ORIGINAL INVESTIGATION

# Thiazolidinediones and Progression of Renal Disease in Patients with Diabetes

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## ABSTRACT

**Objective:** Thiazolidinediones (TZDs) are used in the treatment of type 2 diabetes mellitus (T2DM) and appear to have beneficial effects on markers of cardiovascular or renal risk that are independent of glycemic control. We examined the effects of TZDs on renal survival in a predominantly black population with T2DM.

**Methods:** We performed a retrospective case-control study in patients with T2DM seen in our nephrology clinic in 2001 to 2002. Cases had T2DM and were on a TZD at presentation or for ≥ 6 months over follow-up. Controls were matched for sex, age, duration of T2DM, and initial creatinine. Reaching end-stage renal disease (ESRD) was the primary end point.

**Results:** From 387 records, 43 cases (34 blacks, 31 females) and 106 controls (96 blacks, 83 females) were identified. The baseline characteristics were similar for both groups. Both groups had moderate renal disease (estimated glomerular filtration rate ≈ 40–45 mL/min). Cases had lower systolic blood pressure over follow-up ($p = .02$), but there was no difference in glycemic control or use of insulin. Renal survival was better among cases (age- and gender-adjusted odds ratio for reaching ESRD 0.17 [95% confidence interval 0.03–0.8]; $p = .03$). When adjusted for systolic blood pressure over follow-up, the tendency for improved renal survival in cases remained but was no longer significant.

**Conclusion:** We conclude that TZDs may protect against the progression of renal disease in T2DM. Prospective studies are required to determine the effects of TZDs on renal survival in T2DM.


**Key Words:** type 2 diabetes mellitus, thiazolidinedione, end-stage renal disease, African American, blood pressure

Diabetes mellitus is the most common primary cause of end-stage renal disease (ESRD) in the United States, accounting for about 40% of new cases of ESRD.[1,2] Control of blood pressure and blood glucose is essential in delaying the onset and progression of renal disease in diabetic patients.[2–4] It is usually necessary to use several drugs to reach recommended blood pressure targets in patients with diabetes and renal disease, and among these should be an inhibitor of the renin-angiotensin system (RAS).[3,4] Several novel glucose-lowering agents have been developed over the last 20 years. However, unlike recommendations for blood pressure control, there are no specific recommendations for which glucose-lowering agents to use in patients with diabetes and renal disease with regard to improving renal survival.

Thiazolidinediones (TZDs) are now widely used in the treatment of type 2 diabetes mellitus (T2DM) and appear to have beneficial effects on cardiovascular and renal biomarkers independent of their action on glycemic control.[5–7] Data from animal and cell culture studies have demonstrated reductions in albuminuria and synthesis and secretion of the extracellular matrix products that accumulate in the diabetic mesangium.[8–12] In addition, several studies have demonstrated that treatment with TZDs leads to reductions in albuminuria in patients with diabetes and early nephropathy.[7,13–16] Consequently, we hypothesized that TZDs would slow the progression of renal disease in patients with T2DM and moderate to severe renal disease. In this retrospective case-control study, we observed improved renal survival in patients with T2DM and established renal disease who were treated with TZDs when compared with patients naive to TZDs.

## METHODS

The study was approved by the Wayne State University School of Medicine Human Investigation Committee. We identified and reviewed all charts of pre-ESRD patients with diabetes presenting to the nephrology clinic at Wayne State University from January 1, 2001, to December 31, 2002. Patients were designated as having diabetes if a history of the diagnosis was recorded in the chart or if they were on glucose-lowering medications. Data on demographics, blood pressure, renal function, antihypertensive agents, cardiovascular disease, lipids, diabetic medication use, diabetic complications, and glycemic control at the initial visit and over follow-up were extracted from clinic and hospital records. Cases were pre-ESRD patients with T2DM from two groups: (1) subjects who were on TZDs at presentation to clinic and (2) those who were started on

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TZDs after presentation and remained on the agents for at least 6 months of follow-up. Controls were pre-ESRD patients with T2DM who were not on TZDs at presentation or over follow-up. Controls were matched to cases for age (± 5 years), gender, duration of diabetes (± 5 years), and initial serum creatinine (± 0.5 mg/dL). Given the predominance of blacks in our clinic population (> 80%), we did not consider race as a matching criterion. Each case had to have at least one matching control, but we did not limit the number of controls for any case. In many situations, controls met the criteria for matching more than one of the cases.

