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Metformin Has a Positive Therapeutic Effect on Prostate Cancer in Diabetes Mellitus 2 Patients

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Abstract

Objective—Prostate cancer and type 2 diabetes mellitus are both common diseases found in the elderly male population. The diabetic drug, metformin, has been shown to have anti-neoplastic properties and demonstrated better treatment outcomes when used as adjuvant therapy in breast cancer patients. The hormonally-sensitive cancer analogous to breast in men is prostate. We investigated improved survival, lower risks of recurrences, and lower, more stable levels of prostate specific antigen (PSA) in DM2 patients with prostate cancer on metformin.

Methods—Prostate cancer patients with type 2 diabetes that remained on metformin were compared to controls not on metformin matched by age, weight, race, and Gleason score cancer staging. The endpoints of our study included final PSA values, number of recurrences, metastases and number living for each group.

Results—There were significantly fewer deaths (23% vs 10%), fewer recurrences (15% vs 8%), and fewer metastases (5% vs 0%), and fewer secondary cancers (17% vs 6%) in the metformin

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group (p<0.004). The final PSA value was lower in the metformin-treated group with a result approaching significance (p=0.067). The primary treatments for prostate cancer (i.e. surgery, radiation, androgen depletion) were found to be comparable in both groups.

Conclusions—Our retrospective study shows that adjuvant metformin therapy leads to a better prognosis in prostate cancer. Not only are PSA levels controlled for several years, but there are significantly fewer cancer recurrences in metformin treated patients. Overall, these results are promising and should be followed up with a prospective study to assess long-term survival.

Keywords

prostate cancer; type 2 diabetes; metformin; PSA; prognosis

Introduction

Metformin is a widely used, inexpensive, non-toxic drug used as first-line therapy for patients with type 2 diabetes mellitus. There is a relationship between insulin-resistant diabetes and cancer with insulin as a growth factor for certain tumors [1, 2]. Since metformin has been shown to improve insulin sensitivity, the anti-neoplastic effects of metformin has been explored in pre-clinical, clinical, and epidemiological studies.

Several retrospective and prospective studies have shown a positive outcome of metformin as adjuvant therapy for breast cancer [3], particularly hormonally sensitive tumor types. It is believed that metformin also leads to improved outcomes in patients diagnosed with prostate cancer, the analogous hormonally sensitive cancer in men. However, there have been fewer studies conducted. One study estimates a 44% risk reduction in Caucasian men with prostate cancer [4]. Another study did not find a significant change with metformin therapy; however, this study was limited to patients undergoing radical prostatectomy [5] without chemotherapy.

Although the mechanism of action of metformin has not been elucidated, there have been several proposed molecular pathways in which metformin exerts its anti-cancer effects. The most significant pathway is the activation of AMPK which inhibits mTOR, an energy-signaling molecule found in several cancers [6, 7]. Metformin induces activation of several tumor suppressor genes including ATM, LKB1, and p53 [7, 8]. Additionally, studies have shown metformin is active in the cell cycle and plays a key role in decreasing the expression of genes involved in mitosis [8]. Thus, metformin may work synergistically with chemotherapy to enhance its cytotoxic effects toward cancer cells and improve prognostic factors for prostate cancer.

The growing evidence of metformin's anti-cancer effects in the form of retrospective clinical chart reviews and molecular studies leads us to study the effect of metformin on prostate cancer. We believe that metformin will lead to longer post-treatment survival, a reduced risk of cancer recurrence, as well as a lower and more stable level of PSA in prostate cancer patients.

Methods

A list of prostate cancer patients was provided by the Tumor Registry at the Memphis VA Medical Center. A total of 287 patients were found to meet the criteria of a diagnosis of both prostate cancer and type 2 diabetes. Outpatient pharmacy records were used to determine if (1) patients were on metformin during the period of their last PSA value recorded and (2) metformin use was for at least 6 months. Those who did not meet this condition were considered to be in the non-metformin control group. A chart review of the urology notes written at VAMC was conducted under the approval of the Institutional Review Board for Human Subjects Research, the Research and Development Committee, as well as the appropriate approving committees at the NIH Medical Student Research Fellowship (MSRF) and UTHSC. Parameters obtained through the urology notes included Gleason score, presence of metastasis, treatment undergone, presence of recurrence, beginning PSA, nadir PSA, and final PSA. Laboratory values for hemoglobin A1C and creatinine were obtained. Since patients were drawn from the same pool at random, both groups are equally matched for age, race, and BMI.

Results

The non-metformin group (n = 149) and the metformin group (n = 138) were found to have comparable baseline parameters such as years with prostate cancer and Gleason score staging (Table 1). From these findings, both groups have prostate cancer similar in their grade and severity at the time of diagnosis. Several of the endpoints (Table 2) of our study, including final PSA and PSA velocity showed nearly significant results. The final PSA taken from the urology notes showed a decrease in those that took metformin compared to controls (0.57 ± 0.78 vs 0.84 ± 1.38; $p = 0.067$). The PSA velocity that showed the rate of change in the PSA value from the time of treatment was slower for patients in the metformin group (0.12 ± 0.31 vs 0.27 ± 0.82; $p = 0.076$). Cohen's d analysis for final PSA and PSA velocity ($d = .244$ and .240, respectively) shows small effect sizes. These results suggest there is some practical significance with regard to this study.

