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Original Article

Development of vascular complications and bladder carcinoma in diabetics using pioglitazone: A five-year Indian review

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ARTICLE INFO

Article history:

Received 23 October 2015

Accepted 13 June 2016

Keywords:

Diabetes mellitus type-2

Pioglitazone

Bladder carcinoma

Vascular complications

Thiazolidinedione

ABSTRACT

Background: Pioglitazone has better cardiovascular outcomes and a questionable relationship with bladder carcinoma in diabetes mellitus, type II (DM-2). We sought to evaluate the role of pioglitazone in the Indian population.

Methods: This is a retrospective study at an academic medical center in India. All DM-2 patients in 2008 with a new prescription of pioglitazone were age- and gender-matched with non-users. We excluded patients with gestational DM or DM type I. They were followed forward for five years and demographic data, micro- and macro-vascular complications, mortality, and bladder carcinoma were recorded. Two-tailed $p \leq 0.05$ was considered statistically significant.

Results: Two cohorts of 260 patients, with mean age of 58 ± 11 years with 413 (79.4%) males, were followed for five years. Pioglitazone users had higher hypertension, obesity, DM-2 family history (all $p < 0.003$), and use of insulin and oral hypoglycemics (all $p < 0.0001$) in comparison to non-users. HbA1c was not different between groups. Over five years, pioglitazone users had lesser retinopathy and myocardial infarctions (all $p < 0.01$). Five cases of bladder carcinoma were noted, all in the pioglitazone group, however without statistical significance. Baseline variables, including mean daily pioglitazone dose, were not statistically different between patients with and without bladder carcinoma. Nephropathy and MI were independent predictors for development of bladder carcinoma within pioglitazone users.

Conclusions: Pioglitazone users had significantly lesser myocardial infarctions and retinopathy despite more difficult to control DM 2. In an age- and gender-matched cohort of users and non-users, pioglitazone did not contribute to development of bladder cancer in the Indian population.

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<http://dx.doi.org/10.1016/j.mjafi.2016.06.004>

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Introduction

Thiazolidinediones (TZD) medications, which act on the proliferator-activated receptor gamma (PPAR- γ) a nuclear transcription factor, are used in the management of diabetes mellitus, type 2 (DM-2).¹ TZDs increase insulin sensitivity, reduce blood glucose and hemoglobin A1c (HbA1c) levels, inhibit adipose-tissue lipolysis, and inflammation and reduce blood pressure.² These medications offered a lot of hope for the management of DM-2 in which cardiovascular causes are responsible for nearly 75% of the deaths.² A landmark meta-analysis in 2007 showed a higher risk of myocardial infarction (MI) and cardiovascular mortality with rosiglitazone resulting in this medication being withdrawn from the market.³ Subsequently, pioglitazone was promoted as the cardioprotective TZD with multiple studies demonstrating good cardiovascular profile in these patients.^{2,4,5} More recently, a controversial correlation between pioglitazone and bladder cancer in male patients has been proposed, which has tapered our enthusiasm for this group of drugs.^{1,4} However, most of these data are from the Western literature,^{1,6} with data from Indian authors limited to expert opinions and case series despite India being the diabetic capital of the world.^{7–14} Over the years, epidemiological data have highlighted the significant differences in cardiovascular risks and bladder carcinoma in the Indian population in comparison to other countries.^{14,15} This lack of robust data had resulted in a Indian government ban on pioglitazone and subsequent rapid revocation in 2013 following global trends.¹⁵ In this context, we sought to evaluate data on pioglitazone in the Indian population.

