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Predictive factors of durability to sitagliptin: Slower reduction of glycated hemoglobin, older age and higher baseline glycated hemoglobin

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ABSTRACT

Aims/Introduction: The goal of the present study was to evaluate predictive factors for good efficacy and durability to sitagliptin with ongoing metformin or metformin plus glimepiride therapy in a real practice situation. The present observational study was carried out over a 60-week period and involved Korean patients with type 2 diabetes mellitus.

Materials and Methods: A total of 100 mg of sitagliptin were added once daily to the two most popular therapy regimens (group 1: metformin, group 2: metformin plus glimepiride). Before adding sitagliptin, mean initial glycated hemoglobin (HbA1c) levels were 7.8% (62 mmol/mol) and mean diabetes duration was 8.3 years.

Results: After 60 weeks, the mean change in HbA1c from baseline was −0.9% (−10 mmol/mol) in group 1 and −1.0% (−11 mmol/mol) in group 2. Decreased HbA1c levels were significantly associated with higher initial HbA1c and lower log-transformed C-peptide levels in a multivariate regression analysis. Logistic regression analysis showed that a sustained reduction in HbA1c levels after 12 weeks was significantly associated with older age (≥60 years), higher baseline HbA1c (group 1 ≥ 7.0% [53 mmol/mol], group 2 ≥ 7.5% [58 mmol/mol]) and slower reduction of HbA1c (ΔHbA1c <1.0% [11 mmol/mol]) in group 1 and group 2. In group 2, a higher ratio of reduction of postprandial glucose/reduction of fasting plasma glucose (ΔPPG/ΔFPG) during 12 weeks was also associated with a sustained reduction in HbA1c levels after 12 weeks.

Conclusions: The effects of sitagliptin lasted more than 12 weeks in older patients with a higher baseline HbA1c, and slower reduction of HbA1c during 12 weeks.

INTRODUCTION

It is often difficult to attain target glucose levels in patients with type 2 diabetes mellitus using treatment with a single antidiabetic drug[1,2]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that after 3 years, type 2 diabetes mellitus was adequately controlled with a single drug in just 50% of patients, and after 9 years this percentage decreased to 25%[1–3]. The UKPDS clearly showed that type 2 diabetes mellitus is a progressive disease, and as a result, it is necessary to maintain combination therapy with the addition of antidiabetic drugs over time. Most current therapeutic guidelines recommend metformin as initial monotherapy for the treatment of type 2 diabetes mellitus[4]. If metformin does not achieve target glycemic control, insulin secretagogues are frequently used as a second-line therapy[4]. The present study investigated the effects of sitagliptin on glycemic control in patients who were also being treated with metformin or a metformin and glimepiride combination.

Sitagliptin is a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor given once daily and approved in many countries for the treatment of type 2 diabetes mellitus. DPP-4 is an

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enzyme involved in the degradation of the active incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) into inactive metabolites. GLP-1 and GIP are released into the circulation by the intestine in response to a meal, and both hormones stimulate glucose-dependent insulin secretion as well as insulin biosynthesis[2,5–7]. When considering combination therapy with sitagliptin, metformin is the most commonly used agent, and was effective and well-tolerated in many studies[8–11]. Glimepiride improves blood glucose levels by stimulating insulin secretion from pancreatic β-cells in a non-glucose-dependent manner[12]. Although they operate through different mechanisms, both glimepiride and sitagliptin regulate insulin secretion from β-cells.

In the hierarchy of research design, results from randomized, controlled trials are considered to produce data of the highest grade, whereas observational studies are viewed as having less validity. However, the results of well-designed observational studies do not necessarily overestimate the magnitude of treatment effects when compared with similar studies that involved randomized, controlled trials[13]. During the process of developing sitagliptin, some studies were based on randomized prospective clinical trials, but it is also meaningful to observe the effects of sitagliptin in a 'real practice' situation.

The present 60-week observational study investigated the factors for durability and good efficacy of adding 100 mg sitagliptin to ongoing treatment with metformin alone or to a dual combination treatment of glimepiride and metformin in a real practice situation. Of those patients who responded during the first 12 weeks of treatment, two different types of patients were identified. One type had elevated glycated hemoglobin (HbA1c) levels after 12 weeks, and the other type had similar or decreased HbA1c levels after 12 weeks. The study also assessed parameters that affect the outcome of sitagliptin treatment beyond 12 weeks, and investigated parameters that might allow for prediction of therapeutic effects during 60 weeks. The risk of hypoglycemia and other factors associated with the addition of sitagliptin to ongoing glimepiride and metformin therapy was also investigated.

