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Title: Efficacy of dipeptidyl peptidase-4 inhibitors in patients with glucocorticoid-induced diabetes assessed by continuous glucose monitoring

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Abstract

Objective 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 that may result in more 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 for 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 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 diagnosed with kidney disease or other diseases with renal involvement were recruited for retrospective analysis in this study. After starting DPP-4 inhibitors, the mean and the SD of glucose levels, and the mean amplitude of glycemic excursion (MAGE) were significantly improved compared with baseline. Furthermore, the area over the curve for glucose levels <70 mg/dL was not increased compared with baseline after initiating DPP-4 inhibitors. Treatment of patients with glucocorticoid-induced diabetes using DPP-4 inhibitors can thus 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.

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

Introduction

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 causes hyperglycemia is multifactorial and includes augmentation of hepatic gluconeogenesis, inappropriate secretion of glucagon, inhibition of glucose uptake in adipose tissue, and alteration of insulin receptor and post-receptor signals [1-4]. Patients with persistent hyperglycemia due to glucocorticoid therapy sometimes require insulin therapy. In fact, according to the Endocrine Society guidelines for management of hyperglycemia in hospitalized patients, insulin therapy is recommended for patients with glucocorticoid-induced diabetes [5]. However, insulin therapy itself can result in more 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, scant evidence is available 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 pose a risk of developing medication-associated adverse events such as prolonged hypoglycemia and lactic acidosis. The dipeptidyl peptidase (DPP)-4 inhibitors are a new class of oral antidiabetic drugs which increase the action of the incretin hormones. DPP-4 inhibitors can also be used in CKD patients with dose adjustment. 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 scarcely any evidence about the efficacy of DPP-4 inhibitors for glucocorticoid-induced diabetes.

Precise circadian variations of blood glucose levels have not been clarified in patients with glucocorticoid-induced diabetes. The continuous glucose monitoring (CGM) system can evaluate changes in interstitial glucose levels all day long. It has high monitoring accuracy to measure blood glucose levels, is easy to use, and has good utility in the daily management of diabetes. In this study, we evaluated the efficacy of DPP-4 inhibitors determined by using CGM for the treatment of patients with glucocorticoid-induced diabetes.

Materials and Methods

Patients

We retrospectively analyzed 15 Japanese patients, diagnosed as having glucocorticoid-induced diabetes and 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 ethical committee at both institutions 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 poor CGM recording, and 1 patient who had received DPP-4 inhibitor treatment for only 2 days at the second CGM. Eleven patients (4 men and 7 women; 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 received a previous diagnosis of diabetes mellitus. They also fulfilled the following criteria: hemoglobin A1c (HbA1c) level <6.5 % and fasting plasma glucose level <126 mg/dL prior to glucocorticoid administration. 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 elevation of casual plasma glucose levels over 200 mg/dL at least twice during glucocorticoid treatment. Each patient was prescribed an energy-restricted diet with about as much energy as 30 kcal/kg before glucocorticoid-induced diabetes was diagnosed.

CGM

Glucose profiles were assessed using the iPro®2 CGM system (Medtronic, Northridge, CA). The first CGM test was carried out at least 1 week after energy-restricted diet therapy was started. This CGM device collects, records, and stores data concerning interstitial glucose levels every 5 min, and is calibrated with capillary blood glucose samples 4 times daily. After baseline glucose monitoring for 72 h by CGM, patients were prescribed a DPP-4 inhibitor (sitagliptin, vildagliptin, alogliptin, linagliptin, or teneligliptin) by attending physicians. The following values were calculated from the CGM data: 1) mean 24 h glucose levels, 2) SD of glucose levels, 3) mean amplitude of glycemic excursion (MAGE), 4) area under the curve for glucose levels (AUC) >180 mg/dL per 24 h (24 h AUC), 5) area over the curve for glucose levels (AOC) <70 mg/dL per 24 h (24 h AOC), 6) mean, AUC>180 mg/dL, and highest glucose levels within 3 h postprandially (breakfast: 8:00-11:00 am; lunch:

12:00-3:00 pm; and supper: 6:00-9:00 pm), and 7) pre-prandial glucose levels defined as the lowest glucose levels within 1 h before each meal (breakfast: 7:00-8:00 am; lunch: 11:00 am-12:00 pm; supper: 5:00-6:00 pm). Glycemic AUCs and AOCs were calculated according to the rule of trapezoidal area. One to 4 weeks after initiating DPP-4 inhibitors, patients underwent CGM for another 72 h.

Statistical analysis

Results are presented as the means±SD. The effects of DPP-4 inhibitors were analyzed using the paired t-test and one way repeated ANOVA with the Student-Newman-Keuls method as a post hoc test. The unpaired t-test was used for comparisons between the group in which the glucocorticoid dose was reduced or the group in which it was not. Changes in HbA1c during treatment with DPP-4 inhibitors were assessed using by ANOVA. Statistical analyses were performed using SPSS statistical software version 17.0. Results were considered significant when $P < 0.05$.

