Review Article

ICUrology 2016;57:157-164.
http://dx.doi.org/10.4111/icu.2016.57.3.157
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Potential role for metformin in urologic oncology

Rashid Khalid Sayyid, Neil Eric Fleshner

Department of Urology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Metformin is one of the most commonly used drugs worldwide. It is currently considered first-line pharmacological agent for management of diabetes mellitus type 2. Recent studies have suggested that metformin may have further benefits, especially in the field of urologic oncology. Use of metformin has been shown to be associated with decreased incidence and improved outcomes of prostate, bladder, and kidney cancer. These studies suggest that metformin does have a future role in the prevention and management of urologic malignancies. In this review, we will discuss the latest findings in this field and its implications on the management of urologic oncology patients.

Keywords: Kidney neoplasms; Metformin; Prostatic neoplasms; Urinary bladder neoplasms

INTRODUCTION

Diabetes mellitus (DM) is an epidemic with an ever-growing influence worldwide. Currently, the global prevalence of diabetes is estimated to be 9% among adults aged more than eighteen years. In 2012, it was estimated that 1.5 million deaths were directly caused by diabetes. By the year 2030, it is estimated that diabetes will become the 7th leading cause of death worldwide [1]. These figures highlight the significant impact DM has on our population.

There are many treatment modalities available for managing DM. Metformin is currently considered the initial agent of choice for pharmacologic management of DM type 2 [2]. Metformin, a biguanide agent, is currently approved by the U.S. Food and Drug Administration as an adjunct to diet and exercise to enhance glycemic control in adults and children with DM type 2 [3]. It exerts its effects at the liver, primarily, by decreasing glucose output, and secondarily, by increasing glucose uptake in peripheral tissues, such as muscle. This is mediated by activation of liver kinase B1, which subsequently regulates adenosine monophosphatase protein kinase (AMPK). Via its phosphorylating effect, AMPK inactivates the transcriptional coactivator, transducer of regulated CREB protein 2, consequently resulting in downregulation of transcriptional events that promote synthesis of gluconeogenic enzymes [4]. Metformin is also known to inhibit mitochondrial respiration, which reduces the energy supply for gluconeogenesis [5].

Metformin is one of the most commonly prescribed drugs, with almost 120 million prescriptions filled yearly worldwide [6]. Naturally, there has been an interest to determine whether this drug could have potential benefits beyond its classical indications. There is a growing belief that metformin has a potential role in the prevention and treatment of cancer, particularly in the field of urologic oncology. Thus, the goal of this review is to present and discuss the latest evidence regarding the potential benefits of metformin in the field of urologic oncology, particularly

Received: 28 March, 2016 • **Accepted:** 22 April, 2016
Corresponding Author: Neil Eric Fleshner
Department of Urology, Princess Margaret Cancer Centre, 610 University Avenue, M5G 2M9, Toronto, ON, Canada
TEL: +1-416-946-2899, FAX: +1-416 946-6590, E-mail: neil.fleshner@uhn.ca

prostate cancer, bladder cancer, and renal cell cancer.

METHODS

PubMed and MEDLINE databases were searched for the MeSH (medical subject headings) headings: urology and metformin. Further searches were conducted as required. Articles were restricted to those published between January 2010 and January 2016, in keeping with our goal of presenting the latest evidence.

The inclusion criteria were: metformin use, prostate cancer, bladder cancer, renal cell cancer, randomized controlled trials (RCT), systematic reviews, metanalyses, prospective or retrospective cohort studies, and case-control studies, and English language. Studies deemed by the authors to be not relevant to the topic or of low methodological quality were excluded, after thorough assessment by both authors.

The bibliographies of the retrieved articles were searched manually, and relevant, significant articles were included in this review.

