Original Article

15 mg Pioglitazone 투여로 혈당이 조절되지 않는 제2형 당뇨병 환자에서 Pioglitazone 증량이 혈당 조절에 미치는 효과에 대한 후향적, 관찰연구

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Retrospective Observational Dose-Titration Study of Subjects with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on 15 mg of Pioglitazone

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Abstract

Background: The 30 mg pioglitazone tablet was recently introduced in Korea; no study has yet compared its glucose-lowering or weight gain effects to the 15 mg tablet in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: The electronic medical records of 45 patients with T2DM with glycated hemoglobin (HbA1c) levels > 7.0%, despite taking 15 mg/day pioglitazone and a stable dose of other diabetes drugs for 3 months, were retrospectively reviewed.

Results: After dose up-titration, HbA1c levels decreased at 3- and 6-month follow-ups compared with baseline (8.5% at baseline vs. 8.2% at 3 months vs. 7.9% at 6 months; baseline vs. 3 months, $P = 0.106$; baseline vs. 6 months, $P = 0.005$; 3 months vs. 6 months, $P = 0.096$). In the subgroup analysis of 36 patients taking pioglitazone, sulfonylurea, and metformin, HbA1c levels also decreased at 3- and 6-month follow-ups compared with baseline (8.5 % vs. 8.2 % vs. 7.9%; baseline vs. 3 months, $P = 0.289$; baseline vs. 6 months, $P = 0.014$; 3 months vs. 6 months, $P = 0.232$). There was no significant body weight change (70.8 kg vs. 70.7 kg vs.

71.0 kg).

Conclusion: Up-titrating from 15 mg to 30 mg of pioglitazone in patients with inadequate glycemic control (HbA1c > 9%) who were also taking sulfonylurea and metformin showed additive glucose-lowering effects without significant weight gain in Korean patients with T2DM.

Keywords: Body weight, Diabetes mellitus, Glycated hemoglobin, Thiazolidinediones

INTRODUCTION

Pioglitazone, a type of thiazolidinedione, is known to improve insulin sensitivity, glycemic control, dyslipidemia, hypertension, and microalbuminuria in patients with type 2 diabetes mellitus (T2DM) [1]. Pioglitazones are effective as combination therapy in patients who have failed monotherapy and are included as an option in the American Diabetes Association consensus algorithm [2]. The 2011 Clinical Practice Guidelines for Type 2 Diabetes by the Korean Diabetes Association recommended metformin as the initial preferred monotherapy; in cases with glycated hemoglobin (HbA1c) levels greater than 7.5%, they recommended metformin-based dual therapies with sulfonylurea, pioglitazone, or dipeptidyl peptidase 4 inhibitors as an initial regimen [3].

Although several studies in Western countries and Japan have shown the glucose-lowering effects of a pioglitazone dosage of 30 mg [4-10], until 2012 only pioglitazone 15 mg/day was available in Korea. Because pioglitazone 30 mg/day was not available until January 2013, there are no data on the glucose-lowering efficacy of pioglitazone 30 mg/day in Korea. It is possible that differences in the glucose-lowering efficacy of pioglitazone 30 mg/day exist based on ethnicity.

We aimed to examine the efficacy and safety of pioglitazone when the dose was up-titrated to 30 mg in subjects with T2DM with inadequate glycemic control on 15 mg of pioglitazone combined with other oral hypoglycemic agents.

MATERIALS AND METHODS

1. Study design and participants

The present study is a single-arm, retrospective study. Medical records of patients with T2DM who visited the Inje University Ilsan Paik Hospital Diabetes-Endocrinology Center between January and June 2013 were reviewed. In this analysis, we excluded subjects 25 years or younger in age and those with a history of diabetic ketoacidosis in order to minimize the possibility of including type 1 diabetics in the study population. Although we did not evaluate for the presence of autoantibodies of type 1 diabetes in our subjects, we assumed that the diabetics identified in our study were type 2 diabetics because the incidence of autoantibodies in late-onset diabetes is markedly low in the Korean population [11]. In the Inje University Ilsan Paik Hospital database, patients with T2DM who underwent a dose up-titration of pioglitazone from 15 to 30 mg for 24 weeks were analyzed. We enrolled a study population of patients

on a stable dose of 15 mg of pioglitazone for at least 3 months before dose titration. Combined treatments with stable doses of other antidiabetics drugs were allowed. The doses of other oral hypoglycemic agents used before and after the study were kept constant, and the dose of pioglitazone was increased from 15 to 30 mg/day. Clinical characteristics, including HbA1c, fasting plasma glucose (FPG) levels, and body weight were analyzed at baseline, 3 months, and 6 months after dose up-titration.

