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Original Article

Effect of pioglitazone on decreasing of proteinuria in type 2 diabetic patients with nephropathy☆

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ABSTRACT

Introduction: Diabetic nephropathy that means albuminuria greater than 30 mg/day, affects about one third of diabetic patients. There are many studies about the effect of different medications for diabetic nephropathy with controversy in their results. So, the aim of the study was to investigate the effect of pioglitazone on decreasing of proteinuria in type II diabetic patients and nephropathy.
Methods and materials: It is a double blind clinical trial. At first, 2356 medical carts of the patients were evaluated and 76 patients with type 2 diabetes mellitus with proteinuria greater than 250 mg / day were enrolled in 2 equal groups. In the case group, pioglitazone 15 mg/day was prescribed and patients in the control group received placebo for two months. At the beginning of the study and after 2 months, urinary protein during 24 h was measured in all of the patients and data were entered to SPSS (version23) and evaluated by using Chi- square, Mc Nemar, paired t-test and logistic regression model.
Results: At the beginning of the study, urine protein during 24 h in the case and control groups were 957.7 ± 385.1 and 972.1 ± 378.6 respectively ($P = .872$). So, after 2 months the mean proteinuria in the case and control groups were 647.3 ± 367.2 and 896 ± 372.4 respectively that is valuable ($P = 0.005$). Pioglitazone had the considerable effect on FBS,HbA1c and blood triglyceride too.
Conclusion: The study showed that low dose of pioglitazone is an effective, safe and inexpensive method in reducing of proteinuria in type2 diabetic patients with nephropathy.

1. Introduction

Type 2 diabetes is a type of the metabolic disorder that is recognized with high levels of glucose in the blood which is due to a resistance status against insulin and relative insulin deficiency.

Type 2 diabetes is recognized by three pathophysiologic abnormalities: insulin secretion, insulin resistance, and excessive glucose production by the liver. Diabetes is common in both developed and developing countries. Obesity is common in type 2 diabetes mellitus. The rate of diabetes has risen dramatically over the 50 years ago as obesity has increased. Over the two decades ago, the global prevalence of diabetes has increased from an estimated 30 million in 1985 to 382 million in 2013. 90% of individuals with diabetes suffer from type 2 diabetes, and 10% have type 1 diabetes mellitus and gestational diabetes, respectively. The cause of resulting type 2 diabetes is related to lifestyles and genetic factors. Some factors related to life style such as lack of physical activity, unsuitable diet, stress, obesity, and urbanization. Moreover, nutritional factors increase the risk of developing type 2 diabetes. Most people with type 2 diabetes have had a strong genetic basis, and Its incidence is among identical twins between 70% and 90%. Recent studies have revealed the role of more than 70 genes for the appearance of this disease. Diabetes is one of the main causes of mortality. In the United States, diabetes was reported as the seventh major cause of death in 2010. It has been shown in one of recent estimates that 8% of mortality caused by diabetes disease in 2013 in all over the world.

life expectancy has decreased in type 2 diabetes, because of cardiovascular and renal diseases. In developed countries, type 2 diabetes is the major cause of blindness and renal failure. In addition, the risk of mental impairment and dementia is increased by involving cerebrovascular accidents. Diabetic nephropathy illustrates with a progressive increase in protein excretion (proteinuria), which is observed in prolonged diabetes, decrease renal function and ultimately led to renal failure. Type II diabetes mellitus is the most important factor of chronic renal failure, followed by final stage of renal failure that causes death in diabetic patients. About 40% of End Stage Renal Disease(ESRD) was due to diabetes leaded to spend more than $ 4 billion per year in the

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United States. Also, about 30% of patients with type 1 diabetes and less percentage of patients with type 2 diabetes eventually develop ESRD. Of course, because of the higher prevalence of type 2 diabetes, the number of cases of type II diabetes is higher. Although infections and inflammatory diseases such as types of glomerulonephritis in the past were the most common causes of ESRD, diabetes and high blood pressure are now the most common causes of this disease [1].

