Metformin in prostate cancer: two for the price of one
Department of Medical Oncology, Westmead Cancer Care Centre, Sydney, Australia

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Background: Androgen deprivation therapy (ADT) for prostate cancer treatment induces a metabolic syndrome, which may contribute to non-cancer-related morbidity and mortality. Metformin may abrogate these effects. Additionally, metformin has potential antineoplastic activity in various malignancies including prostate cancer.

Materials and methods: A literature review using PubMed with the keywords: AMPK, androgen deprivation therapy, insulin resistance, metabolic syndrome, metformin and prostate cancer was undertaken.

Results: This overview will look at the current evidence linking ADT and metabolic syndrome while discussing ongoing clinical trials under way assessing the effectiveness of metformin in abrogating these effects. The potential antineoplastic activity of metformin, mediated by multiple proposed mechanisms based on evidence from preclinical and clinical studies, will also be elucidated in this review.

Conclusions: Overall available data support the potential dual benefit of metformin on ADT-induced metabolic syndrome and in its antineoplastic activity in prostate cancer, justifying the need for ongoing clinical trials to confirm these effects as the evidence currently available for standard practice is lacking.

Key words: AMPK, androgen deprivation therapy, insulin resistance, metabolic syndrome, metformin, prostate cancer

introduction
Prostate cancer is the most frequently diagnosed cancer in Western men and among the leading causes of death in men with cancer [1]. Androgen deprivation therapy (ADT) is the mainstay of treatment of advanced prostate cancer but can be associated with significant metabolic consequences, such as insulin resistance and metabolic syndrome. Metabolic syndrome is present in >50% of prostate cancer patients undergoing long-term ADT and may contribute to the all-cause morbidity and mortality for patients with prostate cancer. Some but not all studies have shown that ADT-induced insulin resistance and metabolic syndrome are associated with cardiovascular disease (CVD) [2–7], which is one of the most common causes of non-cancer-related deaths in men with prostate cancer [8]. This review will discuss the hypothesis that metformin may abrogate insulin resistance and metabolic syndrome in patients receiving ADT and will also highlight the potential additional effect of the drug: an anticancer effect mediated by multiple proposed mechanisms.

metabolic syndrome
The metabolic syndrome is variously defined by different bodies including the National Cholesterol Education Program (NCEP), the World Health Organisation and the International Diabetes Federation but all describe a cluster of both non-lipid and lipid features of metabolic origin [9]. The NCEP Adult Treatment Panel III suggests that a diagnosis of metabolic syndrome is made where three or more of the following risk factors are present: central obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, raised blood pressure or raised fasting plasma glucose. This constellation of risk factors is associated with insulin resistance and, in combination, increases the risk of type 2 diabetes mellitus (T2DM) and CVD. The clinical management of metabolic syndrome focuses on effective treatment of underlying risk factors. Recommended management of metabolic syndrome comprises lifestyle interventions including weight reduction, regular exercise and dietary changes as well as medical intervention with lipid lowering, anti-hypertensive and hypoglycaemic drugs such as metformin [9].

ADT and metabolic syndrome in prostate cancer
Metabolic syndrome has been noted to be present in up to 55% of prostate cancer patients who received long-term ADT (≥12 months) as compared with 22% of patients in the non-ADT group [10]. Cross-sectional and longitudinal studies in non-cancer patients have shown that low testosterone levels independently predict the development of insulin resistance and metabolic syndrome [11]. ADT, through its effect on testosterone levels, increases fat mass, body mass index, low-
density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides while decreasing lean mass and insulin sensitivity [12]. Studies have shown that even short-term (12 weeks) use of ADT significantly increased fat mass and decreased insulin sensitivity in men with prostate cancer [13]. The presence of metabolic syndrome is not only associated with CVD but may also have an adverse effect on the prognosis of prostate cancer. A recent retrospective study showed that the presence of metabolic syndrome was associated with a shorter median time to progression (16 versus 36 months) and median overall survival (36.5 versus 46.7 months) in prostate cancer patients receiving ADT [14].

**obesity and abnormal metabolic state: link with cancer risk**

Recently, epidemiological studies have suggested a link between obesity and an abnormal metabolic state with the risk of prostate, colon, breast and renal cancers [15–17]. It has been proposed that this link may relate to multiple factors including an increase in insulin resistance, aromatase activity, adipokine production, angiogenesis, glucose utilisation and oxidative stress DNA damage [18]. Other studies have found a positive association between cancer incidence and exogenous insulin administration and that this risk may be higher with the use of glargine analogues (as opposed to aspart or lispro insulin analogues) [19]. Adipocytes from white adipose tissue secrete adipokines, in the form of leptin and adiponectin, which may be instrumental in linking obesity and prostate cancer [20]. Circulating leptin, which is elevated in obese individuals, is thought to be stimulatory to prostate cancer development [21]. In contrast, circulating adiponectin, which is thought to be inhibitory to prostate cancer development, is reduced in obese individuals [21]. However, the relationship between obesity, metabolic syndrome and risk of cancer remains complicated justifying the need for further investigations.

