The Low-Dose (7.5 mg/day) Pioglitazone Therapy

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Abstract

Pioglitazone is one of thiazolidinedione derivatives, which stimulates nuclear peroxisome proliferator-activated receptor gamma and improves glucose and lipid metabolism and insulin sensitivity. A recent systematic review and meta-analysis showed that pioglitazone therapy was associated with a lower risk of major adverse cardiovascular events (MACEs) in patients with pre-diabetes or insulin resistance (-23%), and diabetes (-17%) [4]. Another meta-analysis demonstrated that pioglitazone therapy in stroke patients with insulin resistance, pre-diabetes, and diabetes was associated with lower risk of recurrent stroke (-32%) and future major vascular events (-25%) [5]. Further, in a European multi-database cohort study of patients with type 2 diabetes, pioglitazone therapy was associated with a statistically significant decrease in the risk of all-cause mortality [6]. Despite these beneficial effects, pioglitazone therapy had higher risks of heart failure (+32%), bone fractures (+52%), edema (+63%) and weight gain (+60%) in the meta-analysis [4].

We previously reported that the low-dose (7.5 mg/day) pioglitazone therapy is beneficial to the improvement in metabolic parameters without weight gain and an increase of risk for heart failure [7]. To find out the efficacy and safety of the low-dose pioglitazone therapy, we reviewed the dose-response of pioglitazone on favorable effects and adverse effects due to pioglitazone, by searching the reports on effects of daily dose of 7.5 mg and/or 15 mg and/or 30 mg of pioglitazone. The low-dose pioglitazone therapy may show the same degree of improvements in glucose and lipid metabolism, fatty liver, insulin resistance, and adiponectin as the standard- and high-dose pioglitazone therapy. Furthermore, the low-dose pioglitazone therapy may also show less adverse effects on weight gain, edema and heart failure as compared with the standard- and high-dose pioglitazone therapy.

Keywords: Body weight; Heart failure; Lipid metabolism; Liver function; Pioglitazone

Introduction

Pioglitazone is one of thiazolidinedione derivatives, which stimulates nuclear peroxisome proliferator-activated receptor gamma (PPARγ) and improves insulin sensitivity by acting on adipose tissue, muscle and liver [1, 2]. Pioglitazone improves serum lipids in addition to glucose-lowering [3]. A recent systematic review and meta-analysis showed that pioglitazone therapy was associated with a lower risk of major adverse cardiovascular events (MACEs) in patients with pre-diabetes or insulin resistance (-23%), and diabetes (-17%) [4]. Another meta-analysis demonstrated that pioglitazone therapy in stroke patients with insulin resistance, pre-diabetes, and diabetes was associated with lower risk of recurrent stroke (-32%) and future major vascular events (-25%) [5]. Further, in a European multi-database cohort study of patients with type 2 diabetes, pioglitazone therapy was associated with a statistically significant decrease in the risk of all-cause mortality [6]. Despite these beneficial effects, pioglitazone therapy had higher risks of heart failure (+32%), bone fractures (+52%), edema (+63%) and weight gain (+60%) in the meta-analysis [4].

Effects of Low-, Standard- and High-Dose Pioglitazone Therapy on Efficacy and Safety of Pioglitazone

Effects of low- (7.5 mg/day), standard- (15 mg/day) and high-dose (30 mg/day) pioglitazone therapy on efficacy- and safety-related parameters due to pioglitazone were shown in Table 1 [7-10].

In the study by Rajagopalan et al, all three groups showed a significant reduction in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) [8]. However, there was no significant difference in HbA1c reduction among three groups. Dose dependency could not be obtained for reduction of HbA1c (r = 0.09; P = 0.42), FPG (r = 0.114; P = 0.175) and PPG (r = 0.06; P = 0.58) [8]. There was a significant reduction in triglyceride and C-peptide and a significant elevation in adiponectin and HDL-cholesterol (HDL-C). However, a significant difference among three groups was not obtained in any laboratory parameters. Adiponectin is a serum protein secreted by adipocytes and suppresses pro-inflammatory state which is observed in the metabolic syndrome including insulin resistance, hyperglycemia, hypertension, and dyslipidemia.
Pioglitazone may increase adiponectin concentrations in patients with type 2 diabetes independently of improvements in blood glucose [11]. The low-dose pioglitazone therapy seems to improve dyslipidemia, insulin resistance and increase adiponectin which is one of the most important therapeutic targets of pioglitazone as well as the standard- and high-dose pioglitazone therapy. Aso et al also reported that the low-dose pioglitazone (7.5 mg/day) therapy increases serum high molecular weight adiponectin and improves glycemic control in Japanese patients with poorly controlled type 2 diabetes [12]. Vu et al reported that the low-dose pioglitazone (7.5 mg/day) therapy increases serum high molecular weight adiponectin and improves glycemic control in patients with the metabolic syndrome without type 2 diabetes [13].

