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Impact Of Metformin On Prostate Cancer Outcomes After Radical Prostatectomy

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Abstract

Objective—Recent studies have shown a relative risk reduction in the incidence of prostate cancer in patients taking metformin. However there are conflicting findings on the impact of metformin on established cases of prostate cancer. In this study we evaluated the impact of metformin on survival and pathological outcomes in established prostate cancer.

Materials and Methods—We retrospectively identified 12,052 patients who underwent radical prostatectomy (RP) between 1997 and 2010 at Mayo Clinic. Among these 885 (7.3%) were diabetics, including 323 taking and 562 not taking metformin. Kaplan-Meier method was utilized to calculate rates of biochemical recurrence (BCR), systemic progression (SP), and all-cause mortality (ACM). Cox models were used to estimate the metformin hazard ratio (HR) adjusted for clinical and pathologic variables.

Results and Conclusions—Median follow-up was 5.1 years. In univariate analysis, metformin HR [95% CI] was not significant for BCR (1.13 [0.84, 1.52], p=0.40), SP (1.37 [0.69, 2.72], p=0.37), and ACM (1.32 [0.84, 2.05], p=0.23). After adjusting for covariates of interest, the HRs for metformin among diabetics remained non-significant for BCR (0.91 [0.67, 1.24], p=0.56), SP (0.83 [0.39, 1.74], p=0.62), and ACM (1.16 [0.73, 1.86], p=0.53). No difference was seen between metformin users and non-users in the final pathologic Gleason score (p=0.33), stage (p=0.1), rate of positive surgical margins (p=0.29), or tumor volume (p=0.76). Metformin use was not associated with a risk reduction in BCR, SP, or ACM. Besides presenting survival data, our results describing metformin's effect on final pathology are unique.

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Keywords

Disease progression; Metformin; Prostate cancer; Prostatectomy; Survival rate; Biochemical-recurrence

Introduction

Worldwide, prostate cancer is the second most commonly diagnosed cancer in men, with 914,000 new cases, and the sixth leading cause of cancer mortality in men, with 258,000 deaths in 2008. [1] Type 2 diabetes mellitus (T2DM) is a common disease, and an inverse association with risk of prostate cancer has been observed. [2-4]

Metformin (1, 1-dimethylbiguanide hydrochloride) is a widely prescribed hypoglycemic agent and is used as first-line therapy for T2DM. It inhibits gluconeogenesis, controls insulin levels, and promotes AMP-activated protein kinase (AMPK). There have been several observational studies, which have shown that diabetics who have taken metformin have lower risk of cancer incidence (ranging from 10% to 50%) than diabetics who are on different glucose lowering regimens. [5-7] This has led to the hypothesis that metformin plays a role in cancer protection. Numerous in-vitro studies have been performed to determine the mechanism of action against cancer cells, which includes inhibition of tumor migration [8], promotion of apoptosis [9], and AMPK pathway activation. [10]

Metformin's role in prostate cancer is evolving. While one large observational study revealed no risk reduction [11], another study revealed 44% risk reduction in prostate cancer incidence. [12] Regarding established cases of prostate cancer, there have been 4 observational studies evaluating the impact of metformin, 2 showing improved survival [13, 14], 1 showing a non-significant decreased odds of high-grade tumor and cancer progression [15], and 1 finding no effect of metformin after radical prostatectomy (RP) on biochemical recurrence. [16]

Currently, there are 7 clinical trials evaluating the role of metformin in prostate cancer. In this context, it is essential to acknowledge that most epidemiological studies done on metformin and its role in prostate cancer are related to risk of developing prostate cancer. Because of a paucity of data regarding impact of metformin on survival and pathological outcomes on established cases of prostate cancer, and discordant findings among existing studies, we sought to perform a retrospective review of diabetic patients with prostate cancer who underwent RP at our institution. We report clinically relevant endpoints of biochemical recurrence (BCR), systemic progression (SP), cause-specific mortality (CSM), all-cause mortality (ACM), and pathologic features after controlling for clinico-pathological variables.