METFORMIN AND PROSTATE CANCER

1. Does metformin use reduce risk of prostate cancer?

There has been considerable debate as to whether metformin consumption is associated with a reduced risk of developing prostate cancer. A metanalysis of 21 studies determined that history of metformin use is associated with a decreased prostate cancer risk (odds ratio [OR], 0.91; $p<0.05$) [7]. Similarly, a metanalysis conducted by Deng et al. [8] demonstrated that metformin use is associated with a decreased incidence of prostate cancer (risk ratio [RR], 0.88, $p<0.05$). This risk significantly improves with increasing duration (p-trend<0.001) and cumulative dose of metformin (p-trend<0.001) [9]. Interestingly, statin use seems to modulate metformin's impact on risk of prostate cancer. Chen-Pin et al. [10] determined that patients using metformin demonstrated a lower risk of prostate cancer (hazard ratio [HR], 0.89; $p<0.02$), with those concurrently using a statin having an even lower risk of prostate cancer (HR, 0.73; $p<0.001$), highlighting the potential benefit of concurrent use of both medications.

These data are supported by considerable evidence from preclinical studies demonstrating a favorable effect for metformin on prostate cancer cells. Metformin was shown to have an antiproliferative effect on a wide range of prostate cancer cell lines via disruption of the androgen receptor (AR) translational MID-1 (midline-1) regulator complex leading to release of the associated AR mRNA and downregulation of AR protein in AR positive cell lines [11,12]. Metformin was also shown to inhibit androgen-dependent insulin-like growth factor (IGF)-1R up-regulation, thus reducing IGF-1-mediated proliferation of prostate cancer cells [13,14]. Interestingly, metformin decreases glucose oxidation and increases prostate cancer cell dependency on reductive glutamine metabolism [15], in addition to inhibiting lipogenesis via decreasing available ATP in a dose-dependent manner [16].

Metformin has been shown to inhibit epithelial-mesenchymal transition by upregulating miR30a (microRNA 30a), a tumor suppressor, and downregulating SOX-4 (SRY-box 4), a transcription factor, which is critical in limiting cancer progression and metastasis [17]. This drug has also been shown to repress cancer cell growth differently in N-cadherin expressing and non-expressing cells. Metformin exerts its antitumor effect via repressing N-cadherin, independent of 5' adenosine monophosphate-activated protein kinase (AMPK) in wild-type N- cadherin cancer cells. Whereas in N-cadherin deficient cells, it acts via activation of AMPK [18]. Additionally, metformin inhibits prostate cancer cell growth by decreasing c-MYC levels [19] and increasing REDD1 (regulated in development and DNA damage responses) expression, a negative modulator of mTOR (mechanistic target of rapamycin), in a p53-dependent manner [20].

However, there have been a number of studies suggesting that there is no association between metformin and risk of prostate cancer. A large case-control study of Ontario-based elderly diabetic men found that metformin use was not associated with prostate cancer development [21]. Two metanalyses similarly determined that there was no relationship between metformin use and risk of prostate cancer [22,23]. Analysis of data from the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial (where biopsy-negative men underwent protocol-dictated prostate-specific antigen [PSA]-independent biopsies at 2 and 4 years) demonstrated prospectively that metformin exposure was not associated with total, low-, and high-grade prostate cancer diagnosis. However, considering the long natural history of prostate cancer, it must be noted that the follow-up period (4 years) was insufficient to definitively determine whether metformin has any effect on cancer risk [24]. A number of other studies similarly suggested that metformin had no impact on prostate cancer risk [25-29], with a prospective, population-based screening trial demonstrating that metformin has no effect on PSA levels [25].

http://dx.doi.org/10.4111/icu.2016.57.3.157

2. Does metformin use impact prostate cancer outcomes?

Metformin has also been shown to have positive effects on prostate cancer outcomes after treatment. A metanalysis conducted by Stopsack et al. [30] determined that metformin is associated with improved overall survival (HR, 0.52–0.88; p<0.001) and lower risk of biochemical recurrence (HR, 0.79, p=0.047). Similarly, two other metanalyses suggested that metformin is associated with a 17% lower risk of biochemical recurrence [31,32]. However, it must be noted that two other metanalyses did not demonstrate any positive effect for metformin on risk of biochemical recurrence [7,8]. Significantly, none of these studies demonstrated a positive effect for metformin on prostate-cancer specific mortality [7,8,30-32]. However, a population-based retrospective cohort study by Margel et al. [33] did suggest that metformin use is associated with lower risk of prostate cancer-specific mortality (HR, 0.76 for each additional 6 months of metformin use; p<0.05) and all-cause mortality. Further studies are needed to evaluate this.

