

Original Article**Reduction of proteinuria by pioglitazone in patients with non-diabetic renal disease**

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**Abstract**

**BACKGROUND:** Increased proteinuria would lead to a larger risk for renal failure in the long term. Therefore, proteinuria requires immediate and thorough evaluation. This study was designed to evaluate the effects of pioglitazone on proteinuria in patients with non-diabetic renal disease.

**METHODS:** In this self-controlled clinical trial study, forty four non-diabetic patients aged 18 and more, who had renal disease and a stable proteinuria of over 0.5 g in 24 hour, were studied. All patients received 15 mg of daily pioglitazone for 4 months. Urine protein excretion was measured as a main end point prior to the study, at the end of the 2nd and 4th months of treatment, and 2 and 4 months after the cessation of the active drug. Other evaluated variables included systolic blood pressure, serum creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting blood sugar (FBS), blood urea nitrogen (BUN) and glomerular filtration rate (GFR) levels.

**RESULTS:** Proteinuria (mean  $\pm$  SEM) prior to the study, at the 2nd and 4th months of the treatment, and 2 and 4 months after the cessation of pioglitazone were  $1088.6 \pm 131.1$ ,  $699.9 \pm 118.3$ ,  $433.9 \pm 68.7$ ,  $416.1 \pm 54.9$  and  $646.9 \pm 89.1$ , respectively ( $p < 0.001$ ). In addition, the reduction of 24-hour urine protein was statistically significant for both male and female patients ( $p < 0.001$  for both).

**CONCLUSIONS:** A reduction of proteinuria in patients with non-diabetic renal disease was observed during the 4-month treatment with pioglitazone which continued for 2 months after the cessation of the treatment. However, 4 months after the cessation of the treatment, a little increase was detected in the level of proteinuria.

**KEYWORDS:** Proteinuria, Pioglitazone, Renal Disease, Thiazolidinediones.

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A crucial function of healthy kidneys is the ability to excrete basically protein-free urine. Persistent proteinuria is a manifestation and maybe a cause of renal dysfunction which increases the risk for renal failure in the long term. Therefore, it requires immediate and thorough evaluation. Appropriate

treatment of proteinuric renal disease might delay the progression of renal failure.<sup>1-3</sup>

The thiazolidinediones are drugs that act by binding and activating peroxisome proliferator-activated receptors (PPAR), improving insulin sensitivity mainly in muscles, decreasing plasma insulin levels, protecting the beta cell,

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and having helpful effects on the vasculature. Thiazolidinediones have also been shown to decrease blood pressure and activate PPAR $\gamma$ .<sup>4-6</sup>

Currently, two thiazolidinediones, i.e. pioglitazone and rosiglitazone, are used as oral hypoglycemic agents for the management of type 2 diabetes. Some studies have shown the effect of thiazolidinediones in the reduction of proteinuria of diabetic nephropathy in both animal models and humans with diabetes.<sup>6-10</sup> There is also evidence that the thiazolidinediones have a direct effect on the kidney.<sup>11</sup>

Few data are available regarding the effects of thiazolidinediones on proteinuria in non-diabetic kidney disease. The only available study is an open-label randomized cross-over study performed by Kincaid-Smith et al. on 40 patients with chronic non-diabetic renal disease in 2003. The authors reported that therapy with rosiglitazone improved the reduction of proteinuria in comparison with other treatment methods.<sup>12</sup>

The reduction of proteinuria is assumed to have a key role in the treatment of renal disease and has a main impact on slowing progression of chronic renal disease.<sup>13,14</sup> There have been few studies about the efficacy of thiazolidinediones in reducing proteinuria among patients with non-diabetic nephropathy. Huge costs of renal replacement therapy and its unavailability in much of the world increase the significance of any new treatment which reduces proteinuria. The aim of this study was to evaluate the effect of pioglitazone on proteinuria among individuals with non-diabetic nephropathy.

## Methods

This study was a self-controlled clinical trial conducted in several private nephropathy clinics from September 2008 to June 2010 to assess the effect of pioglitazone on the rate of proteinuria in patients with existing non-diabetic renal disease.<sup>15</sup> Before the study, ethical approval was obtained from the local research ethics committee at School of Medicine, Isfahan University of Medical Sciences.