**metformin: mechanism of action and role in metabolic syndrome**

Metformin is an oral biguanide drug widely used as front-line treatment of T2DM. Its antihyperglycaemic effects occur by multiple mechanisms: through inhibition of gluconeogenesis in the liver by activation of AMP-activated protein kinase (AMPK), delay in glucose absorption from the gastrointestinal tract, an increase in peripheral uptake of glucose, improvement of insulin sensitivity and stimulation of insulin secretion via glucagon-like peptide-1 (a gut hormone produced in response to food) [22, 23]. The Diabetes Prevention Program randomised trial showed that both lifestyle intervention and metformin reduced the development of metabolic syndrome in patients with impaired glucose tolerance [24]. In addition, results from a study at the St Luke’s cancer centre (‘MADAMS’ trial) have also shown that metformin and lifestyle changes may abrogate ADT-induced metabolic syndrome [25].

Another study is currently under way at Westmead Cancer Care Centre (‘MVENT’ trial) [26] to further assess the effect of metformin in preventing ADT-induced insulin resistance and metabolic syndrome. If metformin is proven to reduce ADT-induced metabolic syndrome, further studies will be warranted to determine whether this drug is associated with a reduction in CVD-related deaths and all-cause prostate cancer mortality.

**potential anticancer effect of metformin**

**preclinical studies in cancer cell lines**

A number of *in vitro* and *in vivo* studies show an effect of metformin on inhibiting growth of multiple cancer cell lines including that of prostate and breast cancers. Ben Sahra et al. [27] showed that metformin gave an up to 50% decrease in cell viability in human prostate cancer cell lines (DU145, PC-3 and LNCaP) compared with only a modest effect (20% decrease) in P69 cells, a normal prostate epithelial cell line, indicating that metformin may specifically target the proliferation of prostate cancer cells over normal cells. Other studies also support an inhibitory effect of metformin on breast, colon, glial, lung and pancreatic cancer cell lines [28–32]. Interestingly, metformin was noted to selectively kill cancer stem cells in breast cancer cell lines [33]. This effect was replicated in a xenograft mouse model, where metformin was used in combination with doxorubicin chemotherapy, selectively killing cancer stem cells and non-stem cancer cells, respectively, thereby reducing tumour mass and prolonging remission more effectively than either drug alone [33].

**metformin: potential mechanisms of antineoplastic activity**

The potential mechanism of activity of metformin has been a subject of continuing investigations but to date has not been completely understood. The proposed antineoplastic mechanisms of metformin are as follows:

Firstly, insulin appears to activate several proliferative and anti-apoptotic events through the insulin receptor in association with increased levels of insulin-like growth factor-I (IGF-I). Clinical studies have shown that higher- than- average insulin levels have been associated with a two- to threefold increased risk of cancer recurrence and death [34, 35]. Metformin reduces hyperinsulinaemia in non-diabetic breast cancer patients by up to 22% [36], which may contribute to its potential antitumour effect [22].

Secondly, metformin acts as a growth inhibitor through its effect on the AMPK pathway (Figure 1). AMPK is a regulator of cellular response and sensor to low energy levels and is activated in response to nutrient deprivation and hypoxia. Metformin also activates the AMPK pathway, eventually causing inhibition of the mammalian target of rapamycin (mTOR) pathway and thus a reduction in protein synthesis and cellular proliferation [37]. The activation of AMPK occurs through a liver kinase B1 (LKB1)-dependent mechanism following inhibition of the mitochondrial respiratory chain and activation of protein kinase C, . This results in phosphorylation of tuberous sclerosis complex tumour suppressor gene 2 (TSC2) and subsequently causes
inhibition of the mTOR pathway as summarised in Figure 1 [37, 38]. Metformin can also secondarily activate the AMPK pathway by increasing intracellular AMP through another LKB1-dependent mechanism [39]. Metformin also appears to indirectly reduce Akt activation, through AMPK-mediated phosphorylation of IRS-1, causing inhibition of mTOR pathway. 4E-BP1, 4E-binding protein 1; Akt, v-akt murine thymoma viral oncogene homologue; AMPK, AMP-activated protein kinase; GBL, G-protein b-subunit-like protein; IRS-1, insulin receptor substrate-1; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; P3K, phosphoinositide 3-kinase; raptor, regulatory-associated protein of mTOR; Rheb, Ras homologue enriched in brain; rictor, rapamycin-insensitive companion of mTOR; S6K1, S6 kinase1; TSC1, tuberous sclerosis protein 1; TSC2, tuberous sclerosis protein 2.

