Abstract

Purpose: This study aims to compare the risks of new-onset prostate cancer between metformin and sulphonylurea users with type 2 diabetes mellitus.

Methods: This population-based retrospective cohort study included male patients with type 2 diabetes mellitus presenting to public hospitals/clinics in Hong Kong between 1st January 2000 and 31st December 2009. We only included patients prescribed either, but not both, of metformin or sulphonylurea. All patients were followed up till 31st December 2019. The primary outcome was new-onset prostate cancer, and the secondary outcome was all-cause mortality. One-to-one propensity score matching was performed between metformin and sulphonylurea users based on demographics, comorbidities, anti-diabetic and cardiovascular medications, fasting glucose level, and HbA1c level. Subgroup analyses based on age and use of androgen deprivation therapy were performed.

Results: The final study cohort consisted of 25695 metformin users (mean age, 65.2±11.8 years) and 25695 matched sulphonylurea users (mean age, 65.3±11.8 years) with a median follow-up duration of 119.6 months (interquartile range: 91.7-139.6) after 1:1 propensity score matching of 66411 patients. Metformin users had lower risks of new-onset prostate cancer than sulphonylurea users (hazard ratio (HR): 0.80; 95% confidence interval (CI): 0.69-0.93; P=0.0031) and all-cause mortality (HR: 0.89; 95% CI: 0.86-0.92; P<0.0001) than sulphonylurea users. Metformin use was more protective against prostate cancer but less protective against all-cause mortality in patients <65 years old (P-value for trend <0.0001 for both) compared to patients aged 65 years or above. Metformin users remained to have lower risk of all-cause mortality than sulphonylurea users, regardless of the use of androgen deprivation therapy (P-value for trend <0.0001) among patients who developed prostate cancer.

Conclusions: Metformin use was associated with significantly lower risks of new-onset prostate cancer and all-cause mortality compared to sulphonylurea use in male patients with type 2 diabetes mellitus.

Keywords: Cohort Studies; Diabetes Mellitus Type 2**;** Metformin; Prostatic Neoplasms; Sulfonylurea Compounds

Introduction

Prostate cancer is the most common cancer diagnosis among male patients and in 2019**,** it was one of the main causes of death worldwide with 487000 deaths.[1] Known risk factors for prostate cancer include family history, ethnicity, and age.[2] Type 2 diabetes mellitus (T2DM) increases the risk of developing cancers such as colon cancer, pancreatic cancer, and bladder cancer.[3] However, the relationship between T2DM, glycemic control, and prostate cancer remains inconclusive.[4-6]

In addition, it has been suggested that the altered risk of new-onset prostate cancer in patients with T2DM is partly attributable to the use of antidiabetic drugs.[7] Metformin and sulphonylurea are the two most commonly prescribed oral antidiabetic drugs in the management of T2DM. While most studies found that metformin was associated with lower incidences of new-onset cancers, there is limited discussion on prostate cancer in particular.[8] Among the few studies that focused on the association between the risk of prostate cancer and metformin, results have been inconclusive and, at times, contradictory.[9-11] As such, there is a need for further investigations into the effects of metformin or sulphonylurea on the risk of prostate cancer. Therefore, this study aimed to compare the risks of new-onset prostate cancer between metformin and sulphonylurea users in a population-based cohort of patients with T2DM.

Methods

2.1 Study design and population

This study was approved by The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee and The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. This retrospective population-based cohort investigates the long-term effects of metformin versus sulphonylurea on the risk of new-onset prostate cancer with propensity score matching approach. Patient data were collected from the Clinical Data Analysis and Reporting System (CDARS), a comprehensive territory-wide database from individual

public hospitals or outpatient facilities in Hong Kong. Data on mortality was accessed through the Hong Kong Death Registry, an official government registry with all the registered death records in Hong Kong. No adjudication of the outcomes was performed in this study as it depended on ICD-9 coding or death registry records. The coding was conducted by clinicians and other administrative staff who were not involved in the research process. This system has previously been used by our team and other teams to conduct population-based research on different diseases,[12, 13] including diabetes mellitus.[14-17]