A small study conducted at The Princess Margaret Cancer Center demonstrated that metformin may have a role to play in the neoadjuvant setting. Twenty-four patients were given metformin prior to surgery. Metformin was found to reduce the Ki67 index (measure of cellular proliferation) by 28.6%–29.5% (p<0.01) as well as demonstrating good tolerability [34]. Preclinical data also suggest that metformin sensitizes prostate cancer cells to radiation therapy, leading to improved tumor oxygenation and radiotherapy response [35,36].

Interestingly, metformin may reduce development of castration-resistant prostate cancer (CRPC). A retrospective study of 2,900 patients with localized prostate cancer managed with external-beam radiation therapy demonstrated that metformin use was independently associated with a diminished risk of development of CRPC in diabetic patients experiencing biochemical failure compared with diabetic nonmetformin patients (OR, 14.71; p=0.01) [37]. Additionally, metformin augments the antiproliferative and apoptotic effects of bicalutamide in prostate cancer. The combination of these two drugs significantly reduces prostate cancer cell growth compared to monotherapy with either drug. This appears to be the result of reduced proliferation in AR-positive cells and increased apoptosis in AR-negative cells [38]. Moreover, nonspecific hypoxia-inducible factor 1-alpha (HIF-1α) inhibitors, such as metformin, have been shown to improve median CRPC-free survival (6.7 years vs. 2.7 years, p=0.01) and reduce the risk of developing CRPC by 71% (p=0.02). There also reduce risk of developing metastases (HR, 0.19, p=0.02) with median metastasis-free survival significantly prolonged (5.1 years vs. 2.6 years, p=0.01) [39]. HIF-1α inhibitors when used in combination with enzalutamide in CRPC cells, result in synergistic inhibition of AR-dependent and gene-specific HIF-dependent expression and prostate cancer cell growth [40].

Similar to previous studies assessing whether combined metformin and statin use was associated with lower risk of prostate cancer development, researchers have evaluated whether combination therapy had any effect on prostate cancer outcomes. A retrospective study of diabetic men undergoing radical prostatectomies demonstrated that dual users, compared to nonusers or users of either medication alone, had lower biochemical recurrence risk than would be expected from each medication's independent effects (HR, 0.2; p<0.05) [41].

Interesting preclinical data suggest that metformin and simvastatin combination chemotherapy has a synergistic effect on castrate-resistant prostate cancer. This combination significantly and synergistically decreased C4-2B3/B4 CRPC cell viability and metastatic properties, with limited adverse effects on normal epithelial cells. This therapy also significantly inhibits primary ventral prostate tumor formation, cachexia, bone metastasis, and biochemical failure more effectively than intraperitoneal docetaxel or monotherapy with either metformin or statin, with significantly less toxicity and mortality than docetaxel [42]. These results highlight the potential of combination chemotherapy with metformin and statin. Currently, a randomized, double-blind phase II trial, the LIGAND (Lipitor and Biguanide to Androgen Delay Trial), is examining the effects of combination metformin and Lipitor on men with PSA between 2 and 5 and experiencing rising PSA levels, despite undergoing definitive therapy (surgery and/or radiation). Over a 3-year period, this trial primarily aims to determine whether this combination therapy affects time to disease progression (defined as PSA rise to 10 ng/mL or greater, development of clinical overt metastases) or patient/physician desire for androgen deprivation therapy (ADT) [43].

ADT, a common strategy to control advanced prostate cancer, is associated with development of metabolic syndrome [44-47]. In one randomized trial of 40 men receiving ADT, it was demonstrated that 6-month treatment with metformin, in addition to a low glycaemic index diet and an exercise program, was associated with significant improvement in abdominal girth, weight, body mass index, and systolic blood pressure (p<0.05 for all) [48]. These interesting findings require further evaluation in future RCTs.

