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Comparison of Vildagliptin and Pioglitazone in Korean Patients with Type 2 Diabetes Inadequately Controlled with Metformin

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Background: We compared the efficacies of vildagliptin (50 mg twice daily) relative to pioglitazone (15 mg once daily) as an add-on treatment to metformin for reducing glycosylated hemoglobin (HbA1c) levels in Korean patients with type 2 diabetes.
Methods: The present study was a multicenter, randomized, active-controlled investigation comparing the effects of vildagliptin and pioglitazone in Korean patients receiving a stable dose of metformin but exhibiting inadequate glycemic control. Each patient underwent a 16-week treatment period with either vildagliptin or pioglitazone as an add-on treatment to metformin.
Results: The mean changes in HbA1c levels from baseline were –0.94% in the vildagliptin group and –0.6% in the pioglitazone group and the difference between the treatments was below the non-inferiority margin of 0.3%. The mean changes in postprandial plasma glucose (PPG) levels were –60.2 mg/dL in the vildagliptin group and –38.2 mg/dL in the pioglitazone group and these values significantly differed (P=0.040). There were significant decreases in the levels of total, low density lipoprotein, high density lipoprotein (HDL), and non-HDL cholesterol in the vildagliptin group but increases in the pioglitazone group. The mean change in body weight was –0.07 kg in the vildagliptin group and 0.69 kg in the pioglitazone group, which were also significantly different (P=0.002).
Conclusion: As an add-on to metformin, the efficacy of vildagliptin for the improvement of glycemic control is not inferior to that of pioglitazone in Korean patients with type 2 diabetes. In addition, add-on treatment with vildagliptin had beneficial effects on PPG levels, lipid profiles, and body weight compared to pioglitazone.

Keywords: Dipeptidyl peptidase 4 inhibitor; Metformin; Thiazolidinediones

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INTRODUCTION

The prevalence of diabetes continues to rapidly increase worldwide, including in Korea. In 2013, 382 million people around the world had diabetes and that number is expected to rise to 592 million by 2035 [1]. In Korea, the prevalence of diabetes has increased from 1.5% to 9.9% over the past 40 years [2] and diabetes and its complications have become a major cause of morbidity and mortality [3]. Therefore, public efforts to achieve effective glycemic control are necessary to reduce the impact of the global epidemic of diabetes.

In conjunction with lifestyle interventions, the use of metformin as a first-line treatment for type 2 diabetes is well established [4]. However, when additional treatment is required to achieve or maintain glycosylated hemoglobin (HbA1c) levels at <7%, the Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes recommends concomitant treatment with sulfonylurea, a thiazolidinedione (TZD), a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium/glucose cotransporter 2 inhibitor, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin [4]. As a monotherapy and in combination with metformin, TZDs effectively reduce HbA1c levels, and thus are widely used to treat patients with diabetes [5]. A recently published study from Korea regarding the efficacy of pioglitazone, which is a TZD, as an add-on treatment to metformin found that the mean change in HbA1c levels from baseline was −0.74% [6]. However, despite the efficacies of TZDs in lowering HbA1c levels, they are associated with weight gain [7], decreased bone mineral density [8], and an increased risk of heart failure [9].

Vildagliptin (Galvus; Novartis, Basel, Switzerland), which is a selective inhibitor of DPP-4, improves glycemic control and has a potentially favorable tolerability profile in adult patients with type 2 diabetes [10]. Furthermore, a number of studies have demonstrated the potential for synergistic action when vildagliptin and metformin are administered in combination. Metformin effectively inhibits DPP-4 activity in patients with type 2 diabetes but the activities of insulin and total GLP-1 remain unchanged [11]. The inhibition of DPP-4 by vildagliptin in conjunction with the activities of metformin improve β-cell function and postprandial insulin sensitivity in type 2 diabetes patients [12]. In addition, patients exposed to metformin for prolonged periods of time exhibit an enhancement of basal and nutrient-induced GLP-1 secretion [13,14]. These findings may explain the synergistic effects of vildagliptin in terms of decreased HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) levels in metformin-treated patients.

Both insulin deficiency and insulin resistance are involved in the pathogenesis of type 2 diabetes. Historically in Korea, deficits in early-phase insulin secretion tended to be the initial clinical abnormality that signals the development of type 2 diabetes [15], and thus the focus of treatment has focused on insulin secretion rather than insulin resistance. More recently, the prevalence of obesity in Korea has gradually increased to over 30% [16] and the importance of pharmacotherapy for the treatment of insulin resistance has emerged. Therefore, it is necessary to assess the efficacies of DPP-4 inhibitors, which increase insulin secretion, and TZDs, which improve insulin resistance, for the treatment of patients with type 2 diabetes in Korea.

