Original Article

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Effects of 6-Month Sitagliptin Treatment on Insulin and Glucagon Responses in Korean Patients with Type 2 Diabetes Mellitus

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Background: This study aimed to evaluate the effect of sitagliptin, an oral dipeptidyl peptidase-4 inhibitor, on insulin secretion and glucagon suppression in Korean subjects with type 2 diabetes mellitus.

Methods: Twenty-four subjects underwent a 75-g oral glucose tolerance test (OGTT) before and after 6 months of sitagliptin treatment. Sitagliptin, insulin, and sulfonylurea were withdrawn for 3 days before OGTT to eliminate any acute effects on β-cell insulin or α-cell glucagon secretion. Venous samples were drawn five times during each OGTT to measure plasma glucose, insulin, and glucagon. Indices on insulin secretion and resistance were calculated.

Results: Early phase insulin secretion, measured by the insulinogenic index significantly increased after 6 months of sitagliptin treatment, especially in the higher baseline body mass index group and higher baseline glycosylated hemoglobin (HbA1c) group. There were no significant differences in the insulin resistance indices before and after sitagliptin treatment. Although no significant differences were observed in the absolute levels of glucagon and the glucagon-to-insulin ratio, there was a significant reduction in the percentile change of glucagon-to-insulin ratio at 30- and 120-minute during the OGTT.

Conclusion: Although the HbA1c level did not decrease significantly after 6 months of sitagliptin treatment, an increase in insulin secretion and reduction in early phase postprandial plasma glucagon-to-insulin ratio excursion was confirmed in Korean subjects with type 2 diabetes.

Keywords: Dipeptidyl-peptidase 4 inhibitors; Glucagon; Glucose tolerance test; Insulin; Korea

INTRODUCTION

Type 2 diabetes mellitus in patients from Asian countries differs in several aspects from that seen in patients from Western countries. The clinical characteristics of Asian type 2 diabetes include a rapid increase in the prevalence of diabetes during a relatively short period of time and early disease onset with a lesser degree of obesity compared to that observed in patients from Western countries [1,2]. Pronounced dysfunction in early-phase insulin secretion with a lower degree of compensato-

ry insulin secretion has been suggested as explanations for the ethnic differences [3,4]. Because β-cell dysfunction is one of the key pathogenetic defects in patients with type 2 diabetes, worsening of β-cell function marks the progression of the disease and is a major target for treatment [5].

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide potentiate glucose-dependent insulin release. In addition, GLP-1 suppresses glucagon release and slows down gastric emptying [6]. Augmented insulin release and a reduction in glucagon concentration, reduce the

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postprandial rise in glucose concentration. Given the differences in the contribution of the insulin secretory defect and insulin resistance in the pathophysiology of type 2 diabetes between Asian and Western populations, the glucose-lowering efficacy of dipeptidyl peptidase-4 (DPP-4) inhibitors is thought to differ by ethnic group. Several studies have shown that DPP-4 inhibitors exhibit a better glucose lowering efficacy in Asians than in other ethnic groups [7].

However, only a few studies have measured blood insulin and glucagon concentrations during a 75-g oral glucose tolerance test (OGTT) in Korean patients. We aimed to evaluate the changes in insulin and glucagon secretion during 75-g OGTT before and after 6 months of sitagliptin treatment in Korean patients with type 2 diabetes.

METHODS

Study population
A prospective study was conducted using patients who had begun sitagliptin therapy for type 2 diabetes between February 2009 and May 2009 at Seoul St. Mary's Hospital, Seoul, Korea. Patients aged less than 80 years, who underwent a 75-g OGTT before and after 6-month sitagliptin treatment were included. Subjects with impaired liver or renal function (alanine aminotransferase levels more than 2-fold above the upper limit of the normal range, a serum creatinine level >133 μmol/L, or a glomerular filtration rate [GFR] <60 mL/min/1.73 m^2), type 1 diabetes, active infection or inflammation, or malignancy were excluded. Subjects who were already taking DPP-4 inhibitors or GLP-1 analogues were also excluded from this study. GFR was estimated from serum creatinine and age using the Modification of Diet in Renal Disease study equation as follows: GFR [mL/min/1.73 m^2] $= 186.3 \times Cr^{-1.154} \times age^{-0.203} \times 0.742$ [if female]).