There were consistently fewer cancer-related outcomes, such as recurrences, metastases, and secondary cancers, in patients undergoing metformin therapy (Table 3). Our analysis looked at the proportion of patients that had cancer recurrence, metastases, or secondary cancers in a pooled sample, which were found to be statistically significant ($p = 0.004$). Of these cancer-related outcomes, secondary cancers were the most impacted by the addition of metformin to treatment (6.0% vs. 17.4%, $p = 0.013$). Percent survival from both groups was based upon all-cause mortality and found to be significantly different with a 76.5% survival without metformin and 89.9% survival on metformin ($p = 0.003$). The ages at death for both groups were similar. Hemoglobin A1C levels were comparable for both groups, however, creatinine levels were significantly elevated in the non-metformin group as was expected (Table 1).

Discussion

Our data suggests that metformin has an overall effect of keeping PSA values low for years after treatment and preventing recurrence and spread of the cancer. PSA value is an important prognostic indicator of prostate cancer with large, increasing values from a baseline value indicative of recurrence. Although PSA has been criticized for being a non-specific marker that can be markedly elevated due to age, benign prostatic hyperplasia, or prostatitis, a rise in PSA after diagnosis and treatment of prostate cancer is more specific for recurrence.

When the data was isolated by different primary treatment methods of prostate cancer, only the group on androgen deprivation therapy (ADT) showed a benefit from metformin. The result was not statistically significant because subdividing the groups would make the sample sizes too small. The three other forms of treatment involved physical removal or destruction of prostate tissue. ADT is the only form of chemotherapy that works to block testosterone production. Studies show metformin can reduce levels of circulating testosterone in obese diabetic patients [9], so there is likely a synergistic effect with ADT within our study. Since ADT is used as secondary or neoadjuvant therapy for other forms of treatment, particularly radiation therapy, there may still be some level of activity in the other groups that is masked by the major effect of the primary treatment. These findings are consistent with the study that showed no improvement in radical prostatectomy patients.

Apart from inhibition of testosterone, another proposed anti-neoplastic mechanisms of action for metformin include inhibition of mTOR in the PI3K/AKT/mTOR pathway [6, 7]. Mutations of PTEN commonly found in prostate cancer lead to activation of mTOR via PI3K [10]. Insulin-resistant diabetes has been shown also to activate this pathway through insulin and IRS1 [1, 2]. Metformin can inhibit mTOR directly through the activation of AMPK or indirectly through lowering the levels of circulating insulin and inactivating the PI3K/AKT pathway.

Metformin also seems to have a global effect in reducing the number of secondary cancers and achieving a lower all-cause mortality rate. Given that both groups appear matched by their age of death, metformin may not necessarily prevent deaths specifically from the prostate cancer. Prostate cancer is a common but mostly indolent cancer [11]. Therefore men are more likely to die with the cancer than due to complications from it. It is likely that the metformin has other beneficial mechanisms of action beyond inhibiting the prostate cancer that limits secondary cancers and improves post-treatment survival. Furthermore, the comparable hemoglobin A1C values in both groups demonstrate that increased mortality is not due to uncontrolled diabetes in the non-metformin group.

Conclusion

In conclusion, this study shows metformin has a positive effect on the outcome of treated prostate cancer patient in terms of lower PSA, fewer secondary cancers and metastases, and better overall survival. A prospective study is necessary to follow up on the long-term improvement on metformin and its potentially synergistic therapeutic effects. Preclinical

work should also be done to further elucidate the molecular pathways in which metformin exerts its anti-cancer effects.

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Abbreviations

DM2	type 2 diabetes mellitus
PSA	prostate specific antigen
mTOR	Mammalian Target of Rapamycin
ADT	androgen deprivation therapy

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Table 1

Baseline Parameters of Prostate Cancer Patients with Metformin Versus Controls

Variable	Non-Metformin n = 149 M ± SD or %	Metformin n = 138 M ± SD or %	Cramer's *V*	Cohen's *d*	*p*-value
Still living	76.5	89.9	.177	---	.003
Age at death, years[a]	72.2 ± 8.3	72.4 ± 7.3	---	.015	.964
Years with prostate cancer	5.7 ± 3.4	5.6 ± 2.9	---	.034	.774
Gleason score	6.9 ± 0.8	6.8 ± 0.7	---	.141	.233
Hemoglobin A1c, %	7.3 ± 1.5	7.5 ± 1.5	---	.110	.355
Creatinine, mg/dL	2.0 ± 1.9	1.1 ± 0.2	---	.652	<.001

[a]n = 35, 14 for non-metformin and metformin respectively

Table 2

PSA Endpoints for Prostate Cancer Patients with Metformin Versus Controls

Variable	Non-Metformin n = 149 M ± SD or %	Metformin n = 138 M ± SD or %	Cohen's *d*	*p*-value
PSA nadir, ng/mL	0.28 ± 0.60	0.28 ± 0.54	.013	.915
PSA final, ng/mL [a]	0.84 ± 1.38	0.57 ± 0.78	.244	.067
PSA velocity, ng/mL/year [a]	0.27 ± 0.82	0.12 ± 0.31	.240	.076

[a]n = 112, 116 for non-metformin and metformin respectively. Those who had time since nadir = 0 or PSA > 10 were excluded.

Table 3

Prevalence of Recurrence, Metastases, and Secondary Cancers of Prostate Cancer Patients with Metformin Versus Controls

Variable	Non-Metformin n = 149 %	Metformin n = 84[a] %	Cramer's *V*	*p*-value
Cancer-related outcomes	31.5	14.3	.191	.004
Recurrences	14.8	8.3	.094	.153
Metastases	4.7	0	.132	.051
Secondary cancers	17.4	6.0	.163	.013

Note: Cancer-related outcomes = presence of Recurrences, Metastases, and/or Secondary cancers

[a]Only patients that stayed on metformin during the entire course of their prostate cancer were assessed for cancer-related outcomes