Material and methods

This retrospective cohort study was carried out at a tertiary care academic medical center in India. The Manipal University Institutional Ethics Committee exempted the study from obtaining written informed consent from individual patients due to its retrospective nature. All patients with between January and December 2008 with an International Classification of Diseases-10 code (ICD-10) of DM-2 with a new prescription of pioglitazone (TZD here forth) were reviewed. Patients with a diagnosis of type-1 or gestation diabetes mellitus were excluded from our study. Patient related information including demographic details, past medical history, oncological history, personal-social history and clinical presentations were recorded. Details on DM-2 including HbA1c, evidence of end organ damage and family history of DM-2 were collected. These patients were followed by chart review for a period of five years to assess for micro- and macro-vascular complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, cerebrovascular accident (CVA) and MI. Mortality during this period was also recorded.

For an anticipated hazard ratio of 1.2 in exposed individuals and an exposure rate of 0.485 in unexposed individuals from a previous study,¹⁶ with precision of 15% at 95% level of confidence for a two-sided test, the calculated minimum sample size was 520. Age- and gender-matched cohorts of 260 patients with and without TZD therapy were followed for

the development of malignancy. These patients were followed forward in time for a period of five years. Best attempts were made via the telephone and postal correspondence to contact patients lost to follow-up. Statistical analysis was performed using IBM SPSS Statistics (IBM Corp, Armonk, NY). The association between TZD exposure and outcomes of macro- and micro-vascular complications, patient status, and malignancy were analyzed using chi-square tests or Student's t-test for equal proportions. Where data were insufficient to meet statistical assumptions for chi-square test, Fisher's exact test or Mann-Whitney U-test was employed. All data are presented as mean $\pm$ standard deviation (SD), relative risks (RR) with 95% confidence interval (CI) or number (percentage). Logistic regression analysis is presented as odds ratio (OR) with 95% CI. Kaplan-Meier logistic regression analysis was used to calculate survival and hazard function statistics, with right censoring performed for the patients who did not have an event during the study duration. Cumulative survival and cumulative hazard was plotted against the event-time product. Two-tailed *p*-value of ≤ 0.05 was considered statistically significant.

Results

A total of 520 patients (all Asian Indian race) with DM-2 were studied in the period from January to December 2008. Of these patients, 413 (79.4%) were male with mean age of 58 ± 11 years. Age, gender, and smoking history matched cohorts of 260 new TZD users and non-users were created and followed over a period of five years. Detailed patient demographic characteristics and risk factors in TZD users and non-users are reported in Table 1. TZD users had lesser hypertension and obesity, but had a more prevalent family history of DM-2. TZD users had statistically significant higher usage of insulin, metformin, and sulphonylureas. HbA1c values were available for 160/520 (30.8%) patients with a mean value of $9.9 \pm 2.5\%$, for the total cohort without statistically significant difference between both groups.

Over a five-year period, TZD and non-TZD patients were evaluated for development of micro-vascular (nephropathy, neuropathy, retinopathy) and macro-vascular (CVA, MI) complications. The TZD users had statistically significant higher incidence of neuropathy, but lesser retinopathy and MI as compared to the TZD non-users. Univariate analysis of complications in TZD and non-TZD users is presented in Table 2. In a logistic regression analysis of significant factors univariate variables from Table 1, TZD use remained an independent predictor of diabetic neuropathy as represented in Table 3.

Of the 520 patients, five (1.9%) patients developed bladder cancer over a five-year period. All five belonged to TZD users cohort with none detected in the non-TZD users (*p*-value 0.06). Over the five-year period, one patient developed bladder carcinoma at year one, second in year three, two additional patients in year four, and the last one in year five (Fig. 1). Mean survival time was 120.2 (95% CI 119.5–120.9) months with 515 patients censored at the end of the five-year duration due to absence of event occurrence. Among the TZD users, baseline characteristics of patients with and without bladder cancer are presented in Table 4. Patients with bladder cancer were all males, with no statistically significant differences in baseline

Table 1 – Baseline characteristics of cohorts.