Explanatory variables
All subjects underwent a 75-g OGTT after 12 hours of overnight fasting before and after 6-month treatment with daily 100 mg sitagliptin. Sitagliptin was withdrawn for 3 days before the 75-g OGTT. The 3-day washout period was designed to eliminate any acute effects of sitagliptin on β-cell insulin or α-cell glucagon secretion during the OGTT. Also, insulin as well as sulfonylurea was withdrawn 3 days before the OGTT while avoiding the development of hyperglycemia by prescribing non-insulin secretagogue. Glucose, insulin, and glucagon levels were obtained during the 75-g OGTT from samples collected at 0, 30, 60, 90, and 120 minutes. Plasma glucose levels were measured using the hexokinase method, and insulin was measured using a radioimmunoassay kit (Dainabot, Tokyo, Japan) in our hospital laboratory. We calculated several indices to measure insulin resistance and insulin secretion. The Matsuda index of insulin sensitivity was calculated as follows:

$$\frac{10{,}000}{\sqrt{\begin{array}{c}(\text{fasting plasma glucose (mmol/L)} \times \text{fasting insulin (}\mu\text{U/mL)} \\ \times \text{mean of glucose during OGTT} \\ \times \text{mean of insulin during OGTT)}\end{array}}}$$

The homeostatic model assessment-β (HOMA-β) and homeostatic model assessment for insulin resistance (HOMA-IR) were calculated by using the fasting insulin and fasting glucose levels as follows:

$$\text{HOMA-IR} = \frac{\text{fasting glucose (mmol/L)} \times \text{fasting insulin (}\mu\text{U/mL)}}{22.5}$$

$$\text{HOMA-}\beta = \frac{20 \times \text{fasting insulin (}\mu\text{U/mL)}}{\text{fasting glucose (mmol/L)} - 3.5}$$

The total area under the curve (insulin/glucose) (total AUC [I/G]) was calculated using a trapezoid method. The insulinogenic index was calculated as the early-phase insulin response relative to the glucose stimulus during OGTT as follows: (insulin [μU/mL] at 30 minutes during OGTT$-$fasting insulin)/(plasma glucose [mmol/L] at 30 minutes during OGTT$-$fasting plasma glucose). The subjects' heights and weights were measured, and their body mass index (BMI) was calculated by dividing their weight (kg) by the square of their height (m^2).

Statistical analysis
Data are presented as mean$\pm$standard error, or as numbers with proportions. A chi-square analysis was used for discontinuous variables, and a Wilcoxon signed rank test was used for continuous variables because of the small sample size. Comparison of time course curves during OGTT were analyzed by repeated measures analysis of variance (ANOVA), and is described as "P for trend." Additionally, a Wilcoxon signed rank test was used for each time point to compare the glucose, insulin and glucagon level before and after sitagliptin treatment. The SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and $P < 0.05$ was considered statistically significant.

Ethics statement

This study protocol was approved by the Institutional Review Board of The Catholic University of Korea (KC14RISI0357). Only de-identified patient data from the database were accessed and were analyzed anonymously. Therefore, the Institutional Review Board waived the need for written informed consent from the participants. This study was conducted according to the principles expressed in the Declaration of Helsinki.

RESULTS

Baseline clinical characteristics of subjects

Among the 37 subjects who began taking sitagliptin during the study period, 13 were unable to repeat the OGTT after 6 months of treatment. Therefore 24 subjects were included; 14 men and 10 women (Table 1). Their mean age and BMI were 53.8±10.36 years and 23.1±3.05 kg/m^2, respectively. The baseline glycosylated hemoglobin (HbA1c) was 55.4±9.62 mmol/mol (7.2%±1.27%). Among 24 subjects, three patients were drug naive, three patients switched from or added on insulin therapy, 15 patients switched from sulfonylurea (glimepiride or gliclazide), two patients switched from metformin, and one patient switched from acarbose.