METFORMIN AND BLADDER CANCER

1. Does metformin use reduce risk of urothelial cancer?

Considerable debate exists as to whether history of metformin use is associated with risk of bladder cancer. A population-based, retrospective study of Taiwanese diabetic men demonstrated that metformin is associated with lower risk of bladder cancer. Multivariable analysis revealed the hazard ratio to be 0.60 (95% confidence interval [CI], 0.56–0.64). This risk progressively diminished with increased cumulative duration and dose of metformin (p-trend<0.0001) [49]. Preclinical studies have shown that metformin inhibits the proliferation of bladder cancer cells, both *in vitro* and *in vivo*. This has been suggested to occur through inhibition of cyclin D1, cyclin-dependent kinase 4, and increase of p21waf-1, in addition to activation of adenosine monophosphatase-activated protein kinases (AMPK) and subsequent suppression of mTOR [50,51].

However, two other retrospective studies determined that metformin is not associated with a decreased incidence of bladder cancer compared to sulfonylurea [52,53]. Further studies are obviously needed to clarify this issue.

It must be noted that there have been a number of studies indicating that the commonly used antidiabetic agent, pioglitazone, is associated with increased risk for bladder cancer. A metanalysis concluded that pioglitazone use is associated with a 20% increased risk of bladder cancer (RR, 1.20; p<0.05). The risk of cancer increased with longer duration of use (RR, 1.42 for >2 years) and increased cumulative dose of the drug (RR, 1.64 for >28,000 mg) [54]. These results were confirmed in two other metanalyses [55,56]. This data highlights the hazards of generalizing the results of the metformin studies in bladder cancer to other antidiabetic agents.

2. Does metformin use impact urothelial cancer outcomes?

Evidence to date suggests that metformin use improves urothelial cancer outcomes. Rieken et al. [57] determined that metformin use in diabetic patients with nonmuscle invasive bladder cancer was associated with a lower risk of disease recurrence (HR, 0.50; p=0.03). Similarly, metformin use in diabetic patients treated with radical cystectomy for urothelial carcinoma demonstrated decreased risk of disease recurrence (HR, 0.61; p=0.04), cancer-specific mortality (HR, 0.56; p=0.04), and any-cause mortality (HR, 0.54; p=0.01) [58]. Furthermore, a study by Nayan et al. [59] revealed that metformin use among diabetics patients undergoing radical cystectomy for urothelial carcinoma was associated with significantly improved recurrence-free survival (HR, 0.38; p=0.003) and bladder cancer-specific survival (HR, 0.57; p=0.019). Significantly, use of other oral hypoglycemic or insulin was not associated with improved oncologic outcomes.

Moreover, metformin use is associated with improved oncologic outcomes in upper tract urothelial carcinoma patients following radical nephroureterectomy. Compared to nondiabetic patients, patients with DM had higher disease recurrence (HR, 1.44; p=0.009) and cancer-specific mortality (HR, 1.49; p=0.008). However, metformin use among diabetics led to disease recurrence and cancer-specific mortality rates similar to those present in non-diabetics, thus proving the efficacy of metformin in this setting [60].

METFORMIN AND RENAL CELL CARCINOMA

The majority of studies assessing the impact of metformin on renal cell carcinoma have evaluated whether metformin has an effect on outcome. Results from these studies though have been conflicting. Cheng et al. [61] retrospectively evaluated effect of metformin on 390 diabetic men with renal cell carcinoma, stratified by disease status. Men with localized disease receiving metformin demonstrated significantly superior disease-free survival (HR, 0.47; p<0.01) and cancer-specific survival (HR, 0.21; p<0.01). However, no such improvements existed among patients with metastatic disease. Moreover, two other retrospective studies found that metformin had no effect on risk of progression, cancer-specific mortality, or all-cause mortality in diabetic patients surgically treated for renal cell carcinoma [62,63].

There is evidence though from preclinical studies to suggest that metformin does indeed have a potential role in the management of renal cell carcinoma. Metformin was shown to inhibit renal cell carcinoma growth both *in vitro* and *in vivo*. This was due to downregulation of cyclin D1 expression, which induces cell cycle arrest, and activation if AMPK, an mTOR inhibitor [64]. Additionally, metformin upregulates miR-26a in renal cancer cells, which is associated with increased PTEN expression, an inhibitor of cell proliferation [65,66].

