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Original Article

Predictive Factors for the Therapeutic Response to Concomitant Treatment with DPP-4 Inhibitors in Type 2 Diabetes with Short-Term Follow-Up

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Objectives: To evaluate the efficacy and predictive factors of Dipeptidyl peptidase-4 (DPP-4) inhibitors in type 2 diabetes mellitus (T2DM) patients who were not well controlled with other oral antidiabetic drugs or insulin in real clinical practice.

Methods: From December 2012 to January 2014, retrospective longitudinal observation study was conducted for patients with T2DM who were not reached a glycemic target (glycated hemoglobin [HbA1c] 〉 6.5%) with other oral antidiabetic drugs or insulins. Type 1 diabetes or other types of diabetes were excluded. Responders were eligible with decreased HbA1c from baseline for more than 5% during follow up period.

Results: Of total 135 T2DM patients having an average 9.0 months follow-up period, 84 (62.2%) of patients were responder to DPP-4 inhibitors. After concomitant treatment with DPP-4 inhibitors, patients had a mean decrease in HbA1c of 0.69 ± 1.3%, fasting plasma glucose of 13 ± 52 ㎎/㎗, and postprandial plasma glucose of 29 ± 85 ㎎/㎗ from baseline (all P 〈 0.05). Independent predictive factor for an improvement of glycemic control with DPP-4 inhibitors was higher baseline HbA1c (odds ratio 2.07 with 95% confidence interval 1.15-3.72) compared with non-responders.

Conclusions: A clinical meaningful improvement in glycemic control was seen when DPP-4 inhibitors were added to other anti-diabetic medications in patients with T2DM regardless of age, duration of T2DM, type of combination treatment regimen. Patients who had higher HbA1c were more easily respond to DPP-4 inhibitors treatment in short-term follow-up period.

Key Words: Dipeptidyl peptidase-4 inhibitor, efficacy, predictive factor, type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) has characteristics of insulin resistance with impaired hyperglycemia. Incretin effect, oral glucose loading induced a greater insulin secretion response than that of an isoglycemic intravenous glucose infusion, had lead us to recognize the glucose lowering effect of gut hormones; glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[1] These incretins are rapidly degraded by Dipeptidyl peptidase-4 (DPP-4),[2] and DPP-4 inhibitors improve glycemic control by slowing degradation of incretin hormones.

A meta-analysis in randomized control trials demonstrated that DPP-4 inhibitors treatment significantly reduced HbA1c by 0.6-0.7% compared with a placebo.[3,4] Combination treatment of DPP-4

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inhibitors with metformin,[5] insulin,[6,7] and sulfonylurea[8,9] also induced more favorable glycemic control than monotherapy. Previous meta-analysis[10] and prospective observational studies[11] have shown that the clinical predictors of therapeutic responses to DPP-4 inhibitors were 1) older age, 2) higher baseline glycated hemoglobin (HbA1c), 3) low beta-cell function, 4) short-duration of diabetes. Meanwhile, other studies[12,13] described that non-obese patients were associated with better response to DPP-4 inhibitor. But there were few studies which evaluated the efficacy of DPP-4 inhibitors under concomitant treatment with all kinds of other anti-diabetic drugs, including insulin in clinical practice. We sought to evaluate the efficacy of add-on treatment with DPP4-inhibitors who were not reached to glycemic target goal (HbA1c > 6.5%) with other anti-diabetic drugs, and to analyze the clinical and metabolic parameters in T2DM patients who are more likely response to DPP-4 inhibitors in clinical practice with short-term follow-up.

MATERIALS AND METHODS

1. Study subjects

From December 2012 to January 2014, adults over 20 year-old with T2DM who were not reached glycemic target (HbA1c > 6.5%), and were not previously prescribed DPP-4 inhibitors (sitagliptin/vildagliptin) were enrolled. Patients who already have been prescribed with all other kinds of anti-diabetic drugs were enrolled. They were excluded i) if they had short duration of follow-up (less than 6 months) or took DPP-4 inhibitors irregularly, ii) Patients who were diagnosed with Type 1 diabetes or secondary diabetes, or iii) there were lack of baseline anthropometric (weight, height) and biochemical parameters based on medical records.