In general, blood pressure was measured by nurses or physicians using a standard mercury sphygmomanometer with the patient in the seated position. If blood pressure was checked more than once on any visit, we used the lowest documented measurement for that visit. Blood pressure over follow-up is the mean of the single lowest blood pressure taken at each follow-up nephrology clinic visit. Use of RAS inhibitors at and prior to presentation and/or over follow-up was noted. Patients were considered to have macroalbuminuria if they presented with one of the following: urine albumin to creatinine ratio > 299 µg albumin/mg creatinine, urine dipstick of at least 1+ for protein, or urine protein to creatinine ratio > 0.3. As almost all patients had macroalbuminuria, we designated high urine protein excretion as (in order of preference) a 24-hour urine protein of > 2,000 mg, a urine protein to creatinine ratio > 2, or a value of 3+ or 4+ protein on urine dipstick. We used the primary renal diagnosis as determined by the treating nephrologist. When no primary renal diagnosis was given, diabetic nephropathy was assigned if there was presence of retinopathy, micro- or macroalbuminuria, a diagnosis of diabetes for at least 5 years, and absence of another obvious cause of renal disease.

Measurements for lipids and glycemic control were not uniformly available with respect to who had them and when they were measured. Baseline lipid, glycosylated hemoglobin, or hemoglobin $A_{1C}$ values are the mean of such values performed within ± 6 months of the first visit. Values from more than 6 months after the initial visit were grouped into 2-year time periods, with the first period being > 6 months to 2 years. Means of values within these time periods were determined, and a weighted mean follow-up value was determined from among these means. In general, glycosylated hemoglobin was the primary laboratory measurement and hemoglobin $A_{1C}$ was a calculated value; therefore, we used glycosylated hemoglobin in our analysis.

We used the modified Modification of Diet in Renal Disease equation to estimate the glomerular filtration rate (eGFR), and patients were classified according to chronic kidney disease stage per the criteria of the National Kidney Foundation.[17] Renal survival was the primary end point and was defined in two ways. Primarily, ESRD was used and was defined as chronic initiation of renal replacement therapy or renal transplantation. Since there were relatively few ESRD events, we also used the combined end point of doubling of serum creatinine or ESRD as a measure of renal survival. Cardiovascular events were also noted and included coronary artery disease (unstable angina, myocardial infarction, and asymptomatic occlusive coronary disease), congestive heart failure, and stroke (including transient ischemic attack). Incident congestive heart failure was a hospitalization with heart failure as a primary diagnosis. Extrarenal microvascular complications included documented proliferative diabetic retinopathy and/or diabetic neuropathy.

Data were entered into *STATVIEW* (SAS Institute, Cary, NC) and analyzed. Kaplan-Meier analysis was initially performed to examine the effects of TZDs on renal survival. Cox proportional hazards were used to determine the interaction of other variables on renal survival (as defined above). Logistic regression was used to determine the effects of TZDs on cardiovascular outcomes. Nominal variables were compared by chi-square (Fisher exact *t*-test in 2 × 2 analysis). Student's *t*-test was used to compare continuous variables. A $p$ value < .05 was considered significant.

## RESULTS

The charts of 387 pre-ESRD patients with diabetes were available for review. From these, we identified 43 cases and 106 controls. The baseline characteristics of the cases and controls are shown in Table 1. The majority of both groups were black and female, reflecting the demographics of our clinic population. There was a tendency for controls to be older and to be black. There were no significant differences in the use of insulin, sulfonylureas, statins, or types of blood pressure–lowering medications used. Although data were not available in many instances, 70% and 82% of cases and controls, respectively, presented with macroalbuminuria ($p$ = not significant). There were no significant differences between cases presenting on a TZD ($n$ = 33) or those who had it started after presentation ($n$ = 10). However, those who were started on a TZD after presentation tended to have a shorter duration of diabetes (7.4 vs 14 years; $p$ = .09) and to have a higher eGFR (60.4 vs 42.9 mL/min; $p$ = .11).

