

Dipeptidyl peptidase-4 inhibitors are effective in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher body mass index and insulin resistance

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ABSTRACT

Aims/Introduction: Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have become available in Japan. It has not yet been clarified what clinical parameters could discriminate DPP-4 inhibitor-effective patients from DPP-4 inhibitor-ineffective patients.

Materials and Methods: We reviewed 33 consecutive patients with type 2 diabetes admitted to Osaka University Hospital for glycemic control. All of the patients were treated with medical nutrition therapy plus insulin therapy to improve fasting plasma glucose (FPG) and postprandial glucose below 150 and 200 mg/dL, respectively. After insulin secretion and insulin resistance were evaluated, insulin was replaced by DPP-4 inhibitors. The efficacy of DPP-4 inhibitors was determined according to whether glycemic control was maintained at the target levels.

Results: Dipeptidyl peptidase-4 inhibitors were effective in 16 of 33 patients. DPP-4 inhibitor-effective patients were younger than DPP-4 inhibitor-ineffective patients. Body mass index (BMI) was significantly higher in DPP-4 inhibitor-effective patients. Endogenous insulin-secreting capacity, including insulinogenic index (II), fasting plasma C-peptide (F-CPR) and C-peptide index (CPI), was more sustained in DPP-4 inhibitor-effective patients than DPP-4 inhibitor-ineffective patients. Insulin resistance evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) was significantly higher in DPP-4 inhibitor-effective patients than DPP-4 inhibitor-ineffective patients. In receiver operating characteristic analyses, the cut-off values for predicting the efficacy of DPP-4 inhibitors were 0.07 for II, 1.5 ng/mL for F-CPR, 1.0 for CPI, 23.0 kg/m² for BMI, 1.3 for HOMA-IR and 67.5 years for age.

Conclusions: Dipeptidyl peptidase-4 inhibitors were effective in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher BMI and insulin resistance. (*J Diabetes Invest* doi: 10.1111/jdi.12016, 2013)

KEY WORDS: Dipeptidyl peptidase-4 inhibitor, Insulin secretion, Type 2 diabetes

INTRODUCTION

The prevalence of type 2 diabetes has been rapidly increasing worldwide¹. According to the National Health and Nutrition Survey in Japan, published in 2008, the number of possible cases of diabetes has also been increasing in Japan; the prevalence was estimated at 13.7 million in 1997, 16.2 million in 2002, 18.7 million in 2006 and 22.1 million in 2007². This is also the case in other Asian countries^{1,3}. It is necessary to develop effective and efficient therapeutic strategies for type 2 diabetes. Recently, incretin-related drugs, such as dipeptidyl

peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have become available in Japan. In Caucasian patients with type 2 diabetes, who are in most cases obese or overweight and hyperinsulinemic, DPP-4 inhibitors improve glycemic control with a low risk of hypoglycemia⁴⁻⁶. However, in Japanese or Asian patients with type 2 diabetes, insulin secretion is decreased to varying extents^{3,7-9}. In recent outpatient studies, a DPP-4 inhibitor was more effective in Japanese type 2 diabetic patients with a shorter duration of disease, lower body mass index (BMI) and lower hemoglobin A1c (HbA_{1c})¹⁰⁻¹². However, the characteristics of patients in whom DPP-4 inhibitors are effective, including insulin secretion and insulin resistance, have not yet been clarified in Caucasian, Japanese or other Asian populations. The effectiveness of DPP-4 inhibitor is influenced by each nutrition therapy varying from each other in outpatient study; and characteristics, including insulin secretion and insulin resistance, are easily misjudged by poor glycemic control (glucose toxicity¹³). Therefore, the characteristics

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In this manuscript, the value for hemoglobin A1c (HbA_{1c}%) is estimated as National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society [JDS]%) + 0.4%.

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of DPP-4 inhibitor-effective patients would be evaluated more clearly only after glycemic control is improved on a regular nutrition therapy.

In this in-patient study, we improved glycemic control by medical nutrition plus insulin therapy and reduced glucose toxicity. We then analyzed the clinical characteristics of patients with type 2 diabetes to detect parameters predicting the efficacy of DPP-4 inhibitors.

