Does Pioglitazone Increase the Risk of Bladder Cancer in Japanese Diabetic Patients?

Kanya Kaga, Kazuhiro Araki, Manato Kanesaka, Masahiro Sugira, Kyokushin Ho, Hiroshi Masuda, Satoko Kojima and Yukio Naya*  
Department of Urology, Teikyo Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba 299-0111, Japan

Abstract

Objective: To investigate the risk of bladder cancer with pioglitazone, the data of diabetic patients treated at Teikyo Chiba Medical Center were analyzed retrospectively.

Methods: From February 2009 to October 2011, 720 patients were treated with pioglitazone, and 742 patients were not treated with pioglitazone at Teikyo University Chiba Medical Center. The numbers of newly diagnosed bladder cancers from February 2009 to December 2013 in these patients and the occurrence of bladder cancer among type 2 diabetes mellitus patients were identified. The duration of diabetes, sex, age, smoking, and medication for diabetes were obtained from the medical records. The occurrence of bladder cancer was defined as incident cases after the initiation of pioglitazone. Statistical significance was analyzed by Fisher's exact test.

Results: About 2% of diabetic patients had bladder cancer. The incidence of bladder cancer was not different between the pioglitazone group (15/720, 2.0%) and the no pioglitazone group (14/742, 1.9%). No oral diabetes medication was related to the risk of bladder cancer. However, use of insulin was significantly related to bladder cancer risk (hazard ratio [HR]: 2.83; 95% confidence interval [CI]: 1.15–6.84; p=0.0246), and sex was also significantly related to bladder cancer (HR: 6.001; 95% CI: 1.397–43.06; p=0.0137). The duration of diabetes and smoking were not associated with bladder cancer risk.

Conclusion: In this study, use of pioglitazone was not related to bladder cancer risk, while use of insulin was related to bladder cancer risk.

Keywords: Cancer; Pioglitazone; Diabetes; Insulin

Introduction

The safety of pioglitazone, an oral anti-diabetic agent in the thiazolidinedione class, is controversial. Although pioglitazone is effective at reducing glycated hemoglobin (HbA1c) levels and may decrease the risk of cardiovascular events [1,2], it has also been associated with weight gain and an increased risk of congestive heart failure [1]. Although data are limited, there is now some evidence suggesting that pioglitazone may be associated with an increased risk of bladder cancer. A recent observational study [3] using the Kaiser Permanente Northern California diabetes registry data found that, among 193,099 diabetic patients who were ≥40 years old, use of pioglitazone at any time (n = 30,173) was not associated with the risk of bladder cancer (adjusted HR: 1.2, 95% CI: 0.9–1.5). However, long-term use of pioglitazone (>24 months of therapy) was associated with an increased risk of bladder cancer (adjusted HR: 1.4; 95% CI: 1.03–2.0). More recent data from observational studies show relative risks (RRs) ranging from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with diabetic patients receiving other antidiabetic medicines but not exposed to pioglitazone [4]. Two studies have been reported from England: one suggested an association between pioglitazone and the risk of bladder cancer [5], while the other did not [6]. Two subsequently published Taiwanese studies and one Korean study found no significant association between pioglitazone and bladder cancer [7-9]. Thus, this relationship remains controversial.

Only one study in Japan investigated the risk of bladder cancer with pioglitazone use [10]. In our hospital, half of the patients with type 2 diabetes mellitus (T2DM) were treated by pioglitazone to prevent cardiac or cerebral vascular events. Most pioglitazone was prescribed by cardiologists. Therefore, it seems that this situation facilitated an assessment of the relationship between pioglitazone and bladder cancer. Therefore, the data of diabetic patients treated at Teikyo Chiba Medical Center were retrospectively analyzed.

Patients and Methods

The frequency of bladder cancer in patients with T2DM treated with any medication from February 2009 to October 2011 was retrospectively examined using the computerized medical records system in our hospital. This system was started from February 2009. A total of 720 patients had been treated with pioglitazone, and 742 patients had not during this period. We could access past use of pioglitazone before January 2009, only 248 patients. The numbers of newly diagnosed bladder cancers during the period up to December 2013 in these patients and the occurrence of bladder cancer in T2DM patients were identified. The occurrence of bladder cancer was defined as incident cases after the initiation of pioglitazone. The ratio of cases was calculated, and significance was analyzed using Fisher's exact test. The risk of bladder cancer with several diabetes medicines was calculated by multivariate logistic regression analysis. The study was approved by the Hospital Ethics Committee.

Results

The patients’ characteristics are shown in (Table 1). There were no differences in patients’ age and sex between those treated with pioglitazone and those not. A total of 720 patients (49.6%) were treated with pioglitazone. Most patients were treated with two or more
another meta-analysis indicated a relationship between bladder cancer and diabetes (HR: 1.29; 95% CI: 1.08–1.54; p=0.0000) [19]. In the present study, the risk of bladder cancer was high in diabetic patients, especially in males. About 2% of diabetic patients had a bladder cancer.

