MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2014; 20: 587-593
DOI: 10.12659/MSM.889872

Received: 2013.10.08
Accepted: 2014.01.03
Published: 2014.04.10

Alogliptin improves steroid-induced hyperglycemia in treatment-naïve Japanese patients with chronic kidney disease by decrease of plasma glucagon levels

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Source of support: This study was supported in 2011 and 2012 by the Hamamatsu University School of Medicine Young Investigator Research Projects (both awarded to Naro Ohashi)

Background: Chronic kidney disease (CKD) is a risk factor for end-stage renal failure and cardiovascular disease, and a strategy to counteract CKD must be established. CKD caused by immunological abnormalities is treated by steroids, frequently resulting in steroid diabetes. Although insulin is the most effective drug against steroid diabetes, administering it to patients can be difficult. Dipeptidyl peptidase-4 (DPP-4) inhibitors were developed for diabetes mellitus with a new mechanism of action. However, their efficacies and mechanisms of action for steroid diabetes are unclear.

Material/Methods: We studied 11 CKD patients treated with steroids admitted to our hospital (3 men and 8 women; age, 66.0±15.9 years). DPP-4 inhibitor alogliptin was administered for steroid diabetes. Levels of markers related to glucose metabolism were measured before alogliptin treatment and after alogliptin treatment, before the prednisolone dose was reduced.

Results: Alogliptin treatment significantly increased plasma glucagon-like peptide-1 (GLP-1) levels from 1.16±1.71 pmol/L to 4.48±1.53 pmol/L and significantly reduced levels of plasma glucose recorded 2 h after lunch and hemoglobin A1c (HbA1c). No significant differences were seen in insulin secretory ability of homeostasis model assessment (HOMA) (HOMA-β) and insulin resistance index of HOMA (HOMA-R) before and after alogliptin treatment. In contrast, alogliptin treatment significantly decreased plasma glucagon levels, from 116.1±38.7 pg/mL to 89.6±17.3 pg/mL. Moreover, there were significant correlations among HbA1c, GLP-1, and glucagon levels.

Conclusions: Alogliptin improves steroid-induced hyperglycemia by decrease of glucagon levels through an increase in plasma GLP-1 levels.

Keywords: Alogliptin • Dipeptidyl Peptidase-4 Inhibitor • HOMA-β • HOMA-R • Steroid Diabetes

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Background

Chronic kidney disease (CKD) is a serious risk factor for end-stage renal failure as well as cardiovascular diseases [1,2], and a strategy to counteract this condition must be established urgently. When immunological abnormalities underlie the development of CKD, patients are administered immunosuppressant drugs, including steroids. Steroid diabetes is a major adverse effect of steroid therapy [3], and long-term use of steroids is associated with an elevated risk of developing diabetes mellitus, with the odds ratio ranging from 1.4 to 2.3 [4–6]. The mechanisms underlying the development of steroid diabetes include increases in gluconeogenesis, hepatic glucose output, and insulin resistance, and reports suggest that steroid diabetes is characterized by normal levels of fasting plasma glucose (FPG) and postprandial hyperglycemia [7].

Although insulin therapy is the only compellingly effective treatment for steroid diabetes, it can be difficult to administer insulin to patients with steroid diabetes because of their refusal to use the therapy, reduced visual acuity, or orthopedic impairment. Oral antidiabetic drugs effective in the treatment of steroid diabetes include α-glucosidase inhibitors and thiazolidinediones [8,9]. However, the evidence that supports the effectiveness of these drugs in the treatment of steroid diabetes is not conclusive because the studies were small and lacked a detailed investigation of the drugs' mechanisms of action.