MATERIALS AND METHODS

Patients

A serial group of 506 participants who began taking sitagliptin with other ongoing antidiabetic drugs from October 2008 through July 2009 were enrolled in the study. Of the 506 participants, 404 participants were included in the analysis and 102 participants were excluded because their medical history showed they had undergone an operation, used steroids, been hospitalized or were diagnosed with cancer. Participants were also excluded if their medical records missed data regarding medication or laboratory results, such as HbA1c, fasting plasma glucose (FPG) or 2-h postprandial glucose (2 h-PPG). Inclusion criteria for the study were: (i) men or women subjects; (ii) clinically diagnosed with type 2 diabetes mellitus for at least 6 months; (iii) ongoing treatment with the same antidiabetic drug for at least 6 months; (iv) inadequately controlled type 2 diabetes mellitus (HbA1c >6.5% [48 mmol/mol]); (v) no hypoglycemic event during the past 3 months; and (vi) no abnormal laboratory findings for aspartate transaminase (AST), alanine transferase (ALT), blood urea nitrogen, creatinine or complete blood count. Data were collected from October 2008 to February 2011 by review of medical records and by interview when possible.

Methods

Once-daily 100 mg sitagliptin was added to the treatment regimen of patients currently taking metformin alone, or metformin plus glimepiride. During sitagliptin addition, patients taking glimepiride and metformin who experienced a hypoglycemic event had their glimepiride dose decreased until they did not experience further events. Patients taking sitagliptin and metformin who experienced a hypoglycemic event had the metformin dose reduced. A hypoglycemic rescue regimen was used if the patients experienced one or more episodes of unexplained hypoglycemia as defined by FPG or finger-stick glucose <2.8 mmol/L with or without the symptoms of hypoglycemia, or <3.9 mmol/L with symptoms of hypoglycemia. A physical examination was carried out, and vital signs, body mass index, HbA1c, FPG, and 2 h-PPG were measured at the hospital every 12 weeks. At-home fingerstick glucose checks were recommended if the patient had hypoglycemic symptoms or a previous hypoglycemic event. Pancreatic β-cell function was calculated using the secretory units of islets in transplantation (SUIT) index[14,15]. The SUIT index can be calculated using data obtained from a single blood sample according to the formula: 250 × fasting C-peptide (nmol/L/(FPG [mmol/L] − 3.43), where the SUIT index of normal subjects is 100 ± 11.7. The SUIT index showed a correlation with C-peptide levels in transplanted patients and type 2 diabetes mellitus patients[14]. The factors associated with the good efficacy of sitagliptin was assessed with a multivariate regression analysis that analyzed the change in HbA1c after 60 weeks of sitagliptin treatment with regard to sex, age, body mass index (BMI), weight, creatinine, ALT, AST, initial HbA1c, log-transformed initial C-peptide, log-transformed SUIT index and log-transformed duration of diabetes.

Patients were classified as 'responders' after 12 weeks of treatment if they had a 0.4% (4 mmol/mol) or more HbA1c reduction in the sitagliptin and metformin group, and greater than a 0.6% (7 mmol/mol) HbA1c reduction in the sitagliptin, glimepiride and metformin group. Because the initial HbA1c in the sitagliptin, glimepiride and metformin group was higher than in the sitagliptin and metformin group, we used different standards. We established the standards with reference to the oriental result of HbA1c reduction, in consideration of similar initial HbA1c[16,17]. In responders, we divided patients into the sustained-effective group and late failure group. The sustained-effective group was comprised of patients with a sustained

HbA1c level at 24, 36, 48 and 60 weeks. All the other patients were classified as the late failure group.

Statistical analyses

Data were expressed as mean ± standard deviation or as a number. *P*-values <0.05 were considered statistically significant. All statistical calculations were carried out using the software program PASW 17.0 (SPSS Inc., Chicago, IL, USA). Comparisons were made using Student's *t*-test, Wilcoxon's rank sum test, paired *t*-test, Pearson's correlation analysis, multivariate regression analysis and logistic regression analysis. We compared mean differences factors between the hypoglycemic and non-hypoglycemic event groups using Student's *t*-test, or Wilcoxon's rank sum test when data were not normally distributed. To compare parameters (Hba1c, FPG, 2 h-PPG) between pre- and post-treatment groups, because sphericity was not assumed, we analyzed not repeated measure ANOVA, but paired *t*-test. The Bonferroni correction was applied for multiple testing. Results were considered significant at $P < 0.05$ after this correction. Pearson's correlation analysis was used to assess relationships between changes in HbA1c and other factors. Because the factors of C-peptide, SUIT and duration of diabetes were not normally distributed, we transformed log. Multivariate regression analysis was used to evaluate the independent relationship between changes in HbA1c and other factors. Logistic regression analysis was used to investigate predictive factors for the effects of sitagliptin after 12 weeks.

RESULTS

Patient characteristics

Of the 404 patients, 367 completed the 60-week study: 204/222 (92%) in the sitagliptin and metformin group (group 1) and 163/182 (90%) in the sitagliptin, glimepiride and metformin group (group 2). Patients left the study for the following reasons: use of another antidiabetic drug as a result of sitagliptin non-response ($n = 12$; group 1 $n = 2$, group 2 $n = 10$); lost to follow up ($n = 11$; group 1 $n = 7$, group 2 $n = 4$); drug compliance below 70% ($n = 5$; group 1 $n = 4$, group 2 $n = 1$); steroid use ($n = 3$; group 1 $n = 2$, group 2 $n = 1$); conditions requiring surgery or hospital admission ($n = 3$; group 1 $n = 2$, group 2 $n = 1$); increase in serum creatinine ($n = 2$; group 1 $n = 1$, group 2 $n = 1$); and increase in serum AST/ALT ($n = 1$; group 2 $n = 1$). Baseline characteristics by treatment group are summarized in Table 1. For the entire study population, the average known duration of diabetes was 8.3 years (group 1: 6.0 years; group 2: 11.1 years), average baseline HbA1c was 7.8% (62 mmol/mol); group 1: 7.5% (58 mmol/mol), group 2: 8.2% (66 mmol/mol) and average baseline FPG was 8.8 mmol/L (group 1: 8.5 mmol/L; group 2: 9.2 mmol/L). The mean drug compliance during the follow-up periods was 86.2%.