Two cases (10.5%) and 19 controls (17.9%) progressed to ESRD over the follow-up period ($p$ = .03). On Kaplan-Meier analysis, the 60-month cumulative renal survival rate was 92.3% in cases versus 58.5% in controls ($p$ = .08, log rank [Mantel-Cox]). Owing to the predominance of females and the tendency for older age in controls, we adjusted for gender and age using Cox proportional hazards analysis. Patients treated with TZDs were significantly less likely to reach ESRD over follow-up (Table 2, model 1). Six cases (14.0%) and 31 controls (29.4%) reached the combined end point of doubling of creatinine or ESRD ($p$ = .06). Similar differences in renal survival were seen

**TABLE 1 Baseline Characteristics of Cases and Controls**

| *Characteristic* | *Cases* (n = *43)* | *Controls* (n = *106)* | p *Value* |
|---|---|---|---|
| Race (AA/non-AA) | 34/9 | 96/10 | .10 |
| Gender (M/F) | 12/31 | 23/83 | .52 |
| Age (yr) | 59 (13.6) | 62.5 (9.3) | .08 |
| Initial creatinine (mg/dL) | 1.88 (0.69) | 1.93 (0.77) | .70 |
| Initial eGFR (mL/min) | 43.7 (19.9) | 44.2 (25.4) | .90 |
| Duration of T2DM (yr) | 12.8 (10.4) | 14.4 (10.1) | .39 |
| Systolic BP initial (mm Hg) | 149.7 (27.3) | 155.3 (25.9) | .24 |
| Diastolic BP initial (mm Hg) | 78.9 (11.7) | 81.0 (13.7) | .36 |
| BMI (kg/m$^2$) | 34.1 (6.7) | 33.7 (8.4) | .76 |
| Diabetic nephropathy as primary renal diagnosis, *n* (%) | 20 (46.5) | 64 (60.4) | .15 |
| Cardiovascular disease, *n* (%) | 18 (41.9) | 52 (49.5) | .47 |
| Extrarenal microvascular complications, *n* (%) | 17 (39.5) | 36 (34.0) | .57 |
| High urine protein, *n* (%) | 11 of 36 (30.6) | 41 of 93 (44.1) | .23 |
| Number on insulin (%) | 17 (39.5) | 55 (52.9) | .21 |
| Number on statins (%) | 13 (30.2) | 37 (34.9) | .70 |
| Glycoslylated hemoglobin (% Hgb) | 9.88 (4.81) (*n* = 25) | 10.6 (3.17) (*n* = 28) | .55 |
| Number of BP medications | 2.70 (1.6) | 2.71 (1.5) | .90 |
| High-density lipoprotein (mg/dL) | 43.7 (12.7) (*n* = 23) | 49.4 (18.8) (*n* = 30) | .22 |
| Low-density lipoprotein (mg/dL) | 130.2 (49.6) (*n* = 27) | 117.9 (47.4) (*n* = 49) | .39 |
| Total cholesterol (mg/dL) | 217.0 (51.2) (*n* = 25) | 213.3 (63.4) (*n* = 36) | .81 |
| Triglycerides (mg/dL) | 241.4 (181.7) (*n* = 24) | 197.0 (112.7) (*n* = 30) | .28 |
| Follow-up time (mo) | 24.4 (25.6) | 23.8 (22.5) | .89 |

AA = African American; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; T2DM = type 2 diabetes mellitus. Values are mean (SD) or *n* (%). All variables were not universally available. In those situations, the total *n* for that variable is shown for cases and controls.

**TABLE 2 Cox Proportional Hazards for Relationship of Thiazolidinediones to Renal Survival (Cases Compared with Controls)**

| | | *95% Confidence Interval* | | |
|---|---|---|---|---|
| *End Point* | *Odds Ratio* | *Lower Limit* | *Upper Limit* | p |
| End-stage renal disease (ESRD) | | | | |
| Case (model 1) | 0.163 | 0.034 | 0.803 | .026 |
| Case (model 2) | 0.260 | 0.052 | 1.28 | .097 |
| Combined doubling of creatinine or ESRD | | | | |
| Case (model 1) | 0.303 | 0.115 | 0.793 | .015 |
| Case (model 2) | 0.378 | 0.141 | 1.01 | .052 |

Model 1 includes age and gender; model 2 includes age, gender, and follow-up systolic blood pressure.
ESRD: cases, 2; controls, 19. Combined doubling creatinine or ESRD: cases, 6; controls, 31.

when this combined end point was used (see Table 2). Of the cases reaching either end point, all were from the group that presented on TZDs.