Dipeptidyl peptidase-4 (DPP-4) inhibitors form a drug category developed for the treatment of diabetes mellitus with a new mechanism of action. DPP-4 inhibitors prevent the inactivation of incretin that is released from the gut after food ingestion; incretin, in turn, stimulates insulin secretion [10,11]. Glucagon-like peptidase-1 (GLP-1) is a potent insulinotropic agent that is qualified for the designation of incretin. Alogliptin is a novel quinazolinone-based DPP-4 inhibitor with selectivity for DPP-4 that is more than 10,000-fold greater than that shown by the closely related serine proteases DPP-2, DPP-8, DPP-9, fibroblast activation protein/seprase, prolyl endopeptidase, and tryptase [12]. Alogliptin can be used to treat patients with moderate-to-severe renal failure by adjusting the dose administered. However, only 1 case report has suggested that DPP-4 inhibitors may be effective in the treatment of steroid diabetes [13]. Furthermore, the mechanism of action of DPP-4 inhibitors in the treatment of steroid diabetes is unclear. This study investigated the mechanism of action and effectiveness of the DPP-4 inhibitor alogliptin in the treatment of CKD patients with steroid diabetes.

Material and Methods

Patients and study protocol

This study was approved by ethics committee of Hamamatsu University School of Medicine and was conducted in accordance with the Declaration of Helsinki. All CKD patients provided written informed consent.

We studied Japanese CKD patients treated with steroids who were admitted to our hospital between January 2012 and December 2012. Those who fulfilled the following criteria were recruited for the study: (1) age, >20 years; (2) absence of the symptoms associated with diabetes mellitus before steroids were administered, including thirst, polyposia, polyuria, and body weight (BW) loss; (3) FPG levels <126 mg/dL, plasma glucose levels 2 h after lunch (2-h PG) <200 mg/dL, and hemoglobin A1c (HbA1c) <6.1% (the Japanese Diabetes Society standard) before steroid administration; and (4) FPG levels ≥126 mg/dL, 2-h PG levels ≥200 mg/dL, and/or HbA1c ≥6.1% after steroid administration. The patients were started on DPP-4 inhibitor, alogliptin for steroid diabetes. The patients who received other drugs for diabetes mellitus, except for alogliptin, were excluded from this study.

Upon initiation of alogliptin treatment, baseline values for plasma glucose, HbA1c, immunoreactive insulin, GLP-1, glucagon levels, and serum DPP-4 levels were measured and compared with the values recorded just before the prednisolone dose was reduced. These markers were measured before breakfast and plasma glucose levels were also measured 2 h after lunch.

Alogliptin dose

The alogliptin dose was adjusted based on renal function as follows: patients with an estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2 were given 25 mg alogliptin once a day; patients with 30≤ eGFR <50 ml/min/1.73 m^2, 12.5 mg/day alogliptin once a day; and patients with an eGFR <30 mL/min/1.73 m^2, 6.25 mg alogliptin once a day. eGFR was calculated using the Japanese eGFR equation as follows:

$194 \times (\text{serum creatinine level})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (if female) [14].

Cumulative steroid dose

The administered steroid dose was added together in prednisolone equivalents.

For example, the prednisolone dose of 1000 mg daily of methylprednisolone pulse therapy for 3 consecutive days were calculated as 1000×3×1.25 (methylprednisolone to prednisolone conversion factor) =3750 mg.

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Calculation of homeostasis model assessment-R and homeostasis model assessment-β

The homeostasis model assessment (HOMA)-R, an index of insulin resistance, and the HOMA-β, an index of insulin secretory capacity, were calculated using the following equations [15]:

HOMA-R = FPG (mg/dL) × fasting plasma insulin (μU/mL)/405

HOMA-β = {360 × fasting plasma insulin (μU/mL)}/{FPG (mg/dL) – 63}

Statistical analysis

Each value was expressed as the mean ± standard deviation (SD). The paired t test was used to compare the data recorded before alogliptin administration and just before the steroid dose was reduced. The relationships among HbA1c, GLP-1, and glucagon levels were analyzed using multiple regression analysis. A value of $p<0.05$ was considered statistically significant. All statistical calculations were performed using SPSS software version 20.0 (SPSS-IBM Chicago, IL).