Table 1 | Baseline characteristics

	Group 1 (metformin only) ($n = 222$)		Group 2 (metformin + glimepiride) ($n = 182$)	
	Mean	Standard deviation	Mean	Standard deviation
Sex (men/women)	132/90		105/77	
Age (years)	57.2	6.1	61.0	10.7
BMI (kg/m^2)	25.6	3.0	25.7	3.8
Weight (kg)	69.5	10.8	68.9	13.2
Duration of diabetes (years)	6.0	5.8	11.1	6.4
HbA1c, mmol/mol (%)	58, 7.5	10, 0.9	66, 8.2	11, 1.0
Fasting plasma glucose (mmol/L)	8.5	1.9	9.2	2.5
Post prandial glucose (mmol/L)	13.0	3.3	14.3	3.7
C-peptide (ng/mL)	1.5	14.1	2.7	17.6
SUIT index	44.5	24.7	43.0	23.2
ALT (U/L)	34	24	35	31
AST (U/L)	26	16	28	23
BUN (mg/dL)	14	4	15	4
Creatinine (mg/dL)	0.9	0.2	0.9	0.2
Total cholesterol (mg/dL)	181	31	185	34
Triglyceride (mg/dL)	177	115	179	101
HDL cholesterol (mg/dL)	46	9	46	10
LDL cholesterol (mg/dL)	101	30	94	45
Mean glimepiride dosage (mg)	–	–	3.41	–
Mean metformin dosage (mg)	977	–	824	–

Results are presented as mean ± standard deviation. ALT, alanine transferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SUIT, secretory units of islets in transplantation.

Efficacy

In groups 1 and 2, treatment with 100 mg sitagliptin once daily for 60 weeks significantly decreased HbA1c, FPG and 2 h-PPG values compared with baseline (mean HbA1c change −0.9% (−10 mmol/mol), $P < 0.01$; mean FPG change −1.7 mmol/L, $P < 0.01$; mean 2 h-PPG change −2.7 mmol/L, $P < 0.01$; Figure 1). Greater reductions in HbA1c, FPG and 2 h-PPG were observed during the first 3 months of treatment, after which time glucose levels stabilized. In the group taking sitagliptin and metformin (group 1: $n = 222$, initial mean HbA1c = 7.5% [58 mmol/mol]), HbA1c, 2 h-PPG and fasting glucose levels decreased by 0.9% (10 mmol/mo; $P < 0.01$), 3.1 mmol/L ($P < 0.01$) and 1.6 mmol/L ($P < 0.01$), respectively, at the end of 60 weeks. In the group taking sitagliptin, sulfonylurea and metformin (group 2: $n = 182$, initial mean HbA1c = 8.2% [66 mmol/mol]), HbA1c, 2 h-PPG and fasting glucose levels decreased by 1.0% (11 mmol/mol; $P < 0.01$), 2.1 mmol/L ($P < 0.01$) and 1.8 mmol/L ($P < 0.01$), respectively, at the end of 60 weeks (Figure 1). The proportion of patients with HbA1c <6.5% (48 mmol/mol) at week 60 were 81.9% in group 1 and 21.2% in group 2. Because of a higher initial HbA1c, the proportion that reached target glucose control was lower in group 2 than group 1. However, the total reduction in HbA1c was larger in group 2.

For both groups, 60-week treatment with sitagliptin significantly improved β-cell function as estimated by the SUIT index, but there was no significant change in C-peptide levels (Figure 2). Sitagliptin had a neutral effect on plasma lipid levels and bodyweight (data not shown). The correlation between the reduction in HbA1c and β-cell function was evaluated using Pearson's correlation analysis. Reduction in HbA1c insignificantly correlated with the log-transformed baseline SUIT index and log-transformed baseline C-peptide levels. Three multivariate regression models were then established to evaluate the independent relationship between changes in HbA1c and baseline β-cell function (Table 2). The effects of log-transformed baseline C-peptide levels and log-transformed SUIT index on the changes in HbA1c were examined and adjusted for sex, age, log transformed duration of diabetes, body mass index, weight, creatinine, ALT, AST, and initial HbA1c (model 1). In model 2, adjustment was carried out for log-transformed SUIT index instead of log transformed C-peptide levels. In model 3, adjustment was carried out for log-transformed C-peptide levels instead of log-transformed SUIT index. In group 1, high baseline HbA1c and low log-transformed baseline C-peptide levels were independent predictors of reduced HbA1c (models 1, 2 and 3). In group 2, high baseline HbA1c, low log-transformed baseline C-peptide levels and a low log-transformed SUIT index were independent predictors of reduced HbA1c in model 1. In model 3, high baseline HbA1c was also a significant independent predictor of reduced HbA1c.

