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Efficacy of Sitagliptin When Added to Ongoing Therapy in Korean Subjects with Type 2 Diabetes Mellitus

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Background: To evaluate the clinical efficacy of sitagliptin for reducing plasma glucose levels in Korean subjects with type 2 diabetes mellitus during a 14-week treatment period.
Methods: Our study design involved the addition of 100 mg sitagliptin once-daily to three ongoing combination therapy regimens and changing from glimepiride and metformin to sitagliptin and metformin.
Results: The addition of sitagliptin 100 mg/day produced a statistically significant reduction in mean HbA1c level (mean HbA1c reduction of 0.99±0.85%, $P<0.01$). In the group taking a combination of sitagliptin and metformin ($n=143$, initial mean HbA1c level=7.48%), the reductions in HbA1c, 2-hour postprandial glucose, and fasting glucose levels were 0.72±0.76% ($P<0.01$), 47±65 mg/dL ($P<0.01$), and 15±44 mg/dL ($P<0.01$), respectively. In the group taking a combination of sitagliptin, glimepiride, and metformin ($n=125$, initial mean HbA1c level=8.42%), the reductions in HbA1c, 2-hour postprandial glucose, and fasting glucose levels were 1.09±0.86% ($P<0.01$), 62±64 mg/dL ($P<0.01$), and 31±45 mg/dL ($P<0.01$), respectively. In the group taking a combination of sitagliptin, glimepiride, metformin, and α-glucosidase inhibitor ($n=63$, initial mean HbA1c level=9.19%), the reductions in HbA1c, 2-hour postprandial glucose, and fasting glucose levels were 1.27±0.70% ($P<0.01$), 72±65 mg/dL ($P<0.01$), and 35±51 mg/dL ($P<0.01$), respectively. In the group that had previous hypoglycemic events and that changed from glimepiride to sitagliptin, HbA1c level did not change but fasting glucose increased significantly (14±29 mg/dL, $P<0.01$).
Conclusion: Sitagliptin combination therapy for 14 weeks significantly improved glycemic control and was well-tolerated in Korean subjects with type 2 diabetes mellitus.

Keywords: Efficacy; Fasting plasma glucose; HbA1c; Sitagliptin; 2-hour postmeal glucose

INTRODUCTION

Treatment with a single oral hypoglycemic agent (OHA) is often unsuccessful at achieving glycemic control in subjects with type 2 diabetes mellitus (T2DM) [1,2]. The UK Prospective Diabetes Study (UKPDS) clearly demonstrated that T2DM is a progressive disease. After three years of treatment, for example, T2DM was adequately controlled with a single drug in only 50% of subjects, while this percentage had decreased to 25% after nine years [1,3]. It appears that many T2DM subjects will require combination therapy and the addition of an OHA.

Metformin is the most commonly used OHA, both as a monotherapy and in combination with other agents [4]. Metformin is a biguanide that acts primarily by lowering hepatic glucose production and may also improve insulin resistance [5,6]. Sulphonylureas improve blood glucose levels by stimu-

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lating insulin secretion from pancreatic β-cells in a non-glucose–dependent manner [7]. α-Glucosidase inhibitors slow the breakdown of disaccharides and other carbohydrates in the gut, delaying the absorption of monosaccharides (principally glucose and fructose) in the small intestine [8]. The most popular combination treatment is metformin and sulfonylurea [3]. In cases of inadequate glycemic control in dual combination therapy, α-glucosidase inhibitors may be added to this regimen. In this setting, the use of insulin is often the next therapeutic step. However, insulin requires parenteral administration, which many subjects find undesirable. Hence, there is a need for additional OHA options to improve the options for combination therapy.