MATERIALS AND METHODS

Patients

We retrospectively reviewed 33 consecutive patients (16 males and 17 females) with type 2 diabetes who were admitted to Osaka University Hospital, Suita, Japan, for glycemic control. The mean (\pm standard deviation [SD]) age was 68.2 ± 8.2 years, the mean duration of diabetes was 14.1 ± 8.1 years, and the mean BMI was 24.0 ± 3.8 kg/m². The mean HbA_{1c} level at the time of admission was $9.5 \pm 2.7\%$. Before admission, 25 patients had been treated with oral antidiabetic drugs (OADs), four patients had been treated with OADs plus insulin, three patients had been treated with medical nutrition therapy and one patient had been treated with insulin. OADs included sulfonylurea in 21 patients, biguanide in 11 patients, alpha-glucosidase inhibitor in 10 patients, DPP-4 inhibitor in six patients, thiazolidinedione in five patients and phenylalanine derivative in two patients. Glutamic acid decarboxylase (GAD)-specific antibodies and ketonuria were negative in all patients.

Protocol

After admission, all of the patients were treated by medical nutrition therapy plus insulin therapy to improve preprandial plasma glucose, including fasting plasma glucose (FPG) below 150 mg/dL and postprandial plasma glucose below 200 mg/dL. OADs were discontinued, with the exception of biguanide in seven patients. After glycemic control was maintained at the target levels for at least 3 days, insulin secretion and insulin resistance were evaluated. At the time of evaluation, the mean FPG was 128.9 ± 23.0 mg/dL. Insulin therapy was then replaced by DPP-4 inhibitor administration. The administered DPP-4 inhibitors included sitagliptin in 27 patients, vildagliptin in four patients and alogliptin in two patients. The efficacy of the DPP-4 inhibitors was evaluated by examining whether glycemic control was maintained in the hospital at the aforementioned target levels without additional OAD(s) or insulin administration at least for 3 days.

Evaluation of Insulin Secretion and Insulin Resistance

Insulin secretion was evaluated using the insulinogenic index (II) of a 75 g-oral glucose tolerance test (OGTT), fasting C-peptide (F-CPR) level, C-peptide index (CPI)¹⁴ and homeostasis model assessment of β -cell function (HOMA- β). CPI was calculated by using the following formula: $F\text{-CPR (ng/mL)} \times 100 / FPG \text{ (mg/dL)}$. HOMA- β was calculated by using the following formula: $\text{fasting immunoreactive insulin (F-IRI)}$

$\mu\text{U/mL} \times 360 / (FPG \text{ [mg/dL]} - 63)$. Insulin resistance was evaluated with homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated by using the following formula: $FPG \text{ (mg/dL)} \times F\text{-IRI} \text{ (}\mu\text{U/mL)} / 405$. HOMA- β and HOMA-IR were not evaluated in nine patients treated with intermediate-acting insulin or long-acting insulin, because of the cross-reactivity to exogenous insulin by endogenous fasting insulin concentration, which is necessary for the calculations of HOMA. A total of 12 patients were excluded from the evaluation of II, because they did not undergo 75 g-OGTT randomly. All of these parameters were evaluated after glycemic control had been maintained at the target levels for at least 3 days and before DPP-4 inhibitor therapy was initiated.

Statistics

Data are presented as the mean \pm SD. A receiver operating characteristic (ROC) curve was used to determine the appropriate clinical parameter cut-off values for identifying patients for whom DPP-4 inhibitor therapy was effective. The Mann-Whitney test was used to compare the clinical characteristics of DPP-4 inhibitor-effective patients and DPP-4 inhibitor-ineffective patients. All statistical analyses were carried out with StatView (Statistical Analysis System Inc., Cary, NC, USA) or the SPSS software package (version 11.0.1J; SPSS, Chicago, IL, USA).