The inclusion criteria were patients with T2DM who were prescribed with either metformin or sulphonylurea, who presented to local government hospitals or outpatient clinics between 1st January 2000 and 31st December 2009. The exclusion criteria were concomitant users of both metformin and sulphonylurea, with less than 90 days exposure of metformin/sulphonylurea in the first year after T2DM, with baseline age less than 18 years old, with cancer diagnosis before and within 90 days of T2DM, or before initial metformin/sulphonylurea exposure, and those who died within 90 days of T2DM, with prior renal failure diagnosis, new-onset prostate cancer within 1-year drug exposure, and prior HIV infection.

Key comorbidities of patients prior to initial prescription of metformin/sulphonylurea drugs were extracted using the appropriate *International Classification of Disease*, Ninth Edition (ICD-9) codes **(Supplementary Table 1**) to adjust and measure potential confounding variables. The number of prior comorbidities was also documented. In addition, prescription records of key medications, including insulin, acarbose, meglitinide, ACEI/ARB, beta blockers, calcium channel blockers, diuretics, lipid-lowering agents, antiplatelets, and non-steroidal anti-inflammatory drugs were also recorded. Baseline laboratory test results obtained before the index prescription date of metformin / sulphonylurea were extracted too. The variability measures of fasting blood glucose and HbA1c were calculated; the underlying formulae are shown in **Supplementary Table 2**. The standard deviations (SD) of high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride were

calculated.

2.2 Outcomes and follow-up

The primary outcome was new-onset prostate cancer. The secondary outcome was all-cause mortality. All patients were followed up until 31st December 2019.

2.3. Statistical analyses and sensitivity analyses

Continuous variables were presented as mean (95% confidence interval [CI] or SD) or median (interquartile range [IQR]), while categorical variables were presented as frequency (%). One-to-one propensity score matching was performed between metformin and sulphonylurea users based on demographics, Charlson's standard comorbidity index, past comorbidities, non-metformin/sulphonylurea medications, fasting glucose, and HbA1c, to generate two matched cohorts of metformin and sulphonylurea users, respectively. Standardized mean differences (SMD) were used to evaluate the balance in baseline covariates between treatment groups, and values less than 0.2 post-weighting were considered negligible and indicative of good balance. Univariate Cox regression models were used to compare the risks of new-onset prostate cancer and all-cause mortality between treatment groups.

Sensitivity analyses were performed. First, Cox proportional hazard model with a one-year lag time was performed. Second, multiple propensity adjustment approaches were used, including propensity score stratification,[18] high dimensional propensity score matching (HDPS),[19] and inverse probability of treatment weighting (IPTW).[20] Third, cause-specific and subdistribution hazard models were utilized. Fourth, subgroup analysis by age was performed. Fifth, subgroup analysis was performed on patients who developed prostate cancer, with stratification for androgen deprivation therapy (ADT) usage. The list of ADT agonist and antagonist drugs are available in **Supplementary Table 3**.

Hazard ratios (HRs) with corresponding 95%CIs and P-values were reported. All P-values were two-tailed, and values <0.05 were considered statistically significant. Multiple imputations by chained equations were performed for missing values in fasting glucose and HbA1c. Each missing value was imputed 20 times using other variables. Propensity scores of each patient in the cohort with the confounding variables were calculated with a logistic regression model. There was no blinding for the predictors as the data were obtained automatically and directly from the electronic health records. RStudio software (Version: 1.1.456) and Python (Version: 3.6) were used for data analyses throughout the study.