The primary evidence of nephropathy shows the existence of very low levels of albumin in the urine (30 mg/day), called microalbuminuria and the microalbuminuria patient is considered as primary nephropathy. Then microalbuminuria may progress to macroalbuminuria (higher than 300 mg/day) or severe nephropathy. When severe proteinuria is observed, a continuous decrease in glomerular filtration rate will occur. Hypertension is commonly associated with albuminuria and nephropathy [2].

The main mechanism for diabetic nephropathy is not clear, but several risk factors involve. One of the serious risk factors for nephropathy in diabetic patients is hypertension. The other factor is high hemoglobin glycosylated (higher than 9%) mentioned as increasing risk factor of nephropathy. Diabetic patients with obesity and overweight are also at risk for nephropathy based on Body Mass Index (BMI). Also, the duration of diabetes and the age of the patient predict the progression of nephropathy [1]. In a study, glycosylated hemoglobin, smoking, the duration of diabetes, systolic blood pressure and diastolic blood pressure showed a significant relationship for nephropathy [2].

Hyperglycemia makes injury to arteries by several complex mechanisms. Inflammatory cytokines produced by inflammatory cells cause damage to the renal cells and accelerate changing epithelial cells to mesenchymal cells and increase extracellular matrix. Immunological and inflammatory mechanisms play an important role in the progression of diabetic nephropathy by activating immune cells and increasing the production of inflammatory molecules. The exact control of blood glucose and blood pressure can decrease the progression of the disease in the initial stages of kidney involvement in patients with diabetes and especially when protein excretion is still in low level, and even it is possible to improve this condition. In more advanced stages, protein excretion is more. However, blood glucose control, consumption restriction, and blood pressure control are effective in decreasing the process of the disease, but it does not stop the trend of the disease. Currently, diabetic nephropathy is treated with ACE inhibitors or angiotensin receptor blockers(ARBs) in addition to blood glucose reducing drugs. Also, limited diets of protein and sodium are used, nevertheless, the prevalence of diabetic nephropathy and diabetes-induced renal failure is still at the high level.

By reducing proteinuria, progression of renal damage to ESRD will be slowed. So, it will improve patients' life and decrease morbidity and costs of end- stage renal disease. Such studies are necessary for achieving these purposes.

2. Materials and methods

The present study was done in the year 2017 with clinical trial code IRCT2017080210222N10. This is a double-blind, randomized clinical trial (prescribing person and also patients who received the drugs (placebo or pioglitazone) were not aware of these two consumed drug types. The variable of research was urine protein excretion rate in 24 h. At first, written informed consent was obtained from the patients and the research objectives were explained to them. Patients were assured that their information would remain as a secret and they are not shared with any individual or group. Patients were examined by a nephrologist. The population under study was 2356 cases of patients, documents in the Nephrology ward of Imam Ali Clinic, Shahrekord. Inclusion criteria were: type 2 diabetic patients, 24-h urine protein more than 250 mg/day, without hypothyroidism and heart failure, HbA1C less than 8, blood pressure less than 160/100, creatinine lower than 2 or GFR greater than 50, and exclusion criteria was undesirable cooperation during the study, and considerable drug side effects. Sample size and sampling of patients referred to Imam Ali Hospital with type 2 diabetes, who had inclusion criteria was 76 patients in the study, 38 patients in each group.

76 patients with type 2 diabetes mellitus with 24-hour urine protein >250 mg/day were selected and then they were divided into two groups, including the group receiving pioglitazone 15 mg daily and the placebo group for two months with stratified randomization that is they were identical in terms of proteinuria rates (three groups of proteinuria (less than 600 mg, 600–1200 mg and 1201 mg and above), During the study, one patient in the pioglitazone group and two in the placebo group due to lack of proper cooperation were excluded. 24-h urine protein was determined before intervention and 2 months later. The results were recorded in the checklist and analyzed by statistical tests. Data entered in the SPSS software (version23) and analyzed using descriptive statistics, Chi- square, Mc Nemar, paired t-test and logistic regression model.