Results

We studied 11 Japanese patients with CKD who were being treated with steroids (3 men and 8 women; mean age, 66.0±15.9 years). The underlying kidney diseases were as follows: microscopic polyangiitis (5 patients), membranous nephropathy (1 patient), minimal change nephrotic syndrome (1 patient), focal segmental glomerulosclerosis (1 patient), IgA nephropathy (1 patient), sarcoidosis (1 patient), and lupus nephritis (1 patient). Baseline physical characteristics, vital signs, and laboratory data, including patients' glucose levels 11.4±12.8 days before steroid administration are shown in Table 1. Physical characteristics and laboratory data, including plasma glucose levels before breakfast and 2 h after lunch, HbA1c, immunoreactive insulin, GLP-1, glucagon, and serum DPP-4 levels were measured 12.5±6.8 days after the administration of steroids began (the mean prednisolone dose at that time was 34.5±6.5 mg/day, and the total and oral cumulative prednisolone doses were 1564.1±1662.5 mg and 370.9±225.6 mg, respectively). Once it was confirmed that a patient fulfilled the criteria for steroid diabetes, alogliptin administration (mean, 13.1±8.6 mg/day) was initiated the next day (Table 2). Physical characteristics and laboratory data, including plasma glucose levels before breakfast and 2 h after lunch, HbA1c, immunoreactive insulin, GLP-1, glucagon, and serum DPP-4 levels were recorded 34.8±11.3 days after steroid administration was started, just before the prednisolone dose was reduced (Table 2). A prednisolone dose of 812.7±585.4 mg was administered cumulatively during this period.

Table 1. Baseline physical characteristics, vital signs, and laboratory data before steroid administration.

Age, years	66.0±15.96
Sex	Male 3 / Female 8
Height, m	1.54±0.05
Body weight, kg	49.6±8.2
Body mass index, kg/m^2	20.8±2.8
Systolic BP, mmHg	135.0±26.9
Diastolic BP, mmHg	78.8±13.4
FPG, mg/dl	90.0±7.4
Casual blood glucose level, mg/dl	104.1±13.3
HbA1c, %	5.06±0.34
Creatinine, mg/dl	1.88±1.13
eGFR, ml/min/1.73 m^2	31.0±16.7
Total cholesterol, mg/dl	239.0±129.4
Triglyceride, mg/dl	144.1±38.2
LDL cholesterol, mg/dl	140.4±92.5
Albumin, g/dl	2.78±0.99

BP – blood pressure; FPG – fasting plasma glucose; HbA1c – hemoglobin A1c; eGFR – estimated glomerular filtration rate; LDL – low-density lipoprotein.

Alogliptin significantly increased plasma GLP-1 levels. Although FPG levels did not change significantly, the 2-h PG levels and HbA1c were significantly reduced after alogliptin treatment. No significant differences were apparent in HOMA-R and HOMA-β after alogliptin treatment. However, plasma glucagon levels significantly decreased from 116.1±38.7 pg/mL to 89.6±17.3 pg/mL ($p=0.017$) after alogliptin treatment. After alogliptin treatment, BW tended to decrease and body mass index (BMI) decreased significantly compared with the BMI before treatment.

To investigate whether the decrease in HbA1c was caused by the increase in GLP-1 levels after alogliptin treatment, the correlation between HbA1c and plasma GLP-1 levels was investigated using multiple regression analysis. HbA1c was significantly associated with plasma GLP-1 levels after adjustments were made for age, sex, BMI, and eGFR (Table 3).

To clarify the reasons for improvement in blood glucose levels by GLP-1, the relationships between GLP-1 and glucagon, HOMA-β and HOMA-R were investigated using multiple regression analysis after adjustments were made for age, sex, BMI, and renal function. Significant relationships were found between plasma GLP-1 levels and plasma glucagon levels after adjustments were made for age, sex, BMI, and creatinine.