Results

3.1 Study cohort

A flow diagram of the cohort identification, inclusion, and exclusion is shown in **Figure 1**. In total, 131160 male patients with T2DM were identified. After excluding patients without metformin nor sulphonylurea use (N=22797), with both metformin or sulphonylurea use (N=40311), less than 90 days exposure of metformin/sulphonylurea (N=1015), baseline age less than 18 years old (N=35), cancer diagnosis before and within 90 days of T2DM diagnosis or before initial metformin/sulphonylurea exposure (N=231), those who died within 90 days of T2DM diagnosis (N=117), with prior renal failure diagnosis (N=135), and new-onset prostate cancer within 1-year drug exposure (N=89) or HIV infection (N=19), 66411 male patients were included (mean [±SD] age at initial drug use: 65.3 ± 12.3 years old) with a median follow-up duration of 119.6 months (IQR: 91.7-139.6). After 1:1 propensity score matching, the final, matched study cohort consisted of 25695 metformin users and 25695 sulphonylurea users. HbA1c (%) was similar in both metformin and sulphonylurea users (mean [±SD]: 7.45 ± 1.47 vs. mean [±SD]:7.45 ± 1.42, respectively, SMD<0.01). The baseline and clinical characteristics of the study cohort before and after propensity score matching are shown in **Table 1** and **Supplementary Table 4**. The distributions of propensity scores for metformin and sulphonylurea users

before and after propensity score matching with nearest-neighbor matching strategy and a caliper of 0.1 are presented in **Supplementary Figure 1**.

3.2 Outcomes

The results of Cox regression are shown in **Table 2 and Supplementary Table 5**. Metformin users had significantly lower risks of new-onset prostate cancer (HR: 0.80; 95% CI: 0.69-0.93; P=0.0031) and all-cause mortality (HR: 0.89; 95% CI: 0.86-0.92; P<0.0001) than sulphonylurea users, as visualized in the Kaplan-Meier curves in **Figure 2** and cumulative incidence curves in **Supplementary Figure 2**. The annualized total and drug-specific incidence rate of all-cause mortality and new-onset prostate cancer per 1000 patients per year in the matched cohort are reported in **Supplementary Table 6 and 7, respectively.**

Sensitivity analyses for the study outcomes in the matched cohort were presented in the following sections, which included analyses with a one-year lag time, with different propensity score matching approaches **(Supplementary Table 8)**, with cause-specific and subdistribution hazard competing risks models **(Supplementary Table 9)**, age stratification **(Supplementary Table 10)**, and by the use of ADT **(Supplementary Table 11-14)**.

3.3 Sensitivity analysis with a one-year lag time

When analyzed with a one-year lag time, metformin users remained to have lower risks of new-onset prostate cancer (HR: 0.54; 95% CI: 0.53-0.62; P<0.0001) and all-cause mortality (HR: 0.88; 95% CI: 0.85-0.93; P<0.0001) than sulphonylurea users.

3.4 Sensitivity analysis based on different propensity score matching approaches

Metformin users had consistently lower risk of developing new-onset prostate cancer than sulphonylurea users when analyzed with propensity score stratification (HR: 0.63; 95% CI: 0.54-0.69; P<0.0001), HDPS

matching (HR: 0.67; 95% CI: 0.55-0.75; P<0.0001) and IPTW (HR: 0.72; 95% CI: 0.67-0.81; P<0.0001). Metformin users also had lower risk of all-cause mortality than sulphonylurea users when analyzed with propensity score stratification (HR: 0.89; 95% CI: 0.82-0.95; P<0.0001), HDPS matching (HR: 0.86; 95% CI: 0.75-0.90; P<0.0001), and IPTW (HR: 0.89; 95% CI: 0.85-0.97; P<0.0001). These are summarized in **Supplementary Table 8**.

3.5 Sensitivity analysis based on cause-specific and subdistribution hazard models

Metformin users had lower risk of developing new-onset prostate cancer than sulphonylurea users in both cause-specific (HR: 0.89; 95% CI: 0.75-0.95; P<0.0001) and subdistribution hazard models (HR: 0.83; 95% CI: 0.72-0.89; P<0.0001). Metformin users also had lower risk of all-cause mortality than sulphonylurea users in both cause-specific (HR: 0.61; 95% CI: 0.56-0.72; P<0.0001) and subdistribution hazard models (HR: 0.59; 95% CI: 0.51-0.66; P<0.0001). These are summarized in **Supplementary Table 9**.

