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Predictive Factors for Efficacy of Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus

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Background: Predictive factors for the efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors for lowering glycosylated hemoglobin (HbA1c) remain unclear in patients with type 2 diabetes mellitus. The aim of this study is therefore to clarify predictive factors of the efficacy of DPP-4 inhibitors for lowering HbA1c after 12 months of treatment.
Methods: A total of 191 consecutive type 2 diabetic patients (male sex 55%, mean age, 68.3±35.8 years), who had been treated with DPP-4 inhibitors for 12 months, were enrolled in this study and evaluated retrospectively.
Results: After 12 months of DPP-4 inhibitor treatment, random blood glucose level, and HbA1c level, decreased from 167±63 to 151±49 mg/dL ($P<0.01$), and from 7.5%±1.3% to 6.9%±0.9% ($P<0.01$) respectively, without severe side effects. Multiple regression analysis showed that predictors of DPP-4 inhibitor treatment efficacy in lowering HbA1c level after 12 months were a decrease in HbA1c level after 3 months of treatment, a high baseline HbA1c level, a low baseline body mass index, and the absence of coronary artery disease.
Conclusion: Most suitable candidates for treatment with DPP-4 inhibitors are diabetics who are not obese and do not have coronary artery disease. In addition, long-term efficacy of DPP-4 inhibitors can be predicted by decrement of HbA1c after 3 months of treatment.

Keywords: Coronary artery disease; Diabetes mellitus; Dipeptidyl-peptidase IV inhibitors; Obese; Predictive factors

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glucose metabolism by inhibiting the breakdown of incretins (a group of gastrointestinal hormones), including glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. Glucose in the small intestine stimulates incretin release, and then these secreted incretins stimulate insulin secretion from β-cells and suppress inappropriate glucagon secretion from α-cells. Thus, DPP-4 inhibitors have a glucose-dependent anti-hyperglycemic action with a low incidence of hypoglycemia. DPP-4 inhibitors are widely used for the treatment of type 2 diabetes [1]. Reaching a glycosylated hemoglobin (HbA1c) level <7.0% is recommended as a treatment target [1]; however, predictive factors for the efficacy of these inhibitors in lowering HbA1c levels have not yet been identified. The aim of this study is to clarify factors including age, gender, body mass index (BMI), estimated glomerular filtration rate (eGFR), presence of dyslipidemia, hypertension, and coronary artery disease (CAD), that are predictive of the efficacy of DPP-4 inhibitors in lowering HbA1c level after 12 months of treatment.

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METHODS

We enrolled 191 consecutive type 2 diabetic patients who were recruited from Tokushima University Hospital during the period from April 2010 to January 2012, and who had been treated with DPP-4 inhibitors for at least 12 months with medical records. Anti-hyperglycemic efficacy of DPP-4 inhibitors was assessed by levels of HbA1c (National Glycohemoglobin Standardization Program) before and 12 months after treatment retrospectively.

Subjects with the following diseases/conditions were excluded: active malignant diseases, connective tissue diseases treated by immunosuppressant and/or steroid therapy, renal failure (defined as serum creatinine >3.0 mg/dL), and liver dysfunction (defined as aspartate aminotransferase >100 IU/L, alanine aminotransferase >100 IU/L). Also excluded were patients receiving insulin or steroid therapy and patients whose treatment—e.g., with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, diuretics, or β-blockers—could affect glucose metabolism if that treatment was changed during the observational period. This study was carried out in conformance with the Declaration of Helsinki and the study protocol was approved by the Tokushima University Hospital Ethics Committee (No. 1760).