Table 1. Baseline clinical characteristics

Characteristic	Baseline
Number	24
Age, yr	53.75±2.11
Sex, male:female	14:10
Weight, kg	62.45±2.10
Height, cm	164.37±1.57
BMI, kg/m^2	23.05±0.62
HbA1c, %	7.22±0.26
Duration of diabetes, yr	5.83±5.18
Total cholesterol, mmol/L	4.15±0.13
Triglyceride, mmol/L	3.27±0.71
HDL-C, mmol/L	1.31±0.07
LDL-C, mmol/L	2.21±0.11
AST, IU/L	23.57±2.42
ALT, IU/L	24.45±2.80

Values are presented as number or mean±standard error.
BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Changes in plasma glucose, insulin, and glucagon response during 75-g OGTT.

There were no significant interaction between the effects of time and treatment status for glucose, insulin, and glucagon from repeated measures ANOVA analysis during the 75g- OGTT (Fig. 1). However, the insulin/glucose ratio curve was significantly higher after sitagliptin treatment (P for trend=0.04). Although there was no significant change in the glucagon/insulin curve after sitagliptin treatment (P for trend=0.88), a significant reduction in the percentile change of plasma glucagon/insulin ratio at 30- and 120-minute was observed during the OGTT (P=0.049, P=0.024, respectively).

Changes in insulin sensitivity and secretion

The insulinogenic index and total AUC (I/G) increased significantly after 6-month sitagliptin treatment, even though the medication had been withdrawn for 3 days before the OGTT (Table 2). There were no significant differences in HOMA-IR, Matsuda index, or HOMA-β level after 6 months of sitagliptin treatment. The HbA1c level tended to decrease after sitagliptin treatment, but this change was not significant.

Subgroup analysis according to initial BMI and HbA1c level

Subjects were divided into two groups according to BMI: the lower BMI group (<23 kg/m^2) and the higher BMI group (≥23 kg/m^2). In both groups, total AUC (I/G) significantly increased with sitagliptin treatment (Table 3). However, the insulinogenic index significantly increased only in the higher BMI level group. There were no significant differences in other indices in both groups, with the exception of HOMA-β in lower BMI group. The HbA1c level tended to decrease in both BMI groups, but this change was not significant.

Subjects were also divided into two groups according to initial HbA1c level: the lower HbA1c level group (<7%, 53 mmol/mol) and the higher HbA1c level group (≥7%, 53 mmol/mol). Total AUC (I/G) and insulinogenic index significantly increased only in the higher HbA1c level group. Also, the decrease in HbA1c level was significant only in the higher HbA1c level group.