Majima et al compared the effects of low-dose pioglitazone (7.5 mg/day) with those of standard-dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes [9]. Both groups showed a significant reduction in HbA1c, FPG, immunoreactive insulin (IRI) and triglyceride, and also showed a significant elevation of HDL-C; however, none of the intergroup differences reached statistical significance [9]. However, in terms of safety, % change of body weight during the 6-month treatment in the low-dose pioglitazone group was significantly less than that in the standard-dose pioglitazone group (P < 0.0001). The study by Majima et al almost supported the result of the study by Rajagopalan et al.

Twice as many patients reported edema with pioglitazone than with gliclazide in a randomized, double-blind, parallel-group comparison trial [14]. In the kidney, PPARγ is most abundant in the collecting duct. Thiazolidinediones has been reported to expand body fluid volume through PPARγ stimulation of the epithelial Na+ channel-mediated renal salt absorption [15]. Majima et al also showed that the incidence of peripheral edema was significantly much lower in the low-dose

Table 1. Effects of Low- (7.5 mg/day), Standard- (15 mg/day) and High-Dose (30 mg/day) Pioglitazone on Efficacy and Safety of Pioglitazone

| Author                | Duration of treatment | 7.5 mg  | 15 mg  | 30 mg  |
|-----------------------|-----------------------|---------|--------|--------|
| Rajagopalan et al [8] | 12 weeks              | Efficacy|        |        |
|                       |                       | HbA1c (%)| -0.5** | -0.6** | -0.7** |
|                       |                       | FPG (mg/dL)| -30.6** | -40.3** | -41.1** |
|                       |                       | PPG (mg/dL)| -48.3** | -53.3** | -54.6** |
|                       |                       | C-peptide (ng/mL)| -0.4** | -0.4** | -0.8** |
|                       |                       | Adiponectin (µg/dL)| +10.6** | +11.3** | +12.1** |
|                       |                       | Triglyceride (mg/dL)| -19.6** | -18.1** | -24.1** |
|                       |                       | HDL-C (mg/dL) | +3.3** | +3.2** | +4.2** |
|                       |                       | Safety     | Body weight (kg)| +0.2 | +0.9** | +1.9** |
|                       |                       |           | BMI (kg/m²) | +0.1 | +0.3** | +0.8** |
|                       |                       |           | Body fat (%) | +0.1 | +0.8** | +1.2** |
| Majima et al [9]     | 6 months              | Efficacy   | HbA1c (%)| -0.61** | -0.69** |
|                       |                       | FPG (mg/dL)| -23.91** | -27.87** |
|                       |                       | IRI (µU/mL)| -0.71** | -0.69** |
|                       |                       | Triglyceride (mg/dL)| -21.32** | -26.93** |
|                       |                       | HDL-C (mg/dL) | +3.53** | +4.55** |
|                       |                       | Safety     | Body weight (kg)| +1.14 | +2.79 |
|                       |                       |           | Body fat (%) | +1.97 | +4.75 |
|                       |                       | Edema      | 2/54 (3.7%) | 11/41 (26.8%) |
| Panikar et al [10]   | 6 months              | Efficacy   | HbA1c (%)| ↓      | ↓      |
|                       |                       | Safety     | Body weight (kg)| +0.88** | +1.62** | +2.72** |
| Adachi et al [7]     | 2 months              | Efficacy   | HbA1c (%)| -0.8*  | -0.7*  |
|                       |                       | ALT (U/mL)| -6.8*  | -4.5   |
|                       |                       | Safety     | Body weight (kg)| -1.0  | +0.9   |
|                       |                       | BNP (pg/mL)| +0.8   | +12.1* |

ALT: alanine aminotransferase; BMI: body mass index; BNP: B-type natriuretic peptide; FPG: fasting plasma glucose; IRI: immunoreactive insulin; PPG: postprandial plasma glucose. *P < 0.1 and **P < 0.05 vs. baseline, respectively.
pioglitazone group (3.7%) than in the standard-dose pioglitazone group (26.8%) (P = 0.0014). Further, their study showed that the low-dose pioglitazone therapy was more favorable for peripheral edema as compared with the standard-dose pioglitazone therapy.

Panikar et al studied the effect of low (7.5 mg/day), standard (15 mg/day) and high (30 mg/day) dose of pioglitazone on glycemic control and weight gain in newly diagnosed type 2 diabetes [10]. At the end of 6 months, there was significant weight gain in all three groups from baseline (P < 0.01). Weight gain was greatest in the high-dose pioglitazone group, intermediate in the standard-dose pioglitazone group and least in the low-dose pioglitazone group. The difference was statistically significant between the low-dose pioglitazone group and the high-dose pioglitazone group, and the standard-dose pioglitazone group and the high-dose pioglitazone group, but not between the low-dose pioglitazone group and the standard-dose pioglitazone group. There was no significant difference in HbA1c reduction between the three groups. The dose was significantly correlated with weight gain (r = 0.254; P < 0.001), suggesting the dose-dependent effect of pioglitazone on body weight gain.