Thus, diabetes is associated with bladder cancer. It is important to investigate the relationship between anti-diabetic drugs and bladder cancer. The present study found a relationship between insulin use and bladder cancer. The elevation of insulin and insulin-like growth factor-1 and their role as mitogens is the mechanism cited most often to explain the association between diabetes and cancer risk [20,21]. A single case-control study has found higher circulating levels of these factors in bladder cancer cases than in controls [22].

Newton et al. reported that there were no associations between T2DM and the overall risk of bladder cancer (RR = 1.01; 95% CI: 0.87–1.17), noninvasive disease (RR = 0.93; 95% CI: 0.76–1.14), or invasive disease (RR = 1.13; 95% CI: 0.91–1.40). Compared to participants without T2DM, the risk of invasive bladder cancer was higher among participants who had T2DM for >15 years (RR = 1.63; 95% CI: 1.09–2.43) and among those using insulin (RR 5 1.64; 95% CI: 1.18–2.27) [23]. It is, therefore, important to investigate the relationship between insulin use and the risk of bladder cancer.

In the present study, there was no relationship between pioglitazone use and bladder cancer risk, despite the fact that half of the patients were treated with other antidiabetic drugs.

Table 1: Patients’ characteristics. There are no differences in age, sex, and incidence of bladder cancer between patients treated with pioglitazone and patients treated with other antidiabetic drugs. Alpha-glycosidase inhibitors (AGIs), biguanides, meglitinides, D-phenylalanine derivatives, and sulfonylureas were used significantly more in the pioglitazone group than in the no pioglitazone group. However, insulin was used significantly more in the no pioglitazone group than in the pioglitazone group.

The incidence of bladder cancer was not different between the groups (15/720 [2.0%] in the pioglitazone group and 14/742 [1.9%] in the no pioglitazone group) (Figure 1). There is no difference in tumor characteristics between two groups. (pioglitazone group: G1 is 0, G2 is 8 and G3 is 7, no pioglitazone group, G1 is 1, G2 is 5 and G3 is 5, unknown is 3, p=0.2732, pioglitazone group: PT2 or more is 3, pT1 is 9, pTa is 3, no pioglitazone group: pT2 or more is 4, pT1 is 5, pTa is 5, p=0.2505). However, a very high incidence of bladder cancer was seen in diabetic patients. Male sex was associated with a high risk of bladder cancer in diabetic patients (HR: 6.001; 95% CI: 1.397–43.06; p=0.0137) (Table 3).

No oral diabetes medication was related to the risk of bladder cancer, but insulin use was significantly related to bladder cancer risk (HR: 2.83; 95% CI: 1.15–6.84; p=0.0246) (Table 2).

Duration of diabetes and history of smoking were not associated with bladder cancer risk. However, the duration of diabetes was known in only 248 patients, and history of smoking was known in only 271 patients.

Discussion
Bladder cancer is the 5th most common cancer in the United States [11], the 7th most common cancer worldwide [12], and the 9th most common cancer in Japan [13]. Known risk factors include age, sex (male), ethnicity/race (white), smoking, and several occupations, particularly those involving exposure to aromatic amines [14]. Evidence is accumulating that diabetes may be related to the risk of several cancers, including a reduced risk for prostate cancer [14] and increased risks for cancers of the pancreas, liver, colon, and breast [15,16], but the evidence is not as clear for bladder cancer. A meta-analysis published in 2006 suggested that diabetic patients had a slightly elevated risk of bladder cancer relative to non-diabetic patients [17]. One meta-analysis in 2013 found that diabetic patients had a slightly elevated risk of bladder cancer (HR: 1.11; 95% CI: 0.95–1.31; p<0.001) [18], and

| Antidiabetic drug | Cases of Bladder Cancer | Total Number | Odds ratio 95% CI | P |
|-------------------|------------------------|-------------|------------------|---|
| Pioglitazone      | 15                     | 720         | 1.37             | 0.55-3.42 | 0.4958 |
| Glucagon-like peptide-1 analog | 0          | 7           | NA               | NA      | NA     |
| Dipeptidyl peptidase-4 inhibitor | 5       | 279         | 1.43             | 0.44-3.88 | 0.5249 |
| Alpha-glucosidase inhibitor(AGI) | 9       | 623         | 0.74             | 0.29-1.80 | 0.5096 |
| Biguanides        | 5                      | 606         | 0.43             | 0.13-1.20 | 0.1094 |
| Prandial Glucose regulators | 4       | 200         | 1.41             | 0.39-4.06 | 0.572 |
| Sulfonylureas (Second generation) | 6       | 238         | 2                | 0.76-4.95 | 0.1531 |
| Sulfonylureas (Third generation) | 8       | 376         | 2.05             | 0.70-5.32 | 0.1788 |
| Insulin           | 10                     | 437         | 2.83             | 1.15-6.84 | 0.0246* |