Statistical analysis

Continuous variables were averaged and each value expressed as the mean±standard deviation, or as a percentage for categorical parameters. HbA1c levels, random blood sugar levels, and parameters associated with dyslipidemia including low density lipoprotein cholesterol (LDL-C), triglyceride, high density lipoprotein cholesterol (HDL-C) before and 12 months after treatment with DPP-4 inhibitors were compared using the paired *t*-test. CAD was defined as angina pectoris, myocardial infarction, and silent myocardial ischemia with or without percutaneous coronary intervention or coronary artery bypass surgery. Gender and the presence of dyslipidemia, hypertension, and CAD were coded as dummy variables. The degrees of association among independent variables for HbA1c level after 12 months, including age, gender, BMI, eGFR, presence of dyslipidemia, hypertension, and CAD, were assessed by multiple regression analyses (stepwise regression model). All statistical analyses were performed using SPSS II version 11 software (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P<0.05$.

RESULTS

Clinical characteristics of study subjects

Characteristics of the patients enrolled in this study are shown in Table 1. Overall, these patients had moderate diabetes, with a mean HbA1c level of 7.5%±1.3%.

Effects of DPP-4 inhibitors on blood glucose and HbA1c level

Twelve months of treatment with DPP-4 inhibitors led to a sig-

Table 1. Clinical characteristics of study subjects

Variable	Value
No. of patients	191
Male/Female	105 (55)/86 (45)
Age, yr	68.3±35.8
Body mass index, kg/m^2	24.7±4.2
HbA1c, %[a]	7.5±1.3
Random blood glucose, mg/dL	167±63
LDL-C, mg/dL	108±33
Triglyceride, mg/dL	156±133
HDL-C, mg/dL	58.5±19.1
Serum creatinine, mg/dL	0.83±0.36
eGFR, mL/min/1.73 m^2	69.6±20.6
Complications	
Hypertension	120 (62.8)
Dyslipidemia	119 (62.3)
Coronary artery disease	62 (32.5)
Drugs	
DPP-4 inhibitors	
Alogliptin	74 (38.7)
Sitagliptin	79 (41.4)
Vildagliptin	38 (19.9)
Other anti-diabetic drugs	
α-Glucosidase inhibitors	84 (44.0)
Sulfonylureas	62 (32.5)
Biguanides	29 (15.2)
Glinides	19 (10.0)
Thiazolidinediones	19 (10.0)
Statins	92 (48.2)

Values are presented as number (%) or mean±standard deviation.
HbA1c, glycosylated hemoglobin; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; DPP-4, dipeptidyl peptidase-4.
[a]National Glycohemoglobin Standardization Program reference value.

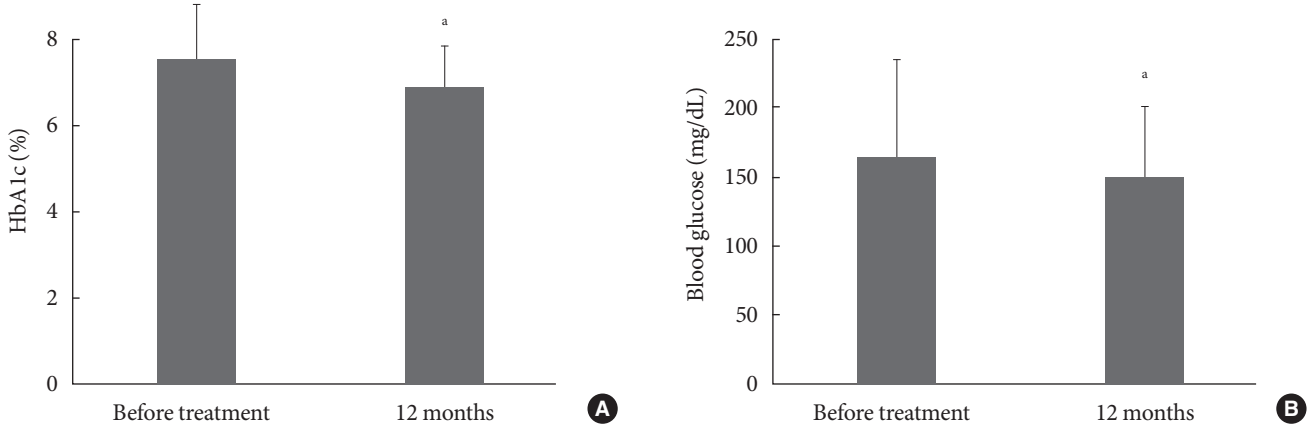

Fig. 1. Effects of dipeptidyl peptidase-4 inhibitor treatment on (A) glycosylated hemoglobin (HbA1c) and (B) blood glucose levels. Values from before the onset of treatment and after 12 months of treatment are compared. [a]$P<0.01$.

