Effect of pioglitazone on proteinuria and cardiovascular events in patients with diabetic nephropathy

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Introduction

Diabetes, as an increasing global disease (1), is presently the prominent reason for end-stage kidney failure, requiring dialysis or kidney transplantation to extend human life (2,3). Therefore, proper controlling of blood glucose is very essential in preventing microvascular complications of diabetes and diabetic nephropathy (DN) (4). There are several drugs for managing blood glucose, all of which are not suitable for diabetic patients with chronic renal failure and low glomerular filtration rate (GFR). Thiazolidinediones may be administered without an adjustment dose for chronic renal failure during treatment (5,6). These medications are exogenous and synthetic agonists of PPARγ (peroxisome proliferator-activated receptor gamma) receptors, which decrease lipolysis in fat cells and enhance insulin sensitivity in target tissues in addition to their anti-inflammatory effects. These medications have also a hepatic metabolism and may be administered without risks of hypoglycemia for patients with chronic renal failure (7,8). Insulin resistance has recently been shown to be one of the mechanisms that increase the risk of cardiovascular events and atherosclerosis. Pioglitazone is a thiazolidinedione that in addition to lowering blood glucose, decreases insulin resistance in adipose tissue, liver, and skeletal muscles by 30–45% (5,8). Furthermore, insulin resistance has recently been shown to be one of the mechanisms that increase the risk of cardiovascular events and atherosclerosis. Pioglitazone is a thiazolidinedione that in addition to lowering blood glucose, decreases insulin resistance in adipose tissue, liver, and skeletal muscles by 30–45% (5,8). Furthermore,
by increasing high-density lipoprotein (HDL) levels, decreasing free fatty acids, and serum adiponectin, this medicine may directly prevent cardiovascular events (9).

**Objectives**

There are insufficient data about the impact of pioglitazone on GFR, the severity of interstitial fibrosis, and cardiovascular events as the main cause of death in patients with DN. Owning to the significance of the topic and the need for additional research on the Iranian population, this study aimed at evaluating the impact of pioglitazone on proteinuria, progression of DN, and cardiovascular events.

**Patients and Methods**

**Study design**

The current prospective study was conducted on 55 participants with type 2 diabetes from Sina and Asadabadi educational and treatment hospitals in Tabriz in April-August, 2020. All patients with DN between the ages of 18 and 75 years having a 15 ≤GFR ≤60 mL/min/1.73 m² participated in the study. Patients with progressive dyspnea, congestive heart failure, body mass index (BMI) greater than 40 kg/m², end-stage liver disease, and generalized edema were excluded from the study. The admitted patients were divided into two groups. Patients in the group 1 received 30 mg of pioglitazone once a day along with other blood glucose-lowering treatments. Patients in the group 2 have been treated with other medications except for pioglitazone.

Demographic characteristics including triglycerides, cholesterol, diastolic blood pressure (DBP), systolic blood pressure (SBP), HDL-c, low-density lipoprotein (LDL-c), hemoglobin, hemoglobin A1c (HbA1c), fasting blood glucose (FBS), and 2-hour post-prandial blood sugar (2hpp) were recorded. Renal function markers including GFR and estimation of 24-hour protein excretion were measured every two months for six months. Moreover, patients were followed up, for cardiovascular events such as unstable angina, acute myocardial infarction, heart failure, and brain stroke that required hospitalization.

**Statistical analysis**

For data analysis, SPPS version 18 was used. After defining the normal distribution of quantitative data, the results were reported as median (first quartile - third quartile) or mean ± standard deviation. The T-test or Mann-Whitney U test was utilized to analyze the quantitative data, and the chi-square test was applied to examine the relationship of qualitative data. The results were considered statistically significant if P < 0.05.

**Results**

**Demographic information of patients**

The group 1 consisted of a total of 33 patients with a median age of 62 years, 16 of whom were women and 17 were men. In the group 2 (n = 22), the median age was 61 years; 13 patients were male and 9 patients were female. The average BMI was 23 kg/m² in both groups. The median history of diabetes in both groups was 6 years.

During the six-month follow-up of the patients, no statistically significant differences between the groups in the term of SBP, DBP, cholesterol, triglycerides, HDL-c, LDL-c, hemoglobin, FBS level, 2hpp, and HbA1c in the second, fourth, or sixth month of follow-up (P < 0.05) were observed. Additional details are provided in Table 1.

**The stage of kidney failure**

During the six months of follow-up, GFR did not alter significantly in the group 1 compared to the group 2. In addition, the proteinuria levels between two groups were not statistically different in the month 2, 4, and 6 of follow-up (P ≥ 0.236; Figure 1).

However, within the group 1, the levels of proteinuria revealed a statistically significant drop in the fourth, and sixth months compared to the second month (P < 0.001; Figure 2).