We assessed and compare the efficacies and tolerabilities of vildagliptin and pioglitazone in Korean patients with type 2 diabetes that exhibited inadequate glycemic control with their existing metformin monotherapy.

METHODS

Study design

The present study was a multicenter, open-label, randomized, active-controlled study conducted at 16 centers in South Korea. The duration of the study was 17 weeks (five visits) and included a 1-week screening period (visits 1 to 2) and a 16-week open-label treatment period. Each patient attended an initial screening visit during which the inclusion and exclusion criteria were assessed. At visit 2, all eligible patients were randomly assigned to receive either vildagliptin (50 mg twice daily, $n=117$) or pioglitazone (15 mg once daily, $n=111$) as an add-on treatment to metformin using a 1:1 ratio. After the randomization procedure, the patients returned to the clinic for the following assessments: visit 3 (week 4), visit 4 (week 12), and visit 5 (week 16). The first patient visit took place on December 22, 2009 and the final patient visit took place on July 9, 2012. All participants provided written informed consent prior to participating. The protocol was approved by the institutional review board at each study site and the study was conducted in accordance with the Declaration of Helsinki (Clinical trial reg. no. NCT01882907).

Study population

Males and females between 18 and 80 years of age with type 2

diabetes were eligible to participate. Additional inclusion criteria consisted of an HbA1c level of 7.0% to 11.0% and an FPG level of <270 mg/dL at the initial screening (visit 1) and treatment with a stable dose of metformin (≥1,000 mg/day) for 4 weeks prior to the initiation of the study.

Patients were excluded from the present study based on the following criteria: pregnant or nursing females or females planning to become pregnant during the study period; reproductive females willing to prevent conception; patients with type 1 diabetes or diabetes due to a secondary cause; those with severe diabetes complications, active infections that could have influenced glycemic status in the 4 weeks prior to visit 1, Torsades de Pointes (clinically significant and persistent ventricular tachycardia and ventricular fibrillation), myocardial infarction, unstable angina, stroke, congestive heart failure (all New York Heart Association classes I to IV), liver disorders such as cirrhosis or chronic hepatitis, or hypersensitivity or allergic reactions to pioglitazone and/or rosiglitazone; those who had undergone percutaneous coronary intervention within the previous 3 months or coronary artery bypass surgery within the previous 6 months; patients receiving insulin treatment without a concomitant illness over the previous 4 weeks; those who had used glucocorticoids within the previous 8 weeks (over 7 days); and those with alanine aminotransferase or aspartate aminotransferase levels >2.5 times the upper limit of normal (ULN), direct bilirubin levels >1.3 times ULN, serum creatinine levels >1.5 mg/dL, and/or clinically abnormal thyroid-stimulating hormone levels.

Study assessments

The body weights and vital signs of each patient were measured at each visit. Fasting lipid profiles (triglyceride [TG], total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], and non-HDL-C levels), standard hematology and biochemistry laboratory assessments, and homeostasis model assessment as an index of insulin resistance (HOMA-IR) and the homeostatic model assessment β-cell function (HOMA-β) were obtained at the initial screening and at weeks 4, 12, and 16. HOMA-IR and HOMA-β represent insulin resistance and pancreatic β-cell function, respectively, and were calculated as follows: HOMA-IR=fasting insulin (FI, μU/mL)×FPG (mmol/L)/22.5, and HOMA-β=20×FI (μU/mL)/[FPG (mmol/L)–3.5]. In addition, electrocardiograms were performed at the screening and week 16.

At each post-baseline visit, all adverse events (AEs) were recorded and assessed for severity and a possible relationship to the study medications. Patients were provided with glucose monitoring devices to determine hypoglycemia, which was defined as symptoms suggestive of low glucose confirmed by a self-monitored glucose measurement of <56 mg/dL. Hypoglycemia was classified into three types: (1) asymptomatic hypoglycemia, which was a glucose level <56 mg/dL without typical symptoms; (2) hypoglycemia grade 1 (mild hypoglycemia), which was typical symptoms and a confirmed glucose level <56 mg/dL; and (3) hypoglycemia grade 2 (severe hypoglycemia), which was an event requiring the assistance of another person regardless of glucose levels.

The primary efficacy parameter was changes in HbA1c levels during the 16-week treatment period following the administration of either vildagliptin (50 mg twice daily) or pioglitazone (15 mg once daily) as an add-on treatment to metformin in the intention-to-treat (ITT) population. The secondary efficacy parameters included assessments of FPG and PPG levels, lipid profiles, and body weight. The mean changes in the HOMA-IR and the HOMA-β from baseline to 16 weeks were also investigated.