DISCUSSION

There is plenty of evidence to date to suggest that metformin has a role to play in the prevention and management of urologic malignancies. This claim is

http://dx.doi.org/10.4111/icu.2016.57.3.157

supported by the multitude of preclinical studies, which have elucidated the mechanism behind which metformin inhibits cancer cell growth. And despite the presence of conflicting studies, plenty of evidence does exist from clinical studies in diabetic patients. These data, while extremely promising, are not the result of RCTs and are subject to inherent biases of observational studies. Thus, RCTs evaluating the impact of metformin on urologic malignancies are now justified. To that end, there is currently a randomized, double-blind, placebo-controlled trial, The Metformin Active Surveillance Trial Study, being conducted across Canada to assess whether metformin can delay the time to progression in nondiabetic men with low risk prostate cancer on active surveillance. Men with biopsy-proven, low-risk (Gleason score≤6), localized prostate cancer choosing expectant management as primary treatment, serum PSA≤10, and clinical stage T1c–T2a will be followed up for 36 months to determine if metformin delays time to progression, defined as: primary therapy for prostate cancer (e.g., prostatectomy, radiation, hormonal therapy) or pathological progression (at least 4 cores involved, at least 50% of any one core involved, or Gleason pattern 4 or higher) [67]. Such studies will help define specific roles for metformin in the field of urologic oncology and will assist urologists, endocrinologists, and primary care physicians to provide better care to their patients. Despite metformin being currently indicated only for the management of glucose levels in diabetic patients [2], this will certainly not remain the case in the future as more research on this drug is conducted.

CONCLUSIONS

History of metformin intake is associated with decreased risk of prostate cancer development. Use in patients with prostate cancer is associated with improved overall survival and lower risk of biochemical recurrence, with reduced risk of development of CRPC and metastases. Combination use with a statin is associated with further decreased risk of disease development and improved biochemical recurrence rates in prostate cancer patients. Metformin is also useful in alleviation of metabolic side effects associated with ADT use.

History of metformin intake is also associated with decreased risk of bladder cancer development and improved recurrence rates post-treatment. Use in diabetic patients with upper tract urothelial carcinoma improves disease recurrence and cancer-specific mortality. In patients with localized renal cell carcinoma, metformin use is associated with superior disease-free survival and cancer-specific survival. These conclusions are all based on retrospective studies, and future RCT are needed to ascertain these data.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. World Health Organization. Diabetes [Internet]. Geneva: World Health Organization; 2016 [updated Mar 2016; cited 2016 Mar 1]. Available from: http://www.who.int/mediacentre/factsheets/fs312/en/.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Harper W, Clement M, Goldenberg R, Hanna A, Main A, et al. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37 Suppl 1:S61-8.
3. U.S. Food and Drug Administration. Metformin Hydrochloride Tablets [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; c2016 [updated Apr 29, 2016; cited 2016 Mar 1]. Available from: www.fda.gov/ohrms/dockets/dailys/02/May02/053102/800471e6.pdf.
4. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005;310:1642-6.
5. El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 2000;275:223-8.
6. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? Mol Cancer Ther 2010;9:1092-9.
7. Yu H, Yin L, Jiang X, Sun X, Wu J, Tian H, et al. Effect of metformin on cancer risk and treatment outcome of prostate cancer: a meta-analysis of epidemiological observational studies. PLoS One 2014;9:e116327.
8. Deng D, Yang Y, Tang X, Skrip L, Qiu J, Wang Y, et al. Association between metformin therapy and incidence, recurrence and mortality of prostate cancer: evidence from a meta-analysis. Diabetes Metab Res Rev 2015;31:595-602.
9. Tseng CH. Metformin significantly reduces incident prostate cancer risk in Taiwanese men with type 2 diabetes mellitus. Eur J Cancer 2014;50:2831-7.
10. Chen-Pin W, Javier H, Lorenzo C, Downs JR, Thompson IM, Pollock B, et al. Statins and finasteride use differentially modify the impact of metformin on prostate cancer incidence in men with type 2 diabetes. Ann Transl Med Epidemiol 2014;1(1). pii: 1004.

