Association Between Thiazolidinedione Treatment and Risk of Macular Edema Among Patients With Type 2 Diabetes

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Background: Findings of prior studies have been inconclusive about the ocular effects of thiazolidinediones on diabetic macular edema (DME). We evaluated, in patients with type 2 diabetes (T2D), the short-term and long-term risks of developing DME among users vs nonusers of thiazolidinediones.

Methods: A retrospective cohort study of 103,368 patients with T2D and no DME at baseline using The Health Improvement Network (THIN) database. Clinical, biochemical, and demographic information was obtained for the period January 1, 2000, through November 30, 2009.

Results: At 1 year, the incidence of DME was 1.3% (n=41) and 0.2% (n=227) among thiazolidinedione users (n=3227) and nonusers (n=100,141), respectively (odds ratio [OR], 5.7 [95% CI, 4.1-7.9]). After Cox multiple regression analysis (adjusted for age; systolic blood pressure; levels of lipids and hemoglobin A1c; and use of aspirin, fibrates, insulin, oral antidiabetic drugs, or renin-angiotensin system blockers), multiple imputation analysis to adjust for missing values, and propensity score analysis to exclude for any selection bias, thiazolidinedione use was associated with an increased risk of DME at 1-year follow-up (OR, 2.3 [95% CI, 1.5-3.6]) and 10-year follow-up (hazard ratio [HR], 2.3; [95% CI, 1.7-3.0]). The effect was similar for pioglitazone and rosiglitazone. Combination therapy with insulin plus a thiazolidinedione was associated with a higher risk of DME after propensity score adjustment (HR, 3.0 [95% CI, 1.5-5.9]), while aspirin use (HR, 0.6 [95% CI, 0.4-0.9]) and angiotensin-converting enzyme inhibitor use (HR, 0.4 [95% CI, 0.2-0.7]) were associated with a reduced risk of DME.

Conclusion: Among patients with T2D, treatment with a thiazolidinedione was associated with an increased risk of DME at 1-year and 10-year follow-up evaluations.


The thiazolidinediones, pioglitazone and rosiglitazone, are peroxisome proliferator–activated receptor γ (PPAR-γ) agonists that ameliorate peripheral and hepatic insulin resistance and are effective glucose-lowering treatments for patients with type 2 diabetes mellitus.1 The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend thiazolidinediones as second- or third-line therapy in combination with other oral agents or insulin to achieve target levels of glycemic control.2 The risk-benefit ratio for thiazolidinedione use has been the subject of intense discussion following a series of metabolic and cardiovascular outcome studies.3-4 Several analyses have highlighted the major adverse effects of thiazolidinediones, including an increased incidence of bone fractures,5 fluid retention and edema,6 increased risk of heart failure,7 and, more recently, potentially increased risk of bladder cancer.8 The PPAR-γ receptors are expressed abundantly in endothelial, renal, and retinal vascular tissues.9,10 Thiazolidinedione-induced peripheral and pulmonary edema is well recognized, and the underlying mechanisms are likely to include vasodilation, renal sodium reabsorption, and direct effects on vascular endothelial permeability.11-13 More recently, however, small clinical studies have suggested an association between thiazolidinediones and diabetic macular edema (DME),14 one of the major sight-threatening complications that affects up to 20% of patients with type 2 diabetes.15
A cohort study from the Kaiser Permanente database reported an increased incidence of DME following short-term (1-year) exposure to pioglitazone, but no association between thiazolidinediones and DME was observed in a cross-sectional analysis of baseline data in the ACCORD eye substudy, and neither of these studies investigated the potential longer-term effects of thiazolidinedione use. Accordingly, the aim of this study was to evaluate the short- and long-term effects of thiazolidinedione treatment (pioglitazone and rosiglitazone) on the risks of developing DME in a large population cohort and to identify any risk factors that may influence visual outcome in patients with type 2 diabetes treated with a thiazolidinedione.