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Table 2. Baseline physical characteristics, vital signs, and laboratory data before and after alogliptin treatment.

	Before treatment	After treatment	p value
Body weight, kg	48.7±8.1	46.3±6.9	0.054
Body mass index, kg/m^2	20.5±3.1	19.5±2.9	0.049
Systolic BP, mmHg	125.9±19.6	122.8±18.6	0.61
Diastolic BP, mmHg	70.0±11.0	68.6±11.6	0.76
FPG, mg/dl	81.8±9.0	78.6±5.5	0.21
2hr PG, mg/dl	231.3±45.8	195.8±42.2	0.031
HbA1c, %	5.11±0.24	4.90±0.31	0.0033
DPP-4, ng/ml	390.1±87.4	343.7±76.2	0.14
GLP-1, pmol/l	1.16±1.71	4.48±2.53	0.0014
HOMA-R	1.78±1.32	1.39±0.43	0.39
HOMA-β	171.1±60.3	186.0±96.8	0.52
Glucagon, pg/ml	116.1±38.7	89.6±17.3	0.017
Creatinine, mg/dl	1.76±1.09	1.38±0.39	0.18
eGFR, ml/min/1.73 m^2	34.8±20.7	38.8±19.5	0.052
Total cholesterol, mg/dl	257.2±69.7	254.8±61.6	0.91
Triglyceride, mg/dl	181.1±74.3	155.5±50.9	0.089
LDL cholesterol, mg/dl	155.6±54.5	142.9±53.6	0.41
Albumin, g/dl	2.68±0.78	3.36±0.57	0.026

BP – blood pressure; FPG – fasting plasma glucose; 2 hr PG – plasma glucose levels 2 h after lunch; HbA1c – hemoglobin A1c; DPP-4 – dipeptidyl peptidase-4; GLP-1 – glucagon-like peptidase-1; HOMA – homeostasis model assessment; eGFR – estimated glomerular filtration rate; LDL – low-density lipoprotein.

Table 3. Correlation between HbA1c and GLP-1 using multiple regression analysis after adjustment for age, sex, BMI, and renal function.

	R	R^2	p value
GLP-1	0.050	0.002	0.83
GLP-1 + age	0.40	0.16	0.22
GLP-1 + age + sex	0.42	0.18	0.38
GLP-1 + age + sex + BMI	0.42	0.18	0.51
GLP-1 + age + sex + BMI + Cr	0.72	0.52	0.082
GLP-1 + age + sex + BMI + eGFR	0.82	0.68	0.010

GLP-1 – glucagon-like peptidase-1; BMI – body mass index; Cr – creatinine; eGFR – estimated glomerular filtration rate.

However, there were no relationships between plasma GLP-1 levels and HOMA-β or HOMA-R (Table 4).

Finally, to clarify whether glucagon influences HbA1c, the relationship between glucagon and HbA1c was assessed using multiple regression analysis. A significant relationship was found between plasma glucagon levels and HbA1c after adjustments were made for age, sex, BMI, and eGFR (Table 5).

Discussion

In this study, administration of alogliptin increased plasma GLP-1 levels and decreased HbA1c, and there was a significant relationship between plasma GLP-1 levels and HbA1c. Moreover, administration of alogliptin decreased plasma glucagon levels, and this was significantly correlated with plasma GLP-1 levels. In addition, a significant relationship existed

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Table 4. Correlations between GLP-1 and glucagon, HOMA-β or HOMA-R using multiple regression analysis after adjustment for age, sex, BMI, and renal function.