Sitagliptin is a once-daily, orally active, potent, and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor approved in many countries for the treatment of subjects with T2DM. DPP-4 is an enzyme involved in the degradation of the intact (active) incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to inactive metabolites. GLP-1 and GIP are released into circulation by the intestine in response to a meal, and both hormones increase glucose-dependent insulin secretion. In addition, GLP-1 suppresses glucagon release. By inhibiting the degradation of active incretins, sitagliptin increases active incretin concentrations, thereby enhancing their glucoregulatory effects [2,9-11]. Sitagliptin is licensed for the treatment of T2DM in combination with metformin and/or a sulphonylurea or with a peroxisome proliferator-activated receptor (PPARγ) agonist (thiazolidinediones) [12]. In this study, we looked at the efficacy and safety of adding 100 mg of sitagliptin to ongoing treatment with metformin alone, to a dual combination treatment of glimepiride and metformin, or to a triple combination treatment of glimepiride, metformin, and acarbose in Korean subjects with T2DM. We also investigated the effect of changing from glimepiride and metformin to sitagliptin and metformin in patients that suffered recent hypoglycemic events.

METHODS

Subjects

This retrospective study involved a cohort of 598 subjects. We excluded 258 potential subjects because their medical history included steroids, surgery, hospitalization (for example for infection), cancer, or because they had stopped taking OHAs. Inclusion criteria were: 1) male or female, aged 45 to 75 years; 2) clinically diagnosed T2DM for at least six months; 3) ongoing treatment with the same OHA for at least six months; 4) inadequately controlled T2DM (HbA1c 7.0% to 10.0% or HbA1c 5.5% to 7.5% in the case of changing from glimepiride to sitagliptin); and 5) no abnormal laboratory findings for aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, or complete blood count (CBC). Laboratory data from 340 subjects were finally used for analysis. Data were collected from October 2008 to August 2009 through review of medical records and via interview where possible.

Methods

We collected cases where sitagliptin (100 mg once-daily) had been added to one of three ongoing treatment regimens: a group taking metformin (mean dose 876 mg/day); a group taking glimepiride (mean dose 3.95 mg/day) and metformin (mean dose 956 mg/day); and a group taking glimepiride (mean dose 4.63 mg/day), metformin (mean dose 1,464 mg/day), and acarbose (mean dose 282 mg/day). We also collected the data of patients whose treatment changed from glimepiride (mean dose 3.44 mg/day) and metformin (mean dose 722 mg/day) to sitagliptin (mean dose 100 mg/day) and metformin. Before changing medication, patients had HbA1c levels in the 5.5% to 7.5% range and had experienced a recent hypoglycemic event twice in the last month (SMBG or serum glucose level <70 mg/dL, with or without hypoglycemic symptoms).

Statistical analysis

Data are reported as mean±standard deviation. All statistical computations were performed using the software program PASW version 17.0 (SPSS Inc., Chicago, IL, USA). Comparisons were made using paired *t*-test and one-way ANOVA. A paired *t*-test was used to compare parameters before and after the addition of sitagliptin. One-way ANOVA was used for tertile analysis with baseline characteristics (C-peptide, age, and body mass index [BMI]) and changes in glucose. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The final analysis included 340 subjects (138 women, 202 men) divided according to treatment regimen into group 1 (metformin alone, *n*=132/385), group 2 (glimepiride plus metformin

combination therapy, n=135/385), group 3 (glimepiride plus metformin and acarbose or voglibose, n=73/385), and group 4 (glimepiride plus metformin combination therapy and hypoglycemia, n=45/385). Baseline characteristics of the subjects are summarized in Table 1. Before adding sitagliptin, the mean HbA1c level was 8.24±1.31%, the mean BMI was 25.6±3.6 kg/m^2 and the mean DM duration was 6.4 years. The mean duration of sitagliptin therapy was 14±4 weeks. Subjects in group 3 had the highest mean values for HbA1c, fasting plasma glucose (FPG), and 2-hour postprandial glucose (2h-PPG).

