocorticoid-induced Diabetes by Continuous Glucose Monitoring

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Abstract:

Objective The administration of glucocorticoids usually causes a mild increase in fasting glucose levels and a greater dose-dependent increase in postprandial values in patients without pre-existing diabetes mellitus. Patients with persistent hyperglycemia due to glucocorticoid therapy sometimes require insulin therapy, which might result in increased weight gain and more episodes of hypoglycemia, some of which are severe. On the other hand, scant evidence is available on the efficacy of oral hypoglycemic agents in treating glucocorticoid-induced diabetes. In this study, we evaluated the efficacy of dipeptidyl peptidase (DPP)-4 inhibitors in patients with glucocorticoid-induced diabetes by continuous glucose monitoring (CGM).

Methods We examined the glycemic profiles using CGM at baseline and 1-4 weeks after initiating DPP-4 inhibitor treatment in patients with newly developed glucocorticoid-induced diabetes.

Results Eleven patients who had been diagnosed with kidney disease or other diseases with renal involvement were recruited for the present retrospective study. After starting DPP-4 inhibitors, the mean and standard deviation (SD) of the glucose level, and the mean amplitude of glycemic excursion (MAGE) were significantly improved in comparison to baseline. Furthermore, the area over the curve (AOC) for the glucose levels <70 mg/dL was not increased in comparison to baseline after the initiation of DPP-4 inhibitor treatment. The results indicate that the treatment of patients with glucocorticoid-induced diabetes using DPP-4 inhibitors can minimize the risk of hypoglycemia and reduce glucose variability.

Conclusion DPP-4 inhibitors are potentially useful for blood glucose control in patients with glucocorticoid-induced diabetes.

Key words: dipeptidyl peptidase-4 inhibitor, glucocorticoid-induced diabetes, continuous glucose monitoring

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Introduction

The administration of glucocorticoids usually causes a mild increase in fasting glucose levels. Glucocorticoids also induce a dose-dependent increase in postprandial blood glucose levels, even in patients without pre-existing diabetes mellitus. The mechanism by which glucocorticoids cause hyperglycemia is multifactorial and includes the augmentation of hepatic gluconeogenesis, the inappropriate secretion of glucagon, the inhibition of the glucose uptake in adipose tissue, and the alteration of insulin receptor and post-receptor signals (1-4). Patients with persistent hyperglycemia due to glucocorticoid therapy sometimes require insulin therapy. In fact, insulin therapy is recommended for patients with glucocorticoid-induced diabetes by the Endocrine Soci-

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ety guidelines for the management of hyperglycemia in hospitalized patients (5). However, insulin therapy itself can result in increased weight gain and may cause more episodes of hypoglycemia, some of which are severe. Recent trials have demonstrated the efficacy of thiazolidinediones and acarbose in patients with glucocorticoid-induced diabetes (6, 7); however, there is little evidence on the efficacy of oral hypoglycemic agents for glucocorticoid-induced diabetes. Furthermore, if patients with glucocorticoid-induced diabetes are also diagnosed with chronic kidney disease (CKD), the use of oral hypoglycemic agents such as sulfonylureas, biguanides, or both, is associated with the risk of developing medication-associated adverse events such as prolonged hypoglycemia and lactic acidosis. Dipeptidyl peptidase (DPP)-4 inhibitors are a new class of oral antidiabetic drugs that increase the action of the incretin hormones. With dose adjustment, DPP-4 inhibitors can also be administered to CKD patients. In addition, a meta-analysis by Kim et al. showed that DPP-4 inhibitors are particularly effective in Asian patients with type 2 diabetes (8). However, there is little evidence of their efficacy in patients with glucocorticoid-induced diabetes.

The precise circadian variations in the blood glucose levels of patients with glucocorticoid-induced diabetes have not been clarified. A continuous glucose monitoring (CGM) system can evaluate the changes in a patient's interstitial glucose throughout the day. It is highly accurate, easy to use, and useful in the daily management of diabetes. In the present study, we evaluated the efficacy of DPP-4 inhibitors, as determined by CGM, in the treatment of patients with glucocorticoid-induced diabetes.