Statistical analyses

We compared the efficacies of vildagliptin (50 mg twice daily) to pioglitazone (15 mg once daily) in terms of reducing HbA1c levels from baseline to week 16 (non-inferiority margin: upper limit of the 97.5% confidence interval <0.3%). The primary and secondary endpoints were assessed in the ITT population and missing data were accounted for using the later observation carried forward method. Of the 287 patients who consented to the participation in this study, 59 were excluded during the screening and 228 were randomized. The safety population consisted of the 228 randomized patients that received at least one dose of study drug and had at least one post-baseline safety assessment. After excluding five patients who had no efficacy data available to assess their primary or secondary endpoints, the ITT population consisted of the 223 randomized patients that received at least one dose of a study drug and had at least one post-baseline assessment of the primary or secondary efficacy variables. The analyses of all efficacy endpoints were conducted with paired *t*-tests and a $P<0.05$ was considered to indicate statistical significance. The incidence rates of hypoglycemic events and other AEs through week 16 were assessed using descriptive statistics and used to determine the safety population.

RESULTS

Patients studied

The flow of the study patients from the initial screening to the study endpoint is summarized in Fig. 1. Of the initial 287 patients who were recruited, 49 were excluded during the screening process and 228 were randomly assigned to a drug group. Table 1 summarizes the demographic and baseline metabolic characteristics of the patients in the randomized population. The mean HbA1c levels of the vildagliptin (7.98%±0.77%) and

