

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

Kanya Kaga, Kazuhiro Araki, Manato Kanesaka, Masahiro Sugiura, 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

*Corresponding author: Naya Y, Department of Urology, Teikyo Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba 299-0111, Japan, Tel: +81-4-3662-1211; Fax: +81-4-3661-4773; E-mail: nayayuko@yahoo.co.jp

Received March 17, 2014; Accepted February 10, 2015; Published February 14, 2015

Citation: Kaga K, Araki K, Kanesaka M, Sugiura M, Ho K, et al. (2015) Does Pioglitazone Increase the Risk of Bladder Cancer in Japanese Diabetic Patients? Med Surg Urol 4: 147. doi:10.4172/2168-9857.1000147

Copyright: © 2015 Kaga K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

	Treated with pioglitazone	Treated without pioglitazone	P
N	720	746	
Age, y (average)	65.2	64.3	NS
Sex (male/female)	504/216	495/251	NS
Occurrence of bladder cancer	15	14	NS
Antidiabetic drugs			
Glucagon-like peptide-1 analog	4	3	NS
Dipeptidyl peptidase-4 inhibitor	150	129	NS
Alpha-glucosidase inhibitor (AGI)	385	238	<0.001
Biguanides	391	215	<0.001
Prandial glucose regulators	133	67	<0.001
Sulphonylureas (Second generation)	139	99	0.0126
Sulphonylureas (Third generation)	206	170	0.002
Insulin	164	273	<0.001

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.

drugs. Alpha-glycosidase inhibitors (AGIs), biguanides, meglitinides, D-phenylalanine derivatives, and sulphonylureas 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

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 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

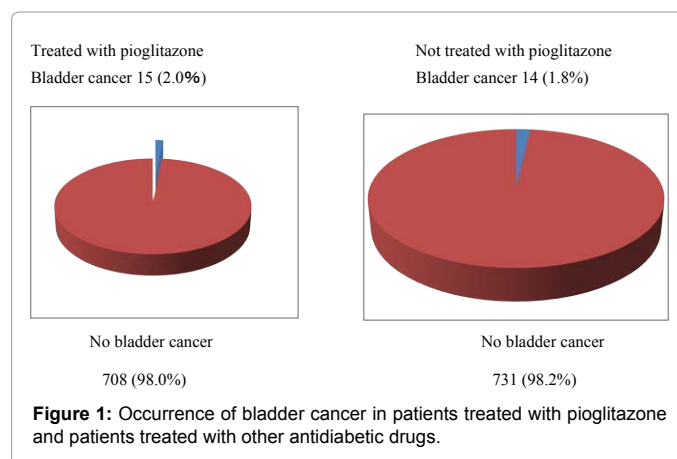


Figure 1: Occurrence of bladder cancer in patients treated with pioglitazone and patients treated with other antidiabetic drugs.

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
Sulphonylureas (Second generation)	6	238	2	0.76-4.95	0.1531
Sulphonylureas (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.

	HR	95% CI	p
Age	1.043	0.975-1.122	0.1416
Sex	6.001	1.397-43.064	0.0137
Smoking	1.552	0.310-8.061	0.5898
Duration of diabetes	1.05	0.996-1.103	0.2255

Table 3: Bladder cancer risk and age, sex, smoking, and duration of diabetes.

treated with pioglitazone. All Asian studies reported that pioglitazone was not associated with bladder cancer risk [7-10], possibly because the incidence of bladder cancer in East Asian countries is lower than that in Western Europe and North America [12]. An 8-year long observational study [24] using the Kaiser Permanente Northern California diabetes registry data found that use of pioglitazone at any time (n= 30,173) was not associated with the risk of bladder cancer (adjusted HR: 1.07; 95% CI: 0.87–1.3), and long-term use of pioglitazone (>48 months of therapy) was not associated with an increased risk of bladder cancer (adjusted HR: 1.30; 95% CI: 0.91–1.86). However, that was an 8-year interim analysis. Any formal conclusions of the KPNC study should be reserved until the study is fully completed.

Morgan et al. reported that metformin with pioglitazone reduced cardiovascular events [25]. There is an abundance of evidence from randomized, controlled trials demonstrating the cardiovascular protective effects of pioglitazone [2,26,27], especially in patients who have already had a myocardial infarction or stroke [26]. In our hospital, many patients with T2DM had cardiovascular disease, and they took pioglitazone to prevent further cardiovascular events.

The limitation of this study is that it was a small, retrospective study. The duration of diabetes was known in only 248 patients, and history of smoking was known in only 271 patients. Because we access the computed medical record system from 2009 February. In almost cases, we could not access the data before 2009 February. Thus we could not clarify the duration of treatment for diabetes. However, this study showed that insulin use might be related to bladder cancer risk in T2DM patients, and pioglitazone was not related to bladder cancer. Further study is necessary to investigate the relationship between pioglitazone and bladder cancer risk.

References

- 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 PROACTIVE Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *The Lancet* 366: 1279-1289.
- 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.
- Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker 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.
- (2011) European Medicines Agency recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer.
- 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.
- Wei L, MacDonald TM, Mackenzie IS (2012) Pioglitazone and bladder cancer: A propensity score matched cohort study. *Brit J Clin Pharmacol* 75: 254-259.
- 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.
- Tseng CH (2012) Pioglitazone and bladder cancer: a population-based study of Taiwanese. *Diabetes Care* 35: 278-280.
- 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.
- Fujimoto K, Hamamoto Y, Honjo S, Kawasaki Y, Mori 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
- Jemal A, Siegel R, Ward E, Hao Y, Xu Y, et al. (2009) Cancer statistics, 2009. *CA Cancer J Clin* 59: 225-249.
- Burger M, Catto JWF, Dalbagni G, Grossman HB, Herr H, et al. (2013) Epidemiology and risk factors of urothelial bladder cancer. *Euro Urol* 63: 234-241.
- Takayama S (2013) Incidence Rate by Cancer site, 2008: Cancer Statistics in Japan 17.
- Schottenfeld D, Fraumeni JF Jr (2006) *Cancer Epidemiology and Prevention*. Oxford University Press, New York.
- 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.
- Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, et al. (2005) Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 293: 194-202.
- Larsson SC, Orsini N, Brismar K, Wolk A (2006) Diabetes mellitus and risk of bladder cancer: a metaanalysis. *Diabetologia* 49: 2819-2823.
- 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.
- 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.
- 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.
- 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. *Amer J Pathol* 176: 2997-3006.
- 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.
- Newton CC, Gapstur 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.
- Lewis JD, Ferrara A, Storm BL, Quesenberry 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 HCI (ACTOS) Study No.01-03-TL-OPI-524 Fourth Interim Analysis Report. 1-20.
- 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.
- 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.
- Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, 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.

Citation: Kaga K, Araki K, Kanesaka M, Sugiura M, Ho K, et al. (2015) Does Pioglitazone Increase the Risk of Bladder Cancer in Japanese Diabetic Patients? *Med Surg Urol* 4: 147. doi:10.4172/2168-9857.1000147