Materials and Methods

Patients

We retrospectively analyzed 15 Japanese patients, who were diagnosed as having glucocorticoid-induced diabetes and who were evaluated by CGM at the Division of Clinical Nephrology and Rheumatology of Niigata University Medical and Dental Hospital and the Division of Internal Medicine in Itoigawa General Hospital, Japan, between April 2012 and March 2013. The study protocol was approved by the human research ethics committees at both institutions and in accordance with the principles embodied in the Declaration of Helsinki, and written informed consent was obtained from all participants. We excluded 2 patients who were finally confirmed to have type 2 diabetes: 1 patient with a poor CGM recording, and 1 patient who had only received DPP-4 inhibitor treatment for 2 days at the second CGM test. Eleven patients (male, n=5 female, n=6 mean age, 62.2±11.7 years) were admitted to either of the hospitals, mainly for kidney disease or other diseases with renal involvement (Table 1). They were glucocorticoid-naive and had not previously been diagnosed with diabetes mellitus. They also fulfilled the following criteria: hemoglobin A1c (HbA1c) level <6.5 % and fasting plasma glucose level < 126 mg/dL prior to the administration of glucocorticoid. The patients received glucocorticoids according to the guidelines for each basic disease. No patients had a family history of diabetes.

Patients took glucocorticoids once or twice a day. Newly developed glucocorticoid-induced diabetes was defined as an elevation of casual plasma glucose levels to >200 mg/dL at least twice during the course of glucocorticoid treatment. Each patient was prescribed an energy-restricted diet (approximately 30 kcal/kg) before glucocorticoid-induced diabetes was diagnosed.

CGM

The patients' glucose profiles were assessed using the iPro®2 CGM system (Medtronic, Northridge, USA). The first CGM test was carried out at least 1 week after starting energy-restricted diet therapy. This CGM device measures and records a patient's interstitial glucose levels every 5 minutes, and is calibrated with capillary blood glucose samples 4 times per day. After baseline glucose monitoring for 72 hours by CGM, the patients were prescribed a DPP-4 inhibitor (sitagliptin, vildagliptin, alogliptin, linagliptin, or teneligliptin) by the attending physician. The following values were calculated from the CGM data: 1) the mean 24 hours glucose level, 2) the standard deviation (SD) of the glucose level, 3) the mean amplitude of glycemic excursion (MAGE), 4) the area under the curve for the glucose level (AUC) >180 mg/dL per 24 hours (24 hours AUC), 5) the area over the curve for the glucose level (AOC) <70 mg/dL per 24 hours (24 hours AOC), 6) the mean, AUC>180 mg/dL, the highest glucose level within 3 hours postprandially (breakfast, 8:00-11:00 AM; lunch, 12:00-3:00 PM; supper, 6:00-9:00 PM), and 7) the preprandial glucose level (defined as the lowest glucose levels within 1 hour before each meal; breakfast, 7:00-8:00 AM; lunch, 11:00 AM-12:00 PM; supper, 5:00-6:00 PM). The glycemic AUCs and AOCs were calculated according to the rule of the trapezoidal area. At 1 to 4 weeks after the initiation of DPP-4 inhibitor treatment, the patients underwent CGM for another 72 hours.

Statistical analysis

The results are presented as the mean ± SD. The effects of DPP-4 inhibitors were analyzed using a paired t-test and a one-way repeated analysis of variance (ANOVA) with the Student-Newman-Keuls method as a post hoc test. The unpaired t-test was used for comparisons within the group in which the glucocorticoid dose was reduced and in the group in which it was not. Changes in the HbA1c level during treatment with DPP-4 inhibitors were assessed using by an ANOVA. Statistical analyses were performed using the SPSS software program (version 17.0). p values of <0.05 were considered to indicate statistical significance.