3.6 Sensitivity analysis by age stratification

The risk of developing the study outcomes was assessed between patients aged 65 and older versus patients aged under 65 **(Supplementary Table 10)**, as visualized in the Kaplan-Meier curves and cumulative incidence curves in **Supplementary Figure 3** and **Supplementary Figure 4**. Among patients aged 65 and older, metformin users had a lower risk of developing prostate cancer (HR: 0.93; 95% CI: 0.79-0.98; P=0.0272) and all-cause mortality (HR: 0.45; 95% CI: 0.44-0.47; P<0.0001). Among patients younger than 65 years old, metformin users had consistently lower risk of developing prostate cancer (HR: 0.78; 95% CI: 0.60-0.95; P=0.0401) and all-cause mortality (HR: 0.57; 95% CI: 0.53-0.61; P<0.0001). There were significant interactions between age groups for the risks of both developing prostate cancer and all-cause mortality (p<0.0001 for both), suggesting that metformin was more protective against prostate cancer but less protective against all-cause mortality in younger patients.

3.7 Sensitivity analysis by use of ADT

Analysis of the effect of ADT, including GnRH agonists and antagonists, on all-cause mortality among metformin and sulphonylurea users who developed prostate cancer was performed **(Supplementary Table 11-14)**. There were no significant differences in the risk of all-cause mortality between ADT users and non-users (HR: 0.80, 95% CI: 0.62-1.04; P=0.1015), which remained insignificant on further analysis by the subgroup of ADT (GnRH antagonists vs non-ADT: HR: 0.71, 95% CI: 0.39-1.30; P=0.2670; and GnRH agonists vs non-ADT: HR: 0.76, 95% CI: 0.58-1.00; P=0.0504). The use of ADT was not associated with significantly different risk of all-cause mortality (metformin and ADT vs. metformin alone; HR: 0.97, 95% CI: 0.45-2.10; P=0.9448), which was consistently observed for both users of GnRH antagonists and agonists as well. Importantly, sulphonylurea users consistently had higher risks of all-cause mortality than metformin users among ADT users, GnRH antagonist, and GnRH agonist users (P value for trend <0.0001 for all).

Discussion

In this population-based cohort study, we showed that long-term metformin use in male patients with T2DM was associated with significantly lower risks of new-onset prostate cancer and all-cause mortality than sulphonylurea use. In addition, such differences appeared to be stronger in younger patients.

Metformin and sulphonylureas are two of the most prescribed drugs for T2DM. Metformin is recommended as first-line therapy for its high efficacy, low cost, weight neutrality, and good safety profile.[21] Sulphonylureas, compared to metformin, is associated with an increased risk of myocardial infarction and all-cause mortality.[22] These findings have led to relegation of sulphonylureas in recent guidelines.[23] These were accompanied by persistent increases in metformin prescriptions and decreases in sulphonylurea prescriptions both locally[24] and internationally.[25] Our findings suggest a further reason to discourage the use of sulphonylureas, particularly in the male population. We acknowledge that our

findings contradict a recent study that metformin use was not associated with any change in risk of developing prostate cancer, although it has a selective protective effect against liver cancer.[4] Nonetheless, the study included patients who, on average, had relatively low HbA1c levels, which may explain the low incidence of new-onset prostate cancer due to better glycemic control.[5]

