

RESEARCH ARTICLE

Renal Outcomes of Pioglitazone Compared with Acarbose in Diabetic Patients: A Randomized Controlled Study

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Abstract

Objective

To assess the effect of pioglitazone on renal outcome, including urinary albumin excretion and estimated glomerular filtration rate (eGFR), in diabetic patients.

Design

A prospective, randomized, open-labeled, controlled study.

Setting

Taipei Veterans General Hospital.

Patients

Sixty type 2 diabetic patients treated with sulfonylureas and metformin, whose glycated hemoglobin (HbA1c) levels were between 7% and 10% and eGFR was between 45 and 125 mL/min/1.73 m².

Intervention

The patients were randomized to receive acarbose or pioglitazone and followed up for 6 months. Thirty patients were randomly assigned to receive acarbose, and 30 patients were assigned to receive pioglitazone.

Measurements

The primary study endpoint was the changes in the urinary albumin-to-creatinine ratio (UACR). The secondary endpoint was the changes in eGFR and other parameters.

Results

After 6 months of treatment, the mean changes in UACR were -18 ± 104 and 12 ± 85 ($p = 0.25$, between groups) for the acarbose and pioglitazone groups, respectively. The mean changes in eGFR were 0 ± 14 and -7 ± 16 mL/min/1.73 m² ($p = 0.09$, between groups) for the acarbose and pioglitazone groups, respectively. The reductions in HbA1c were similar in both groups. Fasting blood glucose was lower in the pioglitazone group than in the acarbose group. Significant body weight gain was observed in the pioglitazone group as compared with the acarbose group (1.3 ± 2.8 vs. -0.6 ± 1.5 kg, $p = 0.002$).

Conclusion

In type 2 diabetic patients who were treated with sulfonylureas and metformin and possessed HbA1c levels between 7% and 10%, additional acarbose or pioglitazone for 6 months provided similar glycemic control and eGFR and UACR changes. In the pioglitazone group, the patients exhibited significant body weight gain.

Trial Registration

ClinicalTrials.gov [NCT01175486](https://clinicaltrials.gov/ct2/show/study/NCT01175486)

Introduction

Diabetic end-stage renal disease increases the risk of cardiovascular events and mortality [1,2]. It is important to prevent or delay progression of diabetic nephropathy in order to reduce the subsequent morbidity and mortality. Thiazolidinediones (TZDs) are one kind of oral anti-diabetic drugs. TZDs are insulin sensitizers that decrease plasma glucose and improve the lipid profile of type 2 diabetic patients [3]. TZDs initiate their action by binding to peroxisome proliferator-activated receptor- γ (PPAR γ) [3]. Although PPAR γ receptors are most abundant in fat cells [3,4], they have also been demonstrated in the mesangium and glomerulus of kidney [5,6]. Studies on rodents have suggested that TZDs can prevent diabetic nephropathy [6–8]. TZDs reduce urinary albumin excretion and proteinuria in diabetic nephropathy [9,10]. TZDs may control blood glucose as well as protect kidney. Till now, studies investigating the impact of TZDs on the estimated glomerular filtration rate (eGFR) are few, and the results are conflicting. Therefore, we conducted a randomized controlled study to investigate the effects of pioglitazone, a kind of TZD, on urinary albumin excretion and eGFR in type 2 diabetic patients as compared with those treated with acarbose.

Materials and Methods

Study design

This prospective, randomized, open-labeled, controlled study was conducted in Taipei Veterans General Hospital to assess the effects of TZDs on diabetic nephropathy. We enrolled type 2 diabetic patients who had been treated with sulfonylureas and metformin, and their glycated hemoglobin (HbA1c) levels were between 7% and 10%. These patients were randomly assigned to additional 50 mg of acarbose treatment three times per day or 30 mg of pioglitazone once per day for a 6-month intervention period. These patients were followed up for 6 months to investigate the short-term effects on diabetic nephropathy. This study was approved by the

Institutional Review Board of Taipei Veterans General Hospital, and all clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was given before the randomization.