Efficacy

In the overall study (groups 1, 2, 3), treatment with 100 mg sitagliptin once daily significantly decreased HbA1c, FPG, and 2h-PPG values from baseline (mean HbA1c change -0.99±0.85%, P<0.01; mean FPG change -25±49 mg/dL, P<0.01; mean 2h-PPG change -58±65 mg/dL, P<0.01). The addition of sitagliptin also led to significant improvements in HbA1c, FPG, and 2h-PPG in each group. In the combination group taking sitagliptin and metformin (group 1: n=132, initial mean HbA1c=7.48%), the reductions in HbA1c, 2h-PPG, and FPG levels were 0.72±0.76% (P<0.01), 47±65 mg/dL (P<0.01), and 15±44 mg/dL (P<0.01), respectively. In the combination group of sitagliptin, sulfonylurea, and biguanide (group 2: n=135, initial mean HbA1c=8.42%), the reductions in HbA1c, 2h-PPG, and FPG levels were 1.09±0.86% (P<0.01), 62±64 mg/dL (P<0.01), and 31±45 mg/dL (P<0.01), respectively. In the combination group of sitagliptin, sulfonylurea, biguanide, and α-glucosidase inhibitor (group 3: n=73, initial mean HbA1c=9.19%), the reductions in HbA1c, 2h-PPG, and FPG levels were 1.27±0.70% (P<0.01), 72±65 mg/dL (P<0.01), and 35±51 mg/dL (P<0.01), respectively (Table 2).

We also analyzed the group whose medication was changed from glimepiride and metformin to sitagliptin and metformin (group 4). A majority of the group experienced an improvement in hypoglycemic events (71%, 32/45). No significant

Table 1. Baseline characteristics

Characteristic	Group 1+2+3 (n=340)	Group 1 (metformin only) (n=132)	Group 2 (metformin+ glimepiride) (n=135)	Group 3 (metformin+ glimepiride +acarbose) (n=73)	Group 4 (substitute sitagliptin for glimepiride) (n=45)
Gender, M/F	202/138	77/55	75/60	50/23	26/19
Age, yr	59.2±10.9	56.2±7.6	59.4±8.8	64.3±5.7	55.3±8.1
BMI, kg/m^2	25.6±3.6	24.8±2.1	25.5±1.9	27.2±3.1	24.6±2.8
Duration of diabetes, yr	6.4±3.1	5.3±2.1	6.6±2.7	8.0±2.1	4.2±1.9
HbA1c, %	8.24±1.31	7.48±1.00	8.42±1.13	9.19±1.08	6.65±0.38
FPG, mg/dL	168±45	150±35	170±44	197±48	97±23
Post prandial glucose, mg/dL	261.0±71	228±53	276±70	293±68	145±34
C-peptide, ng/mL	2.53±1.14	2.82±1.01	2.64±0.85	1.79±0.93	3.12±1.51
ALT, U/L	28.3±16.2	28.2±11.7	24.1±12.6	36.2±8.2	25.3±11.3
AST, U/L	24.7±12.0	24.9±8.3	23.4±10.1	26.7±9.4	25±11.1
BUN, mg/dL	16.5±5.0	16.8±4.6	16.4±2.3	16.1±3.1	15.3±2.1
Creatinine, mg/dL	0.91±0.20	0.92±0.12	0.90±0.11	0.89±0.11	0.87±0.11
Total cholesterol, mg/dL	172.7±36.7	171.3±24.3	174.1±21.5	172.6±31.4	170.1±24.7
Triglycerides, mg/dL	177.9±125.2	177.4±115.7	178.2±107.1	178.2±100.8	168±99.8
HDL-C, mg/dL	45.9±11.0	46.1±4.7	45.5±8.7	46.3±11.9	45.6±10.1
LDL-C, mg/dL	101.4±30.0	100.3±23.1	102.5±24.8	101.4±21.3	100.6±11.4

Data are presented as mean±standard deviation.
BMI, body mass index; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 2. Changes in HbA1c, FPG, 2h-PPG, and weight according to addition of sitagliptin to existing medication and substituting sitagliptin for sulfonylurea