**The incidence of cardiovascular events**

During the six-month period of follow-up, the occurrence of cardiovascular events, including transient ischemic attack and unstable angina was observed in the group 2 in the fourth and sixth months, respectively. Moreover, in the sixth month of the follow-up, 2 cases with cardiovascular events, including transient ischemic attack and unstable angina were identified in the group 1. Thirty (61.2%) patients in the group 1 and 19 (38.8%) patients in the group 2 did not experience any cardiovascular events. However, using Fisher’s exact test with 95% confidence and at an error level of less than 0.05, it was revealed that the ratio of cardiovascular events in the group 1 was not significantly different from the group 2 (P = 0.456). In other words, there was no significant correlation between the use of pioglitazone and the decline in cardiovascular events.

**Discussion**

The present study determined the effect of pioglitazone beyond other glycemic control agents on proteinuria and cardiovascular events in patients with DN. The results of this study demonstrated that this drug reduces 24-hour proteinuria in the group 1, but has no effect on the estimated GFR and the occurrence of cardiovascular events.

The most prevalent cause of chronic renal failure is DN. This disease is characterized by protein excretion of more than 300 mg/d (10). Various studies have indicated that persistent proteinuria is the most significant risk factor for predicting renal injury. Currently, by controlling blood pressure and blood glucose, and using renin-angiotensin-
Table 1. Comparison of the demographic information of the diabetic patients of the two studied groups during 6 months follow-up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2 Months follow-up</th>
<th></th>
<th>4 Months follow-up</th>
<th></th>
<th>6 Months follow-up</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>P value</td>
<td>Group 1</td>
<td>Group 2</td>
<td>P value</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120 (110-140)</td>
<td>130 (120-140)</td>
<td>0.140</td>
<td>120 (110-140)</td>
<td>130 (117.5-140)</td>
<td>0.264</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 (110-130)</td>
<td>130 (117.5-132.5)</td>
<td>0.201</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>80 (80-80)</td>
<td>80 (80-80)</td>
<td>0.928</td>
<td>80 (80-80)</td>
<td>80 (70-80)</td>
<td>0.455</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>80 (72.5-80)</td>
<td>132.5 (109.75-140)</td>
<td>0.459</td>
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<tr>
<td>FBS (mg/dL)</td>
<td>133 (91-146)</td>
<td>130 (116.25-142.5)</td>
<td>0.849</td>
<td>130 (94-140)</td>
<td>140 (117.5-140)</td>
<td>0.339</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 (90-140)</td>
<td>132.5 (109.75-140)</td>
<td>0.459</td>
</tr>
<tr>
<td>2hpp blood sugar (mg/dL)</td>
<td>196 (172-231.5)</td>
<td>200 (180-202.5)</td>
<td>0.755</td>
<td>180 (158-200)</td>
<td>200 (180-200)</td>
<td>0.136</td>
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<td></td>
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<td></td>
<td>180 (155-190)</td>
<td>190 (177.5-200)</td>
<td>0.083</td>
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<tr>
<td>HbA1c (%)</td>
<td>7.1 (6.7-7.65)</td>
<td>7 (6.8-7.5)</td>
<td>0.621</td>
<td>7 (6.9-7.5)</td>
<td>7 (7-7.4)</td>
<td>0.785</td>
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<td>Hemoglobin (g/dL)</td>
<td>12 (10-12)</td>
<td>11 (10-12)</td>
<td>0.509</td>
<td>11.5 (10-12)</td>
<td>11 (10-12)</td>
<td>0.355</td>
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<td></td>
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<td></td>
<td>11.8 (10.5-12)</td>
<td>11 (10-12)</td>
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<tr>
<td>HDL (mg/dL)</td>
<td>35 (35-45)</td>
<td>35 (35-45)</td>
<td>0.482</td>
<td>35 (35-45)</td>
<td>35 (35-45)</td>
<td>0.786</td>
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<td></td>
<td>35 (35-42.5)</td>
<td>40 (35-40.5)</td>
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<tr>
<td>LDL (mg/dL)</td>
<td>70 (65-85)</td>
<td>70 (70-90)</td>
<td>0.238</td>
<td>70 (65.5-90)</td>
<td>70 (70-75)</td>
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<td>70 (65-77)</td>
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<td>Chol (mg/dL)</td>
<td>200 (180-205)</td>
<td>200 (180-200)</td>
<td>0.272</td>
<td>200 (180-200)</td>
<td>200 (180-200)</td>
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<td></td>
<td>190 (180-200)</td>
<td>195 (177.5-200)</td>
<td>0.762</td>
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<tr>
<td>TG (mg/dL)</td>
<td>150 (140-150)</td>
<td>150 (150-150)</td>
<td>0.482</td>
<td>150 (140-150)</td>
<td>150 (147.5-150)</td>
<td>0.876</td>
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</tbody>
</table>

2hpp blood sugar, 2-hour post-prandial blood sugar; Chol, cholesterol; DBP, diastolic blood pressure; FBS, fast blood sugar; HBA1c, Hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride.