Over follow-up, controls had significantly higher systolic blood pressure, but there were no significant differences in follow-up diastolic blood pressure, glycemic control, urine protein excretion, the number of blood pressure medications used, or the number and likelihood of cardiovascular events over the follow-up period (Table 3). The difference in follow-up systolic blood pressure affected renal survival. After adjustment for age, gender, and systolic blood pressure over follow-up, renal survival still tended to be better in cases but was no longer significant (see Table 2, model 2). However, when the combined end point of doubling of creatinine or ESRD was used, the tendency for cases to have improved renal survival with follow-up systolic blood pressure in the model was nearly significant ($p$ = .052). There were no significant differences in the use of RAS inhibitors, use of statins, or serum lipid levels over follow-up.

**TABLE 3 Follow-Up Variables**

| *Characteristic* | *Cases* | *Controls* | p *Value* |
|---|---|---|---|
| No. reaching ESRD | 2 | 19 | .04 |
| No. with incident cardiovascular event | 6 of 42 | 28 of 103 | .13 |
| Follow-up SBP (mm Hg) | 144.9 (20.5) | 154.6 (22.7) | .02 |
| Follow-up DBP (mm Hg) | 78.1 (9.4) | 80.7 (11.1) | .18 |
| No. of BP medications over follow-up | 3.09 (1.4) | 3.07 (1.3) | .94 |
| Urine protein to creatinine ratio | 2.4 (3.32) (*n* = 23) | 2.38 (3.88) (*n* = 56) | .98 |
| Glycosylated hemoglobin (% Hgb) | 9.76 (4.41) (*n* = 28) | 10.6 (3.1) (*n* = 42) | .37 |

DBP = diastolic blood pressure; ESRD = end-stage renal disease; SBP = systolic blood pressure.
Values are number or mean (SD). All variables were not universally available. In those situations, the total *n* for that variable is shown for cases and controls.

## DISCUSSION

In this case-control study, we observed the beneficial effects of TZDs on renal survival in patients with T2DM. This observation parallels and extends findings from animal and cell culture studies demonstrating the potential protective effects of TZDs in diabetic nephropathy.[8–12] This effect of TZDs was independent of differences in glycemic control and may represent a direct vascular and/or renal effect of these agents. This statement is supported by the significantly lower follow-up systolic blood pressure in patients treated with TZDs in the absence of differences in the number and type of blood pressure medications used. However, given the design of this study, we are unable to definitively conclude what, if any, direct effects TZDs may have had. Nonetheless, we believe this study to be the first to examine the effects of TZDs on renal survival in humans with T2DM. It is strengthened by the use of ESRD as an end point and shows that these beneficial effects are still seen in T2DM patients with advanced renal disease.

The TZDs are insulin-sensitizing agents that are selective ligands of the nuclear transcription factor peroxisome proliferator–activated receptor (PPAR) γ.[5] PPARs are nuclear hormone–activated receptors and transcription factors. To date, three different PPAR subtypes have been cloned and characterized: PPAR-α, PPAR-β, and PPAR-γ. PPARs have been shown to be critical factors in regulating diverse biologic processes, including lipid metabolism, adipogenesis, insulin sensitivity, immune response, and cell growth and differentiation. PPAR ligands have been considered potential therapeutic agents for the treatment of the metabolic syndrome and several of its critical components, such as hypertension, atherosclerosis, and insulin resistance.[18]

The effects of TZDs in the kidney have been investigated in human, animal, and cell culture models. TZDs are associated with marked reduction in microalbuminuria in patients with T2DM.[7,13–16] When compared with other hypoglycemic agents, TZDs achieved similar glycemic control but provided superior renal protection in humans with T2DM. PPAR-γ is present in renal mesangial and proximal tubular cells and the renal microvasculature; therefore, their actions in the kidney may be direct.[19–21] In animal models of diabetic nephropathy, treatment with TZDs has significantly reduced urinary albumin excretion and glomerular hyperfiltration, ameliorated mesangial expansion, and inhibited renal matrix protein and transforming growth factor β expression in streptozocin-induced type 1 and Zucker type 2 diabetic rats.[8–12,22] Collectively, these data suggest that PPAR-γ agonists regulate the signaling pathways involved in mesangial extracellular matrix production in diabetes.