Group	ΔHbA1c, %	ΔFPG, mg/dL	Δ2h-PPG, mg/dL	ΔWt, kg
Group 1 metformin+sitagliptin (n=132)	-0.72±0.76[a] (P<0.01)	-15±44[a] (P<0.01)	-47±65[a] (P<0.01)	-1.00±10.04 (P=0.28)
Group 2 glimepiride, metformin+sitagliptin (n=135)	-1.09±0.86[a] (P<0.01)	-31±45[a] (P<0.01)	-62±64[a] (P<0.01)	-0.82±8.11 (P=0.28)
Group 3 glimepiride, metformin, α-glucosidase inhibitor+sitagliptin (n=73)	-1.27±0.70[a] (P<0.01)	-35±51[a] (P<0.01)	-72±65[a] (P<0.01)	-2.00±16.51 (P=0.44)
Group 4 glimepiride & metformin→sitagliptin & metformin (n=45)	0.06±0.73 (P=0.53)	14±29[a] (P<0.01)	10±57 (P=0.25)	-1.08±12.21 (P=0.35)

Paired t-test.
Δ, (after adding or substituting sitagliptin)–(before adding or substituting sitagliptin); FPG, fasting plasma glucose; 2h-PPG, 2 hour-postprandial glucose.
[a]P value<0.05.

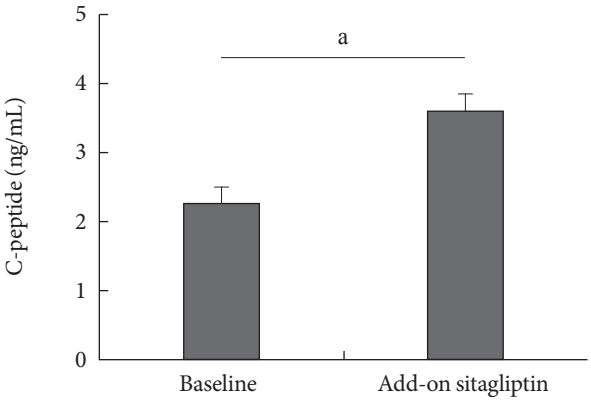

Fig. 1. Fasting C-peptide values after 14-weeks of addition of sitagliptin increased significantly from baseline (P<0.01). Paired t-test, [a]P value <0.01.

change was observed in HbA1c or 2h-PPG level; however, FPG increased significantly (14±29 mg/dL, P<0.01) (Table 2). If we defined a target HbA1c response level as less than 7.0%, the incidence of responders was 82% (108/132), 38% (51/135), and 15% (11/73) for groups 1, 2, and 3, respectively. If we defined an HbA1c response as a reduction of more than 1%, the incidence of responders was 32% (42/132), 47% (64/135), and 47% (34/73) for groups 1, 2, and 3 (initial HbA1c levels: group 1, 7.48%; group 2, 8.42%; group 3, 9.19%). We analyzed the differences between responders (HbA1c<7.0% or HbA1c reduced more than 1%) and non-responders but found no significant factors among initial c-peptide, DM duration, initial weight and initial BMI.

Treatment with sitagliptin significantly improved fasting c-peptide values for all study groups (Fig. 1). Sitagliptin had a neutral effect on plasma lipid level relative to baseline laboratory data (data not shown). We divided the study participants into three groups based on initial fasting C-peptide value: C-peptide<2.27 ng/mL; 2.27 ng/mL≤C-peptide<3.3 ng/mL; and C-peptide≥3.3 ng/mL. After 14 weeks of treatment, we did not observe any significant differences in HbA1c, FPG, or 2h-PPG levels between the tertiles (Fig. 2).

BMI, age, and sex were not independent predictors of response to sitagliptin (Fig. 3). Body weight decreased insignificantly in all treatment groups (groups 1, 2, 3, 4), and we inferred that this result differed from those of other studies because of our short study period (Table 2).