Pioglitazone has an adverse effect of edema that may result in subsequent heart failure, especially in diabetic patients with coronary artery disease [16-18]. We previously studied the effects of pioglitazone on plasma B-type natriuretic peptide (BNP) which is a sensitive biomarker for diagnosing heart failure [19]. We compared the data before the start of pioglitazone with the data at almost 2 months (mean, 52.6 days) after the start of pioglitazone [7]. Body weight showed a non-significant decrease in the daily 7.5 mg pioglitazone-treated group, and showed a non-significant increase in the daily 15 mg pioglitazone-treated group. HbA1c tended to decrease in both groups. Plasma BNP did not change in the daily 7.5 mg pioglitazone-treated group; however, plasma BNP tended to increase in the daily 15 mg pioglitazone-treated group. Our study demonstrated that the daily 7.5 mg pioglitazone-treatment improved HbA1c without increase of body weight and plasma BNP as compared with the daily 15 mg pioglitazone-treatment [7].

The treatment with thiazolidinediones such as pioglitazone reduces hepatocellular lipid levels by 30-50% by modulating insulin sensitivity and endocrine function of adipose tissue in type 2 diabetes [20]. The administration of pioglitazone was reported to reduce steatosis and inflammation in liver in patients with non-alcoholic steatohepatitis and type 2 diabetes [21, 22]. In our study, serum alanine aminotransferase (ALT) tended to decrease in only the daily 7.5 mg pioglitazone-treated group [7].

The Influences of Withdrawal and Daily Dose Reduction of Pioglitazone on Metabolic Parameters in Patients With Type 2 Diabetes

To understand the influences of withdrawal or dose reduction of pioglitazone in patients with type 2 diabetes, we retrospectively picked up patients who had undergone withdrawal or daily dose reduction of pioglitazone after a continuous prescription for 3 months or longer, and compared the data before the withdrawal or dose reduction of pioglitazone with the data at 3 or 6 months [23]. In patients who had undergone daily dose reduction, the mean dose of pioglitazone was 29.6 mg at baseline, 11.9 mg at 3 months, and 11.7 mg at 6 months after the dose reduction. The number of subjects who had taken high-dose metformin (≥ 1,000 mg) and dipeptidyl peptidase-4 (DPP-4) inhibitors increased after the withdrawal or dose reduction of pioglitazone in both groups. Although no significant change was observed in plasma glucose and HbA1c levels, body weight significantly decreased at 3 and 6 months after the dose reduction, suggesting the dose-dependent effect of pioglitazone on body weight gain and also supporting the usefulness of the low-dose pioglitazone therapy.

The Dose-Dependent Effect of Pioglitazone on Other Safety-Related Parameters

A population-based cohort study from France showed that pioglitazone exposure was significantly associated with increased risk of bladder cancer [24]. In this study, a significantly increased risk for high cumulative doses of pioglitazone (≥ 28,000 mg, adjusted hazard ratio (HR): 1.75 (95% confidence interval (CI): 1.22 - 2.50)) and long duration of exposure (≥ 24 months, adjusted HR: 1.36 (1.04 - 1.79)) was observed [24]. Although controversial discussions exist about the association between pioglitazone and bladder cancer, the low-dose pioglitazone therapy may be beneficial to reduce the risk of bladder cancer.

In the nested case-control analysis using the UK General Practice Research Database, a possible association between long-term use of thiazolidinediones and fractures was observed in patients with diabetes mellitus [25]. A meta-analysis reported that pioglitazone was associated with a significantly increased risk of fractures overall in the 10 randomized controlled trials (RCTs) (odds ratio (OR): 1.45, 95% CI: 1.18 - 1.79; P < 0.001) [26]. Five RCTs showed a significantly increased risk of fractures among women (OR: 2.23, 95% CI: 1.65 - 3.01; P < 0.001). Bone mineral density in women exposed to thiazolidinediones was significantly reduced at the lumbar spine and hip in two RCTs [26]. At the moment, the dose-dependent effect of pioglitazone on bone fractures remains unknown.

Conclusion

The summary about efficacy and safety of the low dose (7.5 mg/day) pioglitazone therapy was shown in Figure 1. The low-dose pioglitazone therapy may show the same degree of effects on improvements in glucose and lipid metabolism, fatty liver, insulin resistance and adiponectin as the standard- and high-dose pioglitazone therapy. Furthermore, the low-dose pioglitazone therapy may also show less adverse effects on weight gain, edema and heart failure as compared with the standard- and high-dose pioglitazone therapy. At this moment, the dose-dependent
effect of pioglitazone on bone fractures remains unknown.

**Competing Interests**

The authors declare that they have no competing interests concerning this article.

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