METHODS

STUDY DESIGN AND DATA SOURCE

The study was approved by the National Research Ethics Committee East of England–Cambridge South (reference No. H0305/46). This was a retrospective cohort study using The Health Improvement Network (THIN) database. THIN is an established database that collects anonymized electronic data from a volunteer sample of United Kingdom general practices using the Vision primary care computer system (In Practice Systems, London, England). THIN includes medical records on 9.1 million patients (3.4 million of whom are alive and registered with a practice currently contributing to THIN at the end of the dataset collection) attending approximately 479 general practices in England and Wales. Data recorded in THIN include demographic information, medical diagnoses, prescribed medications, laboratory results, lifestyle characteristics, and referrals to specialists. Past and current medical diagnoses are recorded using READ codes (a thesaurus of coded medical terms maintained and distributed by the United Kingdom Terminology Center). THIN has been shown to be highly representative of the wider United Kingdom population. It has been well validated at both the practice and data set level by comparison with other national data sources for demographics and morbidity, mortality, prevalence, and geographic rates.

STUDY POPULATION

Patients selected for analysis had a diagnosis of type 2 diabetes (defined as diabetes not requiring insulin therapy within 6 months of diagnosis), were 18 years or older, and were registered with the medical practices for at least 1 year from the index date of January 2000. A diagnosis of diabetes was based on READ codes for “diabetes” diagnosis and/or use of glucose-lowering therapies. The index date was chosen based on the licensing of both rosiglitazone and pioglitazone in the United Kingdom. The last date of follow-up for this study was November 30, 2009. According to figures from the THIN database, 95% of repeat prescriptions in general practice have a periodicity (frequency) of 6 months or less. Patients with less than 6 months of exposure to a thiazolidinedione were excluded from the study. Individuals were included in the analysis if they had no history of DME before baseline. The patient cohort was identified using relational database tools that involve strategies to design, code, test, and run programs to identify patients’ information and outcome parameters.

STUDY VARIABLES

Medical and demographic codes for the parameters of interest included age; body mass index (BMI; calculated as weight in kilograms divided by height in meters squared); body weight; levels of hemoglobin A1c (HbA1c) and serum lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides); use of specific antihypertensive drugs, lipid-lowering therapies, insulin, and aspirin; and systolic and diastolic blood pressure (BP).

DME END POINT

The primary outcome measure of the study was a new diagnosis of DME as indicated by READ codes (including all codes relating to a diagnosis of DME and/or focal laser photocoagulation for DME) at 1 year and 10 years from the patient’s entry into the study. A diagnosis of DME recorded on the THIN database would typically originate from a specialist ophthalmologic assessment of the patient following routine yearly eye screening. Specialist-derived diagnoses of DME on THIN have been validated for accuracy, but some degree of measurement error is still possible.

Comprehensive diabetic retinopathy screening in the United Kingdom is free to patients and is based on a standardized protocol, independent of drug prescription, comorbidities, and diabetes consultations. National screening services aim to routinely screen all patients with diabetes yearly for the presence of diabetic retinopathy, including DME. Beginning in 2005, all retinopathy screening performed in England and Wales has been based on digital photographic images, in line with recommendations from the National Diabetic Retinopathy Screening program. Patients with suspected DME at screening are routinely referred for specialist ophthalmologic assessment at the Hospital Eye Service. The coded diagnosis of DME, or a coded diagnosis of focal laser photocoagulation (a specific therapy for DME), is then recorded in the THIN database. Information on visual acuity is unfortunately not available in THIN.

The THIN database was queried to determine the use of prescribed thiazolidinediones prior to the diagnosis of DME or prior to censuring of patients with no diagnosis of DME. Information on drug prescription was extracted from the database.

STATISTICAL ANALYSIS

Baseline clinical and demographic variables were compared between users and nonusers of thiazolidinediones using the t test or the Wilcoxon rank-sum test for continuous variables, and the χ2 test or the 2-tailed Fisher exact test for categorical variables.

A 2 × 2 contingency table was used to calculate the unadjusted odds ratio (OR) of DME incidence at 1 year with rosiglitazone and pioglitazone exposure. Multiple logistic regression analysis was used as the primary analysis to calculate the adjusted OR controlling for the following covariates: systolic and diastolic BP, HbA1c, and lipid levels; body weight; BMI; and the use of insulin, oral antidiabetic therapies, ACE inhibitors, angiotensin II receptor blockers, lipid-lowering therapies, and/or aspirin. All values were measured at baseline. The possible confounding variables were prechosen on clinical grounds, including the thiazolidinedione-insulin interaction, and variables to be included in the final model were chosen by comparing the log-likelihoods of competing models. A diagnostic plot (log-[time] vs log-[log(survival function)]) confirmed that the constant proportionality assumptions were met. In addition, the Hosmer and Lemeshow parameter did not show evidence for lack of fit (P = .44).
The analysis identified 109,295 patients in 464 practices who fulfilled the initial selection criteria. Of these, 5927 patients were not included in the analysis because the baseline date for these records was earlier than the acceptable mortality reporting date for the practice, which made them potentially less reliable. Thus, the cohort for further analysis included 103,368 patients with type 2 diabetes. The baseline characteristics for users and nonusers of thiazolidinediones are listed in Table 1.