2. Variables

Height and weight were obtained using standardized techniques and equipment. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using an HE-23 calibrated balance-beam scale (Sandol TMC, Seoul, Korea). Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Systolic and diastolic blood pressure (BP) were measured by standard methods using a sphygmomanometer with the patient in the sitting position.

Blood samples were collected in the morning after fasting for at least 8 hours. FPG, serum triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum aspartate transaminase/alanine transaminase concentrations were measured with an automated bio-chemical analyzer (Type AU5421; Olympus, Tokyo, Japan). HbA1c was measured using a high-performance liquid chromatography method and a HLC-723 G8 chromatograph (Tosoh Corp., Tokyo, Japan; coefficient of variation 1.66%).

3. Statistics

Statistical analysis of all data was performed using the IBM SPSS ver. 20 for Windows (IBM Co., Armonk, NY, USA). Values are expressed as mean ± standard deviation or as a percentage of the total. We compared clinical characteristics between responder (defined as decrease of HbA1c $\geq$ 1.0% for 6 months on pioglitazone up-titration) and non-responder, using independent samples t-test or x^2 test. To compare HbA1c, FPG, body weight among baseline, 3 months, and 6 months after pioglitazone up-titration of 30 mg/day, analysis of variance with Duncan's new multiple range test (post-hoc analysis) was used. The significance level of the present study was set at $P < 0.05$.

RESULTS

1. Characteristics of the study population (Table 1)

Among the 45 patients included in the study, 29 patients (64.4%) were men and 16 patients (35.6%) were women (age, 60.6 ± 1.49 years old; BMI, 25.9 ± 0.41 kg/m^2; baseline FPG level, 164.3 ± 5.96 mg/dL, and duration of diabetes, 14.9 ± 1.18 years) (Table 1). Five participants (11.1%) were administered sulfonylurea only, 2 participants (4.4%) were administered metformin only, 36 participants (80.0%) were administered both sulfonylurea and metformin, and 2 participants (4.4%) were administered both sulfonylurea and dipeptidyl peptidase 4 inhibitor.

2. Change in HbA1c and FPG (Fig. 1)

In the total study population, compared with

Table 1. Baseline clinical characteristics of subjects (n = 45)

Characteristic	Value
Age (yr)	60.6 ± 1.49
Male	29.6
Weight (kg)	71.0 ± 1.42
Height (cm)	165.8 ± 1.20
BMI (kg/m^2)	25.9 ± 0.41
Systolic BP (mm Hg)	130.2 ± 2.17
Diastolic BP (mm Hg)	72.9 ± 1.85
Baseline FPG (mg/dL)	164.3 ± 5.96
Serum total cholesterol (mg/dL)	149.1 ± 4.63
Serum LDL-cholesterol (mg/dL)	88.6 ± 3.59
Serum HDL-cholesterol (mg/dL)	49.9 ± 1.62
Serum triglyceride (mg/dL)	132.6 ± 7.94
AST (U/L)	22.9 ± 1.11
ALT (U/L)	21.9 ± 1.46
HbA1c (%)	8.4 ± 0.84
Diabetes duration (y)	14.9 ± 1.18
Oral hypoglycemic agents	
Metformin	40 (88.9)
Glimepiride	34 (75.6)
Gliclazide	9 (20.0)
α-glucosidase	2 (4.4)

Values are pressed as mean ± standard deviation, percent only, or number (%).

BMI, body mass index; BP, diastolic blood pressure; FPG, fasting plasma glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; HbA1c, glycated hemoglobin.

baseline measurements, HbA1c continually decreased significantly for 6 months (8.5 ± 0.1% at baseline vs. 8.2 ± 0.1% at 3 months vs. 7.9 ± 0.1% at 6 months; baseline vs. 3 months, $P = 0.106$; baseline vs. 6 months, $P = 0.005$; 3 months vs. 6 months, $P = 0.096$). FPG also significantly decreased (164 ± 6 mg/dL at baseline vs. 146 ± 7 mg/dL at 3 months vs. 146 ± 6 mg/dL at 6 months; baseline vs. 3 months, $P = 0.050$; baseline vs. 6 months, $P = 0.031$; 3 months vs. 6 months, $P = 0.953$). In the subgroup analysis including 36 patients taking pioglitazone, sulfonylurea, and metformin at baseline, HbA1c levels significantly decreased (8.5 ± 0.3% vs. 8.2 ± 0.1% vs. 7.9 ± 0.2%; baseline vs. 3 months, $P = 0.289$; baseline vs. 6 months, $P = 0.014$; 3 months vs. 6 months, $P = 0.232$). In 27 participants who were taking the maximum usual dosage of sulfonylureas (Glimepiride ≥ 6 mg/day, Gliclazide MR ≥ 120 mg/day, or Gliclazide ≥ 320 mg/day) and metformin (≥ 1,500 mg/day), HbA1c levels significantly decreased (8.6 ± 0.3% vs. 8.3 ± 0.1% vs. 8.0 ± 0.2%; baseline vs. 3 months, $P = 0.259$; baseline vs. 6 months, $P = 0.011$; 3 months vs. 6 months, $P = 0.218$).