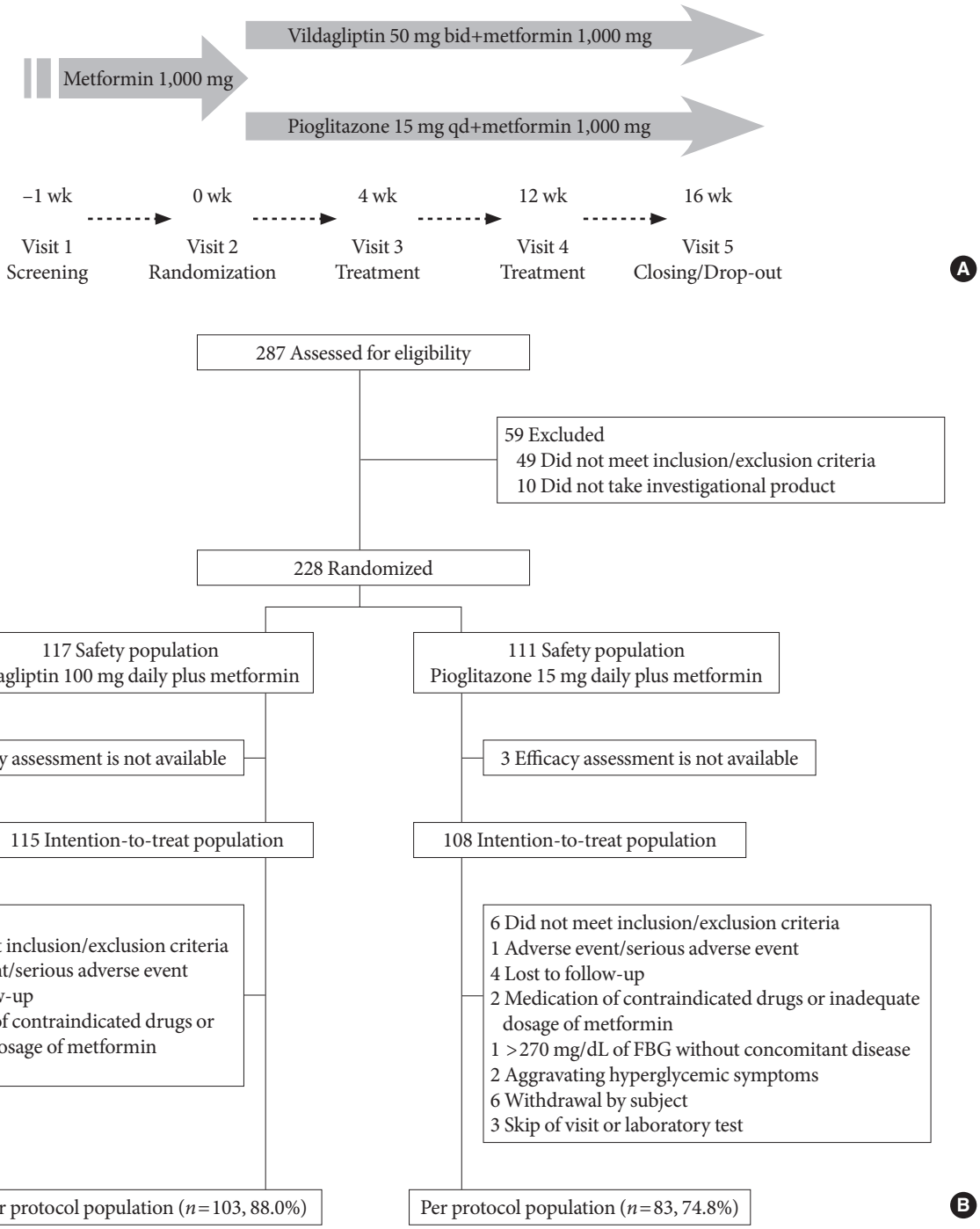

Fig. 1. (A) Study design. (B) Patient disposition. bid, twice daily; qd, once daily; FBG, fasting blood glucose.

Table 1. Baseline characteristics

Characteristic	Vildagliptin 50 mg bid+metformin	Pioglitazone 15 mg qd+metformin	*P* value
Age, yr	55.2±9.8	53.9±9.1	0.293
Sex			0.938
Male	50 (42.7)	48 (43.2)	
Female	67 (57.3)	63 (56.8)	
Body weight, kg	65.00±11.29	64.87±11.56	0.937
Body mass index, kg/m^2	24.9±3.2	25.0±3.3	0.769
Disease duration, mo	68.3±62.0	60.2±58.6	0.316
Glycosylated hemoglobin, %	7.98±0.77	8.08±0.98	0.389
Fasting plasma glucose, mg/dL	147.8±38.6	151.3±35.5	0.480
Postprandial glucose, mg/dL	274.9±73.8	268.4±80.9	0.530
Triglyceride, mg/dL	142.8±69.7	144.7±68.8	0.836
Total cholesterol, mg/dL	170.0±34.5	173.9±34.9	0.409
LDL-C, mg/dL	98.0±28.7	100.2±32.0	0.594
HDL-C, mg/dL	46.3±11.8	48.3±11.6	0.214
Non-HDL-C, mg/dL	123.9±32.1	125.2±34.7	0.769

Values are presented as mean±standard deviation or number (%).
bid, twice daily; qd, once daily; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

pioglitazone (8.08%±0.98%) groups at baseline (visit 1) did not significantly differ (P=0.389). The FPG and PPG levels, lipid profiles, and body weights of the two groups were also similar at baseline and there were no significant differences in medication history between the two groups (Supplementary Table 1).

Primary endpoint

The time-courses of the changes in mean HbA1c levels in the ITT population during the 16-week treatment period following the administration of either vildagliptin (50 mg twice daily) or pioglitazone (15 mg once daily) as an add-on treatment to metformin in patients with type 2 diabetes are provided in Fig. 2B. The mean changes in HbA1c levels from baseline to week 16 were –0.94% in the vildagliptin group and –0.6% in the pioglitazone group (P=0.010) (Fig. 2A). The between-group difference (ITT population) in the changes in HbA1c levels from baseline to week 16 was 0.34%±0.96%. Based on a non-inferiority margin of 0.3%, this finding establishes the non-inferiority of vildagliptin relative to pioglitazone as an add-on therapy to metformin.

Secondary endpoints

The time-courses of the mean changes in FPG and PPG levels during the 16-week treatment period following the administration of either vildagliptin (50 mg twice daily) or pioglitazone (15 mg once daily) as an add-on treatment to metformin in patients with type 2 diabetes are provided in Fig. 2C and D. The mean changes in FPG from baseline to week 16 were –20.4 mg/dL in the vildagliptin group and –15.0 mg/dL in the pioglitazone group (P=0.273). The mean changes in PPG levels from baseline to week 16 were –60.2 mg/dL in the vildagliptin group and –38.2 mg/dL in the pioglitazone group (P=0.040).