DISCUSSION

In this study, we evaluated the effect of sitagliptin on plasma glucose, insulin, and glucagon responses during a 75-g OGTT. As demonstrated by the insulinogenic index, early phase insu-
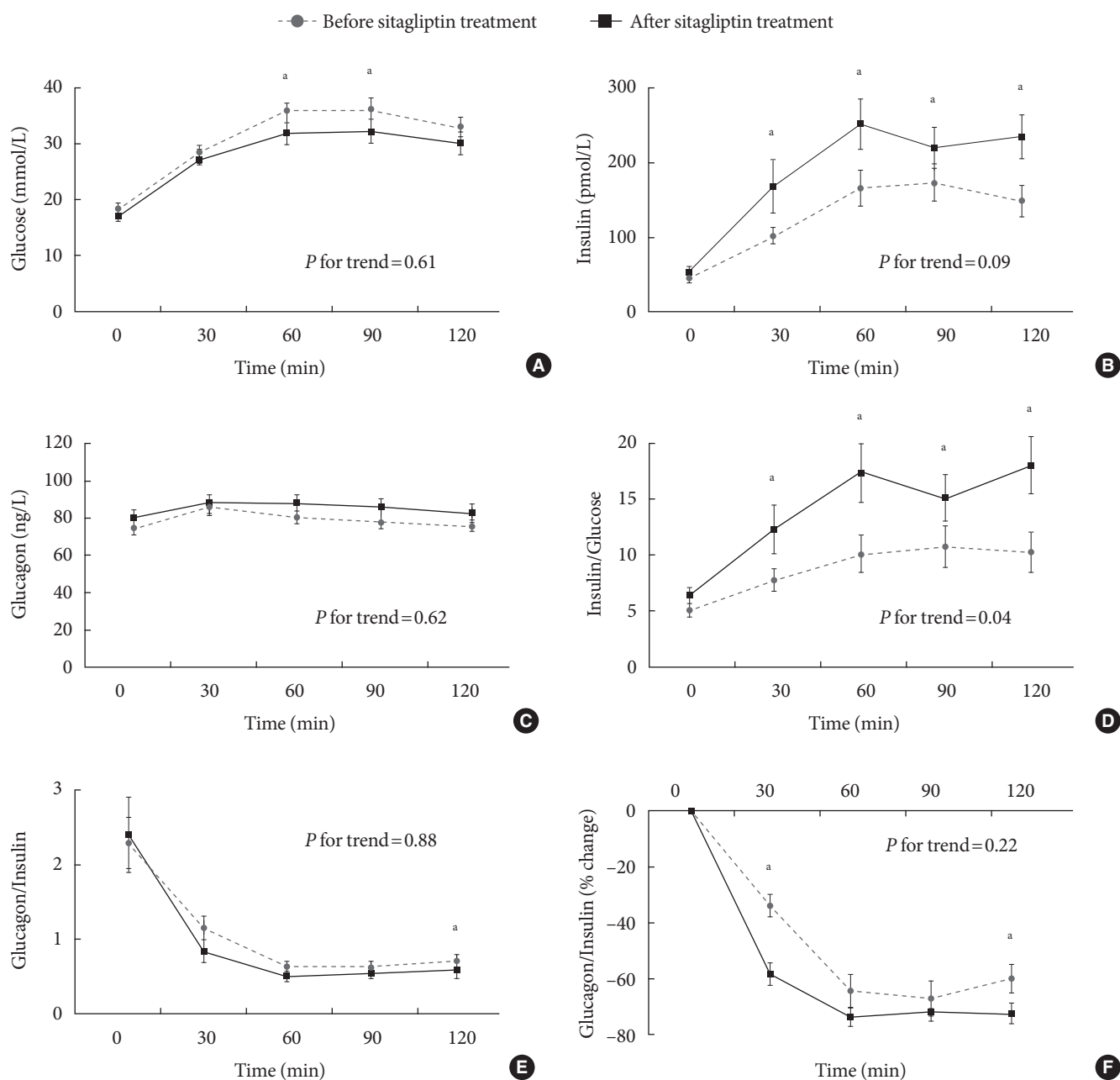
Fig. 1. Changes in plasma glucose (A), insulin (B), and glucagon (C), insulin-to-glucose ratio (D), glucagon-to-insulin ratio (E) and percent change of glucagon-to-insulin ratio (F) response during 75-g oral glucose tolerance test (OGTT) before and after sitagliptin treatment. Values are presented as mean±standard error. (Glucagon/insulin) %change=100×[(glucagon/insulin at 30, 60, 90, or 120-minute)–(glucagon/insulin at 0 minute)]/(glucagon/insulin at 0 minute). Open circles and dashed lines indicate measures before sitagliptin treatment; closed squares and solid lines indicate measures after sitagliptin treatment. "*P* for trend" indicates the comparison of time course curves during OGTT, analyzed by repeated measures analysis of variance. [a]*P*<0.05 at the 0, 30, 60, 90, or 120-minute time points using Wilcoxon signed rank test for paired values.

lin secretion increased after 6 months of treatment with sitagliptin, especially in the higher BMI subgroup and in the higher HbA1c level subgroup. Although no significant differences

in the absolute levels of glucagon and glucagon/insulin ratio were observed, there was a significant reduction in the percentile change of glucagon/insulin ratio at 30- and 120-minute

Table 2. Changes in β-cell function and insulin sensitivity after 6 months of sitagliptin treatment

