

SAFETY AND EFFICACY OF PIOGLITAZONE AMONG TYPE 2 DIABETES MELLITUS PATIENTS RECEIVING LONG TERM HEMODIALYSIS

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Abstract

Background: Type 2 diabetes mellitus (T2DM) frequently causes end stage renal disease (ESRD). Glucose-lowering treatment options for patients with T2DM with ESRD are limited. Thiazolidinedione is an oral glucose lowering agent used to treat patients with ESRD. We evaluated the potential for pioglitazone in combination with other hypoglycemic medications among patients with T2DM receiving long term hemodialysis.

Objectives: To evaluate the safety and efficiency of pioglitazone among patients with ESRD receiving hemodialysis.

Methods: The retrospective study was conducted in the outpatient clinic of Phramongkutklao Hospital during 2006 and 2015. HemoglobinA1C (HbA1c), fasting plasma glucose (FPG), body weight, hematocrit and history of diagnosed chronic heart failure were evaluated after starting medication and 1 year of follow-up.

Results: Data for hemodialysis patients on pioglitazone were analyzed (n=50). Mean FPG changes from baseline were -28.8 ± 80.0 mg/dL after 12 weeks ($p = 0.018$) and -59.2 ± 80.0 mg/dL after 12 months of treatment ($p < 0.001$). Mean HbA1c changes from baseline were also -0.25 ± 1.62 % after 12 weeks ($p = 0.318$) and -1.52 ± 1.77 % after 12 months of treatment ($p < 0.001$). The differences in mean body weight (63.2 ± 13.0 kg vs. 64.6 ± 13.0 kg; $p = 0.139$) and hematocrit (33.4 ± 5.5 vs. 33.6 ± 5.3 ; $p = 0.929$) at baseline and 12 months were not significant, while episodes of congestive heart failure were low (4%). No serious adverse effects such as hypoglycemia with hospitalization or liver failure were observed in any of the patients.

Conclusion: These data suggest that adding pioglitazone to standard hypoglycemic agents among patients with T2DM undergoing hemodialysis improved glucose control and was well tolerated.

Keywords : End stage renal disease, Hemodialysis, Diabetes Mellitus, Thiazolidinedione, Pioglitazone

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Introduction

Patients with Type 2 diabetes mellitus (T2DM) and impaired renal function have become an important public health problem^(1,2) and diabetic nephropathy is the most prevalent cause of end stage renal disease (ESRD) worldwide.^(3,4) Patients with T2DM receiving dialysis have an increased mortality risk and especially a higher risk of cardiovascular death, compared with other diabetic patients without dialysis.⁽⁵⁾ Moreover, hemodialysis patients with T2DM are known to be at a higher risk for cardiovascular disease and muscle wasting than nondiabetic hemodialysis patients.⁽⁶⁾

Altered pharmacokinetics of hypoglycemic medications complicate the treatment of patients with T2DM undergoing dialysis and can present inadequate glycemic control and adverse events. In addition, advanced chronic kidney disease (CKD) and hemodialysis with reduced intake, previous hypoglycemic episodes and longer duration of diabetes are recognized risk factors for prolonged hypoglycemia.⁽⁷⁾ Thiazolidinediones (TZD) are oral hypoglycemic agents used for hemodialysis patients. In addition, patients with T2DM and CKD and/or receiving dialysis or treatment with pioglitazone are associated with a lower all-cause mortality rate.⁽⁸⁻¹⁰⁾ TZD is an insulin sensitizer that reduces insulin resistance, increases glucose uptake in muscle and adipose tissue and decreases hepatic glucose production. It selectively enhances or partially mimics certain actions of insulin, causing a slowly generated hypoglycemic effect among patients with T2DM. The effect is often accompanied by reduced insulin in plasma, triglycerides and fatty acids.⁽¹¹⁾ Several clinical studies have shown that TZD specifically binds to a family of nuclear receptors, and peroxisome proliferation activator receptors (PPAR γ) can improve indices of glucose control. Reduced fasting plasma glucose between 16 and 70 mg/dL and hemoglobinA1C between 0.4% and 2% has been reported.^(12, 13) A few trials have compared the efficacy of TZD among hemodialysis patients.^(14, 15) Here we report the results after assessing efficacy and safety of pioglitazone among patients receiving long term hemodialysis.

Methods

Study Design and population

This retrospective cohort study evaluated the efficacy and safety of pioglitazone treatment among hemodialysis patients during January 2005 and January 2015. The study

was approved by the Ethics Review Committee for Research in Human Subjects, Phramongkutklo Hospital, Thailand. The primary objective was to determine the efficacy of glycemic control and safety after pioglitazone treatment for 12 months. The primary efficacy evaluation was based on the percent change in hemoglobin A1C (HbA1c) levels from baseline to weeks 12 and 54.