Results

For the eleven patients, HbA1c was 6.0±0.4%, fasting plasma glucose was 93.3±9.2 mg/dL, body mass index was 20.9±2.8 kg/m^2, and 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. Patients' clinical characteristics are summarized in Table 1. Four patients had received methylprednisolone pulse therapy before maintenance glucocorticoid therapy. Patients received an initial dose of prednisolone ranging from 25 to 60 mg/day. After the first

CGM test, vildagliptin, or alogliptin was prescribed for 3 patients each, while sitagliptin or linagliptin was prescribed for 2 patients each, and teneligliptin was prescribed for 1 patient.

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

DPP-4 inhibitors further improved postprandial glucose levels and the 3 h mean glucose levels after each meal were significantly lowered (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 h 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 highest postprandial glucose levels were significantly improved with DPP-4 inhibitors 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), but there was no significant difference after breakfast (161.7±40.2 mg/dL vs. 150.7±26.7 mg/dL, P =

0.2). In contrast, pre-prandial glucose levels did not change before breakfast and lunch (87.0±25.0 mg/dL vs. 81.7±15.5 mg/dL, *P* = 0.4, and 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 lowered (Table 4).

Comparison between the group in which the glucocorticoid dose was reduced and the group in which it was not reduced prior to starting DPP-4 inhibitors demonstrated the same tendency toward amelioration of mean glucose levels (6.3±9.2 mg/dL vs. 22.8±24.2 mg/dL, *P* = 0.06), maximum glucose levels (25.4±25.3 mg/dL vs. 50.4±53.3 mg/dL, *P* = 0.2), SD of glucose levels (6.2±7.0 mg/dL vs. 10.6±16.7 mg/dL, *P* = 0.5), MAGE (14.3±23.5 mg/dL vs. 35.7±54.0 mg/dL, *P* = 0.3), and 24 h AUC (>180 mg/dL) (58.3±59.6 mg·24h/dL vs. 180.3±267.5 mg·24h/dL, *P* = 0.2) (Table 5).

Moreover, during the follow-up period of 6 months, the level of HbA1c was not aggravated after treatment with DPP-4 inhibitors (Fig. 3).

Discussion

The effect of DPP-4 inhibitors on blood glucose levels in patients with glucocorticoid-induced diabetes was retrospectively investigated in this study. After starting DPP-4 inhibitors, glycemic profiles as observed by CGM were significantly improved compared with baseline. Measurements of MAGE and SD are widely used to evaluate the variability of blood glucose levels. In our study, we found the level of MAGE to be 127.7±37.5 mg/dL in patients with glucocorticoid-induced diabetes, which is extremely high compared with 25.2 mg/dL reported in healthy controls [9]. The actual daily variations of blood glucose levels in glucocorticoid-induced diabetes patients before and after DPP-4 inhibitor treatment are delineated in Fig. 1. Treatment

with DPP-4 inhibitors, significantly improved CGM findings such as mean glucose levels, SD, MAGE, 24 h AUC (>180 mg/dL) , postprandial mean, AUC (>180 mg/dL), and the highest glucose levels within 3h compared with 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 of 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 its postprandial hyperglycemia. In our study, we might be able to detect glucose variability in glucocorticoid-induced diabetes, and the glucose-dependent effect of DPP-4 inhibitors assessed by CGM.

Recent studies have demonstrated that high levels of MAGE correlate strongly with vascular endothelial dysfunction and 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 glucocorticoid-induced diabetes by lowering the postprandial glucose levels. Moreover, hypoglycemic episodes related to treatment with DPP-4 inhibitors were negligible, since AOC (<70 mg/dL) did not change compared with baseline. Taken together, treatment of glucocorticoid-induced diabetes with DPP-4 inhibitors appears to reduce the variability of glucose levels and minimize the risk of developing hypoglycemia. These favorable effects have the potential to modify patient outcome by reducing the incidence of cardiovascular events.

To investigate the effects of glucocorticoid reduction on glycemic profiles, we divided these patients into two groups: the first with reduction of glucocorticoid dose and the second without reduction of glucocorticoid dose. Both groups demonstrated the same tendency toward amelioration in mean glucose levels, SD, MAGE, and 24 h AUC (>180 mg/dL) (Table 5). We also divided the patients into two groups by the duration of diet therapy before the first CGM test (less than 30 days vs. 30 days or more), by daily frequency of taking glucocorticoid (single daily dosing after breakfast vs. twice daily dosing after breakfast and lunch), and by the duration of DPP-4 inhibitor treatment before the second CGM test (less than 7 days vs. 7 days or more). There were no significant differences in amelioration in glycemic profiles in these groups, respectively (data not shown). These data suggest that administration of DPP-4 inhibitors leads to improvement of CGM data.