nificant decrease in random blood glucose level, from 167±63 to 151±49 mg/dL ($P<0.01$), and in HbA1c level, from 7.5%±1.3% to 6.9%±0.9% ($P<0.01$) (Fig. 1). Single regression analysis showed that the magnitude of decrease in HbA1c level after 12 months was positively associated with the baseline (the initial level at pre-treatment) HbA1c ($P<0.01$) (Fig. 2). In addition, the percentage of patients with a HbA1c level <7.0% after 12 months treatment increased from 36.6% to 60.2%.

There was a significant decrease in LDL-C level, from 108±33 to 104±30 mg/dL ($P<0.05$), in response to treatment with DPP-4 inhibitors; however, no effects were observed for triglyceride, or HDL-C levels. There were no significant changes in eGFR values, and no cases of severe liver dysfunction were reported post-treatment.

Contributors to decreased HbA1c levels after treatment with DPP-4 inhibitors

Stepwise multiple regression analysis was performed to elucidate independent determinants for decreased HbA1c level 12 months after the start of treatment (baseline HbA1c to HbA1c at 12 months). It was shown that the degree of change in HbA1c level 3 months after the start of treatment (baseline HbA1c to HbA1c at 3 months) and baseline HbA1c level were positive contributors to change in HbA1c at 12 months after the start of treatment, and that BMI, and a history of CAD were negative contributors to change. This implies that the decrease in HbA1c level is greater in patients with a high baseline HbA1c level, a low baseline BMI, and an absence of CAD. However, associations with gender, age, eGFR, and presence of hypertension or dyslipidemia, were statistically excluded (Table 2).

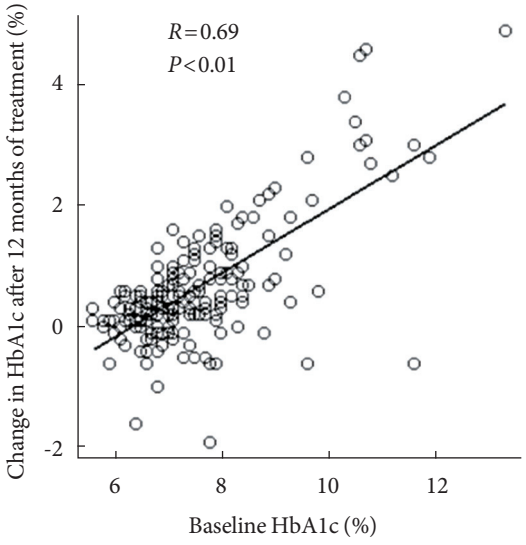

Fig. 2. Association between baseline glycosylated hemoglobin (HbA1c) level and changes in HbA1c after 12 months of treatment.

Safety of DPP-4 inhibitor treatment

Over the 12-month DPP-4 inhibitor treatment period, no patients experienced severe side effects, such as hypoglycemic episodes or pancreatitis, which resulted in a hospital visit or hospitalization.

DISCUSSION

We have shown that DPP-4 inhibitors are effective in decreasing HbA1c level after 12 months of treatment with no severe side effects. We also show that predictors of the efficacy of treat-

Table 2. Multiple regression analysis for determinants of degree of decrease in HbA1c level after 12 months of treatment: ΔHbA1c (baseline to 12 months)

Variable	Coefficient	95% CI	Standardized coefficient	*P* value
ΔHbA1c (baseline–3 mo)	0.5	0.36 to 0.64	0.47	<0.001
Baseline HbA1c	0.32	0.24 to 0.40	0.39	<0.001
Body mass index	–0.02	–0.003 to –0.045	–0.10	0.024
History of coronary artery disease	–0.19	–0.01 to –0.38	–0.10	0.041

CI, confidence interval; HbA1c, glycosylated hemoglobin.

ment were a decrease in HbA1c level after 3 months of treatment, a higher baseline HbA1c level, a lower baseline BMI, and the absence of CAD which is a novel finding of the study.