All patients aged 18 years or older, with a previous diagnosis of T2DM according to the criteria of the American Diabetes Association, received hemodialysis treatment at least 12 weeks and were initially treated with pioglitazone for glycemic control. The primary renal diagnosis of all patients was diabetic nephropathy due to T2DM. Exclusion criteria included acute kidney injury episode, pregnancy, unspecified type of DM and patient life expectancy <1 year. Patients with T2DM and receiving medical care for at least 12 months were included in the present study. T2DM was reviewed using retrieved medical and personal data, including baseline demographic characteristics, hypertension, use of glycemic lowering medications and comorbidities. The patients continued regular medications such as blood pressure lowering agents, lipid lowering agents, recombinant human erythropoietin and phosphate binders during the study period. Safety was assessed by physical examinations, clinical laboratory tests and the incidence and severity of adverse events recorded from treatment. Fasting blood samples were drawn and processed following standardized protocols. Fasting plasma glucose (FPG), HbA1c and hematocrit levels were measured.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD). Continuous variables were assessed using the Paired-*t* test. For all tests, a *p*-value less than 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS, Version 16.0 (SPSS Inc., Chicago, IL, USA). All results were considered significant when *p*-value was <0.05.

Results

A total of 50 subjects (100% Thai ethnicity) with a mean age of 63.3 \pm 11.7 years were included. The average duration

of diabetes was 16.3±3.7years. The mean HbA1C was 7.9±1.9%, and 25% of patients had an HbA1C <7%. The mean systolic and diastolic BP were 133.5±10.2 and 76.0±9.8 mmHg, respectively, In the entire population, 98% had hypertension, 96%, dyslipidemia, 24%,cardiovascular

disease, 6%, malignancy and 6% had autoimmune disease as comorbid diseases. The dosage of pioglitazone was 15-30 mg/day among all subjects. The characteristics and baseline measurements of the patients who entered the study are listed in **Table 1**.

Table 1. Baseline characteristics of the enrolled patients

Characteristics	Total (N=50)
Age (year)	63.3±11.7
Male (N, %)	24 (48%)
Duration of diabetes (years)	16.3±3.7
Body weight (kg)	63.2±13.0
Systolic blood pressure (mmHg)	133.5±10.2
Diastolic blood pressure (mmHg)	76.0±9.8
Co-morbid diseases (N, %)	
Hypertension	49 (98%)
Dyslipidemia	48 (96%)
Cardiovascular disease	12 (24%)
Malignancy	3 (6%)
Autoimmune disease	3 (6%)
Fasting plasma glucose (mg/dL)	176.6±74.9
HemoglobinA1C (%)	7.9±1.9
Hematocrit (%)	33.4±5.6
Insulin monotherapy	25 (50.0)
Insulin + other oral hypoglycemic agents	13 (26.0)
Other oral hypoglycemic agents	12 (24.0)

Data are expressed as mean ±SD or as number (percentage) of patients

Efficacy of treatment

As shown in **Table 2**, significant decreases were observed in FPG levels at 12 weeks after the start of pioglitazone therapy, and the levels continued to decrease throughout the 54-week treatment. Table 2 shows similar results for HA1c: the levels decreased at 12 weeks after the start of pioglitazone therapy and continued to significantly decrease for 54 weeks. Mean FPG changes from baseline were -28.8±80.0 mg/dL after 12 weeks (*p* =0.018) and -59.2±80.0 mg/dL after 12 months of treatment (*p* <0.001). Mean HbA1c changes from baseline were also -0.25±1.62 % after 12 weeks (*p* = 0.318) and

-1.52±1.77 % after 12 months of treatment (*p* <0.001) (**Fig 1**).

Safety of treatment

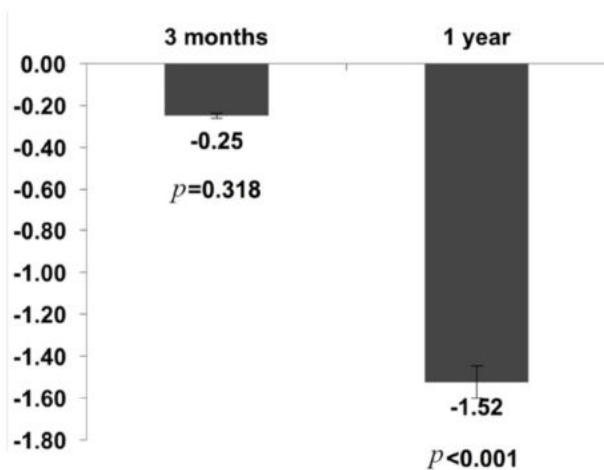
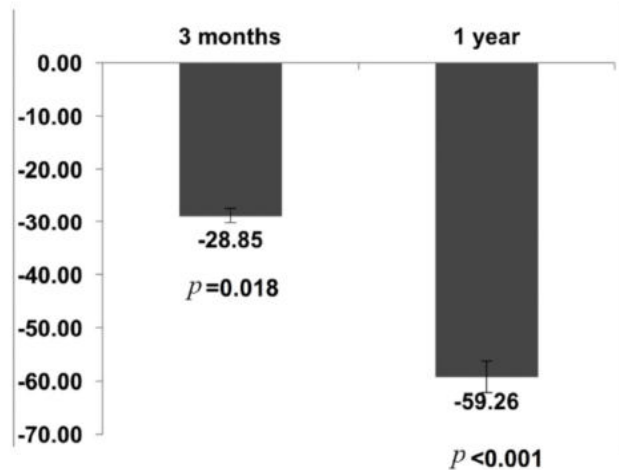
The safety analysis included all patients who entered the study. Two patients with congestive heart failure (4%) were eliminated due to adverse events. No significant changes in body weight were observed after treatment (**Table 2**). No significant differences were found in hematocrit or the erythropoietin dose throughout the 54-week treatment. No serious adverse effects such as hypoglycemia with hospitalization or liver failure were observed among any of the patients.

