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

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ABSTRACT

Introduction: Slowing the progression of diabetes to DN has established a great deal of interest in recent years.
Objectives: Considering the enormous costs of managing patients with diabetes and the lack of similar studies on the Iranian population, the present study aimed at investigating the effect of pioglitazone on the progression of DN and the prevalence of cardiovascular events.
Patients and Methods: The present prospective study was undertaken on 55 patients with type 2 diabetes who were divided into two groups. The group 1 patients received 30 mg of pioglitazone daily in addition to other blood sugar-controlling drugs. Patients in the group 2 recieved other anti-diabetic medications. During a six-month follow-up period, proteinuria and the occurrence of cardiovascular events were assessed.
Results: The 24-hour urinary proteinuria decreased within the group 1 and these intragroup differences were significant ($P<0.001$) during six months of follow-up compared to month two. There was no significant difference in the ratio of cardiovascular events in the group 1 compared to the group 2.
Conclusion: Adding 30 mg of pioglitazone to other blood sugar-lowering medications could lower proteinuria in individuals with type 2 diabetes; however, it had no impact on the risk of cardiovascular events.

Implication for health policy/practice/research/medical education:
Diabetes is an increasing worldwide disease that causes end-stage kidney failure. There are insufficient data about the impact of pioglitazone on renal function and cardiovascular events in patients with diabetic nephropathy. During this study, it was observed that prescribing pioglitazone along with other blood glucose-lowering drugs reduced proteinuria to some extent in patients with type 2 diabetes. However, this drug does not affect the occurrence of cardiovascular events.

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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,

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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 $15 \leq GFR \leq 60$ mL/min/1.73 m^2 participated in the study. Patients with progressive dyspnea, congestive heart failure, body mass index (BMI) greater than 40 kg/m^2, 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/m^2 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 ($P \geq 0.236$; 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

Characteristics	2 Months follow-up			4 Months follow-up			6 Months follow-up		
	Group 1	Group 2	*P* value	Group 1	Group 2	*P* value	Group 1	Group 2	*P* value
SBP (mm Hg)	120 (110-140)	130 (120-140)	0.140	120 (110-140)	130 (117.5-140)	0.264	120 (110-130)	130 (117.5-132.5)	0.201
DBP (mm Hg)	80 (80-80)	80 (80-80)	0.928	80 (80-80)	80 (80-80)	0.455	80 (70-80)	80 (72.5-80)	0.916
FBS (mg/dL)	133 (91-146)	130 (116.25-142.5)	0.849	130 (94-140)	140 (117.5-140)	0.339	120 (90-140)	132.5 (109.75-140)	0.459
2hpp blood sugar (mg/dL)	196 (172-231.5)	200 (180-202.5)	0.755	180 (158-200)	200 (180-200)	0.136	180 (155-190)	190 (177.5-200)	0.083
HbA1c (%)	7.1 (6.7-7.65)	7 (6.8-7.5)	0.621	7 (6.9-7.5)	7 (7-7.325)	0.785	7 (7-7.4)	7 (7-7.5)	0.535
Hemoglobin (g/dL)	12 (10-12)	11 (10-12)	0.509	11.5 (10-12)	11 (10-12)	0.355	11.8 (10.5-12)	11 (10-12)	0.533
HDL (mg/dL)	35 (35-45)	35 (35-40)	0.482	35 (35-45)	37.5 (35-42.75)	0.786	35 (35-42.5)	40 (35-40.5)	0.475
LDL (mg/dL)	70 (65-85)	70 (70-90)	0.238	70 (65.5-90)	70 (70-75)	0.682	70 (65-77)	70 (70-75)	0.319
Chol (mg/dL)	200 (180-205)	200 (180-200)	0.272	200 (180-200)	200 (180-200)	0.819	190 (180-200)	195 (177.5-200)	0.762
TG (mg/dL)	150 (140-150)	150 (150-150)	0.482	150 (140-150)	150 (147.5-150)	0.876	150 (143-150)	150 (147-.5-150)	0.875

