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

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ABSTRACT

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

Methods: Patients with prostate cancer along with DM2 who remained on metformin were compared with controls who were 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% versus 10%), fewer recurrences (15% versus 8%), fewer metastases (5% versus 0%) and fewer secondary cancers (17% versus 6%) in the metformin 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 (ie, surgery, radiation and androgen depletion) were found to be comparable in both the 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 also 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.

Key Indexing Terms: Prostate cancer; Type 2 diabetes mellitus; Metformin; Prostate specific antigen; Prognosis. **[Am J Med Sci 2016;351(4):416–419.]**

INTRODUCTION

Metformin is a widely used, inexpensive, nontoxic 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] As metformin has been shown to improve insulin sensitivity, the antineoplastic effects of metformin have been explored in preclinical, clinical and epidemiologic 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 White 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 anticancer effects. The most significant pathway is the activation of adenosine monophosphate–activated protein kinase that inhibits mammalian target of rapamycin (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 that 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 anticancer 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 would lead to longer posttreatment survival, a reduced risk of cancer recurrence as well as a lower and more stable level of prostate-specific antigen (PSA) in patients with prostate cancer.

METHODS

A list of patients with prostate cancer was provided by the Tumor Registry at the Memphis Veterans Affairs Medical Center. A total of 287 patients were found to

TABLE 1. Baseline parameters of patients with prostate cancer on metformin versus nonmetformin controls.

Variable	Nonmetformin $n = 149$, M ± SD or %	Metformin $n = 138$, M ± SD or %	Cramer's *V*	Cohen's *d*	*P* Value
Still living	76.5	89.9	0.177	-	0.003
Age at death, years[a]	72.2 ± 8.3	72.4 ± 7.3	-	0.015	0.964
Years with prostate cancer	5.7 ± 3.4	5.6 ± 2.9	-	0.034	0.774
Gleason score	6.9 ± 0.8	6.8 ± 0.7	-	0.141	0.233
Hemoglobin A1c (%)	7.3 ± 1.5	7.5 ± 1.5	-	0.110	0.355
Creatinine (mg/dL)	2.0 ± 1.9	1.1 ± 0.2	-	0.652	<0.001

M, mean; SD, standard deviation.
[a] $n = 35$ and 14 for nonmetformin and metformin, respectively.

meet the criteria of a diagnosis of both prostate cancer and type 2 diabetes mellitus. 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 nonmetformin control group. A chart review of the urology record written at Veterans Affairs Medical Center 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 National Institutes of Health Medical Student Research Fellowship and University of Tennessee Health Science Center. Parameters obtained through the urology record 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. As patients were drawn from the same pool at random, both the groups were equally matched for age, race and body mass index.

RESULTS

The nonmetformin group ($n = 149$) and the metformin group ($n = 138$) were found to have comparable baseline parameters like years with prostate cancer and Gleason score staging (Table 1). From these findings, both the groups were found to 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 record showed a decrease in those who took metformin compared with controls (0.57 ± 0.78 versus 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 versus 0.27 ± 0.82; $P = 0.076$). Cohen's *d* analysis for final PSA and PSA velocity ($d = 0.244$ and 0.240, 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 who 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 affected by the addition of metformin to treatment (6.0% versus 17.4%, $P = 0.013$). Percentage survival from both the 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 the groups were similar. Hemoglobin A1C levels were comparable for both the groups, however, creatinine levels were significantly elevated in the nonmetformin 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. The PSA value is an important prognostic

TABLE 2. PSA endpoints for patients with prostate cancer on metformin versus nonmetformin controls.

Variable	Nonmetformin $n = 149$, 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	0.013	0.915
PSA final (ng/mL)[a]	0.84 ± 1.38	0.57 ± 0.78	0.244	0.067
PSA velocity (ng/mL/year)[a]	0.27 ± 0.82	0.12 ± 0.31	0.240	0.076

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