Original Article

A retrospective study to assess the risk of bladder cancer in type-2 diabetic patients treated with pioglitazone

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Abstract

Introduction: Pioglitazone has been a cornerstone of oral hypoglycemic therapy. Concerns have been raised about its association with urinary bladder cancer. Considering the wide usage of this drug, concrete and multiple population-based studies are needed to establish the safety of this drug. The present retrospective study is aimed to assess the association of pioglitazone with urinary bladder cancer.

Materials and Methods: Clinical records of 4170 patients (2085 pioglitazone users and similar number of nonpioglitazone users) attending the diabetes clinic at a tertiary level teaching hospital were accessed, and the patients were subjected to symptom-directed questionnaire, urine examination, and cystoscopy and bladder biopsy (whenever clinically indicated). The risk of bladder cancer was also assessed with respect to cumulative dose and duration of pioglitazone.

Results: We did not observe any increased risk of bladder malignancy with pioglitazone exposure; furthermore, there was no association with cumulative dose and duration of pioglitazone therapy. Pioglitazone was found to be effective and safe in managing glycemic control in diabetic patients.

Keywords: Adverse drug reaction, diabetes, oral hypoglycemic, pioglitazone, urinary bladder cancer

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INTRODUCTION

The number of people with diabetes has risen from 108 million (1980) to 422 million (2014). The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% (1980) to 8.5% (2014).[1] Its prevalence is increasing worldwide, particularly in developing countries like India. India has 40.9 million diabetics (2006) and expected to increase to 69.9 million (2025).[2]

Pioglitazone, a thiazolidinedione, improves glycemic control in people with type-2 diabetes by improving insulin sensitivity through its action at peroxisome proliferator-activated receptor (PPAR) gamma 1 and PPAR gamma 2 and affects lipid metabolism through action at PPAR alpha. The results of these interactions include increased glucose transporters 1 and 4, lowered free fatty acids, enhanced insulin signaling, reduced tumor necrosis factor alpha, and remodeling of adipose tissue. Together, these can increase glucose uptake and utilization in the peripheral organs and decrease gluconeogenesis in the liver, thereby reducing insulin resistance.[3]

It has been reported that in patients with type-2 diabetes mellitus, pioglitazone and metformin significantly improved hemoglobin A1C (HbA1C) and fasting plasma glucose levels, with positive effects on serum lipid levels and no

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evidence of drug-induced hepatotoxicity. These effects were maintained for >1.5 years, including the open-label extension.[4] Kipnes *et al*., 2001 studied the effect of pioglitazone and sulfonylureas on the HbA1C level and found that the combination significantly improves both HbA1C and fasting plasma glucose levels with beneficial effects on serum triglyceride and high-density lipoprotein-cholesterol (HDL-C) levels. Pioglitazone did not show any significant side effects.[5] Pioglitazone has been shown to reduce blood glucose levels in patients with type-2 diabetes. Decreased triglyceride levels and increased HDL-C levels were also observed which could lead to reduction in cardiovascular risk.[6]

Multiple studies have raised concerns about the association of pioglitazone usage with urinary bladder cancer. The US Food and Drug Administration reported that it still believes pioglitazone may pose an increased risk for bladder cancer after updating its review of published research, which has gone back and set forth on issue.[7]

The present study is aimed to associate the risk of urinary bladder cancer with pioglitazone usage and compare the same with nonpioglitazone users.

MATERIALS AND METHODS

Statistical analysis

Unpaired Student's *t*-test was used to determine the significance, and $P < 0.05$ was considered statistically significant. Chi-square test was used to determine the significant risk of bladder cancer with the use of pioglitazone, and $P < 0.05$ was considered statistically significant.

Selection of subjects for the study

The present study was conducted at S N Medical College, Agra, India. Diabetes screening and treatment clinic has been operational for the last 35 years. This clinic facilitates comprehensive outpatient evaluation of diabetic patients including consultation, dietary and life style management, workup and treatment of complications of diabetes mellitus, laboratory services, and free drug distribution. The average outpatient attendance is 300 per week, with approximately 25,000 registered and 8537 follow-up patients. Considering that a large number of patients have been exposed to a variety of oral hypoglycemics (metformin, pioglitazones, and glimepiride), this sourced us ample data to assess safety and tolerance of these drugs. We carefully selected 2085 patients who had taken pioglitazone for variable duration of time. A similar number of nonpioglitazone users were also enrolled. A median duration of pioglitazone therapy exceeding 24 months was considered cutoff for screening for bladder cancer.