Patients who experienced reductions in HbA1c during the first 12 weeks diverged into two types after the 12th week. One

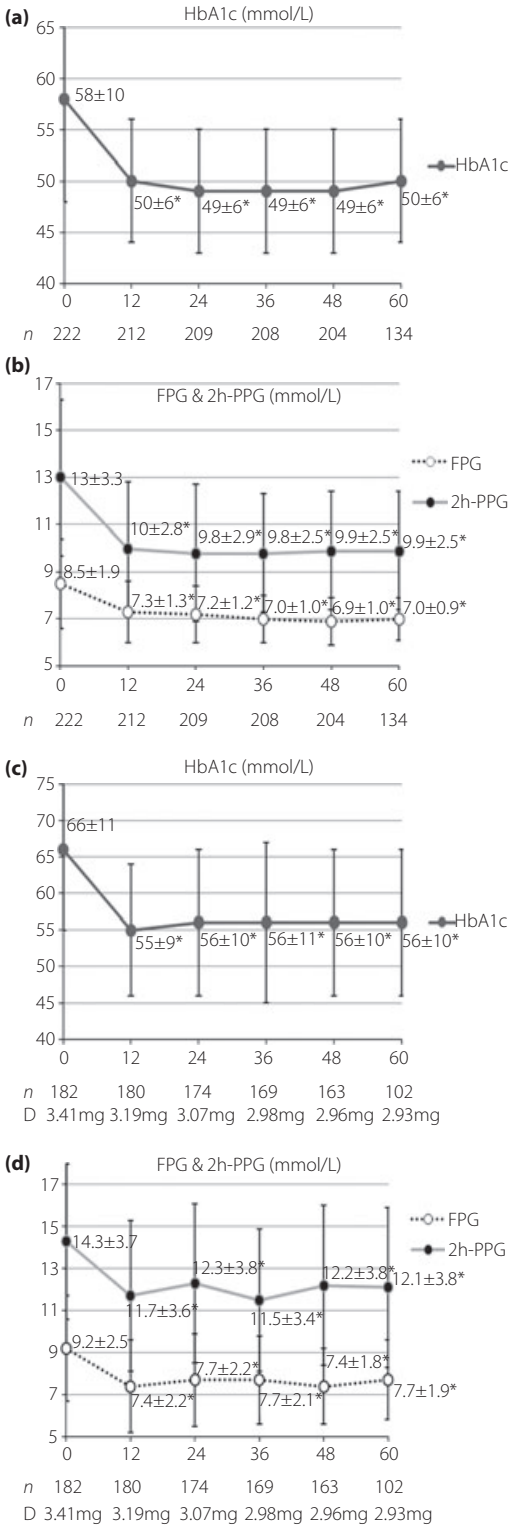

Figure 1 | The addition of once-daily sitagliptin over 60 weeks led to clinically significant reductions in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) and 2-h postprandial glucose (2 h-PPG) levels. (a, b) Sitagliptin addition to metformin therapy. (c,d) Sitagliptin addition to glimepiride and metformin combination therapy. D, Dose of glimepiride.

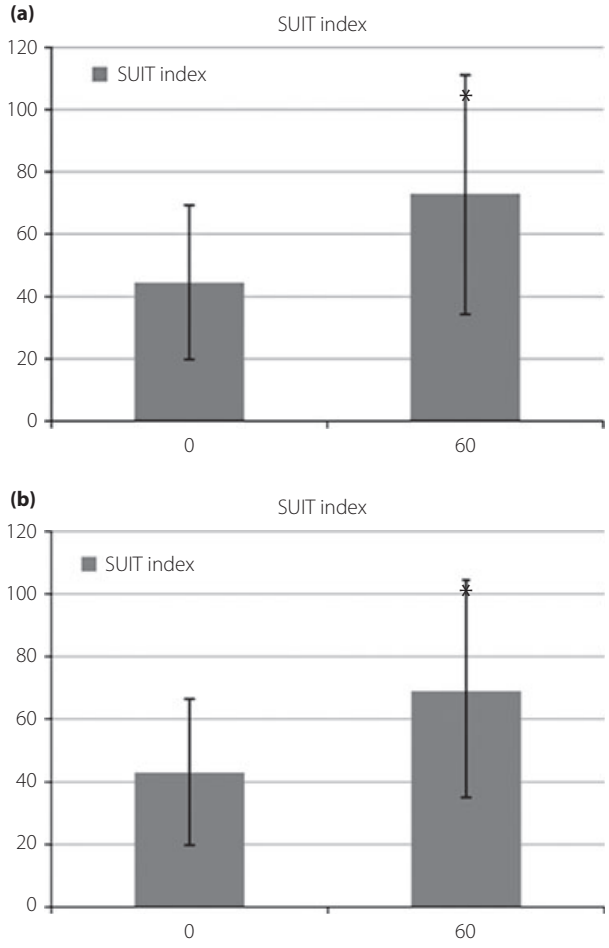

Figure 2 | For both groups, 60-week treatment with sitagliptin significantly improved β-cell function as estimated by the secretory units of islets in transplantation (SUIT) index. (a) Sitagliptin addition to metformin therapy. (b) Sitagliptin addition to glimepiride and metformin combination therapy. *$P < 0.05$ vs baseline, Wilcoxon signed rank test.