* p<0.05, NS: Not significant, CI: Confidence interval

Table 2: Bladder cancer risk and antidiabetic drugs. Pioglitazone use is not related to bladder cancer.
References

1. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, et al. (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the POACTIvE Study (PROspective pioglitAzone Clinical Trial In macrovascular Events): a randomised controlled trial. The Lancet 366: 1279-1289.

2. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 298:1180-1188.

3. Lewis JD, Ferrara A, Peng T, Heddderson M, Blicher WB, et al. (2011) Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 34: 916-922.

4. (2011) European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer.

5. Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, et al. (2012) The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ 344: e3645.

6. Wei L, MacDonald TM, Mackenzie IS (2012) Pioglitazone and bladder cancer: A propensity score matched cohort study. Brit J Clin Pharmacol 75: 254-259.

7. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, et al. (2011) Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology 55: 1462-1472.

8. Tseng CH (2012) Pioglitazone and bladder cancer: a population-based study of Taiwanese. Diabetes Care 35: 278-280.

9. Song SO, Kim KJ, Lee BW, Kang ES, Cha BS, et al. (2012) The risk of bladder cancer in Korean diabetic subjects treated with pioglitazone. Diabetes Metab J 36: 371-378.

10. Fujimoto K, Hamamoto Y, Honjo S, Kawasaki Y, Morii K, et al. (2013) Possible link of pioglitazone with bladder cancer in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 99: e21-23.

11. Jemal A, Siegel R, Ward E, Hao Y, Xu Y, et al. (2009) Cancer statistics, 2009. CA Cancer J Clin 59: 225-249.

12. Burger M, Catto JWF, Dalfagher G, Grossman HB, Herr H, et al. (2013) Epidemiology and risk factors of urothelial bladder cancer. Euro Urol 63: 234-241.

13. Takayama S (2013) Incidence Rate by Cancer site, 2008: Cancer Statistics in Japan 17.

14. Schottenfeld D, Fraumeni JF Jr (2006) Cancer Epidemiology and Prevention. Oxford University Press, New York.

15. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ (2004) Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 159: 1160-1167.

16. Lee SH, Ohr H, Sull JW, Yun JE, Ji M, et al. (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293: 199-202.

17. Larsson SC, Orsini N, Brismar K, Wolk A (2006) Diabetes mellitus and risk of bladder cancer: a metaanalysis. Diabetologia 49: 2819-2823.

18. Xu X, Wu J, Mao Y, Zhu Y, Hu Z, et al. (2013) Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. PLOS ONE 8: e58079.

19. Zhu Z, Zhang X, Shen Z, Zhong Z, Wang X, et al. (2013) Diabetes mellitus and risk of bladder cancer: A meta-analysis of cohort studies. PLOS ONE 8: e58079.

20. Rochester MA, Patel N, Turney BW, Davies DR, Roberts IS, et al. (2007) The type 1 insulin-like growth factor receptor is over-expressed in bladder cancer. BJU Int 100: 1396-1401.

21. Metalli D, Lovat F, Tripodi F (2010) The insulin-like growth factor receptor I promotes motility and invasion of bladder cancer cells through Akt- and mitogen-activated protein kinase-dependent activation of paxillin. Am J Pathol 176: 2997-3006.

22. Zhao H, Grossman HB, Spitz MR, Lerner SP, Zhang K, et al. (2003) Plasma levels of insulin-like growth factor-1 and binding protein-3, and their association with bladder cancer risk. J Urol 169: 714-717.

23. Newton CC, Gaptust SM, Campbell PT, Jacobs EJ (2013) Type 2 diabetes mellitus, insulin-use and risk of bladder cancer in a large cohort study. Int J Cancer 132: 2186-2191.

24. Lewis JD, Ferrara A, Storm BL, Quanberry CP, Bilker WB, et al. (2012) Cohort Study of Pioglitazone and Bladder Cancer in Patients with Diabetes: Fourth Interim Analysis (8-Year) Report with Data from January 1, 1997 to December 31, 2010.Pioglitazone HCl (ACTOS) Study No.01-03-TL-OPI-524 Fourth Interim Analysis Report. 1-20.

25. Morgan CL, Poole CD, Evans M, Barnett AH, Jenkins-Jones S, et al. (2012) What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab 97: 4605-4612.

26. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, et al. (2006) Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 296: 2572-2581.

27. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kuper F, et al. (2008) Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 299: 1561-1567.