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Literature review

THE ASSOCIATION BETWEEN BLADDER CANCERS AND TREATMENT WITH PIOGLITAZONE

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Pioglitazone is an antidiabetic agent belonging to the thiazolinedione class and is used in the treatment of type 2 diabetes mellitus (T2DM). Systematic studies suggest a possible correlation between treatment with pioglitazone and risk of bladder cancer Hypotheses formulated regarding urothelial carcinogenesis include: direct effect of the therapy on the urothelial peroxisome proliferator-activated receptors gamma receptors (PPARγ) and the generation of urinary solids. Several studies are needed to establish the potential correlation between treatment with pioglitazone and bladder cancer and formulate efficient clinical preventive strategies and public health policies.

Keywords: pioglitazone, diabetes, bladder cancers.

INTRODUCTION

Pioglitazone is an antidiabetic agent belonging to the thiazolinedione class and is used in the treatment of T2DM. Thiazolidinediones are ligands of PPARγ and this receptors are expressed in the normal urothelium and bladder cancer cells[1–3]. Clinical studies suggest a possible increased risk of urothelial carcinogenesis in diabetic patients treated with pioglitazone[4–7]. Two hypotheses have been proposed regarding bladder cancer induced by pioglitazone: direct effect of the therapy on the urothelial PPARγ receptors and the generation of urinary solids. In 2004 *Varley CL* and coworkers mention that "*Activation of peroxisome proliferators-activated receptor-γ reverses squamous metaplasia and induces transitional differentiation in normal human urothelial cells*"[2]. In a study on animal models published in 2010 in Toxicological Scienses, Suzuki S and colleagues suggest that the bladder tumors produced by pioglitazone are associated with the formation of urinary solids[8]. The carcinogenic effects of urinary solids are evaluated in several studies. Urine compositional changes produce urinary solids have cytotoxic effect to the urothelium, resulting increased cell proliferation and induction of tumors[9–11].

DISCUSSION

On June, 2011 the French Agency for the Safety and Health Products suspended the use of pioglitazone-containing drugs based on the results of an epidemiological study[12]. Based on observational data, in United States of America, Food and Drug Administration announced in June 15, 2011 that the "*use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer*", and "*recommend that healthcare professionals should: not use pioglitazone in patients with active bladder cancer and use pioglitazone with caution in patients with a prior history of bladder cancer*". The same authority, approved in 2012 the first generic version of pioglitazone hydrochloride[13]. In July 2011 the European Medicines Agency's Committee for Medicinal Products for Human Use had finalised a review of all available data on the occurrence of bladder cancer associated with therapy with pioglitazone. The Agency mention that that therapy with pioglitazone remain a option for certain patients with T2DM but that there is a small increased risk of bladder cancer in patients taking pioglitazone-containing medications. The same authority concluded that "*the small increased risk could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual*

patient's treatment" and contraindicate the treatment with pioglitazone in patients with bladder cancer or in patients with macroscopic haematuria. On March 2012 the European Commission aproved a authorisation throughout the European Union for the first generic version of pioglitazone hydrochloride[14].

Tseng CH published in 2012 in Journal of the Formosan Medical Association a review entitled "Pioglitazone and bladder cancer in human studies: is it diabetes itself, diabetes drugs, flawed analyses or different ethnicities?" The author mentions that result from available studies on the link between treatment with pioglitazone and bladder cancer are not consistent because "*the positive link in patients using pioglitazone in some studies could be due to the drug per se, or due to the underlying disease of diabetes, the interactions with other concomitant drugs, the inherent flaws associated with study designs and statistical analyses, or the different ethnicities between studies*" and recommend further clarification on factors such as duration of treatment with pioglitazone, ethnicity and concomitant bladder cancer risk factors[15].

In the same year, Barbalat Y *et al.*, present in a review entitled "Association Between Pioglitazone and Urothelial Bladder Cancer" results of five clinical studies. The authors concluded that "*Some studies support a minimal increased risk of bladder cancer in diabetic patients using pioglitazone. This risk may be more pronounced for patients who are treated for > 24 months and at cumulative doses ≥ 28,000 mg*"[16].