OUTCOMES AT 1 YEAR

The incidence of DME at 1 year of follow-up according to thiazolidinedione use is listed in Table 2. Patients exposed to a thiazolidinedione had a significantly higher risk of developing DME (OR, 5.7 [95% CI, 4.1-7.9]) (Fisher exact test P < .001).

Following multiple logistic regression to correct for confounding factors and multiple imputation analysis to correct for missing values, we found that exposure to a thiazolidinedione was associated with a significantly increased risk of DME at 1 year (OR, 3.3 [95% CI, 2.2-5.0]). The analysis for pioglitazone and rosiglitazone individually showed that each drug was separately associated with a significantly increased risk of DME at 1 year, and there was no significant difference between the 2 thiazolidinediones (pioglitazone OR, 3.6 [95% CI, 2.0-6.6]; rosiglitazone OR, 3.1 [95% CI, 1.9-5.1]).

The increased risk of DME at 1 year was still present when propensity score methods used to remove selection bias (stratification OR, 2.3 [95% CI, 1.5-3.6]; kernel-matching OR, 2.7 [95% CI, 1.6-4.4]) were used. The potential confounders that did not change the magnitude of associations of interest and were therefore excluded were age, HbA1c level, BMI, lipid measurements, and use of aspirin, fibrates or angiotensin system.

OUTCOMES AT 10 YEARS

Ten years of follow-up data for the patient cohort (n = 103,359) were used to construct Kaplan-Meier curves for time to DME incidence and were further analyzed by Cox regression analysis. The log-rank test yielded an χ2 statistic of 373 (P < .001) and showed a clear difference in DME incidence between users and nonusers of thiazolidinediones (HR, 5.2 [95% CI, 4.3-6.3]) (Figure). A log-rank test was also performed for time since diabetes diagnosis to include all patients, regardless of whether they had used a thiazolidinedione at any time during the study period.
to DME up to 6 months with P < .001, which shows more clearly that the increased risk was also present at short-term follow-up.

Following adjustment for confounding factors using Cox regression and multiple imputation analysis to adjust for missing values, we found that there was a significantly increased risk of developing DME among patients exposed to a thiazolidinedione (HR, 2.8 [95% CI, 2.1-3.5]) (P < .001); after adjusting for selection bias using propensity score stratification, we found a similar result (HR, 2.3 [95% CI, 1.7-3.0]). In this multiple regression model, HbA1c, systolic BP, aspirin use, ACE-inhibitor use, and serum triglyceride levels were variables that produced substantial changes in the magnitudes of the associations of interest (Table 4). A plot to test for the proportional hazard assumption showed that the observed and predicted curves agreed and only deviated when the number of DME events in the thiazolidinedione group small at longer-term follow-up.

Further Cox regression and multiple imputation analysis using an interaction model showed that combination therapy with insulin and a thiazolidinedione increased the HR of DME even further (HR, 4.4 [95% CI, 2.5-7.8]); or HR with propensity score adjustment, 3.0 [95% CI, 1.5-5.9]). Conversely, concurrent use of aspirin (HR, 0.7 [95% CI, 0.5-0.9]) and an ACE inhibitor (HR, 0.5 [95% CI, 0.3-0.9]) was associated with a reduction in the HR of developing DME independent of other covariates and after propensity score stratification: HR, 0.6 (95% CI, 0.4-0.9) and HR, 0.4 (95% CI, 0.2-0.7), respectively (Table 4).

To further strengthen the analysis, propensity scores were derived to exclude indication bias and produce comparable subgroups for a stratified analysis. The potential confounding variables for users and nonusers of thia-
Thiazolidinediones were generally balanced across the propensity score quintiles (Table 5).