Table 1. **Summary of Patient Characteristics.**

Case	Age (years)	Sex	Dx	BH (cm)	BW (kg)	BMI (kg/m^2)	HbA1c (%)	eGFR (mL/min/ 1.73 m^2)	UP (g/gCr)	Prednisolone dose (mg)			Diet therapy (kcal/kg)		DPP-4 inhibitor		Number of days of diet therapy before first CGM test (days)	Number of days of DPP-4 inhibitor before second CGM test (days)
										Initial	Before	After	Before	After	Name	Initial dose (mg)		
1	60	M	IgAN	161.2	67.2	25.9	5.7	61.3	4.7	30*, ##	25, #	25, #	31.5	31.5	Alo	25	14	6
2	47	F	LDKT	158.4	47.8	19.1	5.8	59.8	0.1	25*, ##	15, ##	5, #	32.6	32.6	Lina	5	60	4
3	65	M	MCNS	164.3	61.5	22.8	6.1	53.8	5.9	50, ##	50, ##	50, ##	30.3	33.7	Lina	5	32	5
4	60	F	MPA	152.7	45.6	19.6	6.3	77.4	0.1	50, ##	45, ##	40, ##	27.3	27.3	Teneli	20	43	12
5	42	F	NS	152.0	38.7	16.8	6.4	107.0	7.2	50*, ##	50, ##	40, ##	23.6	31.5	Vilda	100	15	12
6	65	F	MN	157.5	53.7	21.6	5.9	88.5	6.9	40, #	40, #	40, #	29.3	29.3	Sita	50	39	14
7	74	F	CSS	157.1	52.9	21.4	5.2	55.5	0.0	55, ##	50, ##	40, ##	27.6	27.6	Alo	25	56	25
8	74	F	MPA	149.0	41.2	18.6	6.2	7.0	2.5	25, #	25, #	25, #	32.8	32.8	Vilda	100	18	4
9	57	M	DM	174.7	62.7	20.5	5.9	74.5	0.2	60, ##	60, ##	55, ##	29.8	29.8	Vilda	100	13	8
10	82	M	IP	156.0	46.0	18.9	5.8	36.5	0.1	30*, ##	20, #	20, #	29.9	29.9	Sita	25	7	10
11	58	M	MCNS	178.0	78.5	24.8	6.3	66.3	7.8	60, ##	60, ##	60, ##	25.8	25.8	Alo	25	7	9

*These patients received methyl-prednisolone pulse therapy prior to maintenance glucocorticoid therapy, #Single daily dosing after breakfast, ##Twice daily dosing after breakfast and lunch, Alo: alogliptin, After: after DPP-4 inhibitor treatment, Before: before DPP-4 inhibitor treatment, BH: body height, BMI: body mass index, BW: body weight, CSS: Churg-Strauss syndrome, CGM: continuous glucose monitoring, DM: dermatomyositis, DPP: dipeptidyl peptidase, Dx: diagnosis, eGFR: estimated glomerular filtration rate, F: female, IgAN: immunoglobulin A nephropathy, IP: interstitial pneumonia, LDKT: living-donor kidney transplantation, Lina: linagliptin, M: male, MAGE: mean amplitude of glycemic excursion, MCNS: minimal change nephrotic syndrome, MN: membranous nephropathy, MPA: microscopic polyangiitis, MPGN: membranoproliferative glomerulonephritis, NS: nephrotic syndrome, Sita: sitagliptin, Teneli: teneligliptin, UP: urine protein, Vilda: vildagliptin