	Baseline (n=24)	After treatment (n=24)	P value
Glucose, mmol/L			
0 min	9.10±0.64	8.62±0.58	0.209
120 min	16.52±0.89	15.08±1.03	0.072
Insulin, pmol/L			
0 min	45.21±5.36	52.36±7.64	0.361
120 min	148.62±21.27	234.06±29.88	0.001
C-peptide, nmol/L			
0 min	0.68±0.09	0.63±0.36	0.695
120 min	1.94±0.17	1.91±0.98	0.760
Glucagon, ng/L			
0 min	72.73±3.54	79.54±17.32	0.140
120 min	74.07±3.26	82.47±21.06	0.120
Total AUC (insulin/glucose)	8.76±1.53	15.01±2.04	0.001
HOMA-IR	2.78±0.39	3.09±0.70	0.797
Matsuda index	6.37±0.96	5.22±0.73	0.317
Insulinogenic index	0.63±0.11	1.18±0.27	0.001
HOMA-β	26.95±3.31	33.57±4.15	0.061
Total AUC (glucagon/insulin)	1.95±1.09	1.56±1.03	0.303
HbA1c, %	7.22±0.26	6.96±0.20	0.098

Values are presented as mean±standard error.
AUC, area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; HbA1c, glycosylated hemoglobin.

during the OGTT.

In most studies, improvements in the proinsulin-to-insulin ratio and the insulinogenic index were noted with sitagliptin monotherapy or combination therapy [8], the latter being confirmed in our study. An inhibitory effect of GLP-1 analogue on glucagon secretion has been observed in Asian [9] and non-Asian populations [10]. However, only a few studies have reported glucagon responses after use of DPP-4 inhibitors in Asian population. Eto et al. [11] reported a decreased glucagon response after teneligliptin treatment in Japanese patients with type 2 diabetes. Regarding sitagliptin, Herman et al. [12] demonstrated a decreased glucagon and reduced glycemic excursion at 2 and 24 hours during an OGTT in a non-Asian population after single oral dose of sitagliptin (25 or 200 mg). DeFronzo et al. [13] reported 2-week treatment of sitagliptin reduced post-

Table 3. Subgroup analysis according to the initial BMI and HbA1c

	Baseline	After treatment	P value
BMI <23 (n=13)			
Total AUC (I/G)	11.26±2.43	17.52±3.12	0.034
HOMA-IR	1.78±0.42	2.24±0.42	0.116
Matsuda index	7.96±1.46	5.27±0.73	0.152
Insulinogenic index	0.83±0.16	1.46±0.48	0.082
HOMA-β	26.46±4.29	36.86±4.44	0.046
HbA1c, %	6.57±0.26	6.38±0.13	0.357
BMI ≥23 (n=11)			
Total AUC (I/G)	7.51±1.51	11.26±2.26	0.007
HOMA-IR	3.96±0.49[a]	4.09±1.43	0.594
Matsuda index	4.49±0.98[a]	5.15±1.38	0.929
Insulinogenic index	0.49±0.13[a]	0.83±0.15	0.005
HOMA-β	27.52±5.38	29.67±7.45	0.689
HbA1c, %	7.98±0.36[a]	7.64±0.31	0.166
HbA1c <7% (53 mmol/mol) (n=11)			
Total AUC (I/G)	12.51±2.64	17.52±1.89	0.092
HOMA-IR	1.70±0.34	2.28±0.49	0.075
Matsuda index	7.13±1.09	5.40±0.84	0.110
Insulinogenic index	0.83±0.19	1.11±0.17	0.152
HOMA-β	33.66±5.24	42.69±6.68	0.110
HbA1c, %	6.19±0.15	6.27±0.14	0.722
HbA1c ≥7% (53 mmol/mol) (n=13)			
Total AUC (I/G)	6.26±1.04[a]	12.51±3.11	0.003
HOMA-IR	3.69±0.55[a]	3.77±1.22	0.463
Matsuda index	5.73±1.54	5.06±1.17	0.972
Insulinogenic index	0.56±0.14	1.25±0.50	0.003
HOMA-β	21.26±3.69[a]	25.85±4.31	0.294
HbA1c, %	8.08±0.29[a]	7.54±0.27	0.031

Values are presented as mean±standard error.
BMI, body mass index; AUC (I/G), area under the curve (insulin/glucose); HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; HbA1c, glycosylated hemoglobin.
[a]Denotes P<0.05 compared with the baseline value of patients in BMI <23 or HbA1c <7% subgroup.