### Table 5. Distributions of Key Variables by Thiazolidinedione Use and Propensity Score Quintilea

<table>
<thead>
<tr>
<th>Quintileb</th>
<th>Age, y</th>
<th>HbA1c, %</th>
<th>Systolic BP, mm Hg</th>
<th>Insulin Use, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No TZD</td>
<td>TZD</td>
<td>No TZD</td>
<td>TZD</td>
</tr>
<tr>
<td>1</td>
<td>55.7 (13.6)</td>
<td>55.5 (12.2)</td>
<td>8.4 (2.1)</td>
<td>8.5 (2.0)</td>
</tr>
<tr>
<td>2</td>
<td>56.6 (13.7)</td>
<td>58.3 (12.9)</td>
<td>7.6 (1.7)</td>
<td>7.8 (1.6)</td>
</tr>
<tr>
<td>3</td>
<td>59.4 (13.8)</td>
<td>58.9 (13.1)</td>
<td>7.3 (1.5)</td>
<td>7.6 (1.3)</td>
</tr>
<tr>
<td>4</td>
<td>60.4 (14.4)</td>
<td>59.0 (12.7)</td>
<td>7.3 (1.4)</td>
<td>7.7 (1.4)</td>
</tr>
<tr>
<td>5</td>
<td>64.0 (13.9)</td>
<td>59.2 (14.3)</td>
<td>7.3 (1.4)</td>
<td>8.2 (1.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; DME, diabetic macular edema; HbA1c, hemoglobin A1c level; TZD, thiazolidinedione.

COMMENT

This large retrospective cohort study analyzed the primary care electronic medical records of more than 100,000 patients with type 2 diabetes and showed that, even after adjustment for various confounding factors known to influence diabetic retinopathy, exposure to a thiazolidinedione is associated with an increased risk of developing DME. The association was evident with both pioglitazone and rosiglitazone. A previous short-term study from Kaiser Permanente reported a similar increase in risk of DME after 1 year (OR, 2.6), but the analysis did not adjust for several key variables, in particular the use of BP-lowering drugs such as angiotensin receptor blockers and ACE inhibitors, which may affect the progression of diabetic retinopathy.

Diabetic macular edema is a sight-threatening chronic condition, so an important new observation in the present study is that the increased risk of DME continued to accrue during the 10-year follow-up. The patients at greatest risk of developing DME were those taking thiazolidinediones in combination with insulin. Diabetic macular edema has been associated in clinical practice with those patients who develop thiazolidinedione-induced pedal edema, and in large clinical trials the highest incidence of fluid retention and peripheral edema (16%) was observed in the subgroup of patients undergoing combination therapy with a thiazolidinedione and insulin.

Although glycemic control did not modulate the short-term (1-year) risk of DME among users of thiazolidinediones, HbA1c was significant in the longer-term analysis. In addition, the use of aspirin and/or ACE inhibitor drugs was associated with a modest reduction in the HR of DME, which is consistent with previous clinical and experimental studies.

Diabetic macular edema is the leading cause of blindness among patients with type 2 diabetes. The absolute rate of new-onset DME was much lower in the present study (about 1%) than has been reported in previous clinical trials of diabetic retinopathy. This probably reflects the low detection rates in routine clinical practice and highlights the importance of a national systematic screening program for diabetic retinopathy. The cause of DME is complex, but disruption to the blood-retinal barrier (BRB), mediated in part by local release of vascular endothelial growth factor (VEGF), results in chronic leakage of fluid and reduced visual acuity. Important regulators of VEGF include hypoxia, hypergly-
cemia, and angiotensin II, but PPAR-γ agonists also increase VEGF expression,31 and our research group32 has previously shown that thiazolidinediones increase vascular endothelial permeability in vitro. A number of systemic changes associated with thiazolidinediones may also contribute (eg, sodium and fluid retention, vasodilation, changes in BP, microvascular perfusion).32 Thus, there are plausible mechanisms, both local and systemic, by which thiazolidinediones might adversely affect the risk of DME, particularly in insulin-treated patients.

The strengths of this cohort analysis include a very large sample size and a long duration of follow-up. To increase the reliability of the study, we included only patients who were apparently compliant with thiazolidinedione therapy (>6 months and in receipt of repeat prescriptions), and we measured new-onset DME during a 10-year observation period. Diabetic macular edema is a specialist diagnosis that would normally be made only by an ophthalmologist when the patient is referred following routine annual eye screening.