3. Determinants for responders (Table 2 and 3)

When the responder was defined as decrease of HbA1c ≥ 1.0% for 6 months on pioglitazone up-
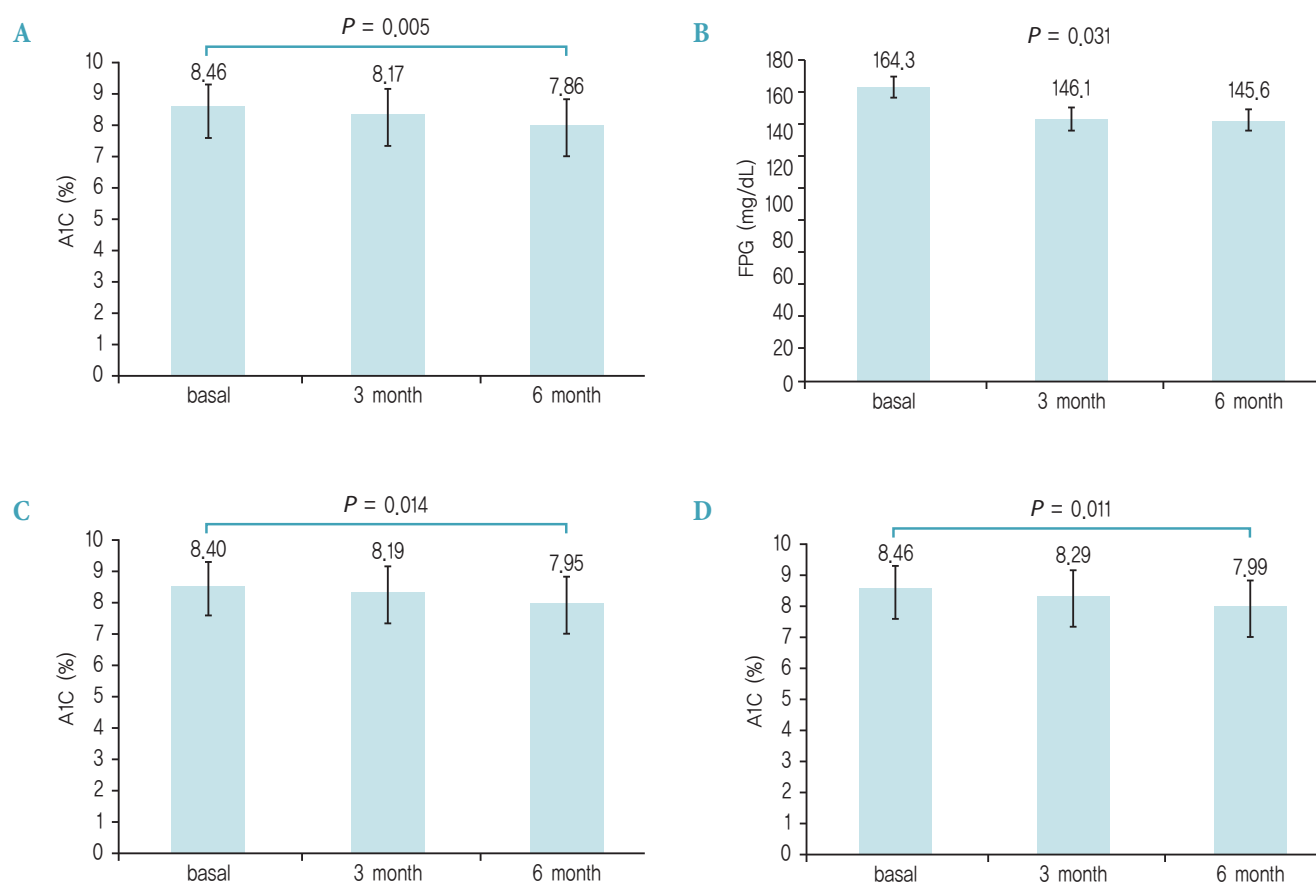
Fig. 1. Effect of dose-up titration of pioglitazone. (A) Effect of dose-up titration of pioglitazone on glycated hemoglobin (HbA1c; n = 45). (B) Effect of dose-up titration of pioglitazone on fasting plasma glucose (FPG; n = 45). (C) Effect of dose-up titration of pioglitazone on HbA1c in sulfonylurea (SU) + metformin (MET) subgroup (n = 36). (D) Effect of dose-up titration of pioglitazone on HbA1c in maximal dose of SU + MET subgroup (n = 27).