Subjects

Type 2 diabetic patients who were regularly followed up in Taipei Veterans General Hospital were invited to participate in this study. Inclusion criteria were type 2 diabetes, between 20 and 80 years old, receiving sulfonylureas and metformin treatment, and HbA1c between 7% and 10%. The exclusion criteria were insulin treatment and/or eGFR <45 or >125 mL/min/1.73 m². Patients with cardiovascular diseases, malignancy, pregnancy, acute illness, congestive heart failure (according to the New York Heart Association functional class III to IV), or liver cirrhosis were also excluded.

Procedures

The baseline information, including age, gender, diabetic duration, body mass index, blood pressure, smoking status, laboratory data, and concomitant medicine, was collected upon enrollment. The body weight, blood pressure, HbA1c concentration, fasting blood glucose, lipid profile, serum creatinine concentration, and urinary albumin-to-creatinine ratio (UACR) were examined at 12 and 24 weeks after randomization. The glomerular filtration rate was estimated using a prediction formula from the four-variable Modification of Diet and Renal Disease study equation [11]. All assessments of urine and blood were performed at a central laboratory.

Patients continued to receive their usual care according to our national guideline for diabetes. Arterial hypertension was treated via a stepwise approach with the target blood pressure <140/90 mmHg. Dyslipidemia was treated with statins to reach the targets of serum total cholesterol <160 mg/dL. No restriction on dietary salt or protein was implemented.

Assays

HbA1c was measured by high-performance liquid chromatography (HLC-723G7, Tosoh, Japan) with a reference range of 4.2%–5.8%. The inter-assay coefficients of variance were <2% at mean HbA1c levels between 4.4% and 8.2%. The urinary albumin concentration was determined by nephelometry, whereas the serum creatinine concentration was examined by Jaffe reaction with a Hoffmann–LaRoche kit. The glomerular filtration rate was estimated using a prediction formula from the four-variable Modification of Diet and Renal Disease study equation [11].

Outcome measures

The primary study outcome was the changes in UACR. The secondary outcome was the alteration in eGFR. Other outcomes were the variation in glycemic control and body weight.

Statistical analysis

Measurements were summarized using the mean \pm standard deviation or using the median with interquartile range (IQR) as appropriate. Comparisons between pioglitazone and acarbose groups were performed using the two sample *t*-test for those variates that were approximately normally distributed and the Wilcoxon-Mann-Whitney test otherwise. Categorical data were summarized using percentages and group comparisons were performed using the χ^2 test. Comparisons between pre and post treatment within each group were performed using the paired

t-test. Comparisons of changes from pre to post treatment between groups were performed using the two sample *t*-test. Statistical significance was declared at the 0.05 level. Statistical analysis was performed with SPSS for Windows version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

We screened 85 type 2 diabetic subjects treated with sulfonylureas and metformin between July 2010 and June 2012 after two years of recruitment. In total, 65 patients were randomly assigned to additional acarbose ($n = 34$) or pioglitazone ($n = 31$) treatment, and 60 patients completed the 6 months of intervention (Fig 1). Baseline characteristics were generally similar between two groups, except there were more women, fewer smokers, and less use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in the pioglitazone group (Table 1). The mean age of the participants was 66.7 years, mean diabetes duration was 11.9 years, mean body weight was 67.4 kg, mean body mass index was 28.1 kg/m², mean systolic blood pressure was 135 mmHg, mean fasting blood glucose was 171 mg/dL, mean HbA1c was 8.26%, mean serum creatinine concentration was 0.84 mg/dL, mean eGFR was 88 mL/min/1.73 m², and median UACR was 18 mg/g.

After 6 months of intervention, HbA1c and fasting plasma glucose improved in both groups. The reductions in HbA1c were similar in both groups. Fasting blood glucose was lower in the pioglitazone group than in the acarbose group. Significant body weight gain was observed in the pioglitazone group as compared with the acarbose group (1.3 ± 2.8 vs. -0.6 ± 1.5 kg, $p = 0.002$). After 6 months of treatment, The mean changes in UACR were -18 ± 104 and 12 ± 85 ($p = 0.25$, between groups) for the acarbose and pioglitazone groups, respectively. The mean changes in eGFR were 0 ± 14 and -7 ± 16 mL/min/1.73 m² ($p = 0.09$, between groups) for the acarbose and pioglitazone groups, respectively.

