Potential role for metformin in urologic oncology

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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 US 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...
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, metaanalyses, 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 metaanalysis 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 metaanalysis 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 metaanalyses 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].
2. Does metformin use impact prostate cancer outcomes?

Metformin has also been shown to have positive effects on prostate cancer outcomes after treatment. A metaanalysis 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 metaanalyses suggested that metformin is associated with a 17% lower risk of biochemical recurrence [31,32]. However, it must be noted that two other metaanalyses 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 enzalutamide 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. 27 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 metaanalysis 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 metaanalyses [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
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 RCTs are needed to ascertain these data.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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