3. Results

In this study, the following results were obtained by comparing the effect of pioglitazone on proteinuria in patients with type 2 diabetes with nephropathy in Imam Ali Clinic, Shahrekord. A total of 73 diabetic patients with type II diabetic nephropathy (37 cases and 36 controls) participated in the current study. The age range of the patients was between 54–71 years with a mean of 62.8 ± 3.8. 35 patients (47.9%) were female and the rest were male. No difference was observed based on sex in the two groups ($P = 0.73$).

Duration of diabetes mellitus, glomerular filtration rate (GFR), systolic and diastolic blood pressure had no valuable difference in the case and control groups The quantitative characteristics of patients in two groups were summarized in Table 1. It showed that the two groups were identical except for age.

The mean of glomerular filtration rate was 66.9 ± 8.5 in the case group and 68.3 ± 8.6 in the control group.

Systolic blood pressure in the case group was 134.9 ± 8.7 and in the control group was 131.7 ± 8.4. Diastolic blood pressure in the intervention group was 80.9 ± 8.9 and in the placebo group was 82 ± 6.3.

Patients' consumed drugs in two groups during the study displayed in Table 2.

Consumption of ACE/ARB, statins, oral hypoglycemic drugs, diltiazem and insulin was compared in the case and control groups. In terms of ACE / ARB consumption, in the first group (intervention group), 94.6% (35 patients) used drug, and 5.4% (2 patients) did not use the drug, and in the second group (placebo), 97.2% (35 patients) had drug use, And 2.8% (1 people) didn't use drug.

Regarding the use of statin in the intervention group, 91.9% (34 patients) use drugs and 8.1% (3 non-drug users) and in the placebo

Table 1
Mean of pretest variables in the intervention and control groups.

Group Variables	Case Mean ± SD	Control Mean ± SD	P-value
Age(year)	63.8 ± 3.9	61.7 ± 3.3	0.012
Duration of diabetes mellitus (year)	11.8 ± 1.8	11.5 ± 2.7	0.526
Glomerular filtration rate	66.9 ± 8.5	68.3 ± 8.6	0.490
Blood pressure Systolic (mmHg)	134.9 ± 8.7	131.7 ± 8.4	0.114
Blood pressure Diastolic (mmHg)	80.9 ± 8.9	82 ± 6.3	0.530

Table 2
Patients' consumed drugs in two groups during the study.

Group Consumed drugs	Case Frequency	Percent	Control Frequency	Percent	P-value
ACE/ARB	35	94.6	35	97.2	1
Statin	34	91.9	33	91.7	1
Oral hypoglycemic drugs	36	97.3	34	94.4	0.615
Diltiazem	10	27	12	33.3	0.557
Insulin	3	8.1	3	8.3	1

group 8.3% (3 people) did not use and 91.7% (33 people) had drug use.

In terms of oral hypoglycemic agents, in the case group 2.7% (1 patients) did not use drugs, 97.3% (36 people) used the drug, and in the control group, 5.6% (2 patients) didn't use, and 94.4% (34 patients) had drug usage.

Regarding the use of diltiazem in the case group, 73% (27 patients) did not use the drug and 27% (10 patients) used the drug, and in the control group, 66.7% (24 patients) did not take drugs and 33.3 Percentage (12 people) took medication.

In the case group, 8.1% (3 patients) used insulin and 91.9% (34 patients) didn't use insulin, and in the control group 8.3% (3 patients) used insulin and 91.7% (33 patients) did not use the drug.

With regard to the meaningful view, there is no difference in patients' consumed drugs in these two groups.

The amount of measured parameters before and after intervention in two groups included in Table 3. Body mass index (BMI) was 28.03 ± 2.08 in the first group (receiving pioglitazone) and 27.67 ± 2.06 in the control group (placebo) ranged from 24 to 33. Regarding the biochemical parameters, there was a significant decrease in 24hr urine protein in the case group compared to the control group. This means that there was no significant difference between the two groups before the intervention, but after the intervention, this difference was significant ($p = 0.005$). The results indicated that the average 24-hour urine protein level at the beginning of the study and before the onset of the intervention (receiving the drug) was 957.7 ± 385.1 mg/d, which after the intervention and consuming pioglitazone within two months the 24hr urine protein reached to 647.3 ± 367.2 mg/d. Mean HbA1C had a significant difference before and after the intervention ($p < 0.001$). The mean before the study was 7.38 ± 0.32 and after the intervention was 7.01 ± 0.22, which was higher than the control group but there was no significant difference in HbA1C before and after intervention in the control group. FBS had a significant difference before and after the intervention ($p < 0.001$) in the case group. The mean before the study was 125.41 ± 16.52 and after the intervention was 110.62 ± 14.5, which was higher than the control group but there was no significant difference in FBS before and after intervention in the control group.