2. Study design

A single-center, retrospective observational study was conducted with on average nine-month follow-up period. We reviewed the medical records of 135 patients with T2DM (aged 30-84 years) at Gyeongsang National University Hospital. The baseline anthropometric (age, gender, weight, height, body mass index, systolic blood pressure, diastolic blood pressure) and biochemical parameters (fasting plasma glucose, 1-hour postprandial glucose, HbA1c, fasting C-peptide) as well as baseline characteristics and comorbidities of T2DM (DM duration, concomitant use of other anti-diabetic drugs, accompanied micro- and macro-vascular complications) were collected based on medical records. After having follow-up of 9.0 ± 1.8 months with DPP-4 inhibitors, anthropometric and biochemical parameters which was recorded at last visit were collected.

Height and weight were measured with patients in light clothing and no shoes. Body mass index (BMI) was calculated weight in kilograms divided by the square of height in meters. Centralized laboratory biochemical analyses were performed on blood samples obtained in fasting condition.

Plasma glucose levels were determined by the hexokinase method using a GLU kit (Roche Diagnostics) on the Roche modular DP analyzer, and HbA1c levels were measured using high performance liquid chromatography on an automated glycohemoglobin analyzer HLC-723G8 (TOSOH, Yokkaichi, Japan). Plasma triglyceride and HDL cholesterol levels were measured by an enzymatic colorimetric method using the Roche modular DP analyzer. The homeostasis model assessment of insulin resistance (HOMA2-IR) and pancreatic beta-cell function (HOMA2%B) calculation was based on model-derived estimates (rather than linear approximations) using the HOMA2 calculator version 2.2.3 (http://www.dtu.ox.ac.uk/homacalculator/download.php, Diabetes Trials Unit, University of Oxford, Oxford, U.K.)

With regard to diabetes-related micro-vascular complications, diabetes retinopathy was diagnosed with fundus exam with whom had more than non-proliferative diabetic retinopathy, performed by expert ophthalmologist. Diabetic nephropathy was diagnosed if spot urine albumin-creatinine ratio was more than 300 ㎍/㎎ or renal function was decreased (estimated GFR ≤ 60㎖/min/1.73㎡, by MDRD equation). Diabetic neuropathy was diagnosed if result of nerve conduction velocity (NCV) was compatible with neuropathy or they have been prescribed with anti-neuropathic drugs under clinical impression.

The primary end-point was the change in HbA1c levels from baseline to last follow-up. Other end-points included fasting plasma glucose (FPG), 1-hr postprandial plasma glucose (PP1). Responders were defined as those who showed decreased HbA1c more than 5% from baseline HbA1c after treatment. Non-responders were defined as those who showed no change or increase in HbA1c after treatment or those who stopped medication with DPP-4 inhibitors under clinical judgement for its effectiveness and compliance.

3. Statistical analysis

The baseline characteristics of patients were described using mean (SD) values for even-distributed continuous variables, and median (interquartile range) for uneven-distributed variables, and numbers and percentages for categorical variables. The student's t-test and Mann Whitney U-test for continuous variables and chi-square test for categorical variables were used to assess the baseline characteristics according to response to DPP-4 inhibitors treatment. The efficacy on glucose control before and after treatment was analyzed with paired t-test and Wilcoxon signed rank test. Univariate and multivariate logistic regression analysis were performed to evaluate predictive factors associated with decreased HbA1c with treatment of DPP-4 inhibitors. All statistical tests were two-tailed, and the significance level was set at $P \leq 0.05$. Analyses were performed using SPSS software (version 18.0. SPSS Inc., Chicago, IL, USA)