Safety

Sitagliptin was generally well-tolerated in this study, resulting in a 9.2% incidence of gastrointestinal trouble. Sitagliptin did not have to be discontinued because of gastrointestinal trouble since the symptoms were mild (diarrhea and abdominal distension). Addition of sitagliptin to an existing treatment resulted in a 0.8% incidence of hypoglycemia. Hypoglycemic events resulted in discontinuation of treatment in one study participant. We did not observe any other clinically significant changes in vital signs or laboratory findings in the study groups.

DISCUSSION

In this study, the addition of once daily sitagliptin led to clinically meaningful reductions in HbA1c, FPG, and 2h-PPG lev-

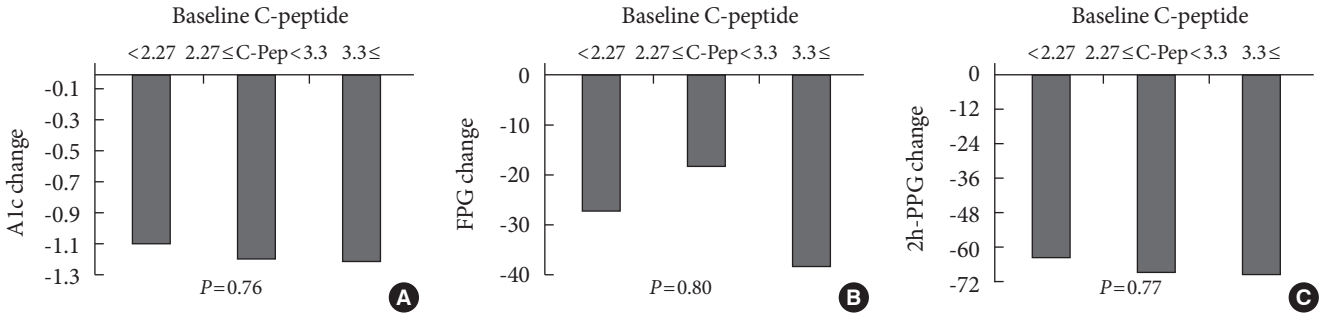

Fig. 2. Changes in HbA1c, fasting plasma glucose (FPG), and 2 hour-postprandial glucose (2h-PPG) values according to baseline C-peptide values were insignificant. (A) Changes in HbA1c according to baseline C-peptide. (B) Changes in FPG according to baseline C-peptide. (C) Changes in 2h-PPG according to baseline C-peptide. One-way ANOVA.

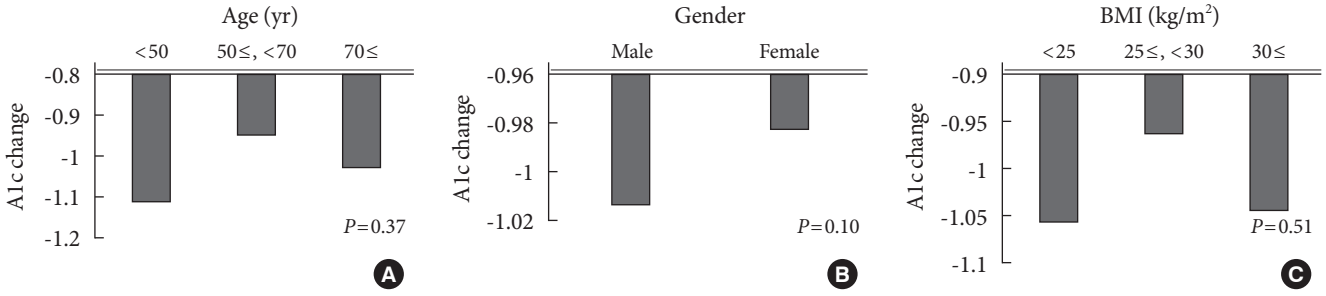

Fig. 3. Changes in HbA1c values according to baseline characteristics (age, gender, BMI) were insignificant. (A) Changes in HbA1c according to age. (B) Changes in HbA1c according to gender. (C) Changes in HbA1c according to BMI. One-way ANOVA. BMI, body mass index.

els in Korean subjects with T2DM with inadequate glycemic control with previous medications (HbA1c 7.0% to 10.0%). Compared to a previous multi-national study by Scott et al. [13], the reduction in HbA1c was similar in the sitagliptin and metformin combination group (HbA1c change, -0.72% vs. -0.73%).