Two-hour post prandial blood sugar (2hrppBS) and LDL had no valuable difference in the case and control groups after intervention($p = 0.149$ and $p = 0.228$ respectively).

Triglyceride level reached from 164.3 ± 48.2 to 138.4 ± 14.07 after intervention in the case group ($p < 0.001$), but in the control group it decreased from 156.1 ± 42.4 to 154.9 ± 40.08 ($p = 0.515$) and significant difference is between these two groups after intervention($P < 0.001$).

The abundance of proteinuria level based on the level of proteinuria reported before and after the study in two groups in Table 4.

We observed after the intervention, the reduction level of proteinuria was more in the intervention group. The McNemar test showed these changes that there was a decrease in the proteinuria level in both groups ($P < 0.01$)

4. Discussion

Diabetic nephropathy is a major microvascular complication in long-standing diabetic patients who eventually undergo renal

Table 3
The average amount of studied parameters before and after the intervention and its changes in two groups.

parameter	Group	Case Mean ± SD	Control Mean ± SD	P-value
Proteinuria(mg/d)	Pretest	957.7 ± 385.1	972.1 ± 378.6	0.872
	Posttest	647.3 ± 367.2	896 ± 372.4	0.005
	Significant rate of pretest and posttest	<0.001	0.011	–
	Difference of pretest and posttest	310.5 ± 112	76.2 ± 170.9	<0.001[a]
FBS(mg/dl)	Pretest	125.41 ± 16.52	122.92 ± 12.85	0.476
	Posttest	110.62 ± 14.5	122 ± 10.24	<0.001
	Significant rate of pretest and posttest	<0.001	0.542	–
	Difference of pretest and posttest	14.8 ± 7.9	0.92 ± 8.9	<0.001[a]
BS -2 hr PP(mg/dl)	Pretest	145.1 ± 14.3	142.4 ± 8.8	0.33
	Posttest	142.3 ± 13.03	142.3 ± 8.82	0.994
	Significant rate of pretest and posttest	<0.001	0.898	–
	Difference of pretest and posttest	2.8 ± 4.4	0.16 ± 7.74	0.149[a]
HbA1c(%)	Pretest	7.38 ± 0.32	7.36 ± 0.28	0.694
	Posttest	7.01 ± 0.22	7.36 ± 0.27	<0.001
	Significant rate of pretest and posttest	<0.001	0.856	–
	Difference of pretest and posttest	0.37 ± 0.14	0.002 ± 0.09	<0.001*
Triglyceride(mg/dl)	Pretest	164.3 ± 48.2	156.1 ± 42.4	0.445
	Posttest	138.4 ± 14.07	154.9 ± 40.08	0.089
	Significant rate of pretest and posttest	<0.001	0.515	–
	Difference of pretest and posttest	25.9 ± 11.2	1.2 ± 11.1	<0.001[a]
LDL(mg/dl)	Pretest	98.03 ± 15.6	98.9 ± 16.3	0.818
	Posttest	97 ± 12.32	100.66 ± 16.77	0.289
	Significant rate of pretest and posttest	0.531	0.352	–
	Difference of pretest and posttest	1.05 ± 10.15	1.78 ± 11.3	0.228[a]
BMI(kg/m2)	Pretest	28.03 ± 2.08	27.52 ± 2	0.301
	Posttest	28.03 ± 2.08	27.67 ± 2.06	0.454
	Significant rate of pretest and posttest	0.324	<0.001	–
	Difference of pretest and posttest	0.005 ± 0.032	0.14 ± 0.099	<0.001[a]

[a] Probability values are corrected for age(logistic regression model).