RESULTS

1. Baseline characteristics of study subjects

Of total 601 patients with T2DM who were newly prescribed DPP-4 inhibitors, 224 patients who have a medical history and baseline anthropometric and biochemical parameters were screened, and 135 patients were enrolled finally. Eighty-nine patients were excluded because of short duration of follow-up or loss of medical records during follow-up. Baseline characteristics of patients were described in table 1. Study analysis demonstrated that an average age was 56.9 ± 10.0 year-old and duration of T2DM was an average of 8.6 ± 7.3 years. Female (n = 53, 39.3%) as well as fifties and sixties (n = 91, 67.5%) were dominant. Among concomitant drugs which were prescribed with DPP-4 inhibitors, 123 patients (91.1%) used metformin, 72 patients (53.3%) used sulfonylurea, 32 patients (23.7%) used thiazolidinedione or alpha-glucosidase inhibitors, and 22 patients (16.3%) used insulin. With regard to diabetes-related microvascular complications, 42 patients (31.1%) had a retinopathy, 34 patients (25.2%) had a neuropathy, and 18 patients (13.3%) had a nephropathy.

2. Efficacy of concomitant use with DPP-4 inhibitor

After an average 9.2 ± 1.8 months of follow-up period, fasting plasma glucose (on average 13 ㎎/㎗; P = 0.019), 1-hr postprandial glucose (29 ㎎/㎗; P = 0.002), and HbA1c (0.7%; P < 0.001) decreased significantly after adding DPP-4 inhibitors (Table 1). In subgroup analysis, add-on treatment with DPP-4 inhibitors showed that it reduced HbA1c by 0.87% with metformin monotherapy (n = 44, P < 0.001), by 0.63% with combination treatment of sulfonylurea and metformin (n = 62, P = 0.001), and by 0.72% with triple combination treatment (n = 27, P = 0.003) (Fig. 1).

3. Difference in anthropometric and biochemical parameters between responders and non-responders

Responders (n = 84, 62.2%) who showed decreased HbA1c about more than 5% from baseline HbA1c had similar baseline anthropometric and biochemical characteristics compared with non-responders (n = 51, 37.8%), except on baseline fasting plasma glucose, HbA1c, and percentage of concomitant insulin usage (Table 2).

Multivariate logistic regression analysis showed that only higher HbA1c at baseline (odds ratio 2.07 with 95% confidence intervals 1.15 – 3.72) was a significant predictive factor of therapeutic response with DPP4-inhibitor after adjusting for several confounding factors such as age, gender, body mass index, duration of diabetes, duration of follow-up, baseline HbA1c, C-peptide, fasting plasma glucose, 1hr-postprandial plasma glucose, and concomitant anti-diabetic drugs (including insulin).

4. Safety and side effects of DPP-4 inhibitors

Hypoglycemia occurred in one patient who was

Table 1. Baseline characteristics of the study subjects and changes of glycemic control after add-on treatment with DPP-4 inhibitors (N=135)

Parameters	n	Baseline	Follow-up	*P* - value†
Age (years)	135	56.9 (10.0)		
Sex (M, %)	135	82 (60.7)		
BMI (kg/m2)	135	25.1 (3.3)		
SBP (mmHg)	131	125 (15)		
DBP (mmHg)	130	72 (10)		
Duration of diabetes (years)	135	8.6 (7.3)		
Laboratory findings				
FPG (mg/dl)	105	148 (42)	134 (41)	0.019
PP1 (mg/dl)	111	247 (72)	218 (68)	0.002
HbA1c (%)	135	8.1 (1.2)	7.4 (1.3)	< 0.001
C-peptide (ng/ml) *	118	2.20 (1.62-2.98)	2.09 (1.59-3.03)	0.423
Total cholesterol (mg/dl)	133	183 (43)	157 (31)	< 0.001
Triglyceride (mg/dl)	133	154 (93)	135 (69)	0.014
HDL (mg/dl)	133	48 (22)	47 (14)	0.864
LDL (mg/dl)	133	105 (34)	90 (28)	< 0.001
Creatinine (mg/dl) *	132	0.80 (0.69-0.95)	0.82 (0.68-0.96)	0.406
uACR (ug/mg) *	128	16.3 (4.4-51.3)	19.7 (9.4-58.3)	0.765
HOMA2-IR	95	2.07 (1.16)	2.00 (1.16)	0.962
HOMA2%B	95	68.49 (43.30)	70.72 (31.81)	0.323
Combination therapy				
Biguanide (n, %)	135	123 (91.1)		
Sulfonylurea (n, %)	135	72 (53.3)		
TZD (n, %)	135	14 (10.4)		
AGI (n, %)	135	18 (13.3)		
Insulin (n, %)	135	22 (16.3)		
Diabetes-related complications				
Retinopathy (n, %)	135	42 (31.1)		
Nephropathy (n, %)	132	18 (13.6)		
Neuropathy (n, %)	135	34 (25.2)		