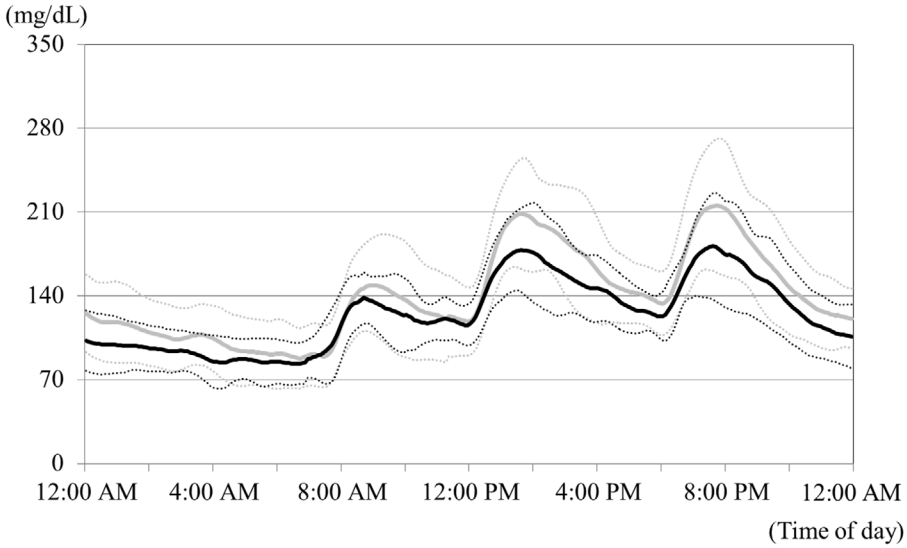

Figure 1. **Daily variation of blood glucose levels as determined by CGM before or after treatment with DPP-4 inhibitors. Gray line: Before treatment with DPP-4 inhibitors±SD. Black line: After treatment with DPP-4 inhibitors±SD**

Table 2. **Comparison of CGM Data before and after Treatment with DPP-4 Inhibitors in 24 Hours.**

	Before	After	p value
Mean glucose (mg/dL)	139.6±22.9	124.7±12.4	0.003
Glucose SD (mg/dL)	43.6±13.1	35.1±13.9	0.007
MAGE (mg/dL)	127.7±37.5	99.7±40.2	0.02
24 h AUC>180 (mg·24h/dL)	172.5±216.6	50.3±62.9	0.01
24 h AOC<70 (mg·24h/dL)	14.4±31.9	7.7±15.7	0.4

AOC: area over the curve for plasma glucose levels, AUC: area under the curve for plasma glucose levels, DPP: dipeptidyl peptidase, MAGE: mean amplitude of glycemic excursions

p value: paired t-test

Results

For the 11 patients, the HbA1c was 6.0±0.4%, the fasting plasma glucose level was 93.3±9.2 mg/dL, the body mass index was 20.9±2.8 kg/m^2, and the estimated glomerular filtration rate (eGFR) was 62.5±26.3 mL/min/1.73 m^2. All of the patients had been diagnosed with kidney disease or other diseases with renal involvement. The patients' clinical characteristics are summarized in Table 1. Four patients had received methylprednisolone pulse therapy before receiving maintenance glucocorticoid therapy. The patients received an initial dose of prednisolone that ranged from 25 to 60 mg/day. After the first CGM test, vildagliptin or alogliptin was prescribed to 3 patients each; sitagliptin or linagliptin was prescribed to 2 patients each; and teneligliptin was prescribed to 1 patient.

After treatment with DPP-4 inhibitors, the mean glucose levels determined by CGM showed significant improvement from 139.6±22.9 mg/dL to 124.7±12.4 mg/dL (p=0.003), the SD of the glucose levels improved from 43.6±13.1 mg/dL to 35.1±13.9 mg/dL (p=0.007), the MAGE improved from 127.7±37.5 mg/dL to 99.7±40.2 mg/dL (p=0.02), and the 24 hours AUC (>180 mg/dL) improved from 172.5±216.6 mg·24 h/dL to 50.3±62.9 mg·24 h/dL (p=0.01). However, the 24 hours AOC (<70 mg/dL) was not significantly changed: 14.4±31.9 mg·24 h/dL to 7.7±15.7 mg·24 h/dL (p=0.4) (Fig. 1, Table 2). Table 3 summarizes the data at baseline and after treatment with DPP-4 inhibitors. Severe treatment-related hypoglycemia was not observed in any of the patients.