type showed an elevated HbA1c after 12 weeks (late failure type), and the other type showed maintained or decreased HbA1c levels after 12 weeks (sustained-effective type). In group 1, 63 patients (39%) had elevated HbA1c after 12 weeks, and 98 patients (61%) had maintained or further decreased HbA1c levels after 12 weeks. In group 2, 46 patients (41%) had elevated HbA1c after 12 weeks, and 65 patients (59%) had maintained or decreased HbA1c levels after 12 weeks. Interactions with diabetes mellitus duration, baseline SUIT index, creatinine, weight, Δ weight during 12 weeks, and BMI between sustained-effective type and late failure type was not found in the logistic regression analyses. In group 1, logistic regression analyses showed that four variables (age, baseline HbA1c, ΔHbA1c and ΔPPG/ΔFPG during 12 weeks) were significantly associated with sitagliptin response after 12 weeks. Regression coefficients (β-coefficients), odds ratios (OR) and 95% CIs of each variable are shown in Table 3. In group 2, age, baseline HbA1c and ΔHbA1c during 12 weeks interacted with sitagliptin response after 12 weeks (Table 3).

Safety

Sitagliptin was generally well-tolerated in the present study. The incidence of gastrointestinal trouble was 10.3%, including symptoms of diarrhea and abdominal fullness. Because side-effects were mild, no participants discontinued sitagliptin as a result of gastrointestinal issues. When sitagliptin was added to an existing treatment, 6.3% of patients in the sitagliptin and metformin group experienced a hypoglycemic event, and 19.2% of patients in the sitagliptin, glimepiride and metformin group experienced a hypoglycemic event. Hypoglycemic events were more severe and more frequent in group 2 compared with group 1 (19.2% vs 6.3%, $P < 0.001$; χ^2-test). Glimepiride dosage was reduced until hypoglycemic events no longer occurred. The mean dose of glimepiride at each point is presented in Figure 1 (initial mean dose of glimepiride: 3.41 mg/day; mean dose of glimepiride after week 60: 2.93 mg/day). The occurrence of hypoglycemia in group 2 appears to be associated with the following factors: old age, extended duration of diabetes, lower initial HbA1c and lower FPG (Table 4). During the 60-week study, there were no cases of pancreatitis among the patients, but temporary elevations in amylase or lipase were observed in 6.1% (25/404) of the patients. All of these elevations were painless and normalized within 3 months. There was one case of a urinary tract infection, two cases of increased serum creatinine and one case of increased serum AST/ALT. These patients discontinued the study. No clinically meaningful changes in vital signs or other laboratory findings were observed in the study groups.

DISCUSSION

In the present study, the addition of once-daily sitagliptin over 60 weeks led to clinically significant reductions in HbA1c, FPG and 2 h-PPG levels in Korean participants with type 2 diabetes mellitus with inadequate glycemic control. As observed in previous sitagliptin studies of shorter duration, reduction in these levels from baseline was sustained over the length of the study[2,11,18–20]. In the group taking sitagliptin and metformin, a reduction in HbA1c was significantly associated with higher baseline HbA1c levels and lower baseline C-peptide levels after adjusting for sex, age, duration of diabetes, BMI, weight, creatinine, ALT, AST and inclusion or exclusion of the SUIT index. In the group taking sitagliptin, glimepiride and metformin, a reduction in HbA1c was significantly associated with high baseline HbA1c levels and low baseline C-peptide levels after adjusting for sex, age, duration of diabetes, BMI, weight, creatinine, ALT, AST, and SUIT index. In a study by Lim *et al.*[21], reduction in HbA1c was significantly associated with high baseline HbA1c levels, low baseline insulinogenic index and short duration of diabetes mellitus after adjusting for age, sex, BMI, blood pressure, triglycerides, creatinine, high sensitivity CRP, gluca-

Table 2 | Multiple regression analysis of changes in glycated hemoglobin after 60 weeks of sitagliptin treatment

	Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*
(a) Sitagliptin addition to metformin therapy						
Sex (1 = men, 2 = women)	0.10	0.61	0.11	0.60	0.11	0.60
Age (years)	−0.14	0.78	−0.02	0.75	−0.08	0.89
Duration of diabetes (years)	−0.08	0.18	−0.08	0.18	−0.08	0.18
BMI (kg/m^2)	−0.11	0.24	−0.11	0.24	−0.11	0.21
Weight (kg)	0.01	0.91	0.01	0.91	0.01	0.88
Creatinine (mg/dL)	0.03	0.61	0.03	0.61	0.03	0.64
ALT (U/L)	0.13	0.19	0.13	0.19	0.13	0.19
AST (U/L)	−0.08	0.43	−0.08	0.43	−0.08	0.43
HbA1c (%)	0.87*	<0.01*	0.75*	<0.01*	0.73*	<0.01*
C-peptide (ng/mL)	−0.75*	<0.01*	–	–	−0.75*	<0.01*
SUIT index	−0.02	0.72	−0.02	0.72	–	–
(b) Sitagliptin addition to glimepiride and metformin combination therapy						
Sex (1 = men, 2 = women)	0.10	0.51	0.10	0.50	0.11	0.48
Age (years)	−0.15	0.88	−0.02	0.86	−0.01	0.92
Duration of diabetes (years)	0.17	0.11	0.17	0.11	0.16	0.12
BMI (kg/m^2)	−0.32	0.12	−0.35	0.15	−0.32	0.13
Weight (kg)	0.26	0.29	0.31	0.25	0.23	0.33
Creatinine (mg/dL)	0.11	0.33	0.11	0.32	0.12	0.31
ALT (U/L)	0.01	0.93	0.02	0.86	0.03	0.83
AST (U/L)	0.07	0.55	0.07	0.55	0.06	0.57
HbA1c (%)	0.56*	<0.01*	0.54*	<0.01*	0.53*	<0.01*
C-peptide (ng/mL)	−0.27*	0.04*	–	–	−0.09	0.08
SUIT index	−0.28*	0.04*	0.03	0.78	–	–

Model 1 included C-peptide and secretory units of islets in transplantation (SUIT) index, model 2 was adjusted for SUIT index instead of C-peptide, and model 3 was adjusted for C-peptide instead of SUIT index. The factors of C-peptide, SUIT and duration of diabetes were not normally distributed, we transformed log. **P*-value < 0.05. ALT, alanine transferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

gon, C-peptide, homeostasis model assessment of β-cell function, and homeostasis model assessment of β-insulin resistance. The study by Lim *et al.*[21] was different from the present study in that their participants had been diabetic for a relatively short period of time. In addition, they targeted drug-naïve patients of type 2 diabetes mellitus using an initial combination therapy of sitagliptin and metformin. In a study by Harashima *et al.*[22], insulin secretion capacity, C-peptide reaction index and SUIT index at baseline did not predict the efficacy of sitagliptin add-on to sulphonylureas therapy. In other Japanese studies, the factor that was most related to a reduction in HbA1c after 3 months of treatment with sitagliptin was baseline HbA1c[23,24]. Other significant baseline factors were higher PPG, lower BMI and shorter duration of diabetes[23,24]. Furthermore, in a meta-analysis by Esposito *et al.*[25] involving 10,467 patients treated with a DPP-4 inhibitor, baseline HbA1c was the best predictor for achieving an HbA1c <7%. We were unsure of the exact relationship among sitagliptin efficacy, duration of diabetes mellitus, BMI, PPG and previous medications, but anticipated that the effects of sitagliptin were closely related to higher baseline HbA1c levels and pancreatic β-cell function.

The greatest reductions in HbA1c, FPG and 2 h-PPG were observed in the first 12 weeks, after which point glucose levels stabilized. Patients who experienced reductions in HbA1c during the first 12 weeks diverged into two types after the 12th week. One type of patient experienced elevated HbA1c after 12 weeks, and the other type of patient had the same or decreased HbA1c levels after 12 weeks. In group 1 and group 2, longer efficacy of sitagliptin was directly proportional to older age (≥60 years) and higher baseline HbA1c (group 1 ≥ 7.0% [53 mmol/mol], group 2 ≥ 7.5% [58 mmol/mol]) and longer efficacy of sitagliptin was inversely proportional to ΔHbA1c (≥1.0% [11 mmol/mol]) during 12 weeks. In responders during 12 weeks, we supposed that the range of HbA1c reduction in sitagliptin is limited, even if the pace of HbA1c reduction is individualized. In group 1, a higher ratio of ΔPPG/ΔFPG during 12 weeks was correlated with a longer efficacy of sitagliptin. There was little difference between group 1 and group 2. Group 1 patients had a relatively short duration of diabetes and thus were likely to have more β-cell function than group 2, and so there was a different response to the same medication.

Table 3 | Factors affecting duration of sitagliptin efficacy (>12 weeks)

	β-coefficients	OR	95% CI
(a) Sitagliptin addition to metformin therapy			
Age (≥60 years)*	1.18	3.13	1.12–9.49
Baseline HbA1c*(≥53, 7.0)	1.14	3.12	1.21–8.09
Δ HbA1c*(≥11,1.0)	−3.57	0.03	0.01–0.28
ΔPPG/Δ FPG	0.26	1.29	1.01–1.66
Constant	−8.26		
(b) Sitagliptin addition to glimepiride and metformin combination therapy			
Age (≥60)†	1.30	3.67	1.19–11.30
Baseline HbA1c†(≥58, 7.5)	1.56	4.59	1.30–16.24
Δ HbA1c†(≥11,1.0)	−1.68	0.19	0.06–0.62
Constant	−16.00		