Patients and Methods

Patient selection

After institutional review board approval, we identified 12,052 consecutive patients who underwent RP between 1997 and 2010 (a time period after the introduction of metformin in US market). Surgical procedures were performed by different surgeons using standard

techniques. Of these, 885 were and 11,167 were not diabetics at the time of RP. Metformin use at time of RP was extracted from the Mayo Clinic electronic medical record (EMR) by searching in the 3 months prior to the RP for the terms- metformin, Glucophage®, Glumetza®, Riomet®, Fortamet®, Obimet®, Gluformin®, Dianben®, Diabex®, Diaformin® or Metsol®. Due to referral nature of the population and the fact that their diabetes was managed by their local care providers, metformin use and duration beyond the RP was not available for all subjects.

Among the diabetics, 323 were and 562 were not taking metformin. Based on a random sample of 100 electronic medical records, metformin was prescribed at a median dose of 1850 mg (IQR 1000-2000) daily. Postoperative assessments, including physical examinations and serum PSA measurements, were done quarterly for the initial 2 years, semi-annually for an additional 2 years, and annually thereafter. Staging was assigned in accordance with the 2009 American Joint Committee on Cancer staging system for prostate cancer [17] and Gleason score was used for grading. For the uniformity of diagnosis and staging, all the cases were reviewed by central pathology laboratory. Adjuvant therapy was defined as treatment received 90 days of RP, and was given at the discretion of the treating physician. BCR was defined as a PSA level of 0.4 ng/mL.

SP was defined as demonstrable metastasis on radionuclide bone scan or on biopsies outside the prostatic bed. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the Mayo Clinic Prostatectomy Registry prospectively monitors outcomes annually by correspondence. Random samples of cases were chosen, and their medical records were carefully reviewed for internal validity.

Statistical analysis

Comparison of clinical and pathological features between diabetics taking and those not taking metformin were made using Wilcoxon test for continuous variables, and Chi-Square or Fisher's exact test for categorical variables. All tests were two-sided, with $P < 0.05$ considered to indicate statistical significance. Kaplan-Meier method was utilized to calculate cumulative rate of BCR, SP, and ACM. Patients were censored at last follow-up or death if the endpoint of interest had not been attained. Cox proportional hazards models were used to estimate the metformin hazard ratio (HR) with 95% confidence intervals (CI) for BCR, SP, CSM, and ACM adjusted for clinical and pathologic variables. Statistical analysis was done using SAS®, version 9.2. (SAS Institute, Cary, NC).

Results

Of 12,052 patients, 885(7%) were and 11,167 were not diabetic. Overall, 36% (323/885) were on metformin at time of RP, with the rate increasing over time: 23% (56/246) in 1997-2001, 35% (106/302) in 2002-06, and 48% (161/337) in 2007-10 ($p < 0.0001$). Table 1 lists the baseline demographics and clinical and pathological variables of metformin non-users versus users among those with diabetes.

Median age was 64 years for non-metformin users and 65 years for metformin users (IQR 59-68 vs. IQR 60-69, $p=0.24$). Median follow-up was 5.1 years for the whole cohort.

Patients on metformin were more likely to have higher BMI (median 31 vs. 29.7; $p=0.0004$), to be on statins (18.3% vs. 9.6%; $p=0.0002$), and to have higher Gleason score 8-10 on biopsy (16.1% vs. 10.4%; $p=0.04$). This difference in Gleason score was not statistically significant on the final pathological analysis (16.5% vs. 12.9%; $p=0.33$). We did not observe any significant group differences in preoperative PSA, rate of positive surgical margins, clinical and pathologic staging, and use of adjuvant therapies after RP (Table 1). No significant difference in final tumor volume was seen (metformin vs. non metformin: 1.6 cc vs. 1.5cc; $p=0.76$). Use of other medications for diabetes was fairly common; glyburide (20.7%), insulin (12.5%), sulfonylureas (10.1%), and thiazolidinedione (12.9%).