In general, long-term administration of glucocorticoids tends to worsen blood glucose control. Recent studies demonstrated that two-thirds of patients with rheumatic or renal disease who received glucocorticoid therapy developed glucocorticoid-induced diabetes [18]. However, in our study, 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 of the incretin effect, and the increase in glucocorticoid-induced insulin resistance was associated with an inappropriate increase in glucagon secretion in 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 which 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, scant evidence is available as to whether DPP-4 inhibitors or GLP-1R agonists are superior to the other in the treatment of glucocorticoid-induced diabetes. A recent report indicated that GLP-1R agonists have superior effects in HbA1c lowering capacity compared with DPP-4 inhibitors [21]. By 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 are given by injection. In this regard, administration of DPP-4 inhibitors for glucocorticoid-induced diabetes is simpler and more convenient than GLP-1R agonists.

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

The limitations of this study are the small number of cases, the short duration of follow-up and the absence of a control group. Since this study was retrospective, 5

kinds of DPP-4 inhibitors were selected for eleven patients. Craddy et al. recently reported that DPP-4 inhibitors have equivalent effects across the class in terms of key efficacy and safety outcomes [24]. Thus, we decided to analyze these eleven patients all together in this study.

Conclusion

In eleven patients with glucocorticoid-induced diabetes, also diagnosed with kidney disease or other diseases with renal involvement and treated with DPP-4 inhibitors, glycemic profiles assessed by CGM improved without increased hypoglycemic episodes during the follow-up period of 6 months. Oral hypoglycemic agents available for CKD patients are limited, thus, DPP-4 inhibitors would be useful for patients with glucocorticoid-induced diabetes.

The authors state that they have no conflict of interest.

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1 Table 1. Summary of patient characteristics

Case	Age (y.o.)	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	Number of days of DPP-4 inhibitor before second CGM test
										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; and Vilda, vildagliptin.

Table 2. Comparison of CGM data before and after treatment with DPP-4 inhibitors in 24 h.

	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; and MAGE, mean amplitude of glycemic excursions.

P value: Paired t-test

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; and 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)

Table 5. Comparison of CGM data between the 2 groups in which the steroid dosage was either reduced or not.

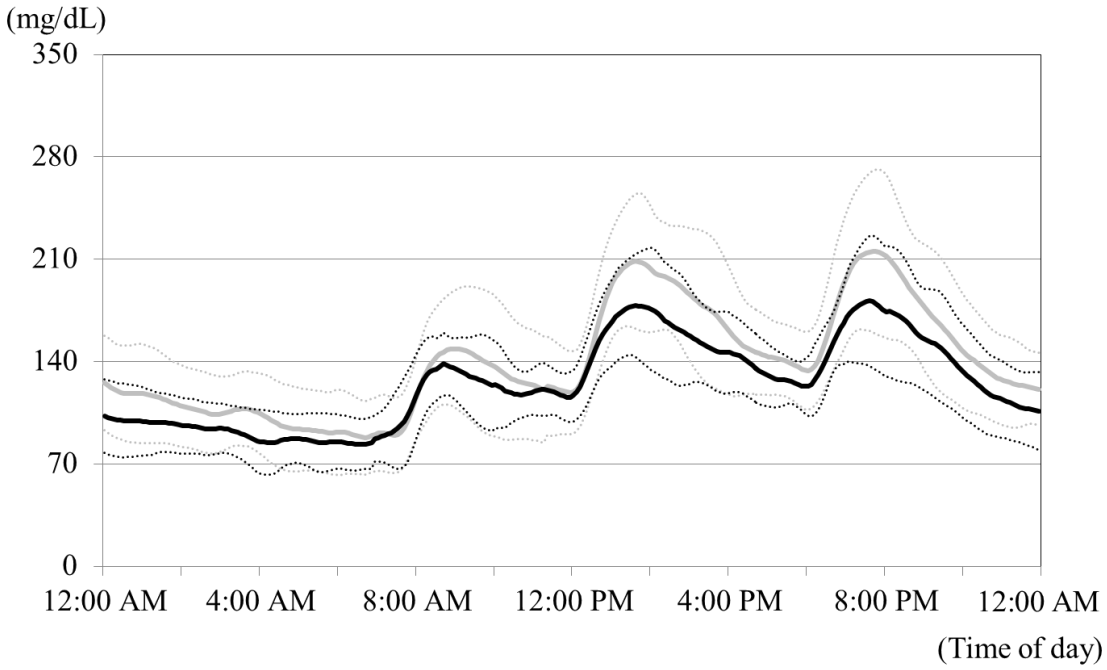
	Δ Mean glucose concentration (mg/dL)	Δ Maximum glucose concentration (mg/dL)	Δ SD (mg/dL)	Δ MAGE (mg/dL)	Δ 24 h AUC (mg·24h/dL)
Reduction of steroid dose (+) (n=5)	6.3±9.2	25.4±25.3	6.2±7.0	14.3±23.5	58.3±59.6
Reduction of steroid dose (-) (n=6)	22.8±24.2	50.4±53.3	10.6±16.7	35.7±54.0	180.3±267.5
P value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

AUC, area under the curve; DPP, dipeptidyl peptidase; and MAGE, mean amplitude of glycemic excursion

P value: Unpaired t-test

Figures and Legends

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.

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