*The reference category of age is <60 years, baseline glycated hemoglobin (HbA1c) <53 mmol/mol, 7.0%, and ΔHbA1c <11 mmol/mol, 1.0%. †The reference category of age is <60 years and baseline HbA1c <58 mmol/mol, 7.5%; and ΔHbA1c <11 mmol/mol, 1.0%. Logistic regression models by sex, age, diabetes mellitus duration, baseline HbA1c, ΔHbA1c, Δ postprandial glucose (PPG)/Δ fasting plasma glucose (FPG), baseline SUIT, baseline C-peptide, creatinine, weight, Δ weight and body mass index. ΔHbA1c = 12 weeks HbA1c–initial HbA1c; ΔPPG/Δ FPG = 12 weeks PPG–initial PPG/12 weeks FPG–initial FPG, Δ weight = 12 weeks weight–initial weight.

Table 4 | Factors affecting the occurrence of a hypoglycemic event in group 2

	Hypoglycemic event (n = 35)	No hypoglycemic event (n = 147)	P-value
Sex (men/women)	21/14	83/64	
Age (years)*	64.3 ± 9.6	60.2 ± 10.8	0.04
Duration of diabetes (years)*	13.5 ± 8.0	10.5 ± 5.8	0.01
Initial HbA1c, (mmol/mol, %)*	62 ± 8, 7.8 ± 0.7	67 ± 12, 8.3 ± 1.1*	<0.01
Initial fasting plasma glucose (mmol/L)*	7.8 ± 1.9	9.6 ± 2.5	<0.01
Initial post prandial glucose (mmol/L)	13.4 ± 3.4	14.5 ± 3.7	0.14
Initial C-peptide (ng/mL)	10.4 ± 38.9	2.8 ± 1.5	0.33
Body mass index (kg/m^2)	25.2 ± 3.6	25.9 ± 3.8	0.32
Weight (kg)	66.1 ± 11.9	69.5 ± 13.3	0.17

*P-value <0.05. HbA1c, glycated hemoglobin.

Although they operate by different mechanisms, both glimepiride and sitagliptin regulate insulin secretion from β-cells[2,26,27]. Sitagliptin, acting through increases in active GLP-1 and GIP levels, increases insulin secretion in a glucose-dependent manner through increased intracellular levels of cyclic adenosine 3′,5′-monophosphate, whereas glimepiride acts in a non-glucose dependent manner through the sulphonylurea receptor[12]. Sitagliptin has also been shown to reduce glucagon concentrations[26], and thus there is a risk of hypoglycemia if sitagliptin is added to ongoing glimepiride therapy. In the present study, group 2 suffered more frequent and more severe hypoglycemic events than group 1, even though group 2 had relatively higher HbA1c levels. Hypoglycemic events occurred more frequently during fasting states than after meals. In a study by Hermansen *et al.*[2], the combination therapy of sitagliptin, glimepiride and metformin resulted in hypoglycemia in 16.4% of patients. The present study showed that 19.2% of patients suffered hypoglycemia in group 2. Careful consideration should be taken when combining sitagliptin and sulfonylureas, especially in elderly patients, who have had diabetes for an extended period of time, and those with lower initial HbA1c and FPG levels. The incidences of gastrointestinal troubles and other side-effects were low.

After 60 weeks of treatment, sitagliptin led to significantly increased β-cell function as evaluated by the SUIT index. DPP-4 inhibitors reportedly increase β-cell differentiation and proliferation, enhance islet architecture remodeling, and preserve islet function in diabetic mice[28]. Experimental and clinical studies suggest that DPP-4 inhibitors could preserve and possibly reverse the progressive elimination of pancreatic β-cells, and the loss of insulin secretory capacity characteristic of type 2 diabetes[29]. However, longer-term studies in patients with type 2 diabetes mellitus are required, to show the clinical significance of these findings.

Type 2 diabetes mellitus arises from dysfunctional pancreatic β-cells, as well as from impaired insulin sensitivity[30,31]. Typically, islet function has already declined by approximately 50% by the time a patient is diagnosed with type 2 diabetes mellitus[30]. Reduced pancreatic β-cell mass as a result of accelerated apoptosis[31] seems to be at least partly responsible for impaired islet function. Most patients with type 2 diabetes mellitus in the Korean population are not obese and have a relatively low volume density of pancreatic β-cell mass[32]. Therefore, the effect of sitagliptin could be more powerful than expected in Korean patients and should be studied further in Asian populations including Korean patients. Although the present study is limited in that it is an observational study, it is meaningful for several reasons. First, although many studies have investigated sitagliptin using randomized prospective clinical trials, this was a study in a 'real practice' setting. Second, over 90% of the study participants completed a 60-week treatment regimen.

