Bladder Cancer 9 (2023) 83–85
DOI 10.3233/BLC-239004
IOS Press

Commentary

Editorial Concerning "The Association Between Diabetes Medication Use and Tumour Characteristics at Diagnosis in Patients with Urothelial Carcinoma: A Retrospective Registry-Based Study"

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Received 3 March 2023
Accepted 5 March 2023
Pre-press 10 March 2023
Published 31 March 2023

In the Western world, and increasingly also in low and middle income countries, there is an epidemic of obesity and type 2 diabetes (T2D), with obesity through chronic inflammation and insulin resistance being one of the main causes (and characteristics) of T2D. And while the individual risk of cancer in the Western world is increasing only slowly, the absolute numbers of new cancer diagnoses are also increasing dramatically. It is logical that this has led to a great deal of interest in the association between T2D and cancer (for an excellent overview of the knowledge in this field, see [1]). This possible association is not only interesting from a public health point of view. Care providers in the clinic are also increasingly dealing with cancer patients who also have obesity and/or T2D.

According to the World Cancer Research Fund (WCRF), there is now strong evidence for the relationship between overweight and obesity and at least 12 cancers, including prostate cancer. According to WCRF, there is still no convincing evidence that overweight/obesity is also a risk factor for bladder cancer [2], despite a meta-analysis of 15 cohort studies with more than 38,000 patients with bladder cancer in which a higher BMI gives a 4.2% higher risk of bladder cancer per increase of 5 kg/m2 [3]. Another meta-analysis of 9 case-control studies and 27 cohort studies suggests that patients with T2D have a 35% higher risk of developing bladder cancer [4].

The prognosis of bladder cancer could also be related to obesity, via a higher insulin and insulin-like growth factor level, low-grade systemic inflammation and PI3K pathway activation [1]. In a meta-analysis of 16 historical cohort studies, NMIBC patients with obesity were found to have a significantly higher risk of recurrence, progression and bladder cancer mortality. Overweight instead of obesity did not appear

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to have such an effect [5]. Overweight MIBC patients had a lower risk of bladder cancer mortality, possibly due to sarcopenia in the reference group. The same authors also reported a significantly higher chance of recurrence and progression among bladder cancer patients with T2D, based on 9 studies, of which only one with a prospective design [5].

A complication in studies of T2D and bladder cancer risk and bladder cancer prognosis is anti-diabetic therapy. Unraveling the influence of the disease or its therapy is a methodological challenge [1, 6]. After all, the severity of T2D may be related both to the risk of cancer and to the choice of therapy. In a cohort of more than 145,000 patients, the thiazolidinedione pioglitazone was found to confer a significantly higher risk of bladder cancer than other anti-diabetic therapies [7], but confounding by indication and other forms of bias may influence this finding. A meta-analysis of the effect of metformin on bladder cancer prognosis did not show a clearly lower recurrence or progression rate [8].

In this issue of Bladder Cancer, Dr. Van Osch and colleagues aim to shed more light on the matter by examining the association between medication for T2D, as a proxy for T2D, and tumor characteristics at diagnosis. They selected all new patients with urothelial carcinoma of the bladder diagnosed between 2000 and 2016 in the southern provinces of the Netherlands in the national cancer registry and linked the records to a pharmacy database. Subsequently, patients with T2D medication (cases: N = 1164) were matched 1:2 on sex and age with patients without T2D medication (controls: N = 2318) and the distribution of stage and grade was compared. In an unmatched analysis, patients taking non-insulin antidiabetic drugs (NIAD) had a 31% higher risk of a T2+ versus Ta tumor and a 31% higher risk of a poorly versus well differentiated tumor.

The question, however, is how much value should be attached to this result. As the authors themselves agree, there are quite a few snags to the design of the study. For example, there was no information about the lifestyle of the patients. Due to the relationship between lifestyle and T2D on the one hand and the possible relationship with tumor characteristics and prognosis on the other hand, the result of the study could be distorted. There was also no information on the duration of T2D treatment and the time between start of treatment and diagnosis of urothelial carcinoma. This potentially leads to prevalent-user bias and hinders the ability to investigate dose-response relationships. Patients treated with T2D medication had more comorbidity than patients without T2D medication, but this was not corrected for. In addition, it is difficult to understand that metformin alone (OR = 1.01) and sulphonylureas alone (OR = 1.07) do not increase the risk of a T2+ versus Ta tumor, but metformin plus sulphonylureas together do (OR = 1.52). The authors speculate that this is because the combination of medications may indicate poorer glycemic control. However, that speculation is contradicted by the finding that NIAD users do have a higher risk of a T2+ and poorly differentiated tumor, but patients who received both NIAD and insulin did not.

Of course, there are many limitations to a study based on existing registries. This is not really a problem for a study that is intended to be exploratory. But several studies already exist on T2D and T2D medication and the risk of bladder cancer and also on the relationship between T2D and T2D medication and bladder cancer outcomes. One may wonder whether an exploratory study adds evidence or confusion in such a case.

What would be the consequences if convincing evidence were provided for a relationship between T2D and/or T2D medication and bladder cancer characteristics or prognosis? Patients known to have T2D may need to be treated more aggressively and follow-up schedules intensified. But perhaps it is even more important that lifestyle medicine finds its way within urology. After all, a better lifestyle not only has a major impact on T2D and the need for NIAD or insulin treatment, but at the same time also on the risk of other comorbidities and quality of life.

ACKNOWLEDGMENTS

The author has no acknowledgements.

FUNDING

The author reports no funding.

AUTHOR CONTRIBUTIONS

Conception/design, drafting the manuscript and critical revision of the manuscript: Lambertus A.L.M. Kiemeney.

CONFLICT OF INTEREST

Lambertus A.L.M. Kiemeney is an Editorial Board member of this journal and acted as reviewer of the manuscript under discussion.

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