Patients aged 18 years or older were eligible for enrolment if they had a level of proteinuria more than 500 mg/day being stable over the past six months and body mass index (BMI) less than 30 kg/m<sup>2</sup> (BMI was calculated as weight in kilograms divided by the square of height in meters). The systolic blood pressure (BP) was required to be controlled (BP  $\leq$  130.85) and stable over the past six months and serum creatinine levels were required to be lower than 4 mg/dl. In addition, patients with diabetes mellitus, class III or IV advanced heart failure, or liver disease (alanine aminotransferase (ALT) > 2.5 fold normal range), as well as those using corticosteroids or other immunosuppressive agents at least 3 months before the admission date were not eligible for the trial. We excluded patients if they had changed their drug dosing of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diltiazem, verapamil and statins, which could have altered urine protein levels. Patients with complication after using pioglitazone, including increased ALT levels three times more than the normal level or progression of heart failure to class III or IV advanced heart failure, were also excluded.

Forty four patients were eligible. After obtaining written informed consents, patients entered the trial and received pioglitazone 15 mg daily for 4 months. The patients were followed up for at least 4 months after completion of their 4-month course of treatment. The primary end point of the study was the reduction of 24-hour urine protein excretion measured prior to the study, at the end of second and fourth months of the treatment and 2 months after cessation of the active drug. The secondary end points included systolic blood pressure, serum creatinine, ALT, aspartate aminotransferase (AST), fasting blood sugar (FBS), blood urea nitrogen (BUN) and glomerular filtration rate (GFR) levels. In this study, we used the Cockcroft-Gault equation as a reliable estimation of GFR. In order to assess their clinical status and monitor the adverse effects, the patients re-

ferred to the clinic every two months during the study.

The descriptive results are shown as mean  $\pm$  SEM (standard error of the mean) for continuous variables and frequency (percentage) for categorical variables. Comparison of various parameters between baseline and different intervals was performed by paired student t-test. Repeated measures analysis of variance (ANOVA) was used to evaluate the changes of 24-hour urine protein excretion levels during the study. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 17.0 (SPSS Inc, Chicago, IL). The level of statistical significance was determined as  $p < 0.01$ .

## Results

Figure 1 shows the flow of the participants through the trial. Of 44 eligible participants, nine patients did not complete the study, i.e. two patients (one male and one female) refused to sign the consent, five (four male and one female) were unwilling to continue, and two (female) discontinued the study due to the side effects. Baseline characteristics of the participants who did not complete the study was not different from those who completed the study (data not shown).

Finally, 35 patients completed the trial. The mean age of patients was  $35.6 \pm 1.7$  years (range: 19 to 56 years). Nineteen patients (59.4%) were male. Averages BMI in patients before the study was  $25.20 \pm 0.56$  kg/m<sup>2</sup> (range: 18.4 to 29.7 kg/m<sup>2</sup>).

At the start of the study (before the intervention), the mean of 24-hour urine protein excretion level was  $1088.6 \pm 131.1$  mg/day which decreased to  $699.9 \pm 118.3$  two months after the intervention, to  $433.9 \pm 68.7$  at the end of the treatment (four months after the intervention), and to  $416.1 \pm 54.9$  six months after intervention (two months after cessation of the drug). However, the average 24-hour urine protein excretion level increased to  $646.9 \pm 89.1$  at the eighth month (four months after the end of the treatment). Overall, results obtained from repeated measures ANOVA indicated

that the trend of reduction in the mean of 24-hour urine protein excretion levels during the study was statistically significant ( $p < 0.0001$ ) (Figure 2).