DPP-4 inhibitors further improved the patient's postprandial glucose levels; the 3 hours mean glucose levels were significantly reduced after each meal (breakfast, 137.1±37.5 mg/dL to 123.9±19.5 mg/dL, p=0.047; lunch, 177.5±43.2 mg/dL to 157.5±28.9 mg/dL, p=0.046; and supper, 188.5±38.2 mg/dL to 155.7±34.4 mg/dL, p=0.005). The AUCs (>180 mg/dL) within 3 hours were also significantly smaller after each meal (breakfast: 3.9±7.9 mg·min/dL vs. 0.2±0.5 mg·min/dL, p=0.04; lunch: 19.0±24.1 mg/dL/min vs. 8.0±10.0 mg/dL/min, p=0.03; and supper: 23.7±30.4 mg·min/dL vs. 8.9±16.8 mg·min/dL, p=0.04). The administration of

Table 3. Summary of Continuous Glucose Monitoring Data.

Case	Mean glucose concentration, (mg/dL)		Maximum glucose concentration, (mg/dL)		Minimum glucose concentration, (mg/dL)		SD (mg/dL)		MAGE (mg/dL)		24 h AUC>180 (mg·24h/dL)		24 h AOC<70 (mg·24h/dL)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	152.5	141.2	303	296	40	40	61.7	58.0	172.0	179.0	310.9	187.6	10.3	14.7
2	138.0	118.6	223	193	82	77	26.8	25.4	80.8	75.5	58.6	2.3	0.0	0.0
3	127.1	115.7	191	208	59	76	45.8	25.8	144.1	78.5	94.1	6.2	2.1	0.0
4	111.6	108.4	260	194	40	63	49.9	35.9	144.8	104.1	38.0	5.9	100.9	6.1
5	138.2	127.6	244	242	64	59	49.0	44.8	136.6	128.1	203.1	76.7	1.6	9.2
6	128.2	115.4	207	208	57	61	32.4	38.7	96.2	107.9	14.6	31.7	9.8	3.0
7	144.7	147.0	278	225	78	79	42.6	32.2	127.3	93.3	141.5	72.0	0.0	0.0
8	136.6	132.1	219	189	92	66	23.4	20.0	63.3	60.0	20.0	4.1	0.0	0.7
9	120.8	120.0	263	238	66	40	47.6	47.0	135.7	138.6	87.0	79.7	2.4	37.7
10	141.3	122.7	268	164	46	79	41.1	13.7	131.3	44.5	108.8	0.0	24.1	0.0
11	196.6	126.8	375	269	95	59	58.0	44.6	163.7	130.9	745.0	64.2	0.0	9.5

After: after DPP-4 inhibitor treatment, AOC: area over the curve, AUC: area under the curve, Before: before DPP-4 inhibitor treatment, MAGE: mean amplitude of glycemic excursion

Table 4. Comparison of CGM Data before and after Treatment with DPP-4 Inhibitors at Meal Time.

	Before	After	p value
Mean of glucose levels within 3 h after each meal (mg/dL)			
Breakfast	137.1±37.5	123.9±19.5	0.047
Lunch	177.5±43.2[a]	157.5±28.9[a]	0.046
Supper	188.5±38.2[a]	155.7±34.4[a]	0.005
The AUC (>180 mg/dL) within 3 h after each meal (mg·min/dL)			
Breakfast	3.9±7.9	0.2±0.5	0.04
Lunch	19.0±24.1[a]	8.0±10.0[b]	0.03
Supper	23.7±30.4[a]	8.9±16.8[b]	0.04
Highest glucose levels within 3 h after each meal (mg/dL)			
Breakfast	161.7±40.2	150.7±26.7	0.2
Lunch	219.0±43.1[a]	192.9±34.3[a]	0.004
Supper	230.1±53.6[a]	192.3±41.8[a]	0.006
Pre-prandial glucose levels (mg/dL)			
Breakfast	87.0±25.0	81.7±18.5	0.4
Lunch	111.3±30.3[a]	110.9±16.4[a]	0.9
Supper	131.3±24.7[ac]	118.7±16.5[ad]	0.04

p value: paired t-test

a: p<0.01 vs. Breakfast. b: p<0.05 vs. Breakfast. c: p<0.01 vs. Lunch. d: p<0.05 vs. Lunch. (ANOVA and Student-Newman-Keuls)