Adenosine monophosphate-activated protein kinase (AMPK) activation is the main mechanism by which metformin inhibits prostate cancer growth.[26] AMPK arrests cell cycle and cell growth by inhibiting the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway.[27] Metformin not only activates AMPK and inactivates AKT but also inactivates p70S6 kinase, which is downstream of mTOR.[28] Metformin's anti-proliferative effect in prostate cancer cells can also be AMPK-independent through acting on regulated in development and DNA damage responses 1 (REDD1),[29] an inhibitor of mTOR, and cyclin D1.[30] In addition, metformin represses the cyclooxygenase 2 (COX-2)/prostaglandin E_2 (PGE2)/signal transducer and activator of transcription 3 (STAT3) axes to inhibit castration-induced epithelial-mesenchymal transition in prostate cancer, which is closely related to drug resistance, tumor relapse, and metastasis.[31] Inhibition of the GTPase Rac1 is a novel mechanism by which metformin reduces metastases in prostate cancer.[32] Furthermore, it was reported that metformin treatment decreases c-MYC oncogene expression and the incidence of prostate intraepithelial lesions formation, and its pro-apoptotic effects are limited to malignant cells.[33]

Our study also found that the protective effect of metformin was stronger in patients below 65 years old. This may again be due related to AMPK activity. In animal models, it was found that the sensitivity of AMPK activation is higher in young tissues.[34] Age-related changes in the function of protein phosphatases (PP2A, PP2Cα, and Ppm1E) may be involved in suppressing AMPK signaling with aging.[35-37] Furthermore, aging and aging-related disorders are associated with oxidative stress[38] which is heavily implicated in the development of prostate cancer.[39] In prostate cancer, a supraphysiological concentration of reactive oxygen species is a hallmark of aggressive disease.[40] In older adults with T2DM, oxidative stress and hyperglycemia can increase the formation of advanced glycation end

products.[41] When combined with elevated levels of reactive oxygen species, advanced glycation end products enhance the anti-apoptotic nuclear factor-kappa B (NF-kB) pathway.[42]

Research is underway to explore the role of metformin in the treatment of prostate cancer. ADT is the first line treatment of prostate cancer, but many patients eventually do not respond well and develop castrate resistance.[43] Metformin, when combined with ADT, is associated with improved survival in advanced prostate cancer.[44] In addition, ADT can cause metabolic[45] and cardiovascular consequences,[46] and metformin is shown to ameliorate these side effects.[47] Metformin may also be used as an adjuvant to chemotherapy, as it reduces the dose necessary to prolong remission.[48] As an adjuvant agent to radical radiotherapy, metformin may improve survival outcomes.[49]

Our study also highlights the importance of pharmacotherapeutic choice for patients with T2DM at high risks of prostate cancer. Although the antineoplastic effects of metformin have been widely studied, they are still not completely understood in different cancer types. More study is needed to determine the dose of metformin required to exert antitumor control in prostate cancer and whether it can be safely recommended in current practice.

Strength and limitations

The main strength of the present study was that a large and representative territory-wide database with long follow-up duration was used. Our findings are thus generalized and may broadly reflect the real-world practice in Hong Kong. Additionally, sensitivity analyses based on different approaches were performed with consistent results, indicating that our findings were robust. However, some limitations are present. First, this study is an observational cohort study, the residual confoundings cannot be excluded. The possible presence of observational bias, coding error and under coding should be noted. Second, data about medication adherence is lacking due to the nature of the data.

Conclusions

Long-term metformin use was associated with significantly lower risk of new-onset prostate cancer and all-cause mortality in male patients with T2DM than sulphonylurea use. Metformin appeared more protective against prostate cancer but less protective against all-cause mortality in those <65 years old.

Declarations

An abstract of this manuscript has been accepted for presentation at the National Comprehensive Cancer Network Annual Conference 2022.

Funding

No funding was received for conducting this study.

Conflicts of interest/ Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material

Available upon request.

Code availability

Available upon request.

Ethics approval

This study was approved by The Joint Chinese University of Hong Kong - New Territories East Cluster

Clinical Research Ethics Committee and The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Consent to participate

Not applicable.

Consent for publication

All authors consent to publication of this manuscript.

References

1.Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

2.Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med. 2018;8(12).

3.Wojciechowska J, Krajewski W, Bolanowski M, et al. Diabetes and Cancer: a Review of Current Knowledge. Exp Clin Endocrinol Diabetes. 2016;124(5):263-75.

