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Original article

Pioglitazone and risk of bladder cancer in type 2 diabetes mellitus patients: A systematic literature review and meta-analysis of observational studies using real-world data

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ABSTRACT

Objectives: Patients with type 2 diabetes mellitus (T2DM) have a higher incidence of bladder cancer (BC); however, the evidence underlining the association between pioglitazone use and BC risk remains inconclusive. We conducted a systematic review and meta-analysis of observational studies to investigate the effect of pioglitazone on risk of BC in T2DM patients.

Methods: We searched all publications regarding risk of BC with pioglitazone use through PubMed, Web of Science and Cochrane library databases from inception to March, 2017. Pooled hazard ratio (HR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Total 15 observational (9 cohort and 6 case-control) studies were meta-analyzed. The pooled results showed a significant association between risk of BC and pioglitazone use (HR 1.20, 95%CI 1.09–1.31; $P < 0.0001$; $I^2 = 4\%$). In subgroup analysis, cumulative dose of pioglitazone (− and >mg) showed a significant association with risk of BC (HR 1.27; 95%CI 1.05–1.54; $P = 0.01$; $I^2 = 0\%$ and HR 1.68, 95%CI 1.36–2.08; $P < 0$ $I^2 = 0\%$ respectively). In addition, a significant association was seen with risk of BC and pioglitazone treatment duration (12–24 months and >24 months) (HR 1.43; 95%CI 1.19–1.71; $P = 0.0001$; $I^2 = 0\%$ and HR 1.58; 95%CI 1.27–1.97; $P < 0.0001$; $I^2 = 29\%$ respectively). Meta-analysis of pioglitazone *vs.* rosiglitazone use, showed a significant association (HR 1.34; 95%CI 1.05–1.71; $P = 0.02$; $I^2 = 0\%$) with BC risk and pioglitazone use.

Conclusion: Pioglitazone use is associated with risk of BC in T2DM patients. Risk of bladder cancer appears to be associated with higher dose and longer duration of pioglitazone use.

1. Introduction

Thiazolidinediones (TZDs), pioglitazone and rosiglitazone are oral hypoglycaemic drugs used for the management of type 2 diabetes mellitus (T2DM). TZDs are insulin sensitizers, widely used for the management of T2DM. Pioglitazone belongs to the TZD group, target PPAR-γ protein, a key transcription factor for adipogenesis and glucose homeostasis.[1] On the other hand, patients with diabetes mellitus have a higher incidence of bladder cancer,[2] but the association between TZD use and bladder cancer still a matter of debate.[3,4] According to American Cancer Society, new cases of bladder cancer and deaths from bladder cancer are expected in 2016 in the United States (US).[5] Incidence of bladder cancer first time observed in a PROactive study, where 14 cases of bladder cancer were found in the pioglitazone treatment arm compared with 5 cases in the placebo group.[6] Preclinical studies reported that pioglitazone and rosiglitazone treatment could develop bladder cancer in diabetic rats.[7,8] It has been also found that pioglitazone exposure caused bladder cancer in male rats, while not observed in mice of either sex. However, mechanism behind the pioglitazone-induced urinary bladder cancer might not be due to PPAR-γ interactions because of differential variation in PPAR-γ expression subsist between the species and sex.[9] Results from a 2 year nonclinical carcinogenicity studies suggested that monotherapy of rosiglitazone were not associated with the bladder cancer.[10] Conversely, another study reveals that rosiglitazone remarkably prop up the bladder neoplasm occurrence in rats pre-treated with hydroxybutyl (butyl) nitrosamine.[7] An independent re-analysis of the RECORD trial data confirmed the original

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results,[11] that rosiglitazone did not increase cardiovascular risk compared to a combination of metformin and sulfonylurea[4]; this has prompted the United States Food Drug Administration (US FDA) to ease some restrictions on rosiglitazone use. An interim report of longitudinal cohort study reviewed by FDA, which showed that short-term use of pioglitazone was not associated with risk of bladder cancer, whereas >2 years use of pioglitazone found to be linked with the bladder cancer in diabetic patients.[12] Additionally, US FDA in 2011 also updated the drug labels of pioglitazone containing medicines and recommended healthcare professionals to avoid prescribing pioglitazone in patient with active bladder cancer and prescribe it with caution in patient having prior history of bladder cancer.[13] Similarly, results of a restrospective cohort study performed in France also reported risk of bladder cancer in pioglitazone users among diabetic patients,[14] and French Medicines Agency (Afssaps) decided to suspend the use of pioglitazone in diabetic patients.[15] Conversely, a recent retrospective cohort study conducted in India documented that pioglitazone was not associated with the bladder cancer in the T2DM patients.[16] Drug Technical Advisory Board (DTAB) of India in 2013 recommended deferment of pioglitazone or manufacture and sale of pioglitazone containing formulation be withdrawn and allowed to be marketed with special caution.[17] Limited real world data regarding safety concern of pioglitazone use and risk of bladder cancer are equivocal and unknown. Information about pioglitazone safety would be important for indemnity and decision making when these drugs are being considered. We therefore performed a systematic literature review and meta-analysis of observational studies to provide more robust evidence regarding the risk of bladder cancer in T2DM patients with pioglitazone use.

