



Metformin and Prostate Cancer: A New Era of Prostate Cancer Research



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Editorial

Metformin, a biguanide, is primarily used in the treatment of type 2 diabetes mellitus (T2DM). Recently, there is a growing interest to examine its role in treatment of different types of cancers [1]. Franciosi and colleagues found a reduction in the risk of development of any cancer due to Metformin use in individuals with T2DM in their systematic review; also, other three systematic reviews assessed the effects of Metformin in individuals with any type of cancer. In meta-analysis of other 20 studies for individuals with T2DM showed that Metformin was associated with a 34% reduction in overall mortality and a 38% reduction in cancer-specific mortality. Two systematic reviews of the association of Metformin with mortality conducted in individuals with any type of cancer with presence or absence of T2DM and came to similar conclusions, but it is also noted that there are differences in the associations between types of cancers and mortality risk with the use of Metformin [2-4].

Prostate cancer (PCa) represents one-third of all new cancer cases each year and the second cause of cancer-related death in US [5]. Development of prostate cancer usually follows premalignant lesions due to a progressive transition from normal prostatic epithelial cells to prostatic intraepithelial neoplasia. By time, most of tumors progress to castration-resistant prostate cancer (CRPC) with development of metastasis [6-8]. Advanced stages of the disease and formation of metastasis are the main causes of most PCa-related mortality. Although there are multiple treatment strategies, the survival rates remain low. The current treatment strategies for PCa include surgery, chemotherapy, radiotherapy, and hormonal therapy. In advanced stage, PCa is characterized by androgen-dependent growth and medical castration through androgen-deprivation therapy (ADT) is the first-line therapy choice for its treatment. This therapy depresses the proliferative function of androgen receptor (AR) but after 12 and 18 months, patients treated with ADT develop resistance to this therapy (CRPC) [6-8].

CRPC is the most aggressive form of PCa and it shows resistance to current available treatment strategies. Recent studies showed that there is existence of a relationship between diabetes, insulin levels, and risk of cancer, including PCa, although, other studies investigating the association between diabetes mellitus and PCa, have reported inconsistent findings. The antineoplastic effect of Metformin was investigated in many recent studies, in which there are evidences that Metformin might have potential benefits on cancer treatment, suggesting a new potential use of this drug beyond its classical indications [9]. The role of Metformin in PCa management was evaluated in many several prospective and retrospective studies. A very interesting meta-analysis conducted by Raval and colleagues in which they retrieved a total of 230 citations through electronic databases and gray literature, after exclusion of certain studies, a total of nine studies were published between 2010 and 2014 were evaluated. In their discussion, they stated that Metformin was marginally associated with a reduction in the risk of biochemical recurrence and Metformin was not associated with all-cause and prostate cancer-specific mortality, also, mixed findings on the association of Metformin and metastases and development CRPC was observed. However, their study findings should be carefully interpreted in the context of the quality and risk of bias present in the included studies as they stated [10].

In conclusion, Metformin may be considered as an ideal agent to be used as adjuvant to standard treatments for PCa, both as monotherapy and combined with chemotherapeutics or other drugs based on data from studies on cancer cell lines and animal models suggest that Metformin lowers the risk of biochemical recurrence and the rates of mortality in PCa through its intrinsic properties and its pleiotropic effects linked with Metformin-mediated fall in plasma glucose and insulin concentrations. Although the potential mechanism of action of Metformin has been largely studied, it is not still completely understood. Other studies are necessary to determine which dose of Metformin

can cause profound direct antineoplastic effects on cancer cell metabolism and if these doses can be safely administered to patients. In addition, randomized controlled studies need to be conducted to assess the efficacy of Metformin in men with prostate cancer with or without diabetes.

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