Parameter	TZD users (n = 260)	TZD non-users (n = 260)	p-value
Males	210 (80.8)	203 (78.1)	0.52
Age (in years)	58 ± 11	59 ± 11	0.30
Hypertension	139 (53.5)	173 (66.5)	0.003*
Obesity	39 (15.0)	56 (21.7)	0.0004*
Malignancy	4 (1.5)	4 (1.5)	1.00
FH malignancy	0 (0.0)	2 (0.8)	0.50
FH DM-2	121 (46.4)	63 (24.1)	<0.0001*
Alcohol abuse	49 (18.8)	44 (17.0)	0.65
Tobacco abuse	49 (18.8)	44 (17.0)	0.65
Radiation therapy	0 (0.0)	4 (1.5)	0.12
DM-2 duration (in years)	9.0 ± 6.9	10.5 ± 8.2	0.89
Insulin	222 (85.4)	184 (70.8)	<0.0001*
Metformin	189 (72.7)	131 (50.6)	<0.0001*
Sulphonylureas	173 (66.5)	103 (39.6)	<0.0001*
HbA1c (in %)	10.1 ± 2.5	9.7 ± 2.5	0.07

Represented as: mean ± SD or number (%).

* p-value ≤ 0.05.

Abbreviations: DM-2, diabetes mellitus, type II; FH, family history; HbA1c, hemoglobin A1c; TZD, thiazolidinediones.

Table 3 – Logistic regression analysis of micro- and macro-vascular complications.

Complications	OR (95% CI)	Unadjusted p-value
Neuropathy	2.9 (1.7–5.1)	0.0001*
Retinopathy	0.6 (0.3–1.0)	0.05
MI	1.1 (0.3–3.4)	0.91

Represented as:

* p-value ≤ 0.05.

Abbreviations: CI, confidence interval; MI, myocardial infarction; OR, odds ratio.

characteristics, tobacco use, mean daily TZD dose or use of other anti-DM-2 medications. Patients with prior nephropathy and MI had a statistically significant high chance of bladder carcinoma and this was confirmed on a subsequent logistic regression analysis with OR 0.04 (95% CI 0.0004–0.071, p-value 0.04) and OR 0.09 (95% CI 0.02–0.16, p-value 0.009).

Discussion

In this study, we evaluated the correlation of TZD use and the risk for vascular complications and occurrence of bladder

Table 2 – Univariate analysis of micro- and macro-vascular complications.

Complications	TZD user (n = 260)	TZD non-users (n = 260)	RR (95% CI)	Unadjusted p-value
Nephropathy	102 (39.2)	89 (34.2)	1.2 (0.9–1.4)	0.28
Neuropathy	169 (65.0)	117 (45.0)	1.4 (1.2–1.7)	<0.0001*
Retinopathy	83 (31.9)	124 (47.7)	0.7 (0.5–0.8)	0.0003*
CVA	7 (2.7)	13 (5.0)	0.5 (0.2–1.3)	0.25
MI	17 (6.5)	35 (13.5)	0.5 (0.3–0.8)	0.01*
Death	8 (3.1)	15 (5.8)	0.5 (0.2–1.2)	0.20

Represented as: number (%).

* p-value ≤ 0.05.

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; MI, myocardial infarction; RR, relative risk; TZD, thiazolidinediones.

Fig. 1 – Kaplan–Meier curve for occurrence of bladder carcinoma over five years.

Table 4 – Baseline characteristics of TZD users with and without bladder carcinoma.

