

## EDITORIAL COMMENT

# Impact of diabetes and metformin use on prostate cancer

Metformin has been a widely used drug in treatment of diabetes for many decades. It is an inexpensive drug with little and manageable side effects. To use it as an anti-cancer agent poses a challenge: who will finance the research if there is no money associated with it. This is where we, as clinicians have to step in and first start with retrospective studies to see whether we believe that Metformin has a potential against cancer and try to identify which patients are most likely to benefit from it. The main effect of Metformin is on glucose metabolism but it also has an interaction with the androgen receptor [1].

Up to date, there are only few published prospective studies on metformin and prostate cancer (Pca) such as the Swiss phase 2 study in chemotherapy-naïve castration-resistant patients (CRPC). In this study, metformin has been shown to stabilize prostate-specific antigen (PSA) progression [2]. Furthermore, we are awaiting the results of the STAMPEDE trial is studying whether metformin in non-diabetic patients with Pca can improve overall survival (OS) [3]. When searching the clinical trials database of the NIH, we found 354 trials with metformin in various cancers, including 27 in Pca. When querying the Canadian clinical trial database, we found 9 ongoing clinical trials with metformin for different cancers, including 4 trials with Pca.

In this issue of the Journal, Linkeviciute-Ulinskiene et al. report their data from the Lithuanian Cancer Registry. Information on drug use was from the mandatory health insurer, the National Health Insurance Fund database.

They found that in the 254 patients (3.8%) who had Pca and diabetes, no differences were seen in prostate cancer-specific survival between men with or without type 2 Diabetes. They defined patients as 'Metformin users' if they ever had been prescribed Metformin. As expected, overall mortality was higher (HR 1.24, 95% CI 1.07–1.43) in diabetics but there was no difference in prostate-specific survival between non-diabetic patients compared to metformin users or metformin non-users. Concerning metformin users, prostate cancer-specific mortality risk was insignificantly lower in diabetic men on metformin (HR 0.74, 95% CI 0.54–1.02,  $p=0.07$ ) compared to non-diabetics. Diabetic non-metformin users had a slightly non-significant decreased prostate-cancer specific survival.

The positive effect of metformin on overall survival is easily explainable. Metformin is a first-line treatment in many countries with universal healthcare. Therefore, these patients are in an early phase of the diabetes. Non-metformin users might already be resistant to metformin and have more progressive disease.

The fact that metformin users have non-significantly better Pca specific survival seems to us to be the most important result of this study.

The strength of this publication is that with the help of the insurance database, ever-users were identified as users. In other studies, drug-use was only recorded once at study entry. On the other hand, we don't know anything about an eventual dose-effect of Metformin. Or, as the authors acknowledge, there is no information on an eventual cumulative effect of Metformin users who often take this medication over several years.

There are several important publications on diabetes and Pca from Nordic countries. In a Swedish nationwide population-based case-control study, men with type 2 diabetes had a 20% reduced risk of being diagnosed with Pca [4]. In a study from Finland, men using antidiabetic drugs had a lower overall Pca risk, and metformin decreased the Pca risk in a dose-dependent manner [5]. A Danish study [6] found that the use of metformin and insulin decreased the incidence of Pca, but for patients who had a previous PSA testing, insulin-use was no longer a significant factor. Lithuania is an interesting country to study the interaction between diabetes and Pca. In a recent publication comparing data from Belarus, Estonia, Latvia, Lithuania, the Russian Federation and the Ukraine [7], it was shown that the highest incidence of Pca was found in the Baltic States such as Lithuania and low incidence in Belarus, the Russian Federation and Ukraine. Furthermore, the annual percentage changes (APC) showed the largest increase in Lithuania. On the other hand, there was a decrease in Pca incidence since 2007. This article was published in October 2019 and has so far one citation.

In a different publication [8] including some of the same authors as in this article, they found a significantly lower risk of Pca in diabetics. The reduction was even higher in metformin-users (than in diabetic who never used metformin (SIR 0.88, 95% CI: 0.80–0.96).

Such important studies are often little noticed, one of the reasons might be that Baltic States are far away for most of us. The effort the authors had to invest to publish their article in an internationally read journal such as the Scand J Urol was visible. We have to continue to support national professional and scientific associations such as the European Association of Urology that supports local associations such as the Baltic ones.

While we are waiting for the results of the mentioned clinical trials, the interest in metformin in general and more specifically in Pca is based and encouraged by studies like the one by Linkeviciute-Ulinskiene et al.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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Received 27 July 2020; accepted 1 August 2020

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