Table 4
Abundance of proteinuria level during the study in two groups based on level of proteinuria.

Group		Case		Control		P-value
Stage		Frequency	Percent	Frequency	Percent	
Pretest	Less or equal of 600	10	27	9	25	0.981
	Between 601-1200	17	46	17	47.2	
	Equal and higher than 1201	10	27	10	27.8	
Posttest	Less or equal of 600	22	59.5	8	22.2	0.005
	Between 601-1200	10	27	20	55.6	
	Equal and higher than 1201	5	13.5	8	22.2	

dialysis or transplantation. Achieving the best metabolic control (A1c < 7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol <100 mg/dl) are effective strategies for preventing the development of microalbuminuria, in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes [1]. To prevent development of this disease and to improve advanced kidney injury, effective therapies directed toward the key molecular target are required. Metabolic and hemodynamic alterations have been considered as the classical factors involved in the development of renal injury in patients with diabetes mellitus. However, the exact pathogenic mechanisms and the molecular events of diabetic nephropathy remain incompletely understood. Nowadays, there are convincing data that relate the diabetes inflammatory component with the development of renal disease [7].

Three subtypes of the PPAR nuclear fatty acid receptors have been identified: alpha, beta/delta and gamma. PPAR alpha is believed to participate in fatty acid uptake (beta- and omega-oxidation) mainly in the liver and heart. PPAR beta/delta is involved in fatty acid oxidation in muscle. PPAR gamma is highly expressed in fat to facilitate glucose and lipid uptake, stimulate glucose oxidation, decrease free fatty acid level and ameliorate insulin resistance. Synthetic ligands for PPAR alpha and gamma such as fibric acid, and thiazolidinediones have been used in patients with type 2 diabetes and pre-diabetic insulin resistance with significantly improved HbA1c and glucose levels. In addition, non-hypoglycemic effects may be elicited by PPAR agonists or dual agonists including improved lipid metabolism, blood pressure control and endothelial function, as well as suppressed atherosclerotic plaque formation and coagulation. However, issues of safety and clinical indication remain undetermined for use of PPAR agonists for the incidence of heart disease in metabolic syndrome and type 2 diabetes [10]. In Brun RP and et al. study, data strongly suggest that PPAR gamma is the predominant receptor regulating adipogenesis; however, they also suggest that PPAR alpha may play a role in differentiation of certain adipose depots in response to a different set of physiologic activators or in certain disease states [8]. In Ko GJ et al study, they investigated the effect and molecular mechanism of the PPAR gamma agonist, pioglitazone, on the progression of diabetic nephropathy in type 2 diabetic rats. It reaveled that pioglitazone not only improves insulin resistance, glycemic control and lipid profile, but also ameliorates renal injury through an anti-inflammatory mechanism in type 2 diabetic rats [16]. There are some evidence that thiazolidinediones had a direct effect on the kidneys through the activation of PPAR receptors identified in the kidneys. The animal studies conducted by Ma et al. [20] and Haraguchi et al. [19], Jin et al [15] have also mentioned the effects. Katavetin et al. [12] reported a significant decrease in the mean of the urinary protein excretion from 1.64 to 0.98 g/day, that is similar to this study and no significant difference in the blood glucose control and blood pressure in both treatment and control groups. In another study by Agarwal et al., it was found that there was a significant decrease in the proteinuria level in the pioglitazone group [13].

The accumulation of advanced glycosylated end-products (AGEs), the activation of isoform(s) of protein kinase C (PKC) and the acceleration of the aldose reductase pathway may explain how hyperglycemia damages tissue. PKC is one of the key signaling molecules in the induction of the vascular pathology of diabetes. A number of gene loci have been investigated to try to explain the genetic susceptibility to diabetic nephropathy [4]. Advanced glycation end products (AGEs) have been implicated in the pathogenesis of diabetic kidney disease [8]. In Myint KM study, they examined whether inhibition of the receptor for advanced glycation end products (RAGE) could attenuate changes in the diabetic kidney. Inactivation of the RAGE gene in a mouse model of diabetic nephropathy results in significant suppression of kidney changes, including kidney enlargement, increased glomerular cell number, mesangial expansion, advanced glomerulosclerosis, increased albuminuria, and increased serum creatinine compared with wild-type diabetic mice [5].