11. Demir U, Koehler A, Schneider R, Schweiger S, Klocker H. Metformin anti-tumor effect via disruption of the MID1 translational regulator complex and AR downregulation in prostate cancer cells. BMC Cancer 2014;14:52.
12. Wang Y, Liu G, Tong D, Parmar H, Hasenmayer D, Yuan W, et al. Metformin represses androgen-dependent and androgen-independent prostate cancers by targeting androgen receptor. Prostate 2015;75:1187-96.
13. Malaguarnera R, Sacco A, Morcavallo A, Squatrito S, Migliaccio A, Morrione A, et al. Metformin inhibits androgen-induced IGF-IR up-regulation in prostate cancer cells by disrupting membrane-initiated androgen signaling. Endocrinology 2014;155:1207-21.
14. Kato H, Sekine Y, Furuya Y, Miyazawa Y, Koike H, Suzuki K. Metformin inhibits the proliferation of human prostate cancer PC-3 cells via the downregulation of insulin-like growth factor 1 receptor. Biochem Biophys Res Commun 2015;461:115-21.
15. Fendt SM, Bell EL, Keibler MA, Davidson SM, Wirth GJ, Fiske B, et al. Metformin decreases glucose oxidation and increases the dependency of prostate cancer cells on reductive glutamine metabolism. Cancer Res 2013;73:4429-38.
16. Loubiere C, Goiran T, Laurent K, Djabari Z, Tanti JF, Bost F. Metformin-induced energy deficiency leads to the inhibition of lipogenesis in prostate cancer cells. Oncotarget 2015;6:15652-61.
17. Zhang J, Shen C, Wang L, Ma Q, Xia P, Qi M, et al. Metformin inhibits epithelial-mesenchymal transition in prostate cancer cells: involvement of the tumor suppressor miR30a and its target gene SOX4. Biochem Biophys Res Commun 2014;452:746-52.
18. Ge R, Wang Z, Wu S, Zhuo Y, Otsetov AG, Cai C, et al. Metformin represses cancer cells via alternate pathways in N-cadherin expressing vs. N-cadherin deficient cells. Oncotarget 2015;6:28973-87.
19. Akinyeke T, Matsumura S, Wang X, Wu Y, Schalfer ED, Saxena A, et al. Metformin targets c-MYC oncogene to prevent prostate cancer. Carcinogenesis 2013;34:2823-32.
20. Ben Sahra I, Regazzetti C, Robert G, Laurent K, Le Marchand-Brustel Y, Auberger P, et al. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1. Cancer Res 2011;71:4366-72.
21. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst 2013;105:1123-31.
22. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol 2013;37:207-18.
23. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2010;3:1451-61.
24. Feng T, Sun X, Howard LE, Vidal AC, Gaines AR, Moreira DM, et al. Metformin use and risk of prostate cancer: results from the REDUCE study. Cancer Prev Res (Phila) 2015;8:1055-60.
25. Randazzo M, Beatrice J, Huber A, Grobholz R, Manka L, Wyler SF, et al. Influence of metformin use on PSA values, free-to-total PSA, prostate cancer incidence and grade and overall survival in a prospective screening trial (ERSPC Aarau). World J Urol 2015;33:1189-96.
26. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer Epidemiol Biomarkers Prev 2011;20:337-44.
27. Kowall B, Stang A, Rathmann W, Kostev K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf 2015;24:865-74.
28. Qiu H, Rhoads GG, Berlin JA, Marcella SW, Demissie K. Initial metformin or sulphonylurea exposure and cancer occurrence among patients with type 2 diabetes mellitus. Diabetes Obes Metab 2013;15:349-57.
29. Nordström T, Clements M, Karlsson R, Adolfsson J, Grönberg H. The risk of prostate cancer for men on aspirin, statin or antidiabetic medications. Eur J Cancer 2015;51:725-33.
30. Stopsack KH, Ziehr DR, Rider JR, Giovannucci EL. Metformin and prostate cancer mortality: a meta-analysis. Cancer Causes Control 2016;27:105-13.
31. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sambamoorthi U. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2015;18:110-21.
32. Hwang IC, Park SM, Shin D, Ahn HY, Rieken M, Shariat SF. Metformin association with lower prostate cancer recurrence in type 2 diabetes: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2015;16:595-600.
33. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol 2013;31:3069-75.
34. Joshua AM, Zannella VE, Downes MR, Bowes B, Hersey K, Koritzinsky M, et al. A pilot 'window of opportunity' neoadjuvant study of metformin in localised prostate cancer. Prostate Cancer Prostatic Dis 2014;17:252-8.
35. Zhang T, Zhang L, Zhang T, Fan J, Wu K, Guan Z, et al. Metformin sensitizes prostate cancer cells to radiation through EGFR/p-DNA-PKCS in vitro and in vivo. Radiat Res 2014;181:641-9.