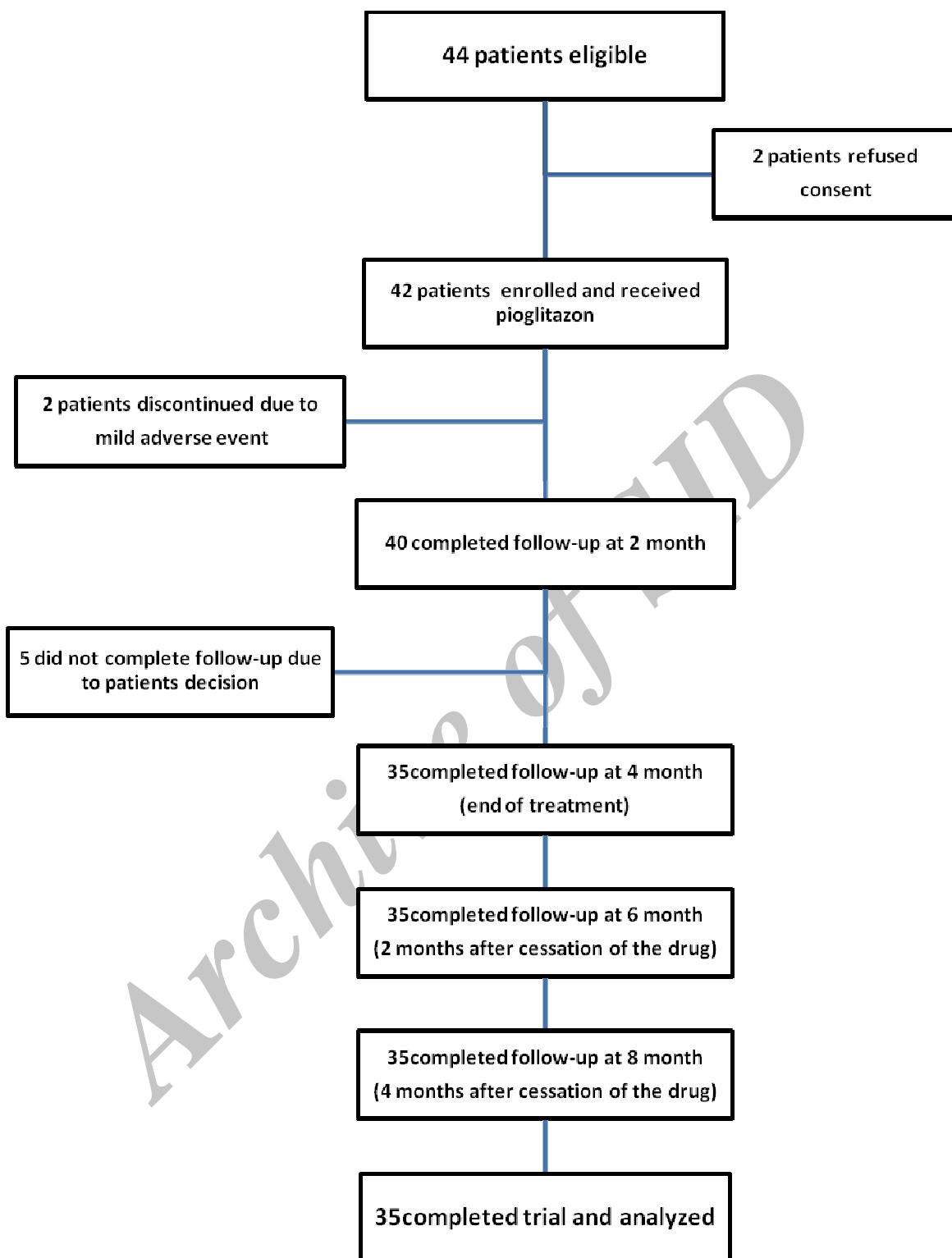
Table 1 shows the results of repeated measures ANOVA that examined the trend in the mean of 24-hour urine protein levels based on sex. Based on the findings in Table 1, the reduction of 24-hour urine protein excretion was statistically significant for both males and females ( $p < 0.001$  for both).

The secondary outcomes showed that four months of pioglitazone therapy had no effects on changes in mean values of serum creatinine, GFR, BUN, systolic blood pressure, FBS, AST, and ALT levels during the treatment phase and the follow-up period. Overall, the results indicated that there were no statistically significant differences in trends of these values ( $p > 0.01$ ) (Table 2).

## Discussion

The reduction of proteinuria is assumed to have a key role in the treatment of renal disease. Pioglitazone is an oral hypoglycemic agent for the treatment of type 2 diabetes.<sup>11</sup> Few studies have shown the effect of pioglitazone on proteinuria in patients with type 2 diabetes.<sup>8,16,17</sup> To the best of our knowledge, this is the first study performed to find the effects of pioglitazone on decreasing proteinuria among patients with existing non-diabetic renal disease. Similar studies were conducted by Ma et al.<sup>18</sup> and Haraguchi et al.<sup>19</sup> to show the effects of thiazolidinediones in animal models.