In summary, the present study showed that treatment with 100 mg sitagliptin once daily in dual combination with metformin and in triple combination with glimepiride plus metformin over a 60-week period appears to be effective and well-tolerated in Korean patients with type 2 diabetes who show inadequate glycemic control. A reduction in HbA1c was significantly associated with baseline HbA1c and C-peptide levels after adjusting for sex, age, duration of diabetes, BMI, weight, creatinine, ALT, AST and SUIT index. After 12 weeks, longer efficacy of sitag-

liptin was associated with older age (≥60 years), higher baseline HbA1c (group 1 ≥ 7.0% [53 mmol/mol], group 2 ≥ 7.5% [58 mmol/mol]) and slower reduction of ΔHbA1c (ΔHbA1c <1.0% [11 mmol/mol]) during 12 weeks. The higher incidence of hypoglycemic events seen in the group taking sitagliptin, glimepiride and metformin was associated with old age, extended duration of diabetes, lower initial HbA1c level, and lower FPG.

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REFERENCES

1. Turner RC, Cull CA, Frighi V, *et al.* Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; 281: 2005–2012.
2. Hermansen K, Kipnes M, Luo E, *et al.* Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab* 2007; 9: 733–745.
3. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 2002; 287: 360–372.
4. Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.
5. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998; 47: 1663–1670.
6. Bergman AJ, Stevens C, Zhou Y, *et al.* Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. *Clin Ther* 2006; 28: 55–72.
7. Herman GA, Bergman A, Stevens C, *et al.* Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2006; 91: 4612–4619.
8. Yasuda N, Inoue T, Nagakura T, *et al.* Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochem Biophys Res Commun* 2002; 298: 779–784.
9. Hinke SA, Kuhn-Wache K, Hoffmann T, *et al.* Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. *Biochem Biophys Res Commun* 2002; 291: 1302–1308.
10. Goldstein BJ, Feinglos MN, Lunceford JK, *et al.* Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2007; 30: 1979–1987.
11. Williams-Herman D, Johnson J, Teng R, *et al.* Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. *Diabetes Obes Metab* 2010; 12: 442–451.
12. Doar JW, Thompson ME, Wilde CE, *et al.* Diet and oral antidiabetic drugs and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. *Br Med J* 1976; 1: 498–500.
13. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342: 1887–1892.
14. Yamada Y, Fukuda K, Fujimoto S, *et al.* SUIT, secretory units of islets in transplantation: An index for therapeutic management of islet transplanted patients and its application to type 2 diabetes. *Diabetes Res Clin Pract* 2006; 74: 222–226.
15. Noguchi H, Yamada Y, Okitsu T, *et al.* Secretory unit of islet in transplantation (SUIT) and engrafted islet rate (EIR) indexes are useful for evaluating single islet transplantation. *Cell Transplant* 2008; 17: 121–128.
16. Nonaka K, Kakikawa T, Sato A, *et al.* Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008; 79: 291–298.
17. Mohan V, Yang W, Son HY, *et al.* Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India, and Korea. *Diabetes Res Clin Pract* 2009; 83: 106–116.
18. Arechavaleta R, Seck T, Chen Y, *et al.* Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2011; 13: 160–168.
19. Aschner P, Katzeff HL, Guo H, *et al.* Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes Obes Metab* 2010; 12: 252–261.
20. Scott R, Loeys T, Davies MJ, *et al.* Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2008; 10: 959–969.
21. Lim S, An JH, Shin H, *et al.* Factors predicting therapeutic efficacy of combination treatment with sitagliptin and metformin in type 2 diabetic patients: the COSMETIC Study. *Clin Endocrinol (Oxf)* 2012; 77: 215–223.
22. Harashima SI, Ogura M, Tanaka D, *et al.* Sitagliptin add-on to low dosage sulphonylureas: efficacy and safety of combination therapy on glycaemic control and insulin secretion capacity in type 2 diabetes. *Int J Clin Pract* 2012; 66(5): 465–476.
23. Nomiyama T, Akehi Y, Takenoshita H, *et al.* Contributing factors related to efficacy of the dipeptidyl peptidase-

4 inhibitor sitagliptin in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2012; 95(2): e27–e28.
24. Maeda H, Kubota A, Tanaka Y, *et al*. The safety, efficacy and predictors for HbA1c reduction of sitagliptin in the treatment of Japanese type 2 diabetes. *Diabetes Res Clin Pract* 2012; 95(1): e20–e22.
25. Esposito K, Cozzolino D, Bellastella G, *et al*. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2011; 13: 594–603.
26. Idris I, Donnelly R. Dipeptidyl peptidase-IV inhibitors: a major new class of oral antidiabetic drug. *Diabetes Obes Metab* 2007; 9: 153–165.
27. Del Prato S, Pulizzi N. The place of sulfonylureas in the therapy for type 2 diabetes mellitus. *Metabolism* 2006; 55: S20–S27.
28. Zhang X, Wang Z, Huang Y, *et al*. Effects of chronic administration of alogliptin on the development of diabetes and beta-cell function in high fat diet/streptozotocin diabetic mice. *Diabetes Obes Metab* 2011; 13: 337–347.
29. Gerich J. DPP-4 inhibitors: what may be the clinical differentiators? *Diabetes Res Clin Pract* 2010; 90: 131–140.
30. Wajchenberg BL. beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 2007; 28: 187–218.
31. Butler AE, Janson J, Bonner-Weir S, *et al*. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; 52: 102–110.
32. Yoon KH, Ko SH, Cho JH, *et al*. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. *J Clin Endocrinol Metab* 2003; 88: 2300–2308.