prandial glucagon secretion relative to baseline in non-Asian subjects. In our study, sitagliptin treatment for 6 months did not suppress the absolute glucagon level or glucagon/insulin ratio. This discrepancy in the glucagon response might be related to

lower level of baseline and peak glucagon level in our study compared to former studies. Differences in ethnicity, treatment duration and baseline HbA1c might have additionally attributed to this discrepancy. Reports on glucagon response during OGTT following sitagliptin treatment in Asian population have been lacking, and further studies are needed to confirm our results.

In contrast to previous studies, there was no significant decrease in HbA1c level after 24 weeks of sitagliptin treatment. However, HbA1c significantly decreased in those with higher baseline HbA1c level (≥7%). Insignificant change of HbA1c in the overall study population might be the consequence of relatively low level of baseline HbA1c in our study, while most outcome studies have included subjects with higher baseline HbA1c levels [14]. Furthermore, the tendency toward increased HOMA-IR level may in part attribute to insignificant change in HbA1c level.

Recent study showed that glimepiride treatment for 24-week appeared to enhance insulin secretion from β-cell, as well as glucagon secretion from α-cell compared to exenatide or sitagliptin, even after 5 days of drug washout to eliminate any acute effects of the study drugs [15]. In our study, 15 out of 24 patients were prescribed with glimepiride (11 patients) or gliclazide (three patients), which may have affected baseline glucagon level. Therefore, studies in subjects who have not been taking sulfonylurea are also needed.

There have been several reports on sitagliptin treatment in Korean populations. Kim et al. [16] evaluated predictive clinical parameters for the therapeutic efficacy of sitagliptin in Korean subjects with type 2 diabetes mellitus. The study showed a greater response among younger subjects with lower BMIs. In another report, Kim et al. [17] showed that the treatment failure group had a longer diabetes duration and higher HbA1c levels compared with the good-response group. In our study, the higher BMI group showed a significantly increased insulinogenic index, which was not observed in the lower BMI group. Moreover, a significant decrease in HbA1c level and improvement in insulinogenic index was observed only in the higher HbA1c level group. The inconsistency between our study and the previous studies might be the result of different baseline characteristics of the enrolled subjects; small number of enrolled patients with lower baseline HbA1c level and BMI in our study. Improved insulinogenic index in the higher BMI subgroup might be associated with higher baseline HbA1c and HOMA-IR level compared with lower BMI subgroup. When subjects were catego-

rized into two groups according to the changes in insulinogenic index (Δinsulinogenic index = insulinogenic index after sitagliptin treatment–insulinogenic index at baseline), those with higher Δinsulinogenic index showed higher baseline HbA1c ($P = 0.01$) and HOMA-IR level ($P = 0.03$) compare to those with lower Δinsulinogenic index levels. While Deacon [18] suggested that a higher baseline HbA1c would be a predictor of a greater HbA1c reduction with a DPP-4 inhibitor, some other reports revealed no effect on baseline HbA1c on the efficacy of DPP-4 inhibitors [7]. Therefore, further studies are required to clarify the parameters associated with the therapeutic efficacy of DPP-4 inhibitors, including sitagliptin.

There are several limitations in this study. First, the sample size was very small, and most of the patients were middle-aged; between 40 and 50 years old. Second, baseline HbA1c was 7.22%, which is close to the recommended target of 7.0%. Also, those who were unable to follow-up OGTT after 6 months of sitagliptin treatment were not evaluated, and therefore we could not rule out the potential selection bias. Finally, diet and exercise were not monitored during the 6-month treatment period.

In this study, we evaluated the changes in insulin and glucagon secretion during 75-g OGTT before and after 6 months of sitagliptin treatment in Korean patients with type 2 diabetes. Although HbA1c level did not decrease significantly after sitagliptin treatment, an increase in insulin secretion and reduction in early phase of postprandial plasma glucagon excursion was confirmed in Korean subjects with type 2 diabetes. Further studies with larger number of patients representative of Korean population are needed to validate our study result.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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