Here, we report that the treatment with pioglitazone 15 mg per day for 4 months improved the reduction of 24-hour urine protein excretion levels. In the only available study, Kincaid-Smith et al. performed an open-label randomized cross-over study on 40 overweight patients with chronic non-diabetic renal disease. They assigned the patients into two groups and observed a drop of 0.24 g/day in urinary protein levels of patients who received rosiglitazone compared with the baseline. They also found an increasing trend of urinary protein level among the subjects on usual treat-

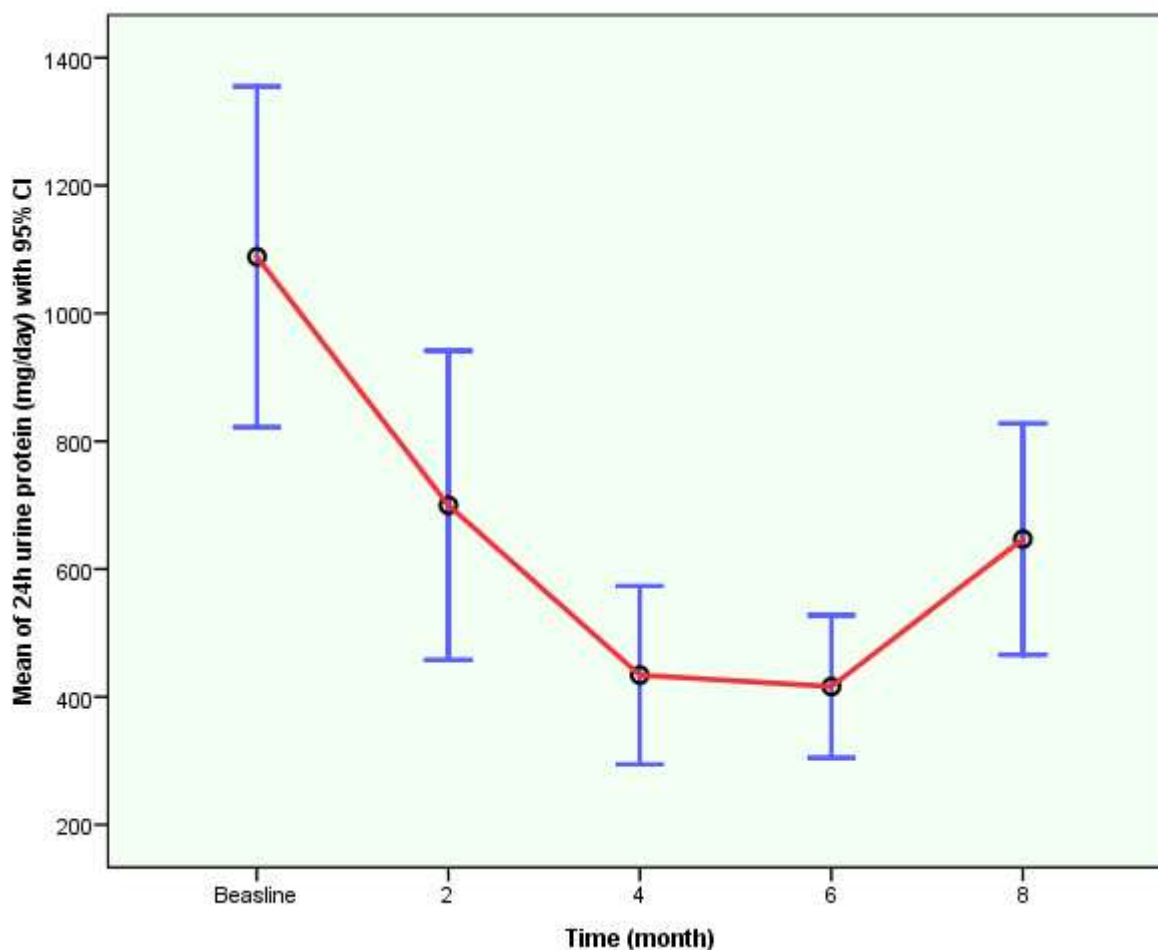


**Figure 1.** Trial Profile

ment (0.12 g/day). On the whole, the investigators reported a statistically significant difference in proteinuria between rosiglitazone

(0.36 g/day) and usual treatments ( $p = 0.002$ ; 95% CI: 0.15-0.58).<sup>12</sup>

