

The Risk of Bladder Cancer in Korean Diabetic Subjects Treated with Pioglitazone (*Diabetes Metab J* 2012;36:371-8)

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Type 2 diabetes mellitus is characterized by insulin resistance as well as progressive pancreatic β -cell dysfunction. Thiazolidinediones (TZDs) are a class of hypoglycemic medications that influence insulin sensitivity in peripheral tissue [1]. Pioglitazone is a TZD, peroxisome proliferator-activated receptor (PPAR)- γ ligand used in the treatment of type 2 diabetic patients [2].

Many preclinical trials have demonstrated that PPAR- γ is a potential molecular target for the development of bladder cancer. Yoshimura et al. [3] found PPAR- γ mRNA in bladder cancer samples. Furthermore, immunohistochemistry revealed that the protein expression of PPAR- γ was significantly higher with increasing grade and increasing stage of bladder cancer [3]. In male rats exposed to muraglitazar, a dual human PPAR- α/γ agonist, there was a dose-related increased incidence of transitional cell papilloma and carcinoma of the urinary bladder [4]. Lubet et al. [5] also reported that another PPAR- γ agonist, rosiglitazone, enhanced bladder tumors in rats pretreated with N-(4-hydroxybutyl)-N-(butyl)-nitrosamine (BBN), a known DNA-reactive bladder carcinogen in several species. However, the mechanisms underlying this pro-tumor potential of pioglitazone for bladder cancer are not fully understood.

In the large prospective pioglitazone clinical trial in macrovascular events (PROactive) study, 14 bladder cancers occurred in the pioglitazone arm (0.5%) versus 6 in the placebo arm (0.2%) [6], and in September 2010, the U.S. Food and Drug

Administration (FDA) announced an ongoing investigation on the possible risk in humans [7]. In July 2011, the European Medicines Agency issued a warning about the potential for bladder cancer with pioglitazone [8]. Subsequent studies also suggested that pioglitazone treatment appears to be associated with a significantly increased risk of bladder cancer in patients with type 2 diabetes [9,10]. However, meta-analysis has demonstrated that this association was not significant [11,12].

Song et al. recently reported the risk of bladder cancer in Korean diabetic patients treated with pioglitazone. In this study, development of bladder cancer in Korean diabetic patients was more related to smoking and hemoglobin level rather than pioglitazone use. However, odds ratio of pioglitazone use was relatively high, although it was not significant (2.09, $P=0.484$). Many factors may be related to this difference between Caucasian and Korean patients. As noted by the authors, ethnic and dose differences may be important factors between Korean and Caucasian studies. In addition, concomitant drug use could be possible confounding factor in those studies. Because pioglitazone is a second-line drug after metformin in the Korean medication system, pioglitazone users usually administer metformin concomitantly. Although the mechanisms underlying the protective potential of metformin are not completely understood, many population studies have shown that metformin is associated with a significant reduction of cancer incidence in general [13]. Also, in contrast to the many Western

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diabetic patients who receive pioglitazone with insulin, only limited Korean patients use pioglitazone with insulin.

Although it is unable to clearly exclude the possibility of a relationship between pioglitazone and bladder cancer, this study provides the meaningful result that the risk of bladder cancer in Korean diabetic patients treated with pioglitazone might be different from that of Caucasians. Pioglitazone is effective in reducing blood glucose and is the only useful TZD that improves insulin sensitivity. However, all therapeutic choices need to be based on the balance of potential risks and benefits. Treatment decisions are not always easy and are best achieved when considering all available evidence. Because the authors are currently analyzing the data from 3,500 patients with bladder cancer across several university hospitals, this result will provide a more definitive conclusion about the relationship between pioglitazone and bladder cancer in Korean diabetic patients.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article was reported.

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