Screening for observation of bladder carcinoma

The medical records of the patients were analyzed with the permission of the administration of the hospital. All the patients with historical exposure of pioglitazone were interviewed with carefully selected questionnaire highlighting symptoms, suggestive of urine tract outflow obstruction and bladder cancer. All patients were subjected to urine examination for red blood cells and malignant cells. Those testing positive in questionnaire and urine examination were subjected to ultrasound, cystoscopy, and bladder biopsy if indicated.

RESULTS

From a total of 8537 registered follow-up diabetic patients, 3700 had an exposure history of pioglitazone exceeding 24 months; of these, 2085 (1100 males and 985 females) consented to be part of the study and participated in interview and questionnaire process; their outpatient record was analyzed for total dose of pioglitazone consumed and other demographic data. An equal number of patients (2085 – 1354 males and 731 females) were selected as control group [Table 1 and Figure 1], who had been following up in the outpatient department and were receiving nonpioglitazone-based oral hypoglycemic. Patients in Group A were taking pioglitazone 15 and 30 mg for >2 years; some of the patients were taking treatment even for >10 years, whereas patients in Group B were on nonpioglitazone-based therapy of oral hypoglycemic agent for diabetes other than pioglitazone. The average HbA1C

Table 1: Gender-wise population selected for the study

Gender	Number of patients (%)	
	Pioglitazone users: Group A	Nonpioglitazone users: Group B
Male	1100 (52.76)	1354 (64.94)
Female	985 (47.24)	731 (35.06)
Total	2085 (100)	2085 (100)

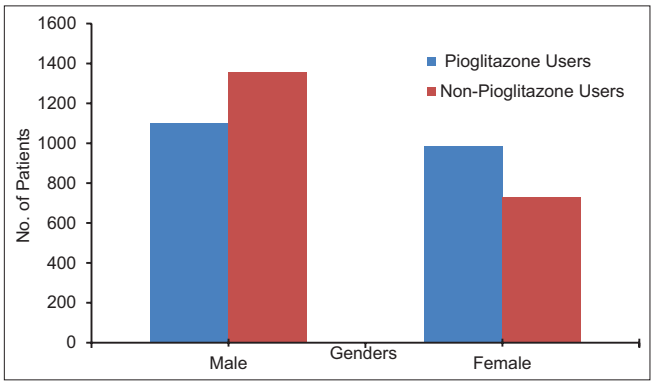

Figure 1: Gender wise distribution of patients

level was 6.4–7.8 (Group A) and 6.1–7.6 (Group B). All the patients were from Indian origin and living in India during the study.

Age-wise distribution of patients

Patients were divided into three age groups, i.e., <40 years, from 41 to 60 years, and >60 years [Figure 2]. The distributions of patients in both the groups are given in Figure 2. The youngest male in Group A was of 27 years and the female was of 29 years, whereas in Group B, the male was of 29 years and the female was of 28 years. The oldest patient in Group A was of 84 years among male and of 74 years among female whereas in Group B was of 82 years among male and of 74 years among female.

There is no significant difference found in the distribution of patients among the male and female population, $P > 0.05$; it represents a uniform selection of subjects among the population.

The significance of duration of therapy and bladder cancer

We observed that 76.13% (587 of 771) males and 76.19% (413 of 542) females had been exposed to pioglitazone 30 mg for a duration exceeding 5 years; similarly, 78.72% (259 of 329) males and 57.78% (256 of 443) females had an exposure to pioglitazone 15 mg exceeding 5 years [Tables 2 and 3]. The study population had majority of patients in both genders in both 15 and 30 mg dosage groups with an exposure exceeding 5 years.

Cumulative lifetime exposure of pioglitazone

The cumulative lifetime exposure of patients to pioglitazone was calculated; and according to this, patients were graded into five groups [Figure 3], group 1: 20–30 g (males 94, females 68); group 2: 30–40 g (males 90, females 104); group 3: 40–50 g (males 254, females 316); group 4: 50–60 g (males 355, females 268); group 5: >60 g (males 307, females 229).