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).
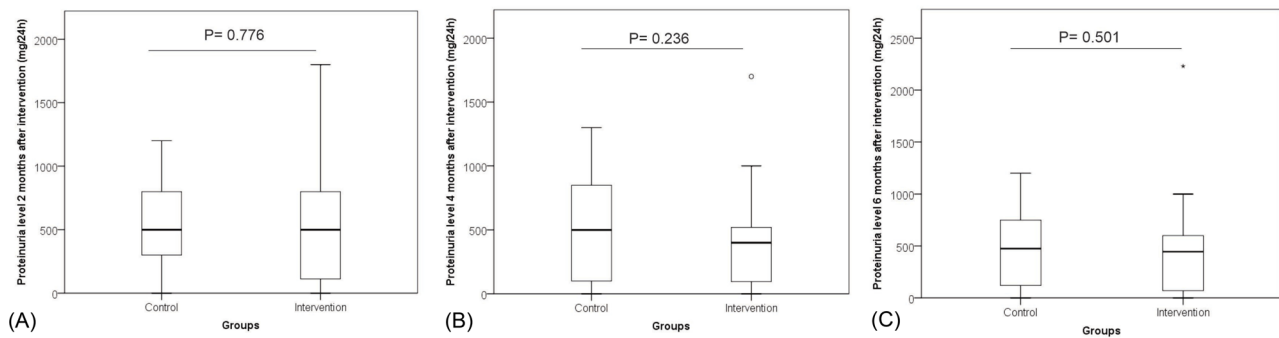
Figure 1. The comparison of 24-hour proteinuria before and after follow-up. The 24-hour proteinuria of diabetic nephropathy patients was shown at 2 months (A), 4 months (B), and 6 months (C) after follow-up. $P < 0.05$ was considered significant.

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
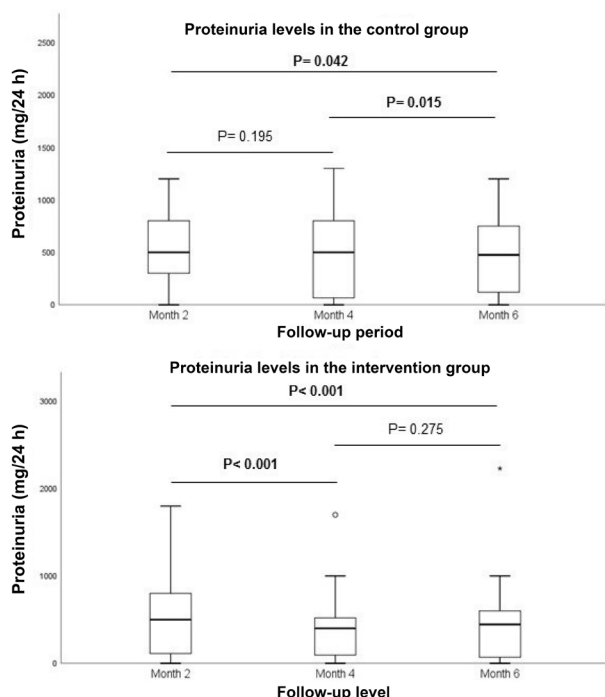
Figure 2. The comparison of 24-hour proteinuria during follow-up months. The 24-hour proteinuria of diabetic nephropathy patients was shown at 2 months (A), 4 months (B), and 6 months (C) after follow-up in the intervention and control groups, separately. *P* value< 0.05 was considered significant.

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 tents 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.