LITERATURE REVIEW

By using the terms of pioglitazone and urothelial carcinogenesis on PubMed and recommendations of the specialized forums, we have identified studies that describe the possible mechanism between treatment with pioglitazone and bladder cancers.

Bladder cancer is a common affection worldwide. Risk factors associated with bladder cancer are representated by: gender, age, smoking, genetics and family history, chronic bladder irritation and infections, certain medicines (pioglitazone) and herbal supplements. Epidemiologic evidence suggests that T2DM patients have a modestly increased risk of bladder cancer than subjects who do not have this condition[17].

According to experimental studies, pioglitazone exhibit antitumor effects mostly due to their capacity to activate PPARγ[18]. Clinical data regarding the risk of bladder cancer in patients treated with pioglitazone are contradictory and inconclusive.

Concern about bladder cancer from pioglitazone first appeared in the PROactive study. In the above-mentioned study were included 5.238 patients from 19 European countries, study in which pioglitazone or placebo was given in combination with pre-existing medication[19]. Study results showed that the incidence of bladder neoplasm was similar but more cases of malignancies (14 *vs* 5) were observed in the pioglitazone versus *placebo* arms of the study[20].

In 2011, Lewis JD *et al.* published in Diabetes Care a report study about "Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone". In this study were included 193.099 diabetic patients the group treated with pioglitazone consisted of 30.173 patients. The authors mention that "*There were 90 cases of bladder cancer among pioglitazone users and 791 cases of bladder cancer among nonpioglitazone users*" and "*short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for more than 2 years was weakly associated with increased risk*"[21]. In 2012 Wei Li, Macdonald TM, Mackenzie IS. published in British Journal of Clinical Pharmacology a study in wich were included 207.714 patients with T2DM, 23.548 in treatment with pioglitazone and 184.166 in treatment with other oral antidiabetic agents .The study revealed that the patients who recived treatment with pioglitazone have no increased risk of bladder cancer compared to those who did not follow this therapy[22].

The most common neoplasms of the bladder are papillary tumors that vary from very well differentiated to highly anaplastic patterns. Macroscopic and microscopic aspects of malignant urothelial proliferation are shown in Figures 1 and 2.

CONCLUSION

Studies are needed to establish the potential correlation between treatment with pioglitazone and bladder cancer and formulate efficient clinical preventive strategies and public health policies.

DECLARATION OF INTERESTS

The authors report no conflicts of interest.

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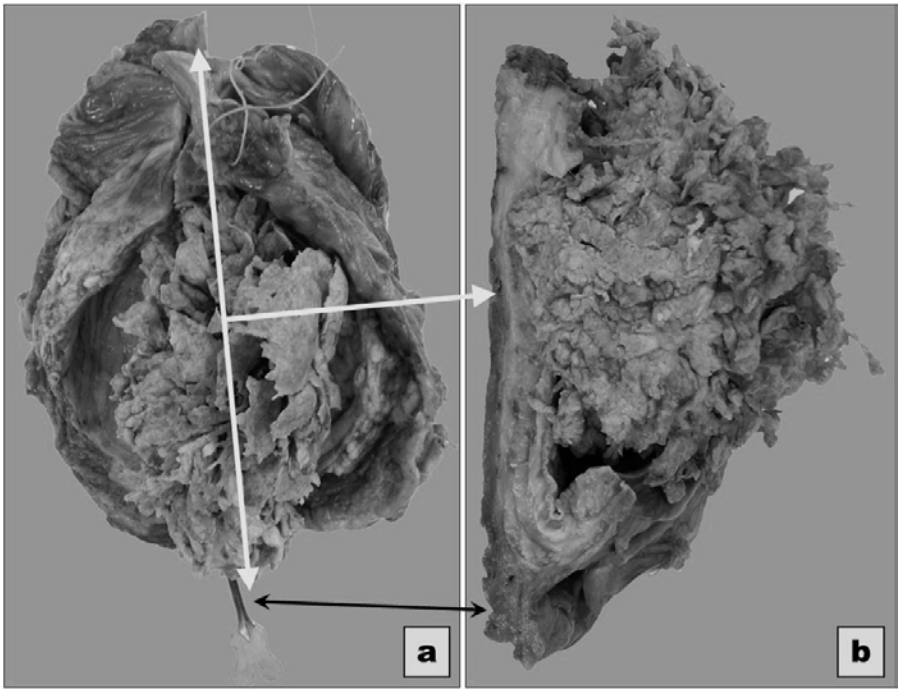