In the ITT population, the fasting lipid levels of the two treatment groups were very similar at baseline. The fasting TG, total cholesterol, LDL-C, HDL-C, and non-HDL-C levels averaged 142.8±69.7, 170.0±34.5, 98.0±28.7, 46.3±11.8, and 123.9±32.1 mg/dL, respectively, in the vildagliptin group and 144.7±68.8, 173.9±34.9, 100.2±32.0, 48.3±11.6, and 125.2±34.7 mg/dL, respectively, in the pioglitazone group. There were significant decreases in the levels of total cholesterol, LDL-C, HDL-C, and non-HDL-C in the vildagliptin group (mean changes from baseline to endpoint: –6.5±25.1, –6.0±21.2, –0.3±8.6, and –8.4±24.7 mg/dL, respectively) but increases in the pioglitazone group (mean changes from baseline to endpoint: 9.6±33.8, 5.4±30.4, 3.7±10.3, and 5.8±32.7 mg/dL, respectively). The fasting TG levels in the vildagliptin group exhibited a greater decrease (–9.2±56.0 mg/dL) than those of the pioglitazone group (–4.8±67.8 mg/dL) and the mean changes in total, LDL-

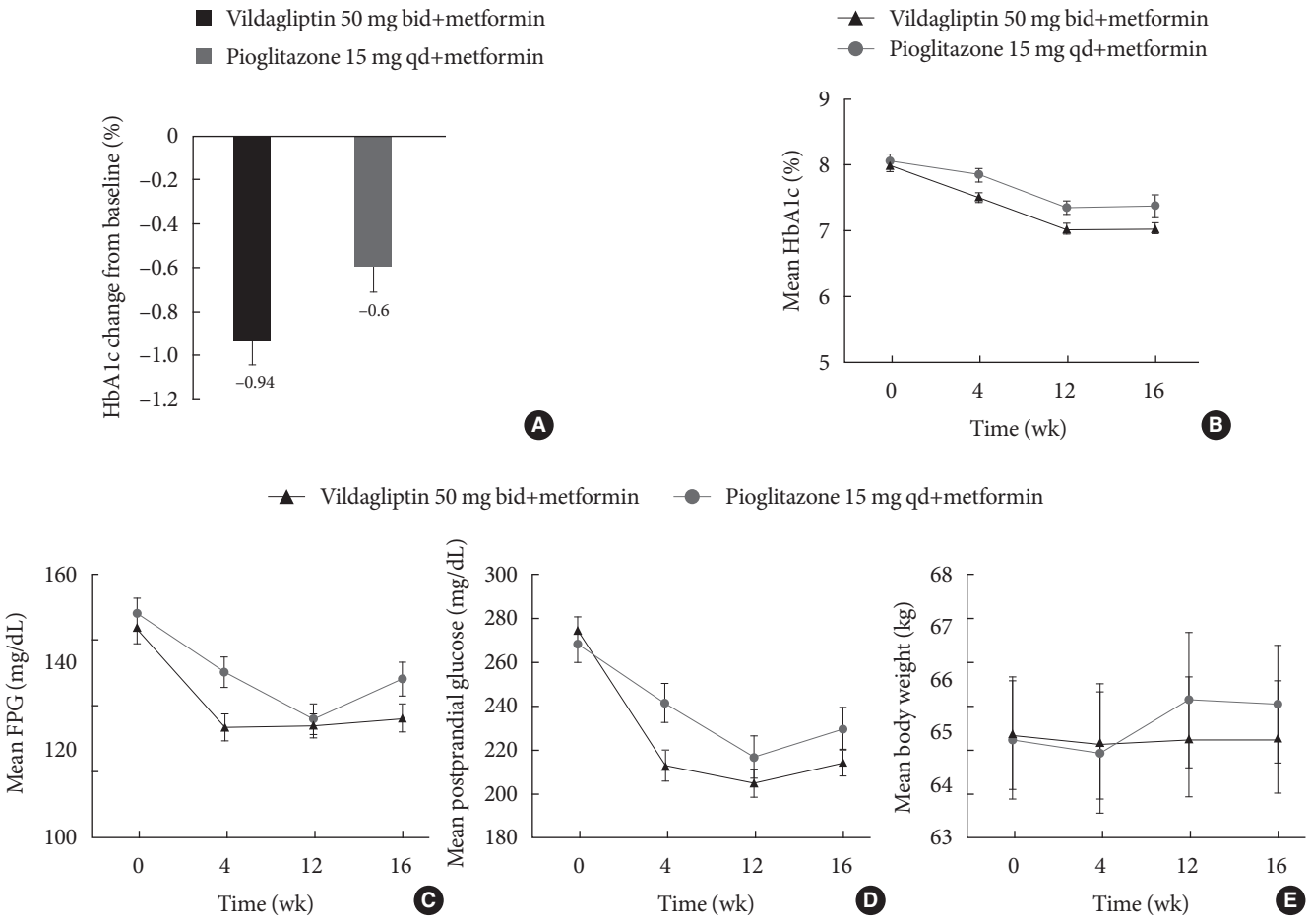

Fig. 2. (A) Change in glycosylated hemoglobin (HbA1c) from baseline at 16 weeks. Time-course of mean HbA1c (B), mean fasting plasma glucose (FPG) (C), mean postprandial glucose (D), and mean body weight (E) during 16-week treatment with vildagliptin (closed triangles) or pioglitazone (closed circles) in patients with type 2 diabetes continuing their previous stable metformin dose regimen. Values are presented as mean±standard error. bid, twice daily; qd, once daily.