The within-group changes before and after intervention are shown in Table 2. Blood pressures and lipid profile were similar before and after treatment, except for a significant reduction in the triglyceride level in the acarbose group. Table 3 illustrates that no significant differences in body weight, HbA1c level, eGFR, and UACR between two groups. The patients in the pioglitazone group had more body weight gain and more reduction in fasting blood glucose than those in the acarbose group.

The adverse events were recorded. No severe hypoglycemia occurred in either group. The overall rates of minor to moderate hypoglycemia showed no significant difference between two groups (Acarbose vs. Pioglitazone: 1.37 ± 1.16 vs. 1.87 ± 1.48 episodes, $p = 0.51$). The most common side-effect was mild to moderate gastrointestinal symptoms in those given acarbose than in those given pioglitazone (Acarbose vs. Pioglitazone: 83% vs. 60%, $p < 0.001$). However in the pioglitazone group, more patients had edema (Acarbose vs. Pioglitazone: 3.3% vs. 36.7%, $p < 0.001$) and body weight increase (Acarbose vs. Pioglitazone: -0.6 ± 1.5 kg vs. 1.3 ± 2.8 kg, $p = 0.002$).

Discussion

This clinical study compared the renal outcomes and glycemic control in diabetic patients who had taken metformin and sulfonylureas via additional pioglitazone or acarbose treatment for 6 months. The results showed similar glycemic control in two groups, and no significant differences of changes in eGFR and UACR between pioglitazone and acarbose treatment. Mean body weight gain was significant in the pioglitazone group. This is the first randomized controlled study using UACR and eGFR as the study outcomes.

The strength of this randomized controlled study is that the baseline HbA1c levels (Acarbose vs. Pioglitazone: $8.2 \pm 0.8\%$ vs. $8.3 \pm 0.8\%$, $p = 0.88$) and HbA1c changes (Acarbose vs.

