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Editorial

Metformin and Prostate Cancer

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Metformin is an FDA-approved antidiabetic agent that manages high blood sugar levels in type 2 diabetes patients. It reduces glucose absorption from the intestines, lowers liver glucose production, and improves insulin sensitivity. [1]

Metformin has numerous antineoplastic effects including an AMP-activated protein kinase–dependent mechanism. Epidemiological studies suggest that obesity and type II diabetes mellitus (T2DM), may play a protective effect on prostate cancer incidence by creating a set of metabolic conditions that lower androgen levels. While the body of evidence to support a role for metformin in prostate cancer therapy is rapidly growing, there is still insufficient data from randomized trials, which are currently still ongoing. However, evidence metformin could be a useful adjuvant agent, particularly in patients on Androgen Deprivation Therapy (ADT). [2]The role of metformin and statins remains promising with several trials showing reduced rates of progression and cancer-specific mortality. Combination therapy strategies have also been evaluated in more advanced patients showing synergism. Dietary interventions especially fruits, vegetables, and fish intake have shown some benefit albeit with mixed results for others like legumes, red meat, coffee, and multivitamins. Several ongoing randomized trials will provide stronger evidence in the future for secondary prevention. [3] Numerous studies of metformin have been completed in a variety of disease states and settings. Future metanalyses may help determine metformin's true benefit in prostate carcinoma. Future larger interventional studies assessing both therapeutic modulation and lifestyle changes will determine whether the survival of men with prostate carcinoma requiring androgen deprivation therapy can ultimately be improved by this approach. [4]

The therapeutic efficacy of metformin in Prostate Cancer (PCa) appears uncertain based on various clinical trials. Metformin treatment failure may be attributed to the high frequency of transcriptional dysregulation, which leads to drug resistance. However, the underlying mechanism is still unclear. It was found that metformin resistance in PCa cells may be linked to cell cycle reactivation. Super-Enhancers (SEs), crucial regulatory elements, have been shown to be associated with drug resistance in various cancers. In Metformin-Resistant (MetR) PCa cells revealed a correlation with Prostaglandin Reductase 1 (PTGR1) expression, which was identified as significantly increased in a cluster of cells with metformin resistance through single-cell transcriptome sequencing. [5]In diabetic patients with PCa, metformin may reduce the metabolic side effects incurred by Androgen Deprivation Therapy (ADT) as well as promote its efficacy. Therefore, metformin used in conjunction with ADT may lower the rate of hospitalization and its related costs. This may help alleviate the economic burden of PCa, which is an increasingly important concern in Asia where its incidence is rising. It was shown that metformin use in patients with PCa receiving ADT was associated with significantly lower risks of all causes and PCa-related mortality, but the healthcare resources and economic implications of such associations have remained unknown. Thus compared the rates of hospital attendances and the associated costs between metformin users and non-users among Asian, diabetic adults with PCa receiving ADT. [6]In another study, 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. Overall mortality was higher in diabetics but there was no difference in prostate-specific survival between non-diabetic patients compared to metformin users or metformin non-users. [7] 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 ¼ 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 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 be the most important result of this study. A meta-analysis supports the concept of randomized clinical trials using metformin in the adjuvant setting, with the strongest supporting evidence in colorectal and prostate cancer, particularly those treated with radical radiotherapy. Such trials could also expand our understanding of the relationships between cancer outcomes and the dose and duration of metformin. In other tumor types, where there is currently less evidence, further observational

studies are needed to advise suitability for investigation in any future randomized, controlled trials. [8]

Current treatments for advanced PCa are limited by drug resistance and toxicity.

Therefore, new cellular targets and novel molecular therapeutic agents with favorable toxicity profiles are needed. Metformin exerts direct effects as a metabolic homeostasis regulator and indirect effects as an anti-proliferative and anti-carcinogenic agent. Considering the potential association between metabolic syndrome and PCa development and progression, metformin may be considered an adjuvant agent, both as a monotherapy and in combination with other therapies. Studies have reported conflicting results regarding the association between metformin use and the risk of PCa incidence and survival outcome. Ongoing trials are exploring the additional effects of metformin combined with androgen receptor axis-targeted agents in patients with Castration-Resistant Pca (CRPC) and patients receiving salvage radiotherapy following radical prostatectomy. Generally, the relationship between the use of metformin and PCa remains controversial. Additional studies are warranted to validate the clinical benefits and potential risks of metformin use. Studies to explore the optimal strategy to maximize the benefits of metformin's intrinsic proprieties are necessary, as are studies of metformin's many effects, especially those related to the reduction of serum glucose and insulin concentrations [9]. Finally, recent findings show that the damages caused by cancer increases with diabetes. Metformin plays a protective role against tissue damage, oxidative stress, antioxidant capacity, and damage within the liver tissue of Copenhagen rats. In addition, this drug may have an anti-carcinogenic effect. Thus, the antidiabetic drug metformin can be repositioned for cancer treatment [10]

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