http://dx.doi.org/10.4111/icu.2016.57.3.157

36. Zannella VE, Dal Pra A, Muaddi H, McKee TD, Stapleton S, Sykes J, et al. Reprogramming metabolism with metformin improves tumor oxygenation and radiotherapy response. Clin Cancer Res 2013;19:6741-50.
37. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol 2013;63:709-16.
38. Colquhoun AJ, Venier NA, Vandersluis AD, Besla R, Sugar LM, Kiss A, et al. Metformin enhances the antiproliferative and apoptotic effect of bicalutamide in prostate cancer. Prostate Cancer Prostatic Dis 2012;15:346-52.
39. Ranasinghe WK, Sengupta S, Williams S, Chang M, Shulkes A, Bolton DM, et al. The effects of nonspecific HIF1α inhibitors on development of castrate resistance and metastases in prostate cancer. Cancer Med 2014;3:245-51.
40. Fernandez EV, Reece KM, Ley AM, Troutman SM, Sissung TM, Price DK, et al. Dual targeting of the androgen receptor and hypoxia-inducible factor 1α pathways synergistically inhibits castration-resistant prostate cancer cells. Mol Pharmacol 2015;87:1006-12.
41. Danzig MR, Kotamarti S, Ghandour RA, Rothberg MB, Dubow BP, Benson MC, et al. Synergism between metformin and statins in modifying the risk of biochemical recurrence following radical prostatectomy in men with diabetes. Prostate Cancer Prostatic Dis 2015;18:63-8.
42. Babcook MA, Shukla S, Fu P, Vazquez EJ, Puchowicz MA, Molter JP, et al. Synergistic simvastatin and metformin combination chemotherapy for osseous metastatic castration-resistant prostate cancer. Mol Cancer Ther 2014;13:2288-302.
43. Clinicaltrials.gov. Lipitor and biGuanide to Androgen Delay Trial (LIGAND) [Internet]. Bethesda (MD): U.S. National Library of Medicine; U.S. National Institutes of Health; U.S. Department of Health and Human Services; 2016 [cited 2016 Mar 3]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02497638?term=LIGAND&rank=8
44. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol 2009;27:3452-8.
45. Tsai HT, Keating NL, Van Den Eeden SK, Haque R, Cassidy-Bushrow AE, Ulcickas Yood M, et al. Risk of diabetes among patients receiving primary androgen deprivation therapy for clinically localized prostate cancer. J Urol 2015;193:1956-62.
46. Keating NL, Liu PH, O'Malley AJ, Freedland SJ, Smith MR. Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. Eur Urol 2014;65:816-24.
47. Chen AC, Petrylak DP. Complications of androgen deprivation therapy in men with prostate cancer. Curr Oncol Rep 2004;6:209-15.
48. Nobes JP, Langley SE, Klopper T, Russell-Jones D, Laing RW. A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. BJU Int 2012;109:1495-502.
49. Mamtani R, Pfanzelter N, Haynes K, Finkelman BS, Wang X, Keefe SM, et al. Incidence of bladder cancer in patients with type 2 diabetes treated with metformin or sulfonylureas. Diabetes Care 2014;37:1910-7.
50. Zhang T, Guo P, Zhang Y, Xiong H, Yu X, Xu S, et al. The antidiabetic drug metformin inhibits the proliferation of bladder cancer cells in vitro and in vivo. Int J Mol Sci 2013;14:24603-18.
51. Zhang T, Wang X, He D, Jin X, Guo P. Metformin sensitizes human bladder cancer cells to TRAIL-induced apoptosis through mTOR/S6K1-mediated downregulation of c-FLIP. Anticancer Drugs 2014;25:887-97.
52. Goossens ME, Buntinx F, Zeegers MP, Driessen JH, De Bruin ML, De Vries F. Influence of metformin intake on the risk of bladder cancer in type 2 diabetes patients. Br J Clin Pharmacol 2015;80:1464-72.
53. Tseng CH. Metformin may reduce bladder cancer risk in Taiwanese patients with type 2 diabetes. Acta Diabetol 2014;51:295-303.
54. Bosetti C, Rosato V, Buniato D, Zambon A, La Vecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. Oncologist 2013;18:148-56.
55. He S, Tang YH, Zhao G, Yang X, Wang D, Zhang Y. Pioglitazone prescription increases risk of bladder cancer in patients with type 2 diabetes: an updated meta-analysis. Tumour Biol 2014;35:2095-102.
56. Zhu Z, Shen Z, Lu Y, Zhong S, Xu C. Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract 2012;98:159-63.
57. Rieken M, Xylinas E, Kluth L, Crivelli JJ, Chrystal J, Faison T, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. BJU Int 2013;112:1105-12.
58. Rieken M, Xylinas E, Kluth L, Crivelli JJ, Chrystal J, Faison T, et al. Effect of diabetes mellitus and metformin use on oncologic outcomes of patients treated with radical cystectomy for urothelial carcinoma. Urol Oncol 2014;32:49.e7-14.
59. Nayan M, Bhindi B, Yu JL, Hermanns T, Mohammed A, Hamilton RJ, et al. The effect of metformin on cancer-specific survival outcomes in diabetic patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Urol Oncol 2015;33:386.e7-13.
60. Rieken M, Xylinas E, Kluth L, Trinh QD, Lee RK, Fajkovic H,