Figure 1. Gross aspect of a papillary tumor developed on the left lateral of the bladder. (a) Frontal anterior view, with a median sagittal opening of the wall, revealing the exophytic papillary proliferation (the grooved stylet is introduced in the urethra, to mark the bladder neck); Yellow vertical line marks the parasagittal plane passing through middle of the tumor. (b) Parasagittal section through the cauliflower like tumor and the vesical wall.

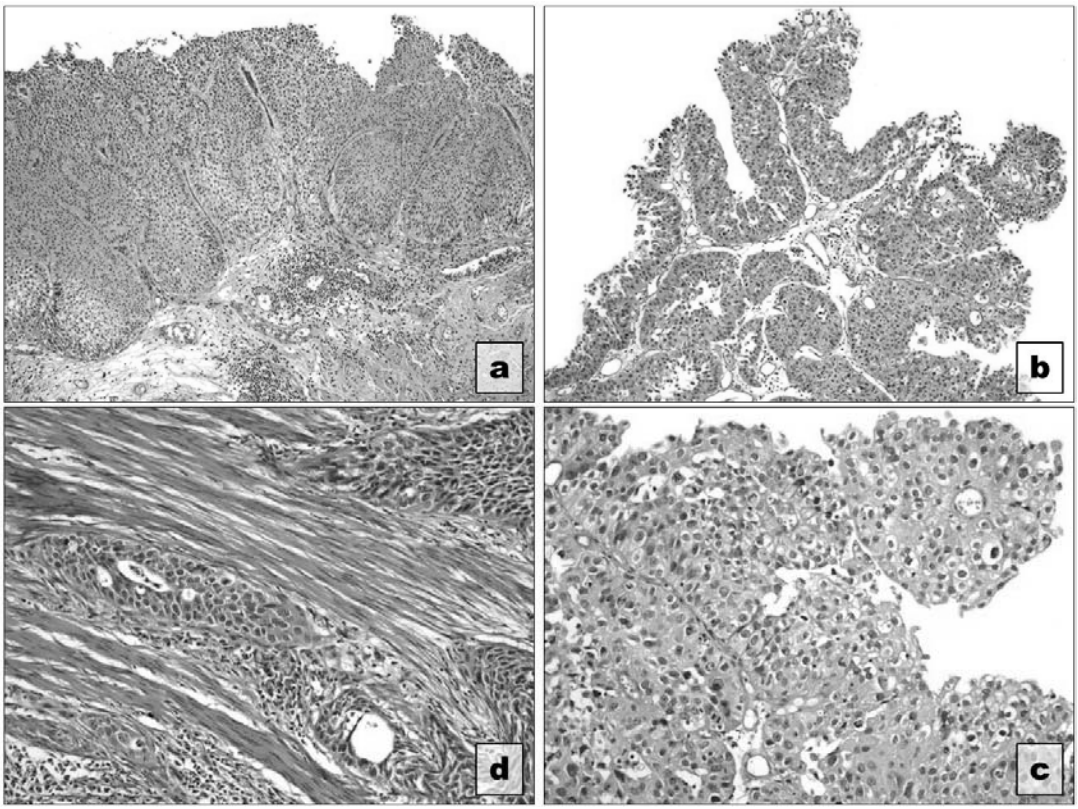

Figure 2. Poorly differentiated papillary urothelial carcinoma of the bladder with deep invasion in tunica muscularis; (a) Larger view of an urothelial malignant papillary proliferation, without invasion of the subepithelial connective tissue; (b) Malignant papillary, branched projection covered by poorly differentiated urothelial cells (HE, ×40); (c) Detail of a papillary branch: malignant urothelial proliferation with loss of polarity, nuclear and cellular pleomorphism, prominent single or double nucleoli, and numerous mitoses (HE, ×100); (d) Tumor invasion in the muscular layer of the bladder wall (HE, ×100).

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