titration, only baseline HA1c level was different between responders and non-responders (9.1 ± 0.8% vs. 8.2 ± 0.7%, P = 0.001). There was no difference in age, sex, BMI, systolic and diastolic BP, and lipid profile. In logistic regression analysis for the responder with variables of P < 0.6 in univariate analyses (maximal dosage of sulfonylurea [SU] + metformin [MET], systolic BP, baseline HbA1c, serum LDL cholesterol, serum TG, and diabetes duration) as covariates, only baseline HbA1c was associated with decrease of HbA1c ≥ 1.0% for 6 months on pioglitazone

up-titration.

4. Body weight and other adverse events

Excluding the 2 patients who did not undergo body weight follow-up, 43 of 45 patients were monitored for changes in body weight at baseline, 3-month, and 6-month follow-ups. Thirteen of 43 patients (30.2%) had an increase in body weight of approximately 1.8 kg through the study period. Eighteen of 43 patients showed no weight change. Twelve of 43 patients

Table 2. Comparison of clinical characteristics between responder and non-responders on pioglitazone up-titration responder, defined as decrease of HbA1c ≥ 1.0% for 6 months

Characteristic	Non-responder (n = 31)	Responder (n = 14)	P-value
Age (y)	60.3 ± 9.8	61.5 ± 10.9	0.719
Men	20 (64.5)	9 (64.3)	1.000
Maximal dosage of SU + MET	20 (64.5)	7 (50.4)	0.512
BMI (kg/m^2)	25.8 ± 2.1	26.1 ± 3.5	0.765
Systolic BP (mm Hg)	129.4 ± 14.4	132.0 ± 14.8	0.593
Diastolic BP (mm Hg)	73.1 ± 13.6	72.4 ± 9.4	0.843
FPG (mg/dL)	168.3 ± 42.2	155.6 ± 34.5	0.295
HbA1c (%)	8.2 ± 0.7	9.1 ± 0.8	0.001
Serum total cholesterol (mg/dL)	147.8 ± 27.7	151.8 ± 30.3	0.705
Serum LDL-cholesterol (mg/dL)	86.3 ± 22.4	92.5 ± 21.4	0.417
Serum HDL-cholesterol (mg/dL)	50.5 ± 8.6	48.9 ± 12.7	0.702
Serum triglyceride (mg/dL)	127.6 ± 48.4	142.3 ± 49.1	0.394
Diabetes duration (y)	13.5 ± 6.3	16.8 ± 8.5	0.217

Responder, defined as decrease of HbA1c ≥ 1.0% for 6 months. Value arepressed as mean ± standard deviation or number (%).
SU, sulfonylurea; MET, metformin; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3. Logistic regression analysis for responder on pioglitazone up-titration

Variable	Odds ratio (95% CI)	P-value
Maximal dosage of SU + MET	0.34 (0.05~2.52)	0.290
Systolic BP (mm Hg)	0.95 (0.87~1.04)	0.239
Baseline HbA1c (%)	9.37 (1.84~47.7)	0.007
Serum LDL-cholesterol (mg/dL)	1.02 (0.97~1.07)	0.491
Serum triglyceride (mg/dL)	1.00 (0.97~1.02)	0.788
Diabetes duration (y)	1.06 (0.91~1.23)	0.476

CI, confidence interval; SU, sulfonylurea; MET, metformin; BP, blood pressure; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein.

showed a decrease in body weight of approximately 1.6 kg. For all participants, there was no significant change in body weight (70.8 ± 1.4 kg vs. 70.1 ± 1.4 kg vs. 71.0 ± 1.5 kg; baseline vs. 3 months, $P = 0.996$; baseline vs. 6 months; $P = 0.926$, 3 months vs. 6 months, $P = 0.892$).

No severe adverse events were observed during the study among the 44 subjects (excluding 1 patient lost to follow-up).