Parameter	Bladder cancer (n = 5)	No bladder cancer (n = 255)	p-value
Age (in years)	54.0 ± 6.5	58.0 ± 11.0	0.96
Male gender	5 (100.0)	205 (80.4)	0.59
Hypertension	3 (60.0)	136 (53.3)	1.00
Obesity	1 (20.0)	38 (14.9)	0.56
Malignancy	1 (20.0)	3 (1.2)	0.08
FH malignancy	0 (0.0)	0 (0.0)	1.00
FH DM-2	1 (20.0)	120 (47.1)	0.38
Alcohol abuse	2 (40.0)	47 (18.4)	0.24
Tobacco abuse	2 (40.0)	47 (18.4)	0.24
Radiation therapy	0 (0.0)	0 (0.0)	1.00
HbA1c (in %)	10.1 ± 0.6	10.1 ± 2.5	1.00
Insulin	5 (100.0)	217 (85.1)	1.00
Metformin	4 (80.0)	185 (72.6)	1.00
Sulphonylurea	3 (60.0)	170 (66.7)	1.00
Daily TZD dose (in mg)	32.0 ± 15.7	16.1 ± 9.6	0.82
Nephropathy	5 (100.0)	101 (39.6)	0.01*
Neuropathy	5 (100.0)	170 (66.7)	0.17
Retinopathy	0 (0.0)	87 (34.1)	0.17
CVA	0 (0.0)	8 (3.1)	1.00
MI	2 (40.0)	15 (6.0)	0.04*
Death	0 (0.0)	8 (3.1)	1.00

Represented as: mean ± SD or number (%).

* p-value ≤ 0.05.

Abbreviations: CVA, cerebrovascular accident; DM-2, diabetes mellitus, type II; FH, family history; HbA1c, hemoglobin A1c; MI, myocardial infarction; TZD, thiazolidinediones.

carcinoma. Our study is the largest single-center Indian study evaluating bladder carcinoma in patients using TZD. The major findings are as follows: (a) In an age- and gender-matched cohort of DM-2 patients, TZD use was associated with lesser diabetic retinopathy and MI; (b) despite all bladder carcinoma cases occurring in the TZD cohort, this did not achieve statistical significance; (c) all bladder carcinoma patients in our population were male which is consistent with existing literature; and (d) mean TZD dose and concurrent use of insulin or other oral hypoglycemic agents were not statistically different between patients with and without bladder carcinoma.

In DM-2 patients, TZD act by improving insulin sensitivity in the liver, muscle and other peripheral organs and is currently licensed for combination use with metformin or insulin in obese patients.^{8,9,14,15} TZD act by agonistic action on PPAR-γ, which in addition to being expressed in the normal urothelium, has been known to be associated with proliferating bladder tumors.^{1,17} This association has been best studied in the laboratory, with TZD serving to alter the urinary milieu in male rats which has not been noted in the human population.^{4,17,18} However, PPAR-γ has been studied from both a tumorigenesis and cancer prevention perspective due to its potential dual action. TZDs could increase, decrease, or have a neutral cancer risk in this population.⁹ Between 2004 and 2009, the Food and Drug Administration (FDA) of the United States of America received 93 post-marketing reports of bladder carcinoma associated with pioglitazone that had triggered large scale trials to evaluate this association.^{16,18} This

hypothesis was supported in two meta-analysis of all studies and only controlled trials that also showed a dose-response relationship with pioglitazone use.^{17,18} However, more recent data including a large scale clinical trial by Kaiser Permanente Northern California group showed absent to weak association with bladder carcinoma.^{4,6,16} Multiple arguments can be made for this discrepancy in literature including the difference in rat and human bladder milieu, baseline worse diabetic status, and cardiovascular disease in patients with pioglitazone, pro-carcinogenic state of DM-2, pro-carcinogenic effects of insulin, and use of primarily epidemiological or observational databases.^{1,4,8–10,15–18} In an enlightening opinion piece on the controversies in pioglitazone,⁴ Ryder discusses the pitfalls of the PROactive trial¹⁹ that pioneered the focus on this correlation. Additionally, these patients due to worsening diabetes are more likely to be tested for proteinuria, and thereby be diagnosed with incidental bladder carcinoma on the same urinalysis.¹