RESULTS

DPP-4 inhibitors were effective in 16 of 33 patients. The mean duration of the hospitalization in all the patients was 31.5 ± 10.0 days. There was no significant difference between DPP-4 inhibitor-effective and DPP-4 inhibitor-ineffective patients. The clinical characteristics of the studied patients are shown in Table 1. There were significant differences in age, BMI and the insulin secretion parameters, including II, F-CPR and CPI, between DPP-4 inhibitor-effective and DPP-4 inhibitor-ineffective patients (Table 1). There was also a significant difference in HOMA-IR between these patient groups (Table 1). Therefore, the insulin-secreting capacity and the degree of insulin resistance of DPP-4 inhibitor-effective patients were larger than those of DPP-4 inhibitor-ineffective patients. There was no significant difference in HbA_{1c} at the time of admission or insulin requirement before DPP-4 inhibitor treatment initiation. Biguanide was used throughout the study to treat four DPP-4 inhibitor-effective patients and three DPP-4 inhibitor-ineffective patients. No other OADs were used during insulin therapy or DPP-4 inhibitor therapy before the evaluation of the efficacy of the DPP-4 inhibitors. The appropriate cut-off values for predicting the efficacy of the DPP-4 inhibitors and the area under the curves (AUCs) in the ROC analyses are shown in Table 2, in addition to the positive and negative predictive values. All parameters, including II, F-CPR, CPI, BMI, HOMA-IR and age, had high AUCs, and all cut-off values showed high positive and negative predictive values. Of these parameters, II had the highest AUC, and its cut-off value

Table 1 | Clinical characteristics of the patients with type 2 diabetes for whom dipeptidyl peptidase-4 inhibitor was effective or ineffective

	Effective	Ineffective	P-value
n (Male/female)	16 (8/8)	17 (8/9)	
Age (years)	64.8 ± 8.5	71.3 ± 6.8	0.028
Duration (years)	11.6 ± 8.4	16.4 ± 7.2	N.S
Body mass index (kg/m ²)	25.3 ± 2.6	22.7 ± 4.3	0.0069
HbA _{1c} † (%; NGSP)	10.1 ± 3.5	8.8 ± 1.5	N.S
Fasting plasma glucose‡ (mg/dL)	126.9 ± 16.8	130.9 ± 28.1	N.S
Fasting C-peptide‡ (ng/mL)	1.9 ± 0.7 (n = 15)	1.3 ± 0.7	0.0038
C-peptide index‡	1.5 ± 0.5 (n = 15)	1.1 ± 0.7	0.0055
Insulinogenic index‡	0.16 ± 0.15 (n = 9)	0.08 ± 0.06 (n = 12)	0.017
HOMA-β‡	47.9 ± 54.9 (n = 10)	23.8 ± 23.2 (n = 14)	N.S
HOMA-IR‡	2.1 ± 2.0 (n = 10)	1.1 ± 0.8 (n = 14)	0.035
Insulin dose‡ (unit/kg)	0.30 ± 0.18	0.33 ± 0.14	N.S

Data are means ± standard deviation. †On admission. ‡After glycemic control. HbA_{1c}, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta-cell function; NGSP, National Glycohemoglobin Standardization Program.

(0.07) showed the high positive and the highest negative predictive values. After II, the AUCs decreased, in order, as follows: F-CPR, CPI, BMI, HOMA-IR and age.

DISCUSSION

In the present study, we showed that DPP-4 inhibitors are effective for glycemic control in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher BMI and insulin resistance, and younger age. This is the first report on the clinical characteristics of DPP-4 inhibitor-effective patients that evaluated both insulin secretion and insulin resistance. All of the parameters, including II, F-CPR, CPI, BMI, HOMA-IR and age, were thought to be useful parameters for predicting the efficacy of DPP-4 inhibitors. II in OGTT was the most valuable parameter for discriminating DPP-4 inhibitor-effective patients from DPP-4 inhibitor-ineffective patients, based on II having the highest AUC. This finding is consistent with our previous study, which showed that liraglutide, another incretin-related drug, was effective in type 2 diabetic patients with sustained endogenous insulin-secreting capacity¹⁵. After II, the AUCs decreased, in order, as follows: F-CPR, CPI, BMI, HOMA-IR and age. All of these parameters are easier to use than II in a clinical setting. Insulin secretion has often deteriorated to varying degrees in Japanese and other Asian patients with type 2 diabetes^{3,7-9}.

In patients with type 2 diabetes, the prevalence of metabolic syndrome-oriented type 2 diabetes, which is characterized by insulin resistance¹⁶, increases as much as 45.9% in males and 28.0% in females¹⁷. These findings suggest that insulin secretion insufficiency, insulin resistance or both might be present in Japanese and other Asian patients with type 2 diabetes. The present study showed that both the insulin-secreting capacity and insulin resistance could be predictive markers for the effectiveness of DPP-4 inhibitors. Therefore, an evaluation of the insulin-secreting capacity and insulin resistance is recommended before initiating DPP-4 inhibitor treatment.