4.Murff HJ, Roumie CL, Greevy RA, et al. Metformin use and incidence cancer risk: evidence for a selective protective effect against liver cancer. Cancer Causes Control. 2018;29(9):823-32.

5.Murtola TJ, Vihervuori VJ, Lahtela J, et al. Fasting blood glucose, glycaemic control and prostate cancer risk in the Finnish Randomized Study of Screening for Prostate Cancer. Br J Cancer. 2018;118(9):1248-54.

6.Crawley D, Chamberlain F, Garmo H, et al. A systematic review of the literature exploring the interplay between prostate cancer and type two diabetes mellitus. Ecancermedicalscience. 2018;12:802.

7.Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Antidiabetic medication and prostate cancer risk: a population-based case-control study. Am J Epidemiol. 2008;168(8):925-31.

8.Yu H, Zhong X, Gao P, et al. The Potential Effect of Metformin on Cancer: An Umbrella Review. Front Endocrinol (Lausanne). 2019;10:617.

9.Lee MJ, Jayalath VH, Xu W, et al. Association between metformin medication, genetic variation and prostate cancer risk. Prostate Cancer Prostatic Dis. 2021;24(1):96-105.

10.Azoulay L, Dell'Aniello S, Gagnon B, et al. Metformin and the incidence of prostate cancer in

patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev. 2011;20(2):337-44.

11.Preston MA, Riis AH, Ehrenstein V, et al. Metformin use and prostate cancer risk. Eur Urol. 2014;66(6):1012-20.

12.Ju C, Lai RWC, Li KHC, et al. Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users. Rheumatology (Oxford). 2020;59(9):2340-9.

13.Ju C, Zhou J, Lee S, et al. Derivation of an electronic frailty index for predicting short-term mortality in heart failure: a machine learning approach. ESC Heart Fail. 2021;8(4):2837-45.

14.Lee S, Liu T, Zhou J, et al. Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. Acta Diabetol. 2021;58(2):171-80.

15.Lee S, Zhou J, Guo CL, et al. Predictive scores for identifying patients with type 2 diabetes mellitus at risk of acute myocardial infarction and sudden cardiac death. Endocrinol Diabetes Metab. 2021;4(3):e00240.

16.Lee S, Zhou J, Leung KSK, et al. Development of a predictive risk model for all-cause mortality in patients with diabetes in Hong Kong. BMJ Open Diabetes Res Care. 2021;9(1).

17.Lee S, Zhou J, Wong WT, et al. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. BMC Endocr Disord. 2021;21(1):94.

18.Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

19.Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology. 2009;20(4):512-22.

20.Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.

21.Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017;60(9):1586-93.

22.Douros A, Dell'Aniello S, Yu OHY, et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. BMJ. 2018;362:k2693.

23.Canadian Diabetes Association Clinical Practice Guidelines Expert C, Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes. 2013;37 Suppl 1:S1-3.

24.Yang A, Wu H, Lau ESH, et al. Trends in Glucose-Lowering Drug Use, Glycemic Control, and Severe Hypoglycemia in Adults With Diabetes in Hong Kong, 2002-2016. Diabetes Care. 2020;43(12):2967-74.

25.Montvida O, Shaw J, Atherton JJ, et al. Long-term Trends in Antidiabetes Drug Usage in the U.S.: Real-world Evidence in Patients Newly Diagnosed With Type 2 Diabetes. Diabetes Care.

2018;41(1):69-78.

26.Zingales V, Distefano A, Raffaele M, et al. Metformin: A Bridge between Diabetes and Prostate Cancer. Front Oncol. 2017;7:243.

27.Tee AR. The Target of Rapamycin and Mechanisms of Cell Growth. Int J Mol Sci. 2018;19(3).

28.Yuan F, Cheng C, Xiao F, et al. Inhibition of mTORC1/P70S6K pathway by Metformin synergistically sensitizes Acute Myeloid Leukemia to Ara-C. Life Sci. 2020;243:117276.