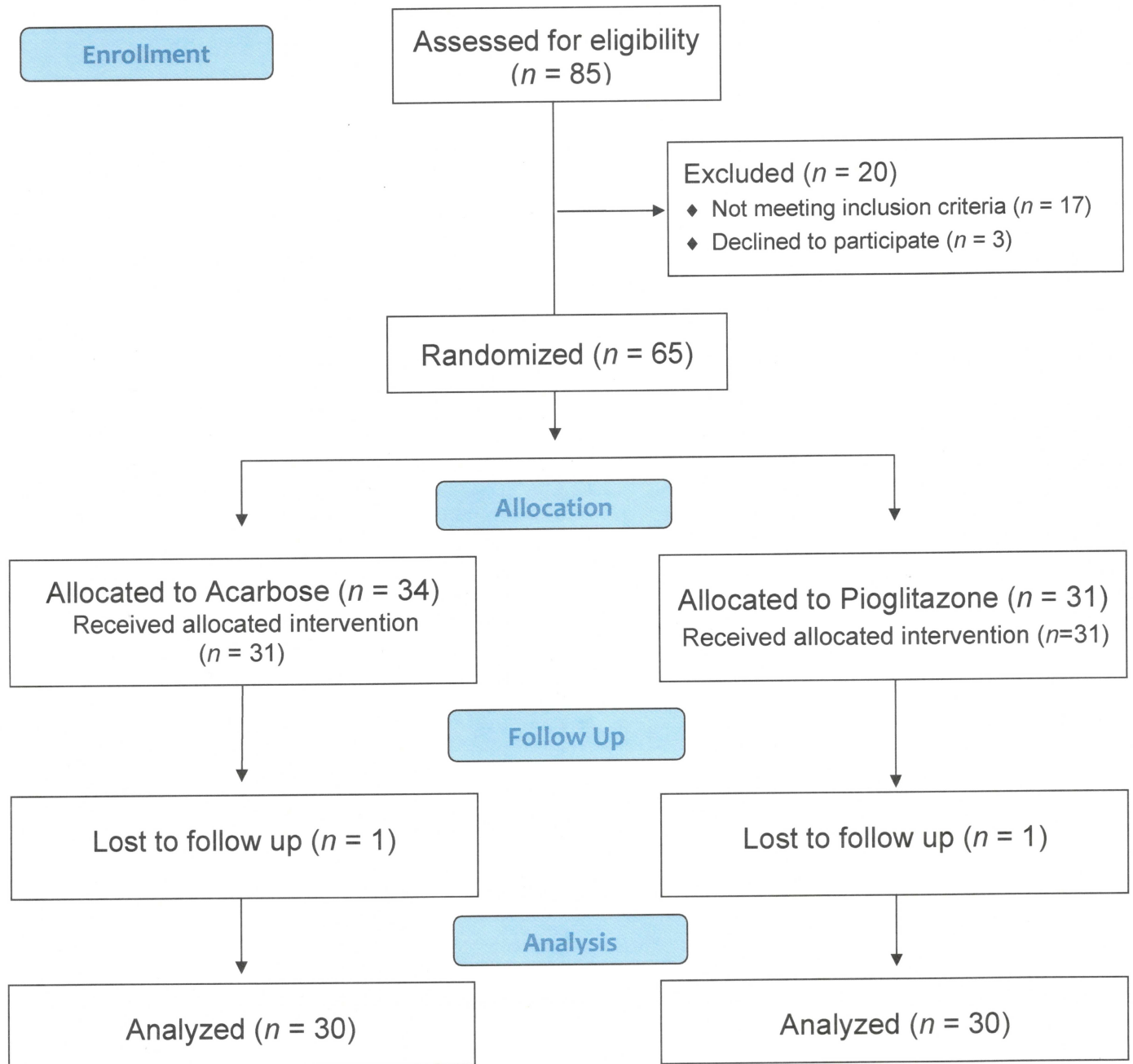


Fig 1. Flow diagram of the study.

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Pioglitazone: $-0.5 \pm 0.9\%$ vs. $-0.5 \pm 0.6\%$, $p = 0.78$) were the same between the two groups. The acarbose group had a similar glycemic control with pioglitazone group before and after intervention. We chose acarbose as a control to make glycemic control comparable. Only one animal study showed that acarbose, an alpha-glucosidase inhibitor, reduced increased albumin excretion in streptozotocin-diabetic rats [12]. No human study has demonstrated the influence of acarbose on renal function. If we used placebo as a control, a different glycemic control might affect the renal outcome.

Table 1. Baseline characteristics of the study patients.

	Acarbose <i>n</i> = 30	Pioglitazone <i>n</i> = 30	<i>p</i>
Age (years)	67.2 ± 7.6	66.3 ± 8.8	0.67
Gender-female (%)	36.7	73.3	0.004
Duration of diabetes (years)	12.3 ± 7.4	11.6 ± 4.0	0.67
Body weight (kg)	69.7 ± 10.1	65.1 ± 11.4	0.10
Body mass index	30.1 ± 18.4	26.0 ± 3.4	0.26
Systolic BP (mmHg)	134 ± 16	136 ± 14	0.69
Diastolic BP (mmHg)	79 ± 10	78 ± 10	0.84
Smoking (%)	23.3	3.6	0.03
Laboratory data			
HbA1c (%)	8.2 ± 0.8	8.3 ± 0.8	0.88
Fasting blood glucose (mg/dL)	167 ± 33	176 ± 43	0.35
Total cholesterol (mg/dL)	181 ± 26	177 ± 40	0.64
HDL cholesterol (mg/dL)	47 ± 10	49 ± 21	0.72
LDL cholesterol (mg/dL)	106 ± 21	101 ± 33	0.52
Triglycerides (mg/dL)	141 ± 58	143 ± 74	0.88
ALT (IU/L)	30 ± 16	25 ± 12	0.20
Creatinine (mg/dL)	0.90 ± 0.24	0.79 ± 0.25	0.07
eGFR (mL/min/1.73 m ²)	85 ± 20	91 ± 24	0.31
UACR (median, IQR) (mg/g)	18 [7–66]	8 [5–54]	0.36
Medicine			
Alpha-blockers (%)	6.7	6.7	1.00
Beta-blockers (%)	33.3	26.7	0.57
Calcium channel blockers (%)	33.3	26.7	0.57
Diuretics (%)	16.7	6.7	0.23
ACE inhibitors/ARBs (%)	60.0	26.7	0.009
Other anti-hypertensive agents (%)	6.7	6.7	1.00
Fibrate (%)	0	0	NA
Statin (%)	43.3	53.3	0.44
Aspirin (%)	20	20	1.00