DPP-4 inhibitors significantly improved the highest postprandial glucose levels after lunch (219.0±43.1 mg/dL to 192.9±34.3 mg/dL, p=0.004) and supper (230.1±53.6 mg/dL to 192.3±41.8 mg/dL, p=0.006), while the highest postprandial glucose levels after breakfast did not differ to a statistically significant extent (161.7±40.2 mg/dL vs. 150.7±26.7 mg/dL, p=0.2). In contrast, the preprandial glucose levels did not change before breakfast (87.0±25.0 mg/dL vs. 81.7±15.5 mg/dL, p=0.4) or before lunch (111.3±30.3 mg/dL vs. 110.9±16.4 mg/dL, p=0.9), but those before supper (131.3±24.7 mg/dL vs. 118.7±16.5 mg/dL, p=0.04) were slightly reduced (Table 4).

The comparison between the group in which the glucocorticoid dose was reduced and the group in which it was not reduced prior to the initiation of DPP-4 inhibitor treatment revealed that both groups showed the same tendency toward the amelioration of the mean glucose level (6.3±9.2 mg/dL vs. 22.8±24.2 mg/dL, p=0.06), the maximum glucose level (25.4±25.3 mg/dL vs. 50.4±53.3 mg/dL, p=0.2), the SD of the glucose level (6.2±7.0 mg/dL vs. 10.6±16.7 mg/dL, p=0.5), the MAGE (14.3±23.5 mg/dL vs. 35.7±54.0 mg/dL, p=0.3), and the 24 hours AUC (>180 mg/dL) (58.3±59.6 mg·24 h/dL vs. 180.3±267.5 mg·24 h/dL, p=0.2) (Table 5).

Moreover, the HbA1c level was not aggravated after treatment with DPP-4 inhibitors during the six-month follow-up period (Fig. 2).

Table 5. Comparison of CGM Data between the Group in which the Glucocorticoid Dose was Reduced and the Group in which It was Not.

	Δ Mean glucose concentration (mg/dL)	Δ Maximum glucose concentration (mg/dL)	Δ SD (mg/dL)	Δ MAGE (mg/dL)	Δ 24 h AUC (mg·24h/dL)
Reduction of glucocorticoid dose (+) (n=5)	6.3±9.2	25.4±25.3	6.2±7.0	14.3±23.5	58.3±59.6
Reduction of glucocorticoid dose (-) (n=6)	22.8±24.2	50.4±53.3	10.6±16.7	35.7±54.0	180.3±267.5
p value	0.06	0.2	0.5	0.3	0.2

AUC: area under the curve, DPP: dipeptidyl peptidase, MAGE: mean amplitude of glycemic excursion
p value: unpaired t-test