Table 2. Changes of fasting plasma glucose, hemoglobinA1C, body weight and hematocrit after pioglitazone treatment

	Body weight (kg)	Fasting plasma glucose (mg/dL)	HemoglobinA1C (%)	Hematocrit (%)
Baseline	63.2±13.0	176.6±74.9	7.9±1.9	33.4±5.6
At 3 month of treatment	63.8±13.2	152.4±62.2	7.8±1.6	33.5±5.0
<i>p</i> - value (at 3 month vs. baseline)	0.463	0.018	0.318	0.858
At 12 month of treatment	64.6±13.0	128.2±37.7	6.8±0.9	33.7±5.3
<i>p</i> - value (at 12 month vs. baseline)	0.139	<0.001	<0.001	0.929

Figure 1. Changes of glycemic control after pioglitazone treatment among hemodialysis patients

Data are expressed as mean±SD. Comparisons between treatment groups using the Independent *t*-test (continuous variables)

A. Mean changes of hemoglobinA1C after pioglitazone treatment at 3 and 12 months**B. Mean changes of fasting plasma glucose after pioglitazone treatment at 3 and 12 months**

Discussion

This study evaluated the efficacy and safety of pioglitazone among patients with T2DM on hemodialysis. Overall, the study demonstrated that pioglitazone was effective to treat Thai patients with T2DM receiving hemodialysis. HbA1c levels among patients with T2DM decreased from 7.9% at baseline to 6.8% after 54 weeks of treatment. The results of this study showed that pioglitazone treatment exhibited high efficacy as previously reported in the general⁽¹⁶⁾ and ESRD populations.^(14,15) In a Japanese population of diabetics

on hemodialysis, pioglitazone was effective in reducing plasma glucose and HbA1c from baseline levels from week 4 after the commencement of treatment and no serious adverse effects were observed among any of the patients.⁽¹⁵⁾ Moreover, TZD produced a number of pleiotropic actions concerning cardiovascular risk factors and TZD treatment could improve survival among CKD with and without hemodialysis.⁽⁸⁻¹⁰⁾

The serious side effects of TZD treatment included congestive heart failure, fluid retention, weight gain and anemia.^(17,18)

The meta-analysis of four randomized, controlled trials comparing rosiglitazone with other oral hypoglycemic agents demonstrated a two-fold significantly increased risk for congestive heart failure in the general population⁽¹⁹⁾ and significant associations of rosiglitazone use with higher cardiovascular and all-cause mortality rate among hemodialysis patients with T2DM.⁽²⁰⁾ The incidence of serious heart failure also increased with pioglitazone vs. placebo among 5,238 patients with T2DM with pre-existing cardiovascular disease.⁽²¹⁾ However, some studies did not detect these adverse events with pioglitazone among patients with normal renal function⁽²¹⁾, CKD⁽⁸⁾ and those receiving hemodialysis.^(9,10) This finding was similar to our findings, in which patients demonstrated a low frequency of treatment limiting weight gain and heart failure among hemodialysis patients receiving pioglitazone treatment. No changes were found in hematocrit values, erythropoietin dose requirements or weight gain in the present study. These results might have been due to the success of the low dose pioglitazone treatment in minimizing the expansion of the intravascular volume.

There remains the possibility of residual confounding regarding the efficacy of TZD treatment. One must consider whether TZD-treated patients received better care and exhibited good compliance. Second, assessment of glycemic control among hemodialysis patients is difficult. Among hemodialysis patients, the use of HbA1c is limited due to the shortened half-life of erythrocytes and recombinant human erythropoietin treatment.⁽²²⁾ Finally, all patients received other hypoglycemic agents and an adjusted dose of anti-diabetic therapy according to standard of care.

This study had some limitations. First, because of the retrospective cohort design, we could not evaluate long term patient outcomes, and could not assess the mechanisms of pioglitazone associated with heart failure. Second, the outcomes of this study were based on primarily Asian patients with long term dialysis and may not be generalizable to a special population, e.g., peritoneal dialysis, advanced renal disease without dialysis and high comorbid illnesses. This cohort consisted of patients with T2DM incident to hemodialysis. Generalization to prevalent hemodialysis patients should be undertaken cautiously; further, generalization to nondiabetic hemodialysis patients is unadvisable. In addition, assessment of outcomes in this study

was limited to one year of follow-up and no control group; further study is needed to clarify longer term effects.

Conclusion

Pioglitazone therapy is safe and effective for patients with T2DM receiving hemodialysis. The long term safety of pioglitazone treatment will require further evaluation in longer duration studies and high risk groups regarding heart failure.

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Competing interests

The authors declare that they have no competing interests.

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