The numbers of patients with BCR, SP, CSM, and death on follow-up were 203, 36, 13, and 94 respectively. Kaplan-Meier plots for cumulative rates of BCR, SP, and ACM for metformin users and non-users after RP are shown in figure 1, 2 and 3 respectively. No statistically significant (univariable Cox model) difference in BCR ($p=0.40$), SP ($p=0.37$), and ACM ($p=0.23$) was seen. The crude metformin HR [95% CI] was not significant for BCR (1.13 [0.84, 1.52]; $p=0.40$), SP (1.37 [0.69, 2.72]; $p=0.37$), and ACM (1.32 [0.84, 2.05]; $p=0.23$).

Next, we used Cox proportional hazards models to adjust for age, BMI, p-Gleason score, p-stage, soft tissue margin, log2 of pre-operative PSA, statins and treatment (BCR only), as shown in Table 2. The HRs for metformin users declined but remained non-significant for BCR (0.91 [0.67, 1.24]; $p=0.56$), SP (0.83 [0.39, 1.74]; $p=0.62$), and ACM (1.16 [0.73, 1.86]; $p=0.53$). For CSM with only 12 events the crude and adjusted (for p-Gleason score) metformin HRs were 2.77 [0.93, 8.28]; ($p=0.07$) and 1.42 [0.44, 4.60]; ($p=0.56$) respectively. An analysis removing those with prior and/or adjuvant therapy found that the adjusted metformin hazard ratios for BCR, SP, and ACM were essentially unchanged (data not shown). Further adjustment for the 4 other diabetes medications (thiazolidinedione, sulfonylureas, glyburide, insulin) resulted in a similar non-significant HR for metformin and BCR (0.91 [0.66, 1.24]; $p=0.54$). The numbers of events precluded such an adjustment for SP, CSM, and ACM.

Discussion

In this large single-center study with a median follow up of 5.1 years, we have shown that metformin use was not associated with BCR, SP, ACM, or p-stage, grade and tumor volume, in men who underwent RP for prostate cancer.

To our knowledge, this represents the largest cohort of patients in which role of metformin, in relation to prostate cancer outcomes after RP, has been assessed. To eliminate diabetes as a confounder, we have intentionally chosen patients with diabetes in whom the only difference is exposure to metformin. As shown in Table 1, the clinico-pathologic features of both metformin and non-metformin user-groups are very similar, with differences in BMI and statin use only, for which we adjusted in the final multivariate model. Hence, we were able to focus on the influence of metformin on prostate cancer progression. In metformin users we did observe a higher Gleason score in biopsy specimens, which was statistically not significant on final pathologic analyses. We are unable to explain this discrepancy.

To date, only one observational study has evaluated the effect of metformin on outcomes after RP. Patel et al. looked at metformin's effect on BCR, in a study including 112 diabetics taking and 98 not taking metformin. No difference in risk of BCR was seen in metformin group compared to non-metformin group (HR 0.94, CI [0.60, 1.5]; $p=0.81$). [16]

Recently, Spratt et al. reported survival outcomes in 157 diabetic patients taking and 162 diabetic patients not taking metformin with localized prostate cancer who were treated with external-beam radiation therapy (ERT). Metformin use was shown to improve BCR-free survival, metastasis-free survival, overall survival (OS), and CSM. [14] This is in sharp contrast to our results and those of Patel, et al. a difference that may have resulted from the analytic approach. In our study and the Patel et al. study, diabetes and metformin use were defined as fixed covariates at the time of RP, with status changes after RP not having been evaluated (intent to treat approach). In the Spratt et al. study metformin use and diabetes were also analyzed as fixed covariates. However, some 29 (18%) men in their metformin group actually began metformin after start of ERT (time zero) and 44 (14%) of men in the diabetes group had diabetes diagnosed after ERT. As the Cox models began at the time of ERT, failure to analyze these effects properly as time-dependent covariates may have resulted in biased HRs, as one has to survive to receive post-ERT metformin. [18] Another plausible explanation for improved survival is that metformin may act as a radio-sensitizer for cancer cells, which, then, would improve the efficacy of ERT. [19, 20]