It is an important limitation of this study that information about duration of diabetes and duration of individual patient exposure to a thiazolidinedione was not available. However, the baseline characteristics of patients in the 2 cohorts were comparable in terms of age, sex, and BMI. The percentage of patients receiving insulin and mean HbA1c, levels were slightly higher in the thiazolidinedione user group, but this was balanced by slightly higher BP and more patients receiving aspirin, ACE inhibitors, and statins in the nonusers group. Furthermore, the propensity score analysis mitigates against indication bias and strengthens the interpretation of a true association between DME and use of a thiazolidinedione.

During the study period (2000-2009), thiazolidinediones were routinely and widely used in clinical practice in patients with diabetes of varying duration (eg, as dual or initial combination therapy with metformin in those with short-duration disease and as third-line agents added to metformin/sulfonylurea combination therapy). Despite propensity score analysis and the similar baseline profiles, it is possible, but in our view unlikely, that the thiazolidinedione users were significantly different than the nonusers either in diabetes duration or in their cardiovascular risk profile. The present study confirms and extends other observations implicating thiazolidinedione use with an increased risk of DME, but the data require cautious interpretation.

In conclusion, this large-population study has shown that, even after adjustment for a range of confounding variables, thiazolidinediones are associated with an increased risk of DME in patients with type 2 diabetes, especially those undergoing insulin therapy. The risk increased continuously over the 10-year duration of this study. The explanation for this association is unclear, but plausible mechanisms described previously exist by which these drugs might adversely influence this important ocular complication of type 2 diabetes. A larger and more detailed meta-analysis of randomized controlled trials (ideally in high-risk patients) will be needed to clearly establish the risk-benefit profile of thiazolidinediones in patients with, or at risk of, DME. In addition, future clinical trials to evaluate new PPAR-γ (or dual α,γ) agonists should prospectively evaluate the ocular safety of these drugs. Clinicians should be vigilant in the clinical screening for DME among those patients taking thiazolidinediones.

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Author Contributions: Dr Idris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Idris and Donnelly. Acquisition of data: Idris. Analysis and interpretation of data: Idris and Warren. Drafting of the manuscript: Idris and Donnelly. Critical revision of the manuscript for important intellectual content: Idris, Warren, and Donnelly. Statistical analysis: Idris and Warren. Obtained funding: Idris. Administrative, technical, and material support: Donnelly. Study supervision: Donnelly.

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Thiazolidinediones and Macular Edema

The thiazolidinediones, rosiglitazone and pioglitazone, are peroxisome proliferator-activated receptor γ (PPAR-γ) agonists. They effectively reduce glycated hemoglobin among patients with type 2 diabetes mellitus by approximately 1 to 1.5 percentage points compared with placebo and are used as second-line treatment agents. However, rosiglitazone and pioglitazone have been associated with peripheral edema, congestive heart failure, and bone fractures. An increased risk of myocardial ischemia has been attributed to rosiglitazone. An increased risk of bladder cancer associated with pioglitazone is noted in the current label. Spontaneous reports of macular edema with the use of thiazolidinediones has resulted in regulatory warnings on this potential association. However, the causality remains unclear.

The prevalence of diabetic macular edema (DME) in one or both eyes among patients with diabetes is estimated to be 7.1%. Approximately one-third of these affected eyes lose vision. Since PPAR-γ receptors are present in the retinal vasculature, PPAR-γ–mediated fluid retention has been postulated to contribute to DME. In this issue of the Archives, Idris et al report the results of a retrospective, population-based study of adult patients with type 2 diabetes in the United Kingdom. The investigators used data from The Health Improvement Network (THIN), which allowed for long observation of the exposed patients and adequate adjustment for important confounders, including body weight, glycated hemoglobin levels, and concomitant medications. After propensity score adjustment, the authors reported a significantly increased odds of DME in users of thiazolidinediones compared with nonusers (odds ratio [OR], 2.3 [95% CI, 1.5-3.6]) at 1 year. Both pioglitazone and rosiglitazone were associated with a similar increased risk. This increased risk persisted at 10 years of follow-up.

Importantly, the authors appropriately used multiple imputation methods to handle missing data in this cohort and used propensity score methods to address confounding by indication, which is a prominent risk with observational data; however, several limitations preclude definitive conclusions. First, the authors did not have information on the duration of thiazolidinedione exposure or duration of diabetes in the THIN data; that is, they compared prevalent users of thiazolidinediones—