Despite multiple studies internationally, the Indian literature on pioglitazone is sparse and restricted to opinion pieces and editorials.^{7–14} This is a crucial gap in literature since the Indian population is significantly different from the predominantly white European/American population in these published data.^{1,4} India has a higher incidence of cardiovascular diseases and insulin resistance than the Western population.^{4,8} The incidence of bladder cancer in the western world is between 80 and 100 cases per 100,000 person-years in comparison to 2–4 per 100,000 person years in the Indian population.^{10,17} In a recent article, Balaji et al.¹⁴ evaluated a population of 1077 patients and noted 20 instances of bladder carcinoma with only one case in a pioglitazone user. However, due to the lack of a control group, lack of detailed comments on comorbidities, and retrospective review with small numbers, it is tough to opine on this association. In our study, pre-selected sample size and age- and gender-matching for TZD and non-TZD user population and relative similarity of baseline cohorts helped make this comparison more meaningful. Mean daily TZD doses in our population are consistent with literature from other Indian authors and are significantly lower in comparison to reports from our Western colleagues.^{7,9,14} In a similar study evaluating Taiwanese and Korean patients, bladder cancer was noted with much smaller daily and cumulative doses, making us hypothesize that racial, ethnic, and body mass factors could have a role in this relationship.^{7,14,20} Additionally, Asian studies including ours reported a paradoxical cumulative dose relationship inconsistent with Western literature making us wonder on the generalizability of current literature.^{14,20}

Over the last many years, pioglitazone has proven its efficacy in providing cardiovascular benefit in DM-2 patients by reducing the risk of stroke, MI, and cardiovascular mortality across multiple studies.^{4,9,15} Its ability at stroke prevention and plaque stabilization has been validated in the Asian population too.^{8,21} In addition to its action on decreasing triglycerides, low-density lipoproteins, HbA1c skeletal muscle insulin resistance, pioglitazone has also decreased daily insulin usage in patients with DM-2 and impaired glucose tolerance ('pre-diabetes').^{8,9,15,22} Consistent with the same, our study demonstrated statistically significant decrease in diabetic retinopathy and MI in TZD users compared to non-users. The use of

insulin, metformin, and sulphonylureas were significantly higher in our TZD population leading us to hypothesize that their DM-2 was significantly worse controlled than the non-users. Though the HbA1c levels were higher in our TZD users, it did not achieve statistical significance. The MI protective action of TZD in our population despite the complex interplay of baseline comorbidities and worse DM-2 status is an encouraging sign and needs further validation in more dedicated randomized trials. Experimental data have advocated a likely role for pioglitazone in improvement of outcomes with ischemia/reperfusion injury, pending further studies.² The higher cardiovascular risks in the Indian population in combination with increased insulin resistance, difficult to control DM-2 often on multiple medications and low incidence of bladder carcinoma make pioglitazone an attractive choice for this population.^{9,10} However, reports of a higher incidence of heart failure in TZD population need us to carefully evaluate the risk-benefit ratio of pioglitazone use in DM-2 patients.^{5,7,21}

Our study has certain limitations as well. We performed a single center study using a retrospective design with inherent selection and informational biases. As a consequence we were limited to relying on an administrative database for diagnosis using ICD-10 codes. Due to the lack of background information, we are unable to comment on pre-existing bladder carcinoma cases that could have been incidentally discovered during this time period. Additionally, the diagnosis of bladder carcinoma was ascertained using ICD-10 codes without further information on disease staging, histology patterns, and management. Due to the low economic status, prevalence of migrant labor, and lack of fixed occupation among our patient population, we are unable to determine the complex interplay of socioeconomic dynamics and their influence on medication compliance and environmental risk factors. Tobacco abuse, which is a known risk factor for bladder cancer, was noted in <20% of our population.

In conclusion, our study highlights the largest single-center Indian case series of bladder carcinoma related to TZD use. We report no significant increase in bladder carcinoma in age- and gender-matched cohorts of TZD users in comparison to non-users. We also highlight the positive effect of TZD on micro- and macro-vascular complications in DM-2. We strongly advocate for more robust Asian, and specifically Indian, literature to evaluate this controversial group of medications.

Conflicts of interest

The authors have none to declare.

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