	Glucagon			HOMA-β			HOMA-R		
	R	R^2	p value	R	R^2	p value	R	R^2	p value
GLP-1	0.16	0.026	0.50	0.28	0.076	0.23	0.23	0.052	0.32
GLP-1 + age	0.26	0.066	0.56	0.33	0.11	0.37	0.23	0.054	0.61
GLP-1 + age + sex	0.28	0.079	0.72	0.43	0.18	0.32	0.49	0.24	0.20
GLP-1 + age + sex + BMI	0.37	0.13	0.68	0.45	0.20	0.42	0.64	0.41	0.062
GLP-1 + age + sex + BMI + Cr	0.79	0.63	0.023	0.65	0.43	0.19	0.67	0.45	0.13
GLP-1 + age + sex + BMI + eGFR	0.77	0.59	0.053	0.53	0.22	0.50	0.71	0.51	0.092

HOMA – homeostasis model assessment; GLP-1 – glucagon-like peptidase-1; BMI – body mass index; Cr – creatinine; eGFR – estimated glomerular filtration rate.

Table 5. Correlation between HbA1c and glucagon using multiple regression analysis after adjustment for age, sex, BMI, and renal function.

	R	R^2	p value
Glucagon	0.31	0.094	0.21
Glucagon + age	0.54	0.30	0.060
Glucagon + age + sex	0.57	0.32	0.11
Glucagon + age + sex + BMI	0.57	0.32	0.22
Glucagon + age + sex + BMI + Cr	0.69	0.48	0.16
Glucagon + age + sex + BMI + eGFR	0.83	0.69	0.022

BMI – body mass index; Cr – creatinine; eGFR – estimated glomerular filtration rate.

between HbA1c and plasma glucagon levels. These data suggest that the increase in plasma GLP-1 levels after alogliptin administration contributed to the decrease in HbA1c by reduction of plasma glucagon levels. In contrast, administration of alogliptin did not significantly increase HOMA-β or decrease HOMA-R, and plasma GLP-1 levels were not correlated with HOMA-β and HOMA-R. These data suggest that insulin secretory capacity and insulin resistance are not key factors in the improvement of steroid diabetes by alogliptin. In the present study, 1 patient with steroid-induced hyperglycemia required treatment with insulin because alogliptin administration did not alleviate postprandial hyperglycemia. Although this patient could not be included in the analyses, the patient's data before and after alogliptin treatment were: 2-hr PG, 429 mg/dL and 409 mg/dL, respectively; plasma GLP-1 levels, lower than the limit of detection and 3.0 pmol/L, respectively; plasma glucagon levels, 80 pg/mL and 108 pg/mL, respectively; HOMA-R, 3.01 and 2.01, respectively; and HOMA-β 82.5 and 65.5, respectively. These data may support our hypothesis that a decrease in plasma glucagon levels plays an important role in the alleviation of steroid diabetes. Abnormal regulation of glucagon secretion has been implicated in the development of hyperglycemia in patients with type 2 diabetes mellitus [16], and a recent study in animal models indicated that a reduction in glucagon action can have profound effects on mitigating hyperglycemia even in the presence of severe hypoinsulinemia [17]. These results are compatible with our findings that glucagon plays an important role in the induction of steroid diabetes. However, an accumulation of patient numbers, including cases that drop out, is required.

The following mechanism may underlie the effectiveness of alogliptin in the treatment of steroid diabetes. In addition to increasing gluconeogenesis, hepatic glucose output, and insulin resistance [7], steroid treatment increases levels of plasma glucagon secreted from α cells in the basal state and in response to protein ingestion or aminogenic stimulation [18]. GLP-1 inhibits glucose-dependent glucagon secretion in addition to increasing insulin secretion [19,20]. The increase in GLP-1 after alogliptin administration may suppress plasma

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glucagon levels in steroid diabetes, leading to improved plasma glucose levels.

Significant correlations were not found between plasma glucagon levels and GLP-1 and HbA1c by single regression analysis. However, significant correlations were found between plasma glucagon levels and GLP-1 and HbA1c by multiple regression analysis after adjusting for renal function in addition to age, sex, and BMI. Glucagon is secreted from the α cells in the pancreas and excreted from the kidneys, and plasma glucagon levels are elevated in patients with chronic renal failure compared with healthy subjects [21]. In the present study, renal function was remarkably (but not significantly) improved by steroid treatment; therefore, renal function was selected as an independent variable. This led to the detection of significant relationships between glucagon and GLP-1 and HbA1c.