Hitron et al. recently reported results on 153 T2DM patients with prostate cancer who underwent treatment (not specified) and observed time to BCR. Patients on metformin and thiazolidinedione appeared to have slightly statistically non-significant decreased odds of presenting with high-grade disease (OR: 0.62 [0.22–1.70]; $p=0.92$) and cancer progression (27.6 months versus 31.4 months; $p=0.86$) compared to patients on insulin and sulfonylureas. However, unlike our study, no distinction between metformin and thiazolidinedione in survival outcome was performed. [15]

He et al. recently reported results on 132 patients with prostate cancer who were on metformin. [13] On their multivariate analysis, metformin was significantly associated with improved OS (HR: 0.55 [0.31-0.96]; $p=0.035$). However, similar to Spratt et al. study, metformin (ever used) appears to have been analyzed as a fixed covariate at time of oncologic treatment (time zero), even though it may have started after time zero, an approach which can lead to biased hazard ratios. [18]

Several large population-based studies have demonstrated that metformin prevents the development of cancer. [5, 6, 21] Although the precise mechanism has yet to be fully elucidated, numerous preclinical studies have demonstrated potential pathways. For example, in prostate cancer, a key in-vitro mechanism is through activation of the AMPK pathway. [22] The outcome is depression of downstream promoters of mTOR (mammalian target of rapamycin), which is involved in regulating protein synthesis and growth. [23-25] However there is evidence of cross-talk between the mTOR and MAPK (mitogen-activated protein kinase) pathways; resulting in the latter's activation, which improves prostate cancer cell survival. [26] It is plausible that interaction between the aforementioned pathway may have concealed any obvious clinical effect in our study.

Our study, in a relatively large cohort of prostate cancer patients who are taking metformin, reveals two important implications: a) On the final pathologic analysis, metformin did not influence the tumor stage, Gleason score and tumor volume, and b) metformin use did not effect the BCR-free survival, metastatic disease-free survival and overall survival. When these results are viewed in the context of the existing data on risk prevention of prostate cancer, it appears that metformin may play a role in early stages of prostate cancer; however, our data does not show an effect in established cases. Currently, there are 7 clinical trials evaluating the role of metformin in prostate cancer, of which 3 are currently in the recruitment phase (Clinical Trials.gov Identifier: NCT01620593, NCT 01561482, NCT 01433913) and 2 (NCT 01733836, NCT 01677897) have yet to begin recruitment. While we are awaiting results of clinical trials, the survival and pathological information obtained from our data can be utilized for designing future clinical studies. The doses used in these trials range from 1000-2000 mg/day, which is similar to the median metformin dose in our subjects at time of RP, 1850 mg (IQR 1000-2000) daily.

Our study is not without limitations. First, we did not capture the duration of treatment or the initiation of metformin after surgery and our doses were not fixed. Second, due to its retrospective, non-randomized nature, our study is prone to selection and susceptibility bias, and cannot address all potential confounders (e.g. testosterone and hemoglobin A1c). We also acknowledge that the patients evaluated here represent a highly selected cohort, treated at a high-volume, tertiary care-center. Follow-up in our study was only for 5.1 years. It is plausible that with a longer follow-up, differences in metformin vs. non metformin use may be seen. Further, many of these men presumably developed prostate cancer while on metformin for several years, hence, they may represent a population that is in some way resistant to any potential metformin benefit.

Conclusions

This retrospective study found no statistically significant association of metformin on prostate cancer outcome following RP.