In both the sitagliptin, sulfonylurea, and biguanide combination group (group 2: n=135, initial mean HbA1c=8.42%) and the sitagliptin, sulfonylurea, biguanide, and α-glucosidase inhibitor combination group (group 3: n=73, initial mean HbA1c=9.19%), the reductions in HbA1c, 2h-PPG, and FPG levels were significant. It was known that the higher was the initial level of HbA1c, the greater was the reduction in HbA1c level with the same medication. Although the initial levels of HbA1c, 2h-PPG, and FPG were higher in the multiple drug combination group compared to those in the sitagliptin and metformin group, this did not result in inferior reductions in the glucose levels of multidrug groups compared to that in the sitagliptin and metformin group (group 1: n=132, initial mean HbA1c=7.48%). The group that changed from glimepiride to sitagliptin and that previously had a hypoglycemic event, HbA1c did not increase but fasting glucose increased. In addition, the incidence of hypoglycemic events decreased. Changing from glimepiride to sitagliptin should therefore be considered for patients with recurrent fasting hypoglycemia and HbA1c levels relatively close to target due to glimepiride and metformin treatment.

The incidences of hypoglycemia, gastrointestinal troubles, and other side effects were low. In contrast to other studies, the tertile analysis of fasting c-peptide and BMI showed no correlation with reduction in HbA1c; however, it should be noted that the initial C-peptide levels in this study were greater than 1.0 ng/mL.

Treatment with sitagliptin improved fasting c-peptide levels. T2DM arises primarily from dysfunctional pancreatic β-cells rather than from impaired insulin sensitivity [14,15]. Typically, islet function has already declined by approximately 50% by the time a subject is diagnosed with T2DM [14]. Reduced pancreatic β-cell mass, largely because of accelerated apoptosis [15], seems to at least partially account for impaired islet function. Sulphonylureas also improve blood glucose lev-

els by stimulating insulin secretion; however, some kinds of sulphonylureas have been shown to induce apoptosis in a dose- and time-dependent manner in β-cell lines and islets of humans and rodents [16]. Reportedly, DPP-4 inhibitor increases β-cell differentiation and proliferation, enhances islet architecture remodeling, and preserves islet function in diabetic mice [17]. 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 T2DM [18]. However, long-term studies in subjects with T2DM are needed to demonstrate the clinical significance of these findings.

We note that our retrospective study has some limitations. First, we could not confirm that the prescribed lifestyle modifications involving changes in diet or exercise were performed by the participants. Second, medical compliance by the enrolled patients was not guaranteed. Third, because data were obtained through review of medical records, information of hypoglycemic events or the incidence of gastrointestinal trouble could have been omitted.

In the Korean population, most subjects with T2DM are not obese and have a relatively low volume density of pancreatic β-cell mass [19]. Our study is important because the effects of OHAs in Korean subjects are not the same as those seen in Western subjects, and because few studies have been conducted on the effects of sitagliptin in Korean subjects. Additional long-term studies in Korean subjects with T2DM are needed.

In summary, this study shows that treatment with 100 mg sitagliptin once daily appears to be effective and well tolerated in Korean subjects with T2DM who experience inadequate glycemic control with metformin alone, with a combination of glimepiride and metformin, or with a combination of glimepiride, metformin, and acarbose. Treatment with sitagliptin also appears to improve fasting c-peptide values in these subjects.

CONFLICTS OF INTEREST

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

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