**Figure 1.** Effect of metformin on AMPK and mTOR pathway. Metformin activates the AMPK pathway through LKB1, eventually causing inhibition of the mTOR pathway and thus a reduction in protein synthesis and cellular proliferation. Metformin also appears to indirectly reduce Akt activation, through AMPK-mediated phosphorylation of IRS-1, causing inhibition of mTOR pathway. 4E-BP1, 4E-binding protein 1; Akt, v-akt murine thymoma viral oncogene homologue; AMPK, AMP-activated protein kinase; GBL, G-protein b-subunit-like protein; IRS-1, insulin receptor substrate-1; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; P3K, phosphoinositide 3-kinase; raptor, regulatory-associated protein of mTOR; Rheb, Ras homologue enriched in brain; rictor, rapamycin-insensitive companion of mTOR; S6K1, S6 kinase1; TSC1, tuberous sclerosis protein 1; TSC2, tuberous sclerosis protein 2.

**Clinical evidence: effect of metformin on cancer incidence and mortality**

Recent clinical data suggest that patients taking metformin for the management of T2DM may have a lower incidence and mortality for certain malignancies including prostate and breast cancers [48–52]. The prospective ZODIAC-16 (Zwolle Outpatient Diabetes project Integrating Available Care) study found that metformin use for T2DM was associated with a dose-dependent lowering of cancer-related mortality [53].

**Breast cancer**

In a recent study of women with T2DM, a decreased incidence of breast cancer was noted in those who used metformin for several years but not with short-term use [52]. A retrospective study of female diabetic patients receiving neoadjuvant chemotherapy for breast cancer showed a significantly higher pathologic complete response rate of 24% in metformin users compared with 8% in those not receiving metformin [54].

**Prostate cancer**

In an American population-based case–control study of 1001 patients with prostate cancer and 942 controls, metformin use was associated with a 44% risk reduction in prostate cancer incidence in Caucasians [50]. A recent retrospective study was undertaken by Patel et al. of 210 diabetic (metformin and non-metformin users) and 406 non-diabetic (non-metformin users) patients with prostate cancer undergoing radical prostatectomy.
The data indicated that diabetes, regardless of metformin use, was significantly associated with an increased likelihood of biochemical recurrence. However, there was no association shown for metformin use and improved pathologic outcome or biochemical recurrence rate. This study had several limitations including a small sample size of diabetic patients and metformin users, absence of essential data on the type, duration and control of diabetes, unknown duration of metformin usage and a paucity of data on lifestyle and relevant vascular risk factors. Consequently, this study does not exclude a potential anticancer effect of metformin and further investigation is warranted [55].

ongoing clinical trials of metformin in various malignancies

The growing body of clinical evidence supported by in vivo and in vitro data suggests the need for ongoing clinical trials addressing the potential antineoplastic efficacy of metformin not only in prostate cancer but also in other malignancies. A phase II trial (ANIMATE) is currently under way in Toronto investigating the effect of neoadjuvant metformin therapy in the inhibition of growth and proliferation of prostate cancer cells before radical prostatectomy [56]. A large-scale placebo-controlled phase III trial (MA.32), led by the National Cancer Institute of Canada Clinical Trials Group, is currently under way examining the effects of adjuvant metformin on recurrence rate and disease-free survival of early-stage breast cancer [57]. Several trials are ongoing in patients with hormone-receptor-positive or HER2-positive breast cancer, one of which looks at metformin in combination with hormone-receptor-positive metastatic breast cancer [58, 59]. The combination of metformin and temsirolimus, an mTOR inhibitor, is also under investigation in solid tumours and lymphomas [60].

conclusions

While we eagerly await the results of ongoing trials to assess the clinical antineoplastic effects of metformin in the neoadjuvant, adjuvant and metastatic setting, certain questions remain unanswered and deserve further investigation. These relate to whether the effects of metformin apply to all malignancies or to a selected few, its antineoplastic effects in non-diabetic patients, its efficacy in combination with conventional chemotherapy and possible associated toxicity, elucidation of the optimal dosage of metformin and exploring potential biomarkers to identify sensitive tumours.

The potential benefit of metformin in the treatment and prevention of prostate cancer is large due to the putative dual effect on ADT-induced metabolic syndrome and anticancer effect. The preclinical and limited clinical evidence that is available, coupled with the drug’s favourable safety profile and low cost, justifies the need to pursue its further investigation in prostate cancer and other malignancies.

disclosure

The authors declare no conflict of interest.