Values represent the mean (SD) or number (percentage). *values represent the median (interquartile range)† analyzed by the paired t-test for normally distributed variables, and by the Wilcoxon signed rank test for continuous variables with skewed distributions.

BMI, body mass index; FPG, fasting plasma glucose; PP1, post-prandial 1-hr glucose; HbA1c, glycated hemoglobin;SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; uACR, spot urine albumin/creatinine ratio; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor; HOMA2%B, homeostasis model assessment of pancreatic beta-cell function; HOMA2-IR, homeostasis model assessment of insulin resistance.

co-prescribed with insulin. In 123 patients (91.1%), weight was unchanged or decreased and 12 patients (8.9%) experienced a weight gain after follow-up. Major micro- or macro-vascular complications were not occurred during follow-up.

DISCUSSION

This study has demonstrated that DPP-4 inhibitors showed a relatively good glycemic control effect in T2DM patients who were concomitantly prescribed with other anti-diabetic drugs, including insulin in clinical practice. Higher baseline HbA1c levels were an independent predictive factor to be associated with glycemic efficacy of DPP-4 inhibitors.

Add-on treatment with DPP-4 inhibitors produced clinically significant glycemic improvements in HbA1c, fasting plasma glucose as well as postprandial glucose. Reduction in postprandial glucose (on average 29 ㎎/㎗) was more prominent than that of fasting glucose (on average 13 ㎎/㎗), even with short-term follow-up in our study. Incretin effect was induced after oral glucose load and its pharmacologic property of DPP4 -inhibitor explains beneficial effects on postprandial hyperglycemia.[14] Previous long-term (52 weeks) study also demonstrated that initial combination treatment with sitagliptin and metformin induced a better glycemic control, and reduction in postprandial glucose was greater than fasting glucose in drug-naïve T2DM.[11]

In our study, independent predictive factor for therapeutic effectiveness on glucose control with add-on treatment with DPP-4 inhibitors was high baseline HbA1c levels, regardless of concomitant anti-diabetic medications. In previous Korean