It has not yet been established which patients would benefit from the effects of DPP-4 inhibitor treatment. For example, Monami et al. [2] showed that DPP-4 inhibitors were more effective in older patients with a mild/moderate fasting hyperglycemia, while Kim et al. [3] showed they were more effective in Asians than in other ethnic groups, especially in a lower BMI group of <30 kg/m^2. In terms of predicting efficacy, Nomiyama et al. [4] and Maeda et al. [5] showed that a higher baseline HbA1c level, lower BMI, and shorter period since the onset/diagnosis of diabetes were significantly correlated with a greater HbA1c reduction. Iwasaki et al. [6] also reported that increased serum levels of eicosapentaenoic acid and docosahexaenoic acid could predict DPP-4 inhibitor efficacy. Lim et al. [7] showed that low insulinogenic index, indicating β-cell dysfunction, was a predictor of combination therapy of sitagliptin and metformin. Consistent with previous studies, our results also show that a decrease in HbA1c level is dependent on baseline HbA1c. Secondary failure such as desensitization of insulin secretion with sulfonylurea has been known in some antidiabetics [8]; however, we have shown that the decrease in HbA1c level after 12 months of treatment is associated with the decrease seen after 3 months of treatment, suggesting that long-term effects of DPP-4 inhibitors on glucose metabolism can be predicted by the short-term effects of this treatment. Another predictor of DPP-4 inhibitor response is low BMI. Insufficiency in insulin secretion occurs predominantly in patients with low BMI, while insulin resistance occurs predominantly in patients with high BMI. Thus DPP-4 inhibitors, which improve insulin secretion as well as insulin resistance, are more effective in patients with low BMI. Increased DPP-4 activity in patients with high BMI may account for the lower efficacy of DPP-4 inhibitors in this group [9]. Furthermore, DPP-4 inhibitors were more effective in patients without CAD than in patients with CAD. The mechanisms of the results were unknown, further basic studies are therefore needed to clarify the issue. In addition, whether DPP-4 inhibitors decrease cardiovascular events or mortality is still debatable [10-13], further clinical studies are also needed.

HbA1c <7% is known as a treatment target with respect to diabetic complications from the guidelines [1,14]. In this study, 60.2% of patients with moderate diabetes reached this level, indicating that DPP-4 inhibitors are effective in lowering glucose.

Lipid profile is an important determinant of cardiovascular risk in type 2 diabetic patients, and LDL-C is the most important risk factor. DPP-4 inhibitors have been reported to reduce LDL-C in addition to total cholesterol; however, results between studies are not consistent [15-17]. The precise mechanism by which LDL-C is reduced by DPP-4 inhibitors has not been determined; although, DPP-4 inhibitors might reduce the expression of hepatic genes involved in cholesterol synthesis [18] or reduce intestinal secretion of cholesterol and apolipoprotein B-48 [19].

The present study had several limitations. Only patients who had been treated with DPP-4 inhibitors for at least 12 months at our hospital were included, and thus, the study contains a patient selection bias. In addition, patients receiving insulin therapy were excluded, because co-administration of DPP-4 inhibitors and insulin was not permitted in Japan at the time of this study. This was a retrospective study with a small sample size; thus, we could not compare the effects of each DPP-4 inhibitor as the characteristics of patients varied between groups. We also had a comparatively short observation period, and thus could not analyze the long-term effects of DPP-4 inhibitor treatment. Randomized, or large, clinical cohort studies, with a longer observation period are needed to clarify these issues.

In conclusion, suitable candidates for treatment with DPP-4 inhibitors are diabetic patients without obesity or CAD. In ad-

dition, the long-term efficacy of DPP-4 inhibitors can be predicted by a decrease in HbA1c level after 3 months of treatment.

CONFLICTS OF INTEREST

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