2. Materials and methods

2.1. Protocol and registration

Our study protocol is registered on PROSPERO, the international prospective register of systematic reviews.[18] The current systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline.[19]

2.2. Search strategies

We performed a comprehensive literature search by using electronic databases PubMed, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through March, 2017 to identify relevant studies that investigated the association between pioglitazone and risk of bladder cancer in patients withdiabetes mellitus. The PubMed search strategy used the following text words or Medical Subject Headings (Mesh): “diabetes mellitus”, “diabetes”, “bladder cancer”, “urinary bladder neoplasms”, “pioglitazone”, “glitazone”, and “thiazolidinediones”. Manual searches were also performed on Google Scholar and bibliographies of included studies and previous reviews were also examined to identify additional relevant publications. The literature search was performed with no time-frame restrictions. Language other than English was not included in analysis.

2.3. Study selection

Study selection was based on an initial screen of identified titles and abstracts and a second screen of full-text articles. Studies were considered eligible if they met the following criteria: (1) the study design was an observational study (Cohort, nested case-control or case control); (2) the exposure of interest was pioglitazone (3) the outcome of interest was bladder cancer incidence or effect of pioglitazone on bladder cancer; (4) patients with T2DM; (5) reported unadjusted or adjusted estimates [hazard ratio (HR) or odds ratio (OR)] of the association between exposure and outcome, and the corresponding 95% confidence interval (CI), or sufficient raw data to allow their calculation.

2.4. Data extraction

Three independent reviewers (MA, RK and SV) extracted the abstract judiciously according to inclusion criteria. Any discrepancies were arbitrated by the third senior reviewers (AK, PG, and MS) until consent is achieved on every issue. A standard data extraction format was used to collect study information including; name of the first author, year of the publication, age, percentage of male, settings, country, database used, study population, exposure and outcome ascertainment, number of cases/control, exposure *vs.* comparison, duration of follow up, dose and duration of pioglitazone therapy, unadjusted and fully adjusted HR or OR and their 95% CI, and adjusted variables.

2.5. Quality assessment

Two reviewers (MA and RK) independently assessed the quality of each study by using Newcastle-Ottawa Scale (NOS), as recommended by the Cochrane Non-Randomized Studies Methods Working Group.[20] The NOS consists of three parameters of quality: selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The NOS based on star system (with a maximum of nine stars) assigns a maximum of four stars for selection, two for comparability, and three for exposure/outcome. We considered studies with a score of 6 or greater as high quality.

2.6. Statistical analysis

The adjusted effect estimates (HR, or OR) and associated 95% CI for the bladder cancer outcomes and use of pioglitazone were extracted. All analyses were conducted on the natural log scale and standard errors (SE) derived from the formula: [log (95%CI, upper limit)-log (95%CI, lower limit)]/3.92.[21] The OR was considered as equivalent to HR when the disease of interest is not common.[22] We used HR as the common measure of association across studies. Because of the clinical heterogeneity inherent in our data, we used random effects models (DerSimonian and Laird) for meta-analyses of extracted log HR and their SE.[23] Generic inverse variance outcome type was used to pool HR with 95% CI of included studies. Statistical heterogeneity was assessed using the I^2 statistic, with results ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively.[24] Primary analysis focused on assessing the risk of bladder cancer among pioglitazone users. Predefined subgroup meta-analysis was performed for the effect of pioglitazone cumulative dose and duration on risk of bladder cancer. A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result, by excluding each study one by one and recalculating the combined HR on the remaining studies analysis. We also excluded those studies which mentioned only unadjusted estimates and poor quality (score <6) of study according to NOS. The potential publication bias was performed by using a funnel plot for asymmetry and was examined by using the Begg’s adjusted rank correlation test and Egger’s linear regression test, if >10 studies were included in the analysis of the primary outcomes.[25,26] All the statistical analysis was conducted with Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014) and R software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), using the packages

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