Although TZDs may or may not have direct effects in the kidney, they clearly have systemic effects. This is supported by our observation, and that of others, of lower blood pressure with use of these agents.[13,16,23,24] Blood pressure is an established risk factor for renal survival in almost all renal diseases, and the lower systolic blood pressure levels seen in cases in our study may explain their improved renal survival. In fact, systolic blood pressure over follow-up remained a significant predictor of ESRD after adjustment for age and gender in all patients (odds ratio = 1.03 for each 1 mm Hg [95% confidence interval 1.01–1.05]; $p = .02$). However, we are unable to say if lower follow-up blood pressure was due to the TZD or to other factors. For example, cases that presented on a TZD had higher baseline systolic blood pressure than those who had the TZD started later (152.4 vs 140.4 mm Hg; $p > .2$). There was no further lowering of systolic blood pressure in those in whom the TZD was started after presentation. Therefore, the lower mean follow-up systolic blood pressure seen in cases does not appear to be a direct result of TZD administration.

The data on the blood pressure–lowering effects of TZDs are mixed and may be unique to specific agents. A meta-analysis comparing the relative effects of pioglitazone and rosiglitazone demonstrated little effect on blood pressure for the latter and found no data on the former.[25] However, there are studies that have demonstrated significant blood pressure lowering with rosiglitazone in the

ranges that we have observed in this study.[13,24,26,27] When blood pressure reduction has been significant, it has correlated with improvements in insulin sensitivity.[26,27] This improvement in sensitivity may have an indirect effect on arterial stiffness and vascular reactivity.[28] In fact, studies have demonstrated improvements in intima media thickness and pulse wave velocity of the carotid vessels in patients with T2DM and nephropathy.[29] Similarly, reductions in urinary albumin excretion have been correlated with reductions in blood pressure in patients with T2DM nephropathy.[13,16] Taken together, these data suggest a beneficial effect of TZDs on the vasculature that is manifested clinically by lower blood pressure and reductions in albuminuria.

Other studies that have examined the effects of TZDs on renal risk have been largely limited to patients with microalbuminuria and have been limited to 12 to 52 weeks of follow-up. Consequently, improvements in renal survival can only be hypothesized. This hypothesis is supported, however, as blood pressure and urinary albumin reductions have been proven to be beneficial to renal survival.[2,3] We agree with the suggestions of many authors that TZDs should be considered in patients with early nephropathy.[13–16] However, the effects of TZDs in patients with T2DM with gross proteinuria and significant reductions in eGFR have not been studied. Our study demonstrates that the beneficial effects of TZDs on renal risk extend to these patients. In addition, we did not limit our cases to those with diabetic nephropathy as their primary renal diagnosis. The benefits seen were not affected by whether diabetic nephropathy was the primary renal diagnosis. Therefore, TZDs may improve renal survival in all patients with T2DM and significant renal risk. This is important because patients with T2DM have a high prevalence of renal disease of heterogeneous causes and are at high risk of declines in renal function.[2,30]

Although a novel observation, our study is limited in that it is retrospective and relatively small. Owing to the small size and retrospective nature, we are not able to comment on the effects of specific TZDs or on dose effects. In many instances, patients were switched between TZDs and dosing was not done by a similar protocol. We are able to hypothesize only that the differences in systolic blood pressure between the groups were a direct effect of TZDs because we have no direct measures of vascular reactivity or endothelial function. Data on follow-up urine protein excretion were limited, but, in general, almost all patients presented with gross proteinuria and advanced renal disease. In addition, we are limited in our ability to determine the mechanism by which TZDs may have their effects in the kidney of the diabetic patient. Using the case-control design and ESRD as our end point helped overcome some of these limitations and strengthen our observations. In addition, we did not limit our cases and controls to patients with diabetic nephropathy as their primary renal diagnosis, indicating a general benefit for these agents in all patients with T2DM and renal disease.

In summary, we believe that this is the first study showing that TZDs delay progression to ESRD in humans with T2DM. Similar to other studies, patients on TZDs had lower systolic blood pressure over follow-up.[13,16,23,24] These results need to be validated by prospective studies; however, until then, practitioners may consider using TZDs in patients with diabetes who have renal disease and are at significant risk of progression toward ESRD.

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