Continuous data are expressed as the mean ± standard deviation and the comparisons are performed using the two sample *t*-test. UACR are expressed as median with interquartile range and are compared using Wilcoxon-Mann-Whitney test. Categorical data are expressed in percentages and group comparisons are performed using the χ^2 test.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; UACR, urinary albumin-to-creatinine ratio.

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TZDs reduce urinary albumin excretion and proteinuria in diabetic nephropathy [9,10]. Inhibition of transforming growth factor- β 1 and genes involved in collagen/fibronectin formation and reduced serum/renal interstitial tumor necrosis factor- α levels [13,14] have been suggested as potential mechanisms for the renoprotective effect of TZDs [6], but the precise mechanism by which TZDs reduce albuminuria remains unknown. In this study, pioglitazone use for 6 months increased UACR to 12 ± 85 mg/g. As compared with the acarbose group, the change was not significant.

The influence of TZDs on eGFR is not clear. A retrospective study showed that among diabetic patients with normal renal function, rosiglitazone users exhibited a lower decline in renal function than controls during a 3-year follow-up period [15]. Our previous nationwide cohort

Table 2. Within-group changes before and after 6 months of intervention.

	Acarbose (n = 30)			Pioglitazone (n = 30)		
	Change	95% CI	p	Change	95% CI	p
Body weight (kg)	-0.6 ± 1.5	-1.17 to -0.06	0.03	1.3 ± 2.8	0.25 to 2.34	0.02
Systolic BP (mmHg)	-1 ± 15	-6.68 to 4.74	0.73	-2 ± 14	-7.15 to 3.35	0.47
Diastolic BP (mmHg)	-3 ± 11	-6.85 to 1.25	0.17	-1 ± 9	-4.81 to 1.95	0.39
HbA1c (%)	-0.5 ± 0.9	-0.76 to -0.13	0.007	-0.5 ± 0.6	-0.72 to -0.28	<0.001
Fasting blood glucose (mg/dL)	-6 ± 32	-18.26 to 6.05	0.31	-28 ± 41	-42.80 to -12.34	0.001
Total cholesterol (mg/dL)	-6 ± 29	-16.50 to 5.50	0.32	-5 ± 44	-21.31 to 11.64	0.55
HDL cholesterol (mg/dL)	1 ± 9	-2.13 to 5.03	0.41	3 ± 9	-0.34 to 6.68	0.08
LDL cholesterol (mg/dL)	-3 ± 23	-11.47 to 6.07	0.53	-4 ± 41	-19.86 to 11.09	0.57
Triglycerides (mg/dL)	-23 ± 54	-42.90 to -2.24	0.03	-14 ± 42	-30.05 to 1.25	0.07
Creatinine (mg/dL)	0 ± 0.13	-0.06 to 0.04	0.80	0.05 ± 0.14	-0.001 to 0.10	0.06
eGFR (mL/min/1.73 m ²)	0 ± 14	-5.19 to 5.39	0.97	-7 ± 16	-12.88 to -0.68	0.03
UACR (mg/g)	-18 ± 104	-58.16 to 21.29	0.35	12 ± 85	-20.46 to 44.06	0.46

Data are expressed as the mean ± SD. The comparisons are performed using the paired *t*-test.