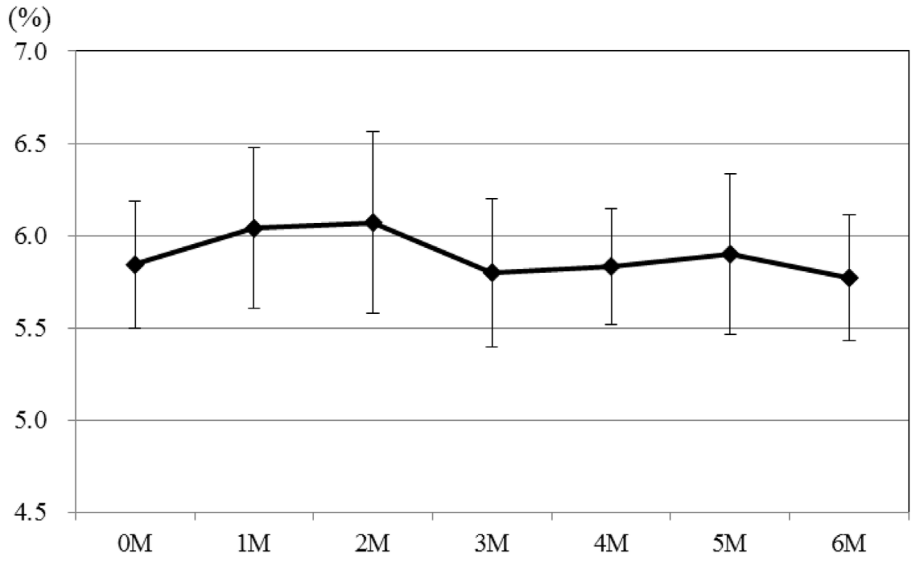

Figure 2. Changes in HbA1c level after the patients started DPP-4 inhibitors. During the follow-up period of 6 months, the level of HbA1c was not aggravated by glucocorticoids after treatment with DPP-4 inhibitors.

Discussion

In the present study, we retrospectively investigated the effect of DPP-4 inhibitors on the blood glucose levels of patients with glucocorticoid-induced diabetes. After starting DPP-4 inhibitors, the glycemic profiles, as observed by CGM, were significantly improved in comparison to baseline. The measurements of MAGE and SD are widely used to evaluate the variability of blood glucose levels. In our study, we found that the level of MAGE in patients with glucocorticoid-induced diabetes was 127.7±37.5 mg/dL, which is extremely high in comparison to the level reported in healthy controls (25.2 mg/dL) (9). The actual daily variations of the blood glucose levels of patients with glucocorticoid-induced diabetes before and after DPP-4 inhibitor treatment are shown in Fig. 1. Treatment with DPP-4 inhibitors significantly improved not only the patients' CGM findings during 24 hours, such as the mean glucose level, SD, MAGE, 24 hours AUC (>180 mg/dL), but also the mean, AUC>180 mg/dL, the highest glucose level within 3 hours postprandially in comparison to baseline. It has been reported that glucocorticoid-induced diabetes is characterized by an increase in postprandial glucose levels (10-12). In our study, as well as a previous study, there was a tendency for blood glucose levels to rise in the evening. Furthermore, because DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner (13, 14), they can improve postprandial hyperglycemia. Our study showed that we might be able to detect glucose variability in glucocorticoid-induced diabetes, and the glucose-dependent effect of DPP-4 inhibitors using CGM.

Recent studies have demonstrated that high levels of MAGE are strongly correlated with vascular endothelial dysfunction and the induction of oxidative stress, abnormalities which directly increase the risk of developing diabetic complications including cardiovascular diseases and diabetic micro-vascular diseases (15, 16). DPP-4 inhibitors are

known to improve glycemic variability in diabetic patients (17). Our data obtained from CGM showed that DPP-4 inhibitors improve glucose variability in patients with glucocorticoid-induced diabetes by lowering the postprandial glucose levels. Moreover, the hypoglycemic episodes related to treatment with DPP-4 inhibitors were negligible, since the AOC (<70 mg/dL) did not change in comparison to baseline. Taken together, the treatment of glucocorticoid-induced diabetes with DPP-4 inhibitors appears to reduce the variability in glucose levels and minimize the risk of developing hypoglycemia. These favorable effects have the potential to modify the patient outcome by reducing the incidence of cardiovascular events.

To investigate the effects of glucocorticoid reduction on the patients' glycemic profiles, we divided the patients into two groups: in the first group, the glucocorticoid dose was reduced; in the second, the glucocorticoid dose was not reduced. Both groups demonstrated the same tendency toward the amelioration of the mean glucose level, SD, MAGE, and 24 hours AUC (>180 mg/dL) (Table 5). We also divided the patients into two groups according to the duration of diet therapy before the first CGM test (<30 days vs. ≥30 days), according to the frequency of taking glucocorticoids (a single daily dose after breakfast vs. twice daily after breakfast and lunch), and according to the duration of DPP-4 inhibitor treatment before the second CGM test (<7 days vs. ≥7 days). There were no significant differences in the amelioration of the glycemic profiles in these groups (data not shown). These data suggest that administration of DPP-4 inhibitors leads to the improvement of CGM data.