One of the possible reasons why these parameters, including BMI and HOMA-IR, were also useful for predicting the efficacy of DPP-4 inhibitors is the correlation between these parameters and insulin secretion parameters in the patients in the present study. BMI was significantly correlated with F-CPR ($r = 0.500$, $P = 0.0035$), CPI ($r = 0.485$, $P = 0.0049$), II ($r = 0.441$, $P = 0.046$) and HOMA-β ($r = 0.554$, $P = 0.0050$). HOMA-IR was also significantly correlated with F-CPR ($r = 0.663$, $P = 0.0006$), CPI ($r = 0.418$, $P = 0.047$) and HOMA-β ($r = 0.879$, $P < 0.0001$). It is also possible that DPP-4 inhibitors

Table 2 | Characteristics of cut-off values of the clinical parameters for predicting the efficacy of dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes

Parameters	Optimal cut-off value	AUC	Sensitivity (%)	Specificity (%)	PV(+) (%)	PV(-) (%)
Insulinogenic index	0.07	0.810	100.0	75.0	75.0	100.0
Fasting C-peptide (ng/mL)	1.5	0.800	73.3	82.4	78.6	77.8
C-peptide index	1.0	0.788	80.0	70.6	68.4	84.6
Body mass index (kg/m ²)	23.0	0.776	87.5	70.6	73.7	85.7
HOMA-IR	1.3	0.757	70.0	85.7	77.8	80.0
Age (years)	67.5	0.724	76.5	62.5	71.4	68.4

AUC, area under the receiving operator curve; HOMA-IR, homeostasis model assessment of insulin resistance; PV(+), positive predictive value; PV(-), negative predictive value.

might ameliorate insulin resistance in our patients, as reported in a previous study¹⁸.

In recent outpatient studies, higher HbA_{1c}, lower BMI and a shorter duration of diabetes were associated with the efficacy of DPP-4 inhibitors^{10–12}. In the present study, HbA_{1c} tended to be higher and the duration of diabetes tended to be shorter in DPP-4 inhibitor-effective patients than in DPP-4 inhibitor-ineffective patients. These findings are consistent with those of the previous studies. However, BMI was significantly higher in DPP-4 inhibitor-effective patients in the present study. We previously reported that insulin secretion was significantly higher in obese Japanese type 2 diabetic patients than non-obese patients¹⁹. It is speculated that insulin secretion is the main determinant of the efficacy of DPP-4 inhibitors, and a higher BMI might reflect more sustained insulin secretion, leading to the effectiveness of the DPP-4 inhibitors in our hospitalized patients. By contrast, in outpatients, a higher BMI might partly reflect overeating, leading to the deteriorating efficacy of DPP-4 inhibitors.

Biguanide is reported to increase the secretion of GLP-1²⁰. However, even though the patients treated with biguanide were excluded in the present study, the results were almost the same as the previous ones. That is to say, DPP-4 inhibitors were effective in patients with sustained endogenous insulin-secreting capacity, a higher BMI and relative high insulin resistance ($P = 0.01$ in II, $P = 0.0086$ in F-CPR, $P = 0.01$ in CPI, $P = 0.029$ in BMI, $P = 0.064$ in HOMA-IR and $P = 0.013$ in age).

In the present study, the efficacy of DPP-4 inhibitors was evaluated in a relatively short period. This is because the glucose levels in patients with good glycemic control using DPP-4 inhibitors for at least 3 days were maintained at the target levels throughout the remaining hospitalization. In contrast, the glucose levels in patients whose glycemic control was poorly controlled for at least 3 days after switching insulin to DPP-4 inhibitors did not reach the target levels despite the longer use of DPP-4 inhibitors.

A total of 12 patients did not undergo 75 g-OGTT randomly. The number of patients who were evaluated for II was smaller than those of the patients who were evaluated for the other parameters. This was a study limitation.

In conclusion, DPP-4 inhibitors were effective in Japanese type 2 diabetic patients with sustained endogenous insulin-secreting capacity, a higher BMI and insulin resistance, and younger age. Insulin secretion evaluated by II, F-CPR and CPI, BMI and insulin resistance evaluated by HOMA-IR were all useful parameters for predicting the efficacy of DPP-4 inhibitors. Further prospective studies of these patients after discharge would confirm the usefulness of these parameters.

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