In addition, there was no significant correlation between GLP-1 and HbA1c by single regression analysis. It is known that the kidney plays a significant role in plasma removal of GLP-1 by a mechanism that involves glomerular filtration and tubular catabolism [22]. Simonsen et al. also reported that the renal extraction rates of N and C terminal GLP-1 were 48.3±5.9% and 56.6±2.6%, respectively [23]. Therefore, we selected age, sex, BMI, and renal function as independent variables, and significant correlations were found between plasma GLP-1 levels and HbA1c.

There are some limitations to this study. First, the number of patients in this study was small. Nevertheless, we demonstrated significant differences before and after alogliptin treatment in levels of 2-h PG, HbA1c, and plasma glucagon, and significant correlations among levels of HbA1c, GLP-1, and glucagon. Second, there may be problems with interpreting the data from patients with steroid-induced hyperglycemia with or without steroid pulse therapy in a lump. However, when only the patients with steroid pulse therapy were analyzed separately, we achieved the same results as the present study before and after alogliptin treatment (HbA1c, 5.23±0.32% and 4.95±0.40%, respectively, p=0.035; GLP-1, 0.98±1.95 pmol/L and 4.50±1.69 pmol/L, respectively, p=0.042; glucagon, 115.8±16.3 pg/mL and 88.3±16.5 pg/mL, respectively, p=0.040; HOMA-β 134.9±37.0 and 155.4±64.4, respectively, p=0.53; HOMA-R, 1.26±0.39 and 1.29±0.53, respectively, p=0.94, data not shown). Third, 5 patients increased their calorific intakes of 200 to 400 kilocalories during the follow-up period because of improvements in the underlying kidney diseases, including microscopic polyangiitis and lupus nephritis. Since the levels of 2-h PG and HbA1c were significantly reduced after alogliptin treatment, the increase in the calorific intake was not considered to have greatly influenced the results of the present study. Fourth, GLP-1 delays gastric emptying, thus enhancing satiety and reducing food intake; consequently, BW declines [19,20]. BW tended to decline in this study before and after alogliptin treatment. However, some patients with nephrotic syndrome whose BW declined as a result of reductions in total body fluid levels were included in this study; therefore, it is difficult to interpret the effect of GLP-1 on BW reduction. Nevertheless, the BW data were analyzed after excluding patients with nephrotic syndrome, and BW tended to decline after alogliptin treatment (BW before and after alogliptin treatment, 45.9±7.4 kg and 44.9±7.8 kg, respectively, p=0.072, data not shown). Trials will be performed shortly to evaluate the effects of GLP-1 on BW reduction in patients with steroid diabetes who do not have excessive levels of total body fluid. Finally, this trial lacked a comparative control. Mean eGFR was 34.8±20.7 mL/min/1.73 m^2 and renal function of some patients was remarkably impaired in the present study. It is prohibited to use thiazolidinediones, sulfonylureas, biguanides, and some parts of glinides for CKD patients with eGFR <30 mL/min/1.73 m^2. In addition, when the present CKD patients with steroid-induced hyperglycemia are treated aggressively with insulin, it is possible that hypoglycemia is caused and dose adjustment is needed with tapering of steroid usage, because the increasing levels of 2-h PG were mild and FPG levels were within normal limits. These are the reasons why this study had no comparative control group by insulin and/or oral antidiabetic drugs.

Conclusions

These data suggest that alogliptin improves plasma glucose levels in patients with steroid-induced hyperglycemia by reduction of glucagon levels through an increase in levels of GLP-1. Thus, alogliptin may be an effective drug for the treatment of steroid diabetes.

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