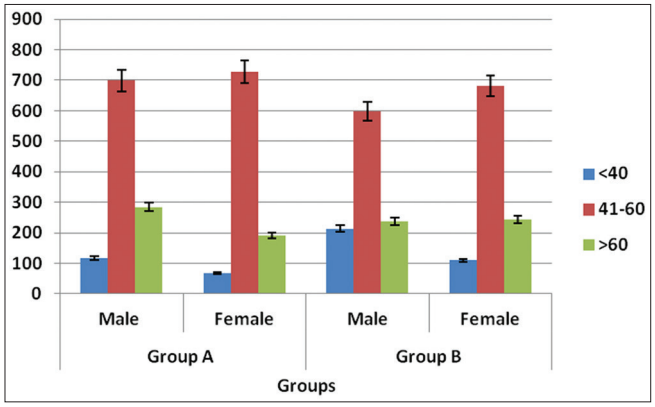

Figure 2: Age-wise distribution of patients in the groups

Evaluation for bladder malignancy in pioglitazone-exposed patients

Patients in the pioglitazone-exposed group were subjected comprehensive assessment for detecting bladder malignancy [Figure 4]; this included symptom-directed questionnaire, urine examination for atypical cells, hematuria, and ultrasound, cystoscopy, and bladder biopsy (wherever indicated).

The symptom-directed questionnaire included responses of the patient for symptoms, suggestive of lower urinary tract symptoms, including dysuria, urgency, frequency, feeling of incomplete evacuation, nocturia, and hematuria. Of the patients in pioglitazone-exposed group, 22 males and 8 females reported having such symptoms for variable duration of time.

Five males and one female had erythrocyturia while no patient had atypical/malignant cells in urine and cystoscopy and bladder biopsy was not performed in any patient as none had clinical indications for the same.

Table 2: Distribution of patients received pioglitazone 30 mg therapy

Duration of therapy (years)	Number of patients	
	Male	Female
>10	307	229
5-10	280	184
2-5	184	129
Total	771	542
Percentage	70.09	55.03

Table 3: Distribution of patients received pioglitazone 15 mg therapy

Duration of therapy (years)	Number of patients	
	Male	Female
>10	75	84
5-10	184	172
2-5	70	187
Total	329	443
Percentage	29.91	44.97

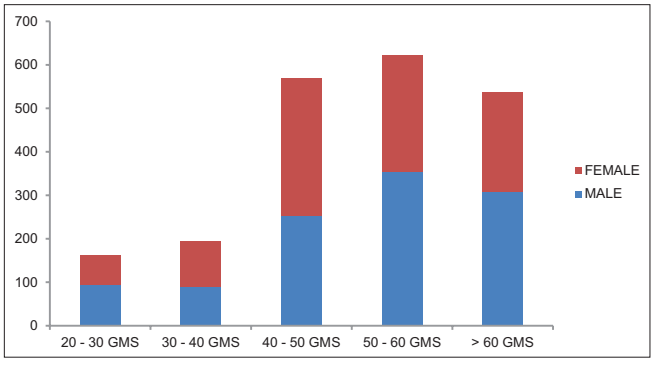

Figure 3: Graded cumulative lifetime exposure of pioglitazone and gender-wise distribution of patients in each group

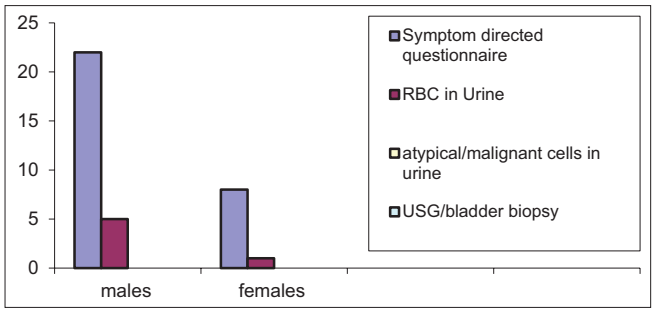

Figure 4: Gender-wise distribution of patient reporting positive findings while evaluating for bladder malignancy

Malignancy in pioglitazone-exposed patients

In the pioglitazone-treated patients, a total of five patients (4 females and 1 male) out of 2085 patients were found to have malignancies, of these 2 cases (females) were of gall bladder malignancy, 1 case had oral carcinoma (male), 2 patient had cervical carcinoma (female), and none of the patient had bladder or other urogenital malignancy.

Malignancy in nonpioglitazone-exposed patients

None of the patients were observed any sign of bladder carcinoma.

Among the female patients of this group, one patient was reported with cancerous cervix and was given the treatment with chemo and radiotherapy. Moreover, among male patients, one patient was reported with chronic myelogenous leukemia, and one patient was found with cancer of the oral cavity [Figure 5].