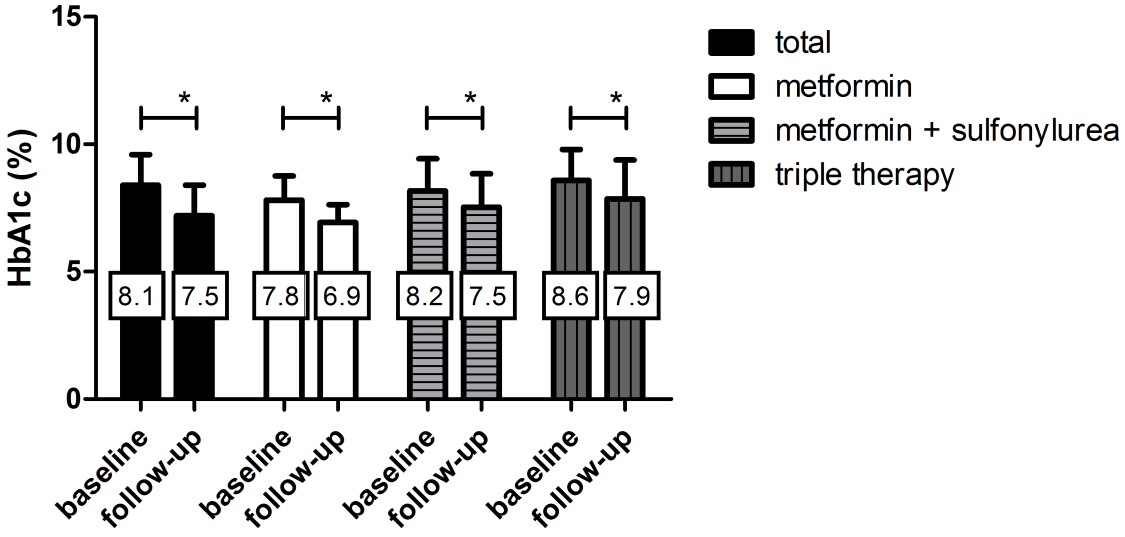

Fig. 1. The efficacy of glycemic control after add-on treatment with DPP-4 inhibitors stratified by concomitant combination treatment. Values in the box represent the mean HbA1c level.
* *P* - value 〈 0.005 by paired t-test.

study by Chung et al,[15] reduction in HbA1c was significantly associated with high baseline HbA1c, low baseline C-peptide levels under the condition that sitagliptin was added to metformin alone or combination with metformin and glimepiride. Lim et al.[11] demonstrated that high baseline HbA1c, lower baseline insulinogenic index, and short duration of diabetes was predictive factors

Table 2. Baseline characteristics according to therapeutic response of DPP-4 inhibitor

Characteristics	Responder	Non-responder	*P* - value†
n	84	51	
Age (years)	57.1 (10.7)	56.6 (8.9)	0.792
Sex (M/F)			
BMI (kg/m2)	24.9 (3.0)	25.5 (3.8)	0.267
SBP (mmHg)	123 (15)	128 (16)	0.069
DBP (mmHg)	72 (10)	73 (10)	0.640
Duration of diabetes (months)	7.8 (7.2)	9.8 (7.3)	0.118
Follow-up duration (months)	9.2 (1.8)	8.6 (1.9)	0.080
FPG (mg/dl)	154 (41)	137 (41)	0.047
PP1 (mg/dl)	245 (67)	250 (79)	0.700
HbA1c (%)	8.4 (1.2)	7.7 (0.9)	0.001
C-peptide (ng/ml) *	2.33 (1.71-3.11)	2.11 (1.54-2.73)	0.172
Total cholesterol (mg/dl)	177 (39)	194 (47)	0.028
TG (mg/dl)	155 (92)	152 (95)	0.816
HDL (mg/dl)	46 (21)	51 (23)	0.259
LDL (mg/dl)	101 (35)	112 (34)	0.073
Creatinine (mg/dl) *	0.81 (0.70-0.96)	0.78 (0.65-0.95)	0.112
HOMA2%B	66.15 (48.12)	72.69 (33.20)	0.437
HOMA2-IR	2.18 (1.27)	1.88 (0.90)	0.177
Combination therapy			
Metformin (n, %)	76 (90.5)	47 (92.2)	〉 0.999
Sulfonylurea (n, %)	41 (48.8)	31 (60.8)	0.214
TZD (n, %)	11 (13.1)	3 (5.9)	0.249
AGI (n, %)	13 (15.5)	5 (9.8)	〉 0.999
Insulin (n, %)	8 (9.5)	14 (27.5)	0.008

Values represent the mean (SD) or number (percentage). *values represent the median (interquartile range). †analyzed by the two-sample t-test for normally distributed variables, and by the Mann Whitney U-test for continuous variables with skewed distributions.

BMI, body mass index;SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PP1, postprandial 1-hr glucose; HbA1c, glycated hemoglobin; TG, triglyceride; HDL, high-dense lipoprotein, HOMA2%B, homeostasis model assessment of pancreatic beta-cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; TZD, thiazolidinedione; AGI, alpha-glucosidase inhibitor.

for efficacy of DPP-4 inhibitor in drug-naïve patients with T2DM. Furthermore, meta-analytic studies also showed that high baseline HbA1c is most prominent predictive factors.[4,16] Even though there are some discrepancies between studies which have different inclusion criteria and characteristics, many studies showed that efficacy of DPP-4 inhibitors was closely associated with high baseline HbA1c.