References

1. McGrath K, Edi R. Diabetic kidney disease: diagnosis, treatment, and prevention. Am Fam Physician. 2019;99:751-9.
2. Lin YC, Chang YH, Yang SY, Wu KD, Chu TS. Update of pathophysiology and management of diabetic kidney disease. J Formos Med Assoc. 2018;117:662-75. doi: 10.1016/j.jfma.2018.02.007.
3. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis. 2018;25:121-32. doi: 10.1053/j.ackd.2017.10.011.
4. Lou J, Jing L, Yang H, Qin F, Long W, Shi R. Risk factors for diabetic nephropathy complications in community patients with type 2 diabetes mellitus in Shanghai: logistic regression and classification tree model analysis. Int J Health Plann Manage. 2019;34:1013-24. doi: 10.1002/hpm.2871.
5. Lebovitz HE. Thiazolidinediones: the forgotten diabetes medications. Curr Diab Rep. 2019;19:151. doi: 10.1007/s11892-019-1270-y.
6. Inzucchi SE, Viscoli CM, Young LH, Furie KL, Gorman M, Lovejoy AM, et al. Pioglitazone prevents diabetes in patients with insulin resistance and cerebrovascular disease. Diabetes Care. 2016;39:1684-92. doi: 10.2337/dc16-0798.
7. Satirapoj B, Watanakijthavonkul K, Supasyndh O. Safety and efficacy of low dose pioglitazone compared with standard dose pioglitazone in type 2 diabetes with chronic kidney disease: a randomized controlled trial. PLoS One. 2018;13:e0206722. doi: 10.1371/journal.pone.0206722.
8. Han L, Shen WJ, Bittner S, Kraemer FB, Azhar S. PPARs: regulators of metabolism and as therapeutic targets in cardiovascular disease. Part II: PPAR-β/δ and PPAR-γ. Future Cardiol. 2017;13:279-96. doi: 10.2217/fca-2017-0019.
9. Deedwania P, Acharya T. Cardiovascular protection with anti-hyperglycemic agents. Am J Cardiovasc Drugs. 2019;19:249-57. doi: 10.1007/s40256-019-00325-9.
10. Furuichi K, Shimizu M, Yuzawa Y, Hara A, Toyama T, Kitamura H, et al. Clinicopathological analysis of biopsy-proven diabetic nephropathy based on the Japanese classification of diabetic nephropathy. Clin Exp Nephrol. 2018;22:570-82. doi: 10.1007/s10157-017-1485-7.
11. Zheng S, Powell DW, Zheng F, Kantharidis P, Gnudi L. Diabetic nephropathy: proteinuria, inflammation, and fibrosis. J Diabetes Res. 2016;2016:5241549. doi: 10.1155/2016/5241549.
12. Strongman H, Christopher S, Majak M, Williams R, Bahmanyar S, Linder M, et al. Pioglitazone and cause-specific risk of mortality in patients with type 2 diabetes: extended analysis from a European multidatabase cohort study. BMJ Open Diabetes Res Care. 2018;6:e000481. doi:

10.1136/bmjdrc-2017-000481.

13. Sun L, Xu T, Chen Y, Qu W, Sun D, Song X, et al. Pioglitazone attenuates kidney fibrosis via miR-21-5p modulation. Life Sci. 2019;232:116609. doi: 10.1016/j.lfs.2019.116609.

14. Wang Z, Liu Q, Dai W, Hua B, Li H, Li W. Pioglitazone downregulates Twist-1 expression in the kidney and protects renal function of Zucker diabetic fatty rats. Biomed Pharmacother. 2019;118:109346. doi: 10.1016/j.biopha.2019.109346.

15. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016;374:1321-31. doi: 10.1056/NEJMoa1506930.

16. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. Diabetes Obes Metab. 2016;18:266-73. doi: 10.1111/dom.12608.

17. Yen CL, Wu CY, See LC, Li YJ, Tseng MH, Peng WS, et al. Pioglitazone reduces mortality and adverse events in patients with type 2 diabetes and with advanced chronic kidney disease: national cohort study. Diabetes Care. 2020;43:e152-e3. doi: 10.2337/dc20-1584.

18. Vaccaro O, Masulli M, Nicolucci A, Bonora E, Del Prato S, Maggioni AP, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol. 2017;5:887-97. doi: 10.1016/s2213-8587(17)30317-0.

19. de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. Cardiovasc Diabetol. 2017;16:134. doi: 10.1186/s12933-017-0617-4.

20. Zhou Y, Huang Y, Ji X, Wang X, Shen L, Wang Y. Pioglitazone for the primary and secondary prevention of cardiovascular and renal outcomes in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis. J Clin Endocrinol Metab. 2020;105dgz252.doi:10.1210/clinem/dgz252.