Comparing the results obtained at the end



**Figure 2.** Trend in the mean of 24-hour urine protein levels with 95% CI during the study on 35 non-diabetic renal disease patients from September 2008 to June 2010. There was a statistically significant difference between baseline and follow-up times after the treatment ( $p < 0.01$ ).

of the present study with baseline measurements ( $p = 0.001$ ; 95% CI: 0.49-0.82) confirms the findings of Kincaid-Smith et al.<sup>12</sup> suggesting thiazolidinediones to have a main role in the management of non-diabetic proteinuria of various etiologies. This study also showed a significant beneficial effect on proteinuria de-

crease in both male and female patients ( $p$  for trend  $< 0.001$ ).

A potential limitation of our study was making the conclusion based on a relatively small number of studies due to the marked lack of investigations examining the effects of pioglitazone on non-diabetic proteinuria.

**Table 1.** Mean of 24-hour urine protein excretion levels by sex in 35 non-diabetic renal disease patients

	Baseline	at the 2 <sup>nd</sup> month	at the 4 <sup>th</sup> month	at the 6 <sup>th</sup> month*	at the 8 <sup>th</sup> month <sup>†</sup>	$p^{\dagger\dagger}$
Male	1060.5 ± 221.5	706.2 ± 172.6	513.1 ± 130.6	400.1 ± 70.9	677.3 ± 161.6	< 0.001
Female	1112.4 ± 1.7	694.5 ± 168.4	367.3 ± 62.3	429.6 ± 83.2	621.3 ± 96	< 0.001

Values are expressed as mean ± SEM.

\* Two months after the cessation of the drug.

<sup>†</sup> Four months after the cessation of the drug.

<sup>††</sup> P-values calculated by repeated measures analysis of variance.

**Table 2.** Clinical and laboratory values for all 35 non-diabetic renal disease patients undergoing pioglitazone treatment during the study

	Baseline	After 2 months	After 4 months	After 6 months*	p
Systolic blood pressure (mm Hg)	114.1 ± 1.5	115.7 ± 1.5	112.9 ± 1.7	115.1 ± 1.3	NS
Fasting blood glucose (mg/dl)	87.6 ± 1.1	87.3 ± 1	86.9 ± 1	87.9 ± 1	NS
Serum creatinine (mg/dl)	1 ± 0.06	1.1 ± 0.08	1.1 ± 0.07	1.1 ± 0.08	NS
GFR <sup>†</sup> (ml/min)	98.1 ± 5.4	94 ± 4.9	94.1 ± 5.8	95.1 ± 5.3	NS
BUN (mg/dl)	22.1 ± 2	26.4 ± 2.1	27.8 ± 2	25.5 ± 2.2	NS
AST (IU/l)	21.3 ± 1.2	19.1 ± 1.2	18.5 ± 1	19.1 ± 1	NS
ALT (IU/l)	20.5 ± 1.2	20.2 ± 1.3	20.3 ± 1.4	20.2 ± 1.1	NS

Data are shown as mean ± SEM. Results given are from repeated measures analysis of variance.

\* Two months after cessation of the drug

<sup>†</sup> Cockcroft-Gault equation was used for an estimation of GFR.

GFR: Glomerular filtration rate; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; NS: Not significant.

Long-term and parallel-group studies with good sample size are needed to define the therapeutic role of thiazolidinediones in the management of proteinuria in other non-diabetic renal disease patients, such as overweight patients or those with cardiovascular diseases or hypertension. In addition, it seems sensible to design new studies to assess the effects of pioglitazone with different doses in longer follow-up time after cessation of the drug. Therefore, more regard should be given to studies that use direct and indirect measures of variables, such as sex

and age, as end points.

Although there have been no adverse events reported during the treatment, there have been concerns whether thiazolidinediones could precipitate congestive heart failure and active liver diseases.<sup>20,21</sup> We believe further studies need to be performed using adverse events as an end point.

In conclusion, the present study showed that regular use of 15 mg pioglitazone daily seems to be effective in the reduction of proteinuria in patients with existing non-diabetic renal disease.

## Conflict of Interests

Authors have no conflict of interests.

## Authors' Contributions

SSh, MM, SS, MA, and BP designed and conducted the study and prepared the manuscript. AA, SAS, ASN conducted the study, prepared the manuscript, and gathered the data. BP also cooperated in data collection. MA performed the data analyses.

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