DISCUSSION

In this study, up-titrating to 30 mg of pioglitazone from 15 mg for patients with inadequate glycemic control showed an additive glucose-lowering effect without significant weight gain in Korean patients with T2DM. To the best of our knowledge, this is the first Korean study evaluating the effects of an increased dose of pioglitazone, from 15 to 30 mg/day on its glucose-lowering efficacy. In this study, HbA1c decreased by about 0.3% at 3 months and about 0.6% at 6 months,

compared to baseline HbA1c after the pioglitazone up-titration. Despite small sample size and limited study design of this study, the finding of significant glucose lowering effect without weight change suggested that up-titrating pioglitazone to the maximum dosage could be one of treatment option for type 2 diabetes, especially in cases with poorer glycemic control (HbA1c > 9%), taking sulfonylurea and metformin.

Until now, only one study reported the efficacy and safety of pioglitazone according to dose up-titration, which examined the effects of an increased dose of pioglitazone from 15 to 30 mg/day on its glucose-lowering efficacy in Japanese diabetes patients undergoing hemodialysis [12]. In that study, the patients were administered pioglitazone 15 mg daily with their morning meal for the first 4 weeks. Subsequently, the doses were titrated by doubling the dose to a maximum of 30 mg/day. During a 24-week period of treatment, HbA1c levels decreased from 6.8% at baseline to 6.1% after 4 weeks and the decreases continued for 24 weeks of therapy without interdialytic body weight gain.

There have been only few studies of the comparison of glucose lowering efficacy of pioglitazone between 15 mg and 30 mg. Aronoff et al. [13] investigated the glucose lowering effect of variable doses of pioglitazone in patients with T2DM. They reported that pioglitazone reduced HbA1C (range 1.0~1.6% in the difference from placebo; when compared with placebo, these were −1.6% with 45 mg, −1.0% with 30 mg, −1.0% with 15 mg, and −0.5% with 7.5 mg) and FPG (39~65 mg/dL difference from placebo; −65 mg/dL with 45 mg, −41 mg/dL with 30 mg, −39 mg/dL with 15 mg, and −28 mg/dL with 7.5 mg). Henry et al. [14] tried to examine the efficacy and safety of mono- or combination therapy with sitagliptin and/or pioglitazone among seven arms that received, once daily 100 mg sitagliptin alone; 15, 30, or 45 mg pioglitazone alone, or 100 mg sitagliptin plus 15, 30, or 45 mg pioglitazone for 54 weeks. In this study, the decrease in HbA1c levels was significantly greater with pioglitazone 30 mg, 45 mg than with pioglitazone 15 mg at week 24 (−1.2% in pioglitazone 30 mg, −1.2% in pioglitazone 45 mg vs. −0.9% in pioglitazone 15 mg). Edema was reported in 0.5% of patients in the sitagliptin monotherapy group and 2.7~5.3% among those in the pioglitazone-treated groups.

In this study, baseline HbA1c level was the only determinant for responders of pioglitazone up-titration. Whereas there was no report about the determinant for responders of pioglitazone up-titration, three Japanese studies showed determinant for responders for newly administrated pioglitazone. Kutoh [15] reported that HbA1c levels and BMI at baseline was significantly higher in responders, defined as > 1% reduction of HbA1c after 3 months, in 81 drug-naïve type 2 diabetes patients. Tajiri et al. [16] showed that age, FPG, and percentage of women at baseline were significantly higher in responders, defined as > 1% reduction of HbA1c after 12 weeks, in 48 type 2 diabetes patients (14 drug naïve, 20 sulfonylurea, 20 biguanide, 5 α-glucosidase inhibitor). Igarashi et al. [17] reported that the values of the BMI, homeostasis model assessment of insulin resistance index, and LDL-cholesterol were significantly higher in the responder group, defined as $\geq$ 1% reduction of HbA1c after 6 months, in 23 type 2 diabetes patients with 5~10 mg glibenclamide alone without other antidiabetics drugs. In this study, there was no other parameter for determining responders for pioglitazone up-titration except for baseline HbA1c,

which could be caused by insufficient statistical power of small sample size. This issue needs to be elucidated in another large sample studies.

There are some limitations to this study. First, it is a small sized study with a limited number of enrollees and restricted to a specific geographic area. Second, it is a retrospective study that used electronic medical record data. Especially there were some possibilities that minor adverse effects could be ignored with limited study design. Therefore, the finding of no increased side effect on pioglitazone up-titration should be confirmed in another prospectively-designed study.

In conclusion, up-titrating to 30 mg pioglitazone from 15 mg in patients with inadequate glycemic control showed additive glucose-lowering effects without significant weight gain in Korean patients with T2DM, especially in cases with poorer glycemic control (HbA1c > 9%), taking sulfonylurea and metformin; however, another prospective, large-sample study is required.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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