Based on non-normal data distribution, results were reported as median (Q1-Q3).
aldosterone system inhibitors, it is possible to slow the development of DN. However, in many cases, despite the use of these methods, kidney damage persists; indicating the involvement of other factors such as inflammation (11). Studies showed that the human nuclear receptor PPAR-γ not only participates in glucose and fat metabolism (12) but also prevents inflammation and fibrosis (13). In an animal study on Zucker rats with diabetes, it was discovered that pioglitazone delays the fibrosis of the interstitial tissue of the kidney in DN by reducing the expression of the Twist-1 gene and thus suppressing the transforming growth factor-β (TGF-β). Based on the findings of this study, the activation of PPAR-γ receptors may be beneficial for preventing DN in rats (14).

Numerous studies have found that insulin resistance is the primary factor linking type 2 diabetes to cardiovascular events. Pioglitazone is the only blood glucose-lowering medication that can improve insulin sensitivity in tissues (15). The 35-month longtime trial on the effect of pioglitazone on 5238 patients with type 2 diabetes highly prone to cardiovascular events showed that this drug could significantly reduce acute unstable angina, stroke, and acute myocardial infarction (16). The defending impacts of pioglitazone on cardiovascular events persevered even in patients with advanced chronic kidney disease, who required dialysis (17). Another study was conducted on 3876 patients with insulin resistance and a history of transient cerebral ischemic attacks or stroke. The result of this study showed that 45 mg of pioglitazone for 4.8 years decreased the risk of acute myocardial infarction, stroke, and acute unstable angina by 24% (15). Although the participants in both studies did not exhibit any symptoms of diabetes and only had insulin resistance, it could be concluded that the positive impacts of pioglitazone on cardiovascular complications of diabetes do not depend on their effects on blood glucose control and related to their effects on reducing insulin resistance. Contrary to these findings, the TOSKA study revealed that pioglitazone did not offer superior protection against diabetic cardiovascular complications when compared to sulfonylureas (18). Likewise, the present study could not find a significant impact of pioglitazone on cardiovascular events.

De Jong et al, in a meta-analysis, concluded that pioglitazone could lower the risk of myocardial infarction and stroke by 23% and 19%, respectively (19). Kernan et al found that the benefits of pioglitazone in reducing non-fatal cardiovascular complications such as unstable angina, myocardial infarction, and the requirement for vascular angiography were not statistically significant, but it could increase non-fatal heart failure. Given the low cost of pioglitazone, some studies suggested that this agent
may be prescribed for diabetic patients (15). Furthermore, Zhou et al discovered that although the prescription of pioglitazone could avoid cardiovascular events in patients with type 2 diabetes, the biggest effect may be seen in individuals having cardiovascular disease backgrounds (20).

Conclusion

Administration of pioglitazone 30 mg along with other blood glucose-lowering drugs to diabetic patients reduces proteinuria to some extent, but this drug does not affect the occurrence of cardiovascular events. It is suggested to perform future studies with a larger sample size and more follow-up to confirm the obtained results.

Limitations of the study

These investigations are still ongoing due to the application of different methods on diverse populations and the contradictory results. Although our study showed the effectiveness of pioglitazone on proteinuria that is in line with most studies, it was not effective on eGFR and reducing the cardiovascular events in the studied groups and it seems that the reason for the mentioned events in both groups is related to the appropriate control of lipid profile and blood pressure (cardiovascular risk factors). Moreover, a long-term clinical follow-up is required for evaluating cardiovascular events.

Authors’ contribution

Conceptualization: FF.
Methodology: FF.
Validation: FF.
Formal analysis: SZV.
Investigation: FF, SZV, SMH.
Resources: SMH.
Data curation: FF.
Writing—original draft preparation: SMH, FF, SZV.
Writing—review and editing: SZV, FF.
Visualization: FF, SZV.
Supervision: FF.
Project administration: FF.
Funding acquisition: BN.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was approved by the Islamic Azad University of Medical Sciences, Tabriz branch, Tabriz, Iran (ethical code # IR.IAU.TABRIZ.REC.1399.049). Written informed consent forms were signed by all participants. This study was extracted from MD., thesis of Nooshin Khadem Haghighi at this university (thesis #13793). Additionally, the authors completely have observed the ethical issues including data fabrication, falsification, plagiarism, double publication misconduct, or submission and redundancy.

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References