DISCUSSION

This retrospective study was aimed to analyze the prevalence of bladder cancer, in the type-2 diabetic patients treated with pioglitazone. This is, to best of our knowledge, the largest retrospective cohort of Indian diabetic patients ever subjected to such evaluation. Since the study was in academic institute with monitored drug usage, the sanctity of data was maintained. We observed that patients on pioglitazone did not have any increased risk of bladder cancer. Previous studies have been ambiguous regarding such observation with some studies reporting positive association of pioglitazone with bladder cancer while other refuting it. It has also been reported that association of bladder malignancy with pioglitazone is dependent on prolonged usage and greater dosage; in this study, most patients in both genders were exposed to >5 years of usage and >30 g cumulative lifetime exposure of pioglitazone. Even with such prolonged and high-dose exposure, we did not observe any increased prevalence of bladder malignancy.

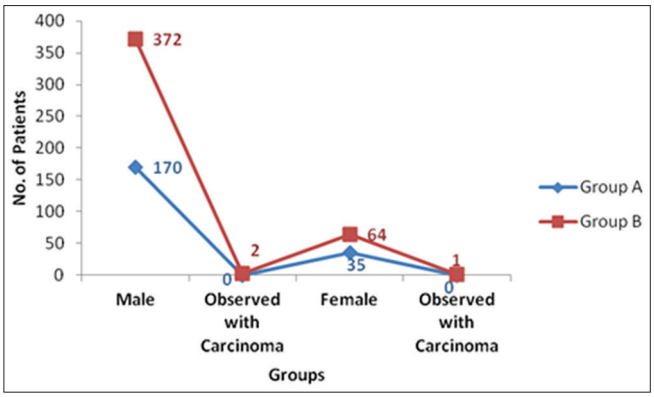

Figure 5: Distribution of malignancy in nonpioglitazone-exposed patients

In a recent study, Tsubaki *et al*. have reported that pioglitazone enhanced the cytotoxic effect of cisplatin and oxaliplatin by suppressing survivin and increasing apoptosis inducing factor (AIF) expression. These results indicated that pioglitazone induced apoptosis via a PPARγ-independent pathway, thus postulating pioglitazone as a potential therapeutic agent for retarding the progression of malignancies.[8]

Tseng has evaluated a cohort of 1,000,000 randomly selected patients from the National Health Insurance Database; 165 incident cases of bladder cancer were observed, of them 10 (0.39%) were ever users and 155 (0.30%) were never users of pioglitazone (adjusted hazard ratio in full model 1.305 [95% confidence interval (CI) 0.661–2.576]).[9] Neumann *et al*. used database from the French National Insurance Information System and studied a cohort of 1,491,060 diabetics and 155,535 on pioglitazone and reported 175 cases of bladder cancer among exposed patients and 1841 among nonexposed patients with incidence rates of 49.4 and 42.8 per 100,000 person-years, respectively. Pioglitazone usage was significantly associated with bladder cancer incidence (adjusted hazard ratio 1.22 [95% CI 1.05–1.43]).[10]

In contrast to studies by Tseng and Neumann *et al*., most other studies have also reported no increased risk of malignancy with pioglitazone usage. Levin *et al*., in a multi-population pooled data of 1.01 million persons over 5.9 million person-years with 3248 cases of incident bladder cancer, 117 exposed cases, and a median follow-up duration of 4.0–7.4 years, reported that cumulative use of pioglitazone or rosiglitazone was not associated with the incidence of bladder cancer.[11]

Few Indian studies have also supported the notion of no increased risk of malignancy among pioglitazone users. Balaji *et al*. in a cohort of 1077 diabetics reported

20 patients of bladder cancer with 31 on them pioglitazone and remaining 1046 on drugs other than pioglitazone, 1 out of 31 developed bladder cancer in pioglitazone compared to 19 out of 1046 in nonpioglitazone users, thus showing no significant association between pioglitazone use and bladder cancer[12] ($P = 0.918$).

Gupta *et al*. studied 2222 type-2 diabetics, 1111 of them being pioglitazone users and remaining on nonpioglitazone-based therapies; they reported that pioglitazone therapy was not associated with occurrence of bladder cancer among Indian type-2 diabetic patients and demonstrated good glycemic control.[13]

An anecdotal Indian case report by Unnikrishnan *et al*. has reported eight cases of bladder cancer among pioglitazone users; their observation also included the first female bladder cancer patient with pioglitazone usage.[14]

CONCLUSION

In this retrospective study, we did not observe any increased risk of bladder malignancy with pioglitazone exposure; furthermore, there was no association with cumulative dose and duration of pioglitazone therapy.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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