C, HDL-C, and non-HDL-C from baseline to week 16 were significantly different between the two groups (all P values <0.05).

The time-courses of the changes in mean body weight during the 16-week treatment period following the administration of either vildagliptin (50 mg twice daily) or pioglitazone (15 mg once daily) as an add-on treatment to metformin in patients with type 2 diabetes are provided in Fig. 2E. The mean changes in body weight from baseline to week 16 were −0.07 kg in the vildagliptin group and 0.69 kg in the pioglitazone group, which were significantly different from each other (P=0.002).

The mean changes in HOMA-IR and HOMA-β from baseline to 16 weeks were analyzed (data not shown). The mean changes in HOMA-IR from baseline were −0.06±2.92 in the vildagliptin group and −3.33±25.16 in the pioglitazone group (P=0.183). And the mean changes in HOMA-β from baseline were 9.77±28.10 in the vildagliptin group and −24.26±294.88 in the pioglitazone group (P=0.183). The mean changes in insulin from baseline were 0.36±6.95 in the vildagliptin group and −8.21±70.06 in the pioglitazone group (P=0.209) and the mean changes in C-peptide were 0.07±0.84 in the vildagliptin group and −0.24±1.14 in the pioglitazone group (P=0.023).

Tolerability and safety

The incidence rates of hypoglycemic events through week 16 are summarized in Table 2. Two patients (1.71%) in the vildagliptin group and three patients (2.70%) in the pioglitazone suffered a hypoglycemic event but these rates did not significantly differ. Likewise, the incidence rates of AEs did not differ between the two groups over the 16-week treatment period.

Table 2. Hypoglycemia (safety population)

Hypoglycemia	Vildagliptin 50 mg bid+metformin (n=117)	Pioglitazone 15 mg qd+metformin (n=111)	P value
Overall	2 (1.7)	3 (2.7)	0.677
Asymptomatic hypoglycemia	2 (1.7)	1 (0.9)	1.000
Hypoglycemia grade 1	0	2 (1.8)	0.236
Hypoglycemia grade 2	0	1 (0.9)	0.487

Values are presented as number (%). Asymptomatic hypoglycemia was defined as glucose level <56 mg/dL but without typical symptoms. Hypoglycaemia grade 1 (mild hypoglycemia) was defined as typical symptoms and a confirmed glucose level <56 mg/dL. Hypoglycaemia grade 2 (severe hypoglycemia) was defined as an event requiring the assistance of another person regardless of glucose levels.
bid, twice daily; qd, once daily.

Both study drugs were relatively safe and well-tolerated and there were no serious drug-related AEs or death. The most commonly occurring AEs in both groups were common colds, upper respiratory tract infections, nausea, diarrhea, dyspepsia, and dizziness (Supplementary Table 2).

DISCUSSION

As an add-on treatment to metformin, vildagliptin is not inferior to pioglitazone in terms of reducing HbA1c levels from baseline to week 16. In addition, it has a beneficial influence on PPG levels, lipid profiles, and body weight compared to pioglitazone. We did not observe any incidences of severe hypoglycemia and the rates of hypoglycemia and AEs did not differ between the two groups. These findings are similar to those of previous Italian studies [17,18]. In the present study, there was a greater decrease in fasting TG levels in patients treated with vildagliptin than in patients treated with pioglitazone (15 mg per day). It could be the result of better glycemic control in the vildagliptin group than in the pioglitazone group. In contrast, an Italian study found that the reduction in fasting TG levels was significantly greater following pioglitazone treatment (30 mg per day) than after vildagliptin treatment as an add-on to metformin [17]. The favorable influence of pioglitazone on TG and HDL levels has been well established [19].

In the present study, compared to pioglitazone, vildagliptin add-on treatment had a beneficial effect on PPG levels and HbA1c levels in Korean patients with type 2 diabetes. Similar to vildagliptin, sitagliptin was more effective than pioglitazone in Japanese patients with type 2 diabetes who had been treated with metformin and/or sulfonylurea [20]. In that multicenter randomized trial, 130 patients with type 2 diabetes whose diabetes had been inadequately controlled with metformin and/or sulfonylurea were assigned to either a sitagliptin group (50 mg/day) or a pioglitazone group (15 mg/day), and they were followed up for 24 weeks. At 16 weeks, if the HbA1c levels of the subjects exceeded 6.5%, then the dose of sitagliptin or pioglitazone was increased by up to 100 or 30 mg/day, respectively. At 24 weeks, the mean changes in HbA1c levels from baseline were –0.86% in the sitagliptin group and –0.58% in the pioglitazone group (P=0.024).