In general, the long-term administration of glucocorticoids tends to worsen blood glucose control. Recent studies have demonstrated that two-thirds of patients with rheumatic or renal disease who received glucocorticoid therapy developed glucocorticoid-induced diabetes (18). However, in our study, the exacerbation of HbA1c was not observed during the 6-month follow-up period because DPP-4 inhibitors were started after the onset of glucocorticoid-induced diabetes. Thus, DPP-4 inhibitors might be expected to prevent the aggravation of glucocorticoid-induced diabetes.

Glucocorticoid-induced insulin resistance and impaired glucose tolerance are both associated with a progressive decline in the incretin effect, and an increase in glucocorticoid-induced insulin resistance was associated with an inappropriate increase in glucagon secretion in the first-degree relatives of patients with type 2 diabetes (4). DPP-4 inhibitors promote insulin secretion via glucagon-like peptide-1 (GLP-1) and inhibit glucagon secretion (19), actions that should be beneficial for the treatment of glucocorticoid-induced diabetes.

Exenatide, an injectable GLP-1 receptor (GLP-1R) agonist, has similar pharmacologic functions to DPP-4 inhibitors and also improves hyperglycemia in patients with glucocorticoid-induced diabetes (20). However, there is little evidence to support the superiority of either DPP-4 inhibitors or GLP-1R agonists in the treatment of glucocorticoid-induced diabetes. A recent report indicated that GLP-1R agonists are superior to DPP-4 inhibitors in their capacity to lower the HbA1c level (21). In contrast, gastrointestinal side effects, particularly nausea, are often reported after treatment with GLP-1R agonists, but such adverse events occur infrequently with DPP-4 inhibitors (19). In addition, DPP-4 inhibitors can be orally administered, whereas GLP-1R agonists must be injected. In this regard, the administration of DPP-4 inhibitors for the treatment of glucocorticoid-induced diabetes is simpler and more convenient in comparison to GLP-1R agonists.

A previous study showed that linagliptin lowered the HbA 1c levels in all patients in a group with a normal renal function and a group with mild-to-moderate renal impairment, and there was no inter-group difference in the HbA1c reduction (22). Another study showed that vildagliptin lowered the level of HbA1c in patients with moderate to severe renal impairment without an increased frequency of hypoglycemic events (23). The present study shows that DPP-4 inhibitors can be used to safely improve glycemic control in patients with glucocorticoid-induced diabetes regardless of their renal function. However, the accumulation of further evidence from prospective studies is needed.

The present study was associated with some limitations, including the small number of cases, the short duration of follow-up and the absence of a control group. Since this study was retrospective in nature, 5 types of DPP-4 inhibitors were selected for 11 patients. Craddy et al. recently reported that DPP-4 inhibitors have equivalent effects across the class in terms of their key efficacy and safety outcomes (24). Thus, we decided to analyze these 11 patients together in the present study.

Conclusion

In 11 patients with glucocorticoid-induced diabetes, who were also diagnosed with kidney disease or other diseases with renal involvement and treated with DPP-4 inhibitors, the glycemic profiles (as assessed by CGM) improved without an increase in the number of hypoglycemic episodes during the 6-month follow-up period. The oral hypoglycemic agents that are available for CKD patients are limited; thus, DPP-4 inhibitors would be useful for patients with glucocorticoid-induced diabetes.

Author's disclosure of potential Conflicts of Interest (COI).
Ichiei Narita: Honoraria, Novartis Pharma K.K., Daiichi Sankyo Co., Ltd, MSD K.K., Mitsubishi Tanabe Pharma Corporation and Kyowa Hakko Kirin Co.,Ltd.

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