The efficacy of renin-angiotensin system (RAS) blockers on type 2 diabetes studied by Fukuda M. This study was undertaken to test the hypothesis that candesartan may enhance the protective effects of pioglitazone against type 2 diabetes. Their work demonstrated that candesartan significantly potentiated the protective effects of pioglitazone against cardiorenal and vascular injury, and diabetes in obese type 2 diabetic mice. Thus, the combination of pioglitazone with candesartan is potentially a promising therapeutic strategy for type 2 diabetes [14]. Angiotensin-converting enzyme (ACE) is a key regulator of the renin-angiotensin system (RAS). ACE2 is a newly described enzyme identified in rodents and humans with a more restricted distribution than ACE, and is found mainly in heart and kidney. ACE2 might act in a counter-regulatory manner to ACE, modulating the balance between vasoconstrictors and vasodilators within the heart and kidney, and playing a significant role in regulating cardiovascular and renal function [5]. It was revealed that pioglitazone reduces pro-inflammatory markers in patients with overt diabetic nephropathy, which indicates potentially beneficial effects on overall cardiovascular risk. This surrogate endpoint needs to be confirmed in trials designed to demonstrate cardiovascular protection [14]. Tanimoto M, showed that the effect of pioglitazone on microalbuminuria might not be due to changing systemic blood pressure and blood glucose levels. It appears that the decrease of urinary albumin excretion might be related to improvement of glomerular enlargement, including hyperfiltration, since the levels of endothelial constitutive nitric oxide synthase (ecNOS) protein were reduced by pioglitazone in the glomerular vessels [17]. In a study by Abe et al in 2007 about the efficacy of pioglitazone in the controlling blood glucose in 20 dialysis patients, patients were treated with 15 mg pioglitazone in the first 4 weeks with a meal in the morning. If the unwanted effects of the drug do not appear, the dosage of the drug can be

increased up to twice as much. In the results, pioglitazone was significantly effective in reducing HbA1c, triglyceride and systolic and diastolic blood pressure [9].

A reduction of proteinuria in patients with the non-diabetic renal disease was observed during the 4-month treatment with pioglitazone which continued for 2 months after the cessation of the treatment was shown in Shahidi S et al. study. However, 4 months after the cessation of the treatment, a little increase was detected in the level of proteinuria [18]. In this study, the group consumed pioglitazone, their urine protein levels decreased significantly compared to the beginning of the trial.

In the current study regarding p-value of less than 0.001, it indicated a positive effect of the drug on the reduction of urine protein. The results of t-test showed that there was a significant decrease in HbA1c, FBS and triglyceride in the case group after intervention but with no considerable effect on LDL, 2hrppBS and BMI. Therefore, the initiation of drug use at lower proteinuria levels will be associated with an increased chance of treatment. Due to the young nature of these studies on the effect of tiazolidinedione drugs family on reducing proteinuria of patients with type 2 diabetes and nephropathy, consideration of the problems and limitations of these studies may play an important role in the continuation of the pathway of researchers. Although there is no specific complication in this study, since the possibility of heart or liver complications with this drug alone and in combination with other common drugs has not yet been addressed, studies are needed to evaluate the tolerable side effects in these patients.

5. Conclusion

Based on the results of this study, the use of pioglitazone was effective in decreasing the level of urine protein in patients with type 2 diabetes and nephropathy for two months and no side effects were observed using this drug. It is suggested to evaluate the benefits and side effects of taking pioglitazone in Diabetic Nephropathy, a similar study should be conducted over a longer period of time.

Limitations of research

Failure to follow up and not referring again patients were problems and limitations of the study. If samples were dropped, new samples were selected according to the criteria for entering and leaving the study and were included in the study.

Conflict of interest

There is no conflict of interest in this project.

Acknowledgment

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