et al. Diabetes mellitus without metformin intake is associated with worse oncologic outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. Eur J Surg Oncol 2014;40:113-20.

61. Cheng JJ, Li H, Tan HS, Tan PH, Ng LG, Ng QS, et al. Metformin Use in Relation With Survival Outcomes of Patients With Renal Cell Carcinoma. Clin Genitourin Cancer 2016;14:168-75.
62. Psutka SP, Boorjian SA, Lohse CM, Stewart SB, Tollefson MK, Cheville JC, et al. The association between metformin use and oncologic outcomes among surgically treated diabetic patients with localized renal cell carcinoma. Urol Oncol 2015;33:67.e15-23.
63. Hakimi AA, Chen L, Kim PH, Sjoberg D, Glickman L, Walker MR, et al. The impact of metformin use on recurrence and cancer-specific survival in clinically localized high-risk renal cell carcinoma. Can Urol Assoc J 2013;7:E687-91.
64. Liu J, Li M, Song B, Jia C, Zhang L, Bai X, et al. Metformin inhibits renal cell carcinoma in vitro and in vivo xenograft. Urol Oncol 2013;31:264-70.
65. Yang FQ, Wang JJ, Yan JS, Huang JH, Li W, Che JP, et al. Metformin inhibits cell growth by upregulating microRNA-26a in renal cancer cells. Int J Clin Exp Med 2014;7:3289-96.
66. Kalogirou C, Schafer D, Krebs M, Kurz F, Schneider A, Riedmiller H, et al. Metformin-derived growth inhibition in renal cell carcinoma depends on miR-21-mediated PTEN expression. Urol Int 2016;96:106-15.
67. Clinicaltrials.gov. The Metformin Active Surveillance Trial (MAST) Study (MAST) [Internet]. Bethesda (MD): U.S. National Library of Medicine; U.S. National Institutes of Health; U.S. Department of Health and Human Services; 2016 [cited 2016 Mar 6]. Available from: https://clinicaltrials.gov/ct2/show/NCT01864096.

http://dx.doi.org/10.4111/icu.2016.57.3.157