The hypoglycemic effects of DPP-4 inhibitors seem to be more effective for Asians than Caucasians, which may be due to the relatively low body mass index (BMI) of Asians [21]. In fact, it has been reported that the differences in insulin sensitivity and β-cell responses between Japanese and Caucasian patients can be explained by BMI [21]. Moreover, Japanese patients with type 2 diabetes are characterized by a larger decrease in insulin secretion and less attribution of insulin resistance [22]. These findings support the hypothesis that the effects of DPP-4 inhibitors would be superior compared to TZDs in Asians.

The peroxisome proliferator-activated receptor γ (PPAR-γ) receptor is the molecular target of the TZD class of anti-diabetes drugs, which includes pioglitazone and rosiglitazone [23]. TZDs enhance insulin sensitivity and improve glycemic control in patients with type 2 diabetes [24] but they also induce AEs such as bone loss, weight gain, and fluid retention, which can exacerbate congestive heart failure. Therefore, the development of the next generation of PPAR-γ ligands with selective therapeutic activities and no AEs is needed.

In the present study, the mean changes in HOMA-IR and HOMA-β from baseline to 16 weeks showed that pioglitazone improved insulin resistance more effectively than vildagliptin and vildagliptin improved insulin secretion more effectively than pioglitazone, although these differences were not statistically significant. A Japanese study found that sitagliptin had similar effects [20].

In humans, chronic treatment with metformin enhances both basal and nutrient-induced GLP-1 secretion [13,14] although its acute administration does not increase circulating levels of GLP-1 [11,13,14,25,26]. These results reinforce the findings of clinical reports describing improved glycemic control in subjects treated with a combination of metformin and DPP-4 inhibitors, which appears to depend on the additive effects of increased GLP-1 release and decreased GLP-1 degradation [14]. Thus, future studies should investigate the underlying mechanisms involved in the metformin-induced enhancement of GLP-1 secretion.

It is an ongoing question in real clinical practice whether to select a DPP-4 inhibitor or a TZD as an add-on therapy to metformin [4]. The medications of patients with type 2 diabetes using oral hypoglycemic agents prescribed at general hospitals in Korea were investigated at approximately the same time the present study was conducted [27] and the frequency of prescriptions for metformin plus a DPP-4 inhibitor (24.3%) was higher than that of metformin plus a TZD (13.6%).

The present study had several limitations. First, the 16-week treatment period may have been too brief to accurately determine the effects of the add-on treatments. Second, the dose of pioglitazone was limited to 15 mg/day. Most of the studies performed in other ethnic groups compared 30 mg/day of pioglitazone with 100 mg/day of vildagliptin [17,18,28]. Thus, additional long-term prospective studies and further trials investigating the effects of higher doses of pioglitazone (30 mg per day) as an add-on treatment are required to confirm our findings.

Unfortunately, 15 mg/day of pioglitazone is the highest dose covered by the Korea national health insurance system during the study period. Although up to 30 mg/day of pioglitazone is approved for clinical use in Korea and is allowed for patients who have a poor response with a dose of 15 mg/day, the use of higher dose incurs an additional cost for patients (without insurance reimbursement) [6]. For this reason, the efficacy and safety of higher doses of pioglitazone could not be compared in this study.

In conclusion, as an add-on treatment to metformin, vildagliptin is as effective and well-tolerated as pioglitazone and also has beneficial effects on PPG levels, lipid profiles, and body weight. Add-on therapy with vildagliptin for Korean patients with type 2 diabetes taking a stable dose of metformin may be more effective than pioglitazone.