Abbreviations: BP, blood pressure; CI, confidence of interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

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study showed that TZD users were associated with a low risk for long-term dialysis [16]. However, the hard endpoint of our previous study, long-term dialysis, might reflect not only the decline in renal function but also the cardiovascular effects of TZDs in patients with advanced chronic kidney disease. Rosiglitazone treatment caused a decline of renal function in diabetic patients as compared with control group over 5 years of follow-up in a retrospective cohort study [17]. In the PROactive study, which enrolled diabetic patients with documented macrovascular disease, the *post hoc* analysis showed pioglitazone group had a greater decline of eGFR as compared with the control group [18]. A randomized controlled trial showed a 5.4% decrease in eGFR after 52 weeks of pioglitazone treatment in stage 3 chronic kidney disease with type 2 diabetes mellitus [19]. They found that the decline in eGFR plateaued after 8 weeks of treatment and improved to a 3.4% decrease from baseline eGFR after 8 weeks of treatment [19]. In our study, the mean eGFR had a non-significant decrement (95% CI -1.04 to 14.77, *p* = 0.09) in the pioglitazone group compared with the acarbose group. To date, the mechanism for eGFR reduction with PPAR γ agonists is not well characterized.

In this study, the patients receiving pioglitazone had significant body weight gain (1.3 ± 2.8 kg) during 6 months of treatment compared with those in the acarbose group (-0.6 ± 1.5 kg). This finding is unsurprising because fluid retention is a known side effect of TZDs. Fluid retention and peripheral edema are described in 5%–7% of patients using TZDs alone or in

Table 3. Between-group differences of outcomes after 6 months of intervention.

	Acarbose	Pioglitazone	95% CI	p
Body weight (Kg)	-0.6 ± 1.5	1.3 ± 2.8	-3.07 to -0.76	0.002
HbA1c (%)	-0.5 ± 0.9	-0.5 ± 0.6	-0.32 to 0.42	0.78
Fasting blood glucose (mg/dL)	-6 ± 32	-28 ± 41	2.32 to 40.62	0.03
eGFR (mL/min/1.73 m ²)	0 ± 14	-7 ± 16	-1.04 to 14.77	0.09
UACR (mg/g)	-18 ± 104	12 ± 85	-74.32 to 19.91	0.25

Data are expressed as the mean ± SD. The comparisons are performed using the two sample *t*-test.

Abbreviations: CI, confidence of interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

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conjunction with other oral agents or up to 15% of patients using pioglitazone with insulin [20]. TZDs can cause fluid retention and peripheral edema in diabetic patients [20–22].

The limitations of this study were a small sample size, short follow-up period, and minimal differences at baseline between two drugs, such as percentage of female patients and smoking status. There were 60.0% and 26.7% of patients in the acarbose and pioglitazone groups receiving ACE inhibitors or ARBs at baseline. Since ACE inhibitors or ARBs may have ameliorated a greater increase in urinary albumin excretion, the decreased urinary albumin-to-creatinine ratio after treatment might partially reflect the increased use of ACE inhibitors or ARBs in the acarbose group.

In conclusion, in patients with type 2 diabetes who were treated with sulfonylureas and metformin and demonstrated HbA1c between 7% and 10%, additional acarbose or pioglitazone treatment for 6 months could improve glycemic control and exert a similar renal effect on eGFR and UACR. However, the patients receiving pioglitazone exhibited more body weight gain than those receiving acarbose. Given the small sample size and short follow-up period in this study, large size studies with longer follow-up period are needed in the future.

Supporting Information

S1 File. Protocol.

(PDF)

S2 File. IRB for Thiazolidinedione.

(PDF)

S3 File. CONSORT 2010 checklist.

(DOC)

Author Contributions

Conceptualization: YHC DCT HSC.

Data curation: YHC DCT HSC.

Formal analysis: YHC DCT HSC.

Funding acquisition: YHC DCT HSC.

Investigation: YHC DCT HSC.

Methodology: YHC DCT HSC.

Project administration: YHC DCT HSC.

Resources: YHC DCT HSC.

Software: YHC DCT HSC.

Supervision: YHC DCT HSC.

Validation: YHC DCT HSC.

Visualization: YHC DCT HSC.

Writing – original draft: YHC HSC.

Writing – review & editing: YHC DCT HSC.

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