In Korea, reimbursement for combination treatment of basal insulin and DPP-4 inhibitor was approved in March 2015. In our study, 22 patients (16.3%) were taking insulin and non-significant HbA1c reduction was observed during follow-up (-0.4 ± 1.7%; P = 0.307). However, previous long-term follow-up studies demonstrated that combination treatment of DPP-4 inhibitors with insulin induced an additional glucose lowering effect compared with insulin monotherapy.[6,17] In these studies, after 24 weeks of combination treatment with basal insulin, HbA1c decreased 0.6% with sitagliptin (n = 641, baseline HbA1c 8.6%), and 0.5% with vildagliptin (n = 296, baseline HbA1c 8.4%), respectively. The therapeutic benefits from combination treatment with DPP-4 inhibitors and basal insulin were suggested by 1) better improvement in glycemic control, including postprandial glucose,[18] 2) minimizing dose of basal insulin uptitration to achieve glycemic target,[19] and 3) reduced incidence of hypoglycemia.[20]

In our study, average BMI of enrolled patients was 25.12 ㎏/㎡, and responders had a non-significantly lower BMI than non-responders (24.87 ㎏/㎡ versus 25.53 ㎏/㎡, P = 0.267). BMI is highly correlated with insulin sensitivity,[21] and Asians patients with T2DM have a different epidemiologic characteristics compared with Caucasians, who have higher BMI with insulin resistance,[22] whereas Asian patients with T2DM had a small amount of insulin beta-cell mass and deficiency in insulin secretion were prominent than Caucasians.[23] Previous study showed that HbA1c-lowering efficacy of DPP-4 inhibitors in T2DM was higher in Asians than in other ethnic groups,[24] and lower BMI was a predictor of a good response to DPP-4 inhibitors.[24,25]

During follow-up period in our study, there was one case (0.74%) of hypoglycemic event (< 70 ㎎/㎗) who were co-prescribed with basal insulin. Hypoglycemia is a major concern with anti-diabetic treatment, especially with sulfonylurea or insulin.[26] DPP-4 inhibitors were known to be well tolerated, and the incidence of hypoglycemia is lower than other oral anti-diabetic drugs.[27]

In our study, weight gain after follow-up occurred in 12 patients (8.9%), and there were no differences in baseline anthropometric and biochemical characteristics and concomitant use of other anti-diabetic drugs with regard to weight changes during follow-up. Weight gain is common among patients taking sulfonylureas, thiazolidinedione, or insulin.[28] Incretin-based therapies, including glucagon-like peptide-1 (GLP-1) agonist[29] and DPP-4 inhibitors[30] were known to induce weight loss or weight neutrality, respectively.

There are several limitations in our study. First,

single-center retrospective study was conducted and follow-up duration was short to evaluate full effects of DPP-4 inhibitors and durability. Second, our study enrolled a small number of patients that is hard to be generalized to a clinical practice. Third, we couldnot evaluate the efficacyof DPP-4 inhibitors by itself because other anti-diabetic medications were not strictly controlled. The possibility that glucose-lowering effect of other anti-diabetic drugs affect the result of study was not fully excluded. Fourth, we did not discriminate and evaluate different pharmacological glucose lowering effects between vildagliptin and sitagliptin. Even though there are many limitations, this study was conducted ina real clinical practice, and concomitant treatment with DPP-4 inhibitor with short-term period also demonstrated a good therapeutic efficacy as shown in previous studies.

In summary, the present study demonstrated that combination treatment with DPP-4 inhibitors and other anti-diabetic drugs, including insulin appears tobe effective and well tolerated. Atherapeutic efficacy of DPP-4 inhibitors was closely associated with high baseline HbA1c after adjustment with age, gender, duration of diabetes, follow-up duration, C-peptide, and concomitant anti-diabetic drugs.

CONFLICT OF INTEREST STATEMENT

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