CONFLICTS OF INTEREST

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REFERENCES

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnen-

kamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103:137-49.
2. Kim DJ. The epidemiology of diabetes in Korea. Diabetes Metab J 2011;35:303-8.
3. International Diabetes Federation. IDF diabetes atlas. 6th ed. Brussels: International Diabetes Federation; 2013.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-9.
5. Stumvoll M, Haring HU. Glitazones: clinical effects and molecular mechanisms. Ann Med 2002;34:217-24.
6. Jin SM, Park CY, Cho YM, Ku BJ, Ahn CW, Cha BS, Min KW, Sung YA, Baik SH, Lee KW, Yoon KH, Lee MK, Park SW. Lobeglitazone and pioglitazone as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial with a 28-week extension. Diabetes Obes Metab 2015;17: 599-602.
7. Hermansen K, Mortensen LS. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. Drug Saf 2007;30:1127-42.
8. Schwartz AV. Diabetes, TZDs, and bone: a review of the clinical evidence. PPAR Res 2006;2006:24502.
9. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370:1129-36.
10. Profit L, Chrisp P, Nadin C. Vildagliptin: the evidence for its place in the treatment of type 2 diabetes mellitus. Core Evid 2008;3:13-30.
11. Lindsay JR, Duffy NA, McKillop AM, Ardill J, O'Harte FP, Flatt PR, Bell PM. Inhibition of dipeptidyl peptidase IV activity by oral metformin in type 2 diabetes. Diabet Med 2005;22: 654-7.
12. Ahren B, Pacini G, Foley JE, Schweizer A. Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. Diabetes Care 2005; 28:1936-40.
13. Mannucci E, Tesi F, Bardini G, Ognibene A, Petracca MG, Ciani S, Pezzatini A, Brogi M, Dicembrini I, Cremasco F, Messeri G, Rotella CM. Effects of metformin on glucagon-like peptide-1 levels in obese patients with and without type 2 diabetes. Diabetes Nutr Metab 2004;17:336-42.
14. Migoya EM, Bergeron R, Miller JL, Snyder RN, Tanen M, Hilliard D, Weiss B, Larson P, Gutierrez M, Jiang G, Liu F, Pryor KA, Yao J, Zhu L, Holst JJ, Deacon C, Herman G, Thornberry N, Amatruda J, Williams-Herman D, Wagner JA, SinhaRoy R. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. Clin Pharmacol Ther 2010; 88:801-8.
15. Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590-3.
16. Kim CS, Ko SH, Kwon HS, Kim NH, Kim JH, Lim S, Choi SH, Song KH, Won JC, Kim DJ, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence, awareness, and management of obesity in Korea: data from the Korea national health and nutrition examination survey (1998-2011). Diabetes Metab J 2014;38:35-43.
17. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab 2008;10:82-90.
18. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab 2009;11:589-95.
19. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, Hanefeld M. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48:1093-104.
20. Takihata M, Nakamura A, Tajima K, Inazumi T, Komatsu Y, Tamura H, Yamazaki S, Kondo Y, Yamada M, Kimura M, Terauchi Y. Comparative study of sitagliptin with pioglitazone in Japanese type 2 diabetic patients: the COMPASS randomized controlled trial. Diabetes Obes Metab 2013;15:455-62.
21. Moller JB, Pedersen M, Tanaka H, Ohsugi M, Overgaard RV, Lynge J, Almind K, Vasconcelos NM, Poulsen P, Keller C, Ueki K, Ingwersen SH, Pedersen BK, Kadowaki T. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. Diabetes Care 2014;37:796-804.
22. Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Mat-

suura T, Suzuki H, Kurose T, Yamada Y, Seino Y. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 2004;53:831-5.
23. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem 2000; 43:527-50.
24. Cariou B, Charbonnel B, Staels B. Thiazolidinediones and PPARgamma agonists: time for a reassessment. Trends Endocrinol Metab 2012;23:205-15.
25. Cuthbertson J, Patterson S, O'Harte FP, Bell PM. Investigation of the effect of oral metformin on dipeptidylpeptidase-4 (DPP-4) activity in type 2 diabetes. Diabet Med 2009;26:649-54.
26. Green BD, Irwin N, Duffy NA, Gault VA, O'Harte FP, Flatt PR. Inhibition of dipeptidyl peptidase-IV activity by metformin enhances the antidiabetic effects of glucagon-like peptide-1. Eur J Pharmacol 2006;547:192-9.
27. Suk JH, Lee CW, Son SP, Kim MC, Ahn JH, Lee KJ, Park JY, Shin SH, Kwon MJ, Kim SS, Kim BH, Lee SH, Park JH, Kim IJ; Relationship between cardiovascular disease and brachial-ankle pulse wave velocity (baPWV) in patients with type 2 diabetes (REBOUND) Study Group. Current status of prescription in type 2 diabetic patients from general hospitals in Busan. Diabetes Metab J 2014;38:230-9.
28. Kaur K, Kaur R, Mittal N, Arora S, Kaushal S. Comparison of efficacy of add-on therapy of vildagliptin versus pioglitazone among type 2 diabetes mellitus patients inadequately controlled on dual therapy of metformin plus sulfonylurea. Asian J Med Sci 2014;5:77-81.