29.Ben Sahra I, Regazzetti C, Robert G, et al. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1. Cancer Res. 2011;71(13):4366-72.

30.Sahra IB, Laurent K, Loubat A, et al. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene. 2008;27(25):3576-86.

31.Tong D, Liu Q, Liu G, et al. Metformin inhibits castration-induced EMT in prostate cancer by repressing COX2/PGE2/STAT3 axis. Cancer Lett. 2017;389:23-32.

32.Dirat B, Ader I, Golzio M, et al. Inhibition of the GTPase Rac1 Mediates the Antimigratory Effects of Metformin in Prostate Cancer Cells. Molecular Cancer Therapeutics. 2015;14(2):586-96.

33.Akinyeke T, Matsumura S, Wang X, et al. Metformin targets c-MYC oncogene to prevent prostate cancer. Carcinogenesis. 2013;34(12):2823-32.

34.Reznick RM, Zong H, Li J, et al. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. Cell Metab. 2007;5(2):151-6.

35.Gimeno-Alcaniz JV, Sanz P. Glucose and type 2A protein phosphatase regulate the interaction between catalytic and regulatory subunits of AMP-activated protein kinase. J Mol Biol. 2003;333(1):201-9.

36.Marley AE, Sullivan JE, Carling D, et al. Biochemical characterization and deletion analysis of recombinant human protein phosphatase 2C alpha. Biochem J. 1996;320 (Pt 3):801-6.

37.Voss M, Paterson J, Kelsall IR, et al. Ppm1E is an in cellulo AMP-activated protein kinase phosphatase. Cell Signal. 2011;23(1):114-24.

38.Zhang Y, Unnikrishnan A, Deepa SS, et al. A new role for oxidative stress in aging: The accelerated aging phenotype in Sod1(-/)(-) mice is correlated to increased cellular senescence. Redox Biol. 2017;11:30-7.

39.Battisti V, Maders LD, Bagatini MD, et al. Oxidative stress and antioxidant status in prostate cancer patients: relation to Gleason score, treatment and bone metastasis. Biomed Pharmacother. 2011;65(7):516-24.

40.Kumar B, Koul S, Khandrika L, et al. Oxidative stress is inherent in prostate cancer cells and is required for aggressive phenotype. Cancer Res. 2008;68(6):1777-85.

41.Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol. 2014;18(1):1-14.

42.Morita M, Yano S, Yamaguchi T, Sugimoto T. Advanced glycation end products-induced reactive oxygen species generation is partly through NF-kappa B activation in human aortic endothelial cells. J Diabetes Complications. 2013;27(1):11-5.

43.Karantanos T, Corn PG, Thompson TC. Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches. Oncogene. 2013;32(49):5501-11.

44.Richards KA, Liou JI, Cryns VL, et al. Metformin Use is Associated with Improved Survival for Patients with Advanced Prostate Cancer on Androgen Deprivation Therapy. J Urol. 2018;200(6):1256-63.

45.Bosco C, Crawley D, Adolfsson J, et al. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS One. 2015;10(3):e0117344.

46.Gheorghe GS, Hodorogea AS, Ciobanu A, et al. Androgen Deprivation Therapy, Hypogonadism and Cardiovascular Toxicity in Men with Advanced Prostate Cancer. Current Oncology. 2021;28(5):3331-46.

47.Aboelnaga EM, Aboelnaga MM, Elkalla HM. Metformin addition to androgen deprivation therapy effect on cancer prostate patients with type 2 diabetes. Diabetes Metab Syndr. 2021;15(5):102251.

48.Iliopoulos D, Hirsch HA, Struhl K. Metformin decreases the dose of chemotherapy for prolonging tumor remission in mouse xenografts involving multiple cancer cell types. Cancer Res. 2011;71(9):3196-201.

49.Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol. 2016;27(12):2184-95.