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Abbreviations

ACM	All-cause mortality
BCR	Biochemical recurrence
CSM	Cause specific mortality
RP	Radical prostatectomy
SP	systemic progression
T2DM	Type 2 diabetes Mellitus
AMPK	AMP-activated protein kinase
mTOR	mammalian target of rapamycin
MAPK	Mitogen-activated protein kinase
OS	Overall survival

Figure 1. Kaplan-Meier plot with numbers at risk for cumulative event rate of biochemical recurrence following radical prostatectomy

Figure 2. Kaplan-Meier plot with numbers at risk for cumulative event rate of systemic progression after radical prostatectomy

Figure 3. Kaplan-Meier plot with numbers at risk for cumulative event rate of all-cause mortality following radical prostatectomy

Table 1
Baseline Demographic And Clinical Characteristics Of Metformin Users Vs. Nonusers

	No. non users (%)	No. users (%)	p value
Age			0.24 ^C
N	562	323	
Median	64	65	
Q1, Q3	59.0, 68.0	60.0, 69.0	
BMI (Kg/m²)			0.0004 ^C
N	562	323	
Median	29.7	31	
Q1, Q3	26.9, 33.1	28.0, 34.1	
Statins users			0.0002 ^A
No	508 (90.4%)	264 (81.7%)	
Yes	54 (9.6%)	59 (18.3%)	
Pre-op PSA (ng/mL)			0.95 ^C
N	527	297	
Median	5.4	5.3	
Q1, Q3	3.9, 7.8	3.8, 8.1	
2009 AJCC Clinical T-stage			0.89 ^A
T1ab	9 (1.6%)	5 (1.6%)	
T1c	290 (52.7%)	180 (56.3%)	
T2a/2b	192 (34.9%)	105 (32.8%)	
T2c	38 (6.9%)	19 (5.9%)	
T3/4	21 (3.8%)	11 (3.4%)	
Biopsy Gleason Score			0.04 ^B
6	319 (57.0%)	166 (51.6%)	
7	183 (32.7%)	104 (32.3%)	
8+	58 (10.4%)	52 (16.1%)	
2009 AJCC Pathologic Stage			0.10 ^A
T2a N0, T2b N0	173 (31.0%)	79 (24.5%)	
T2cN0	275 (49.3%)	163 (50.5%)	
T3aN0	57 (10.2%)	34 (10.5%)	
T3bN0, T4N0	36 (6.5%)	32 (9.9%)	
Tx N+	17 (3.0%)	15 (4.6%)	
Pathological Gleason Score			0.33 ^B
6	250 (44.7%)	135 (41.9%)	
7	237 (42.4%)	134 (41.6%)	
8+	72 (12.9%)	53 (16.5%)	
Positive surgical margin			0.29 ^A
No	432 (76.9%)	238 (73.7%)	
Yes	130 (23.1%)	85 (26.3%)	

	No. non users (%)	No. users (%)	p value
Estimated Tumor volume (cc)			0.76 ^C
N	481	289	
Median	1.5	1.6	
Q1, Q3	0.4, 3.9	0.4, 4.2	
Estimated prostate volume (cc)			0.22 ^C
N	562	320	
Median	33.5	35.3	
Q1, Q3	25.7, 46.5	26.4, 48.1	
Radiation treatment— prior to surgery			0.20 ^D
No	560 (99.6%)	319 (98.8%)	
Yes	2 (0.4%)	4 (1.2%)	
Hormonal treatment— prior to surgery			0.56 ^A
No	492 (87.5%)	287 (88.9%)	
Yes	70 (12.5%)	36 (11.1%)	
Radiation treatment— adjuvant(<90days)			0.42 ^A
No	539 (95.9%)	306 (94.7%)	
Yes	23 (4.1%)	17 (5.3%)	
Hormonal treatment— adjuvant(<90days)			0.20 ^A
No	511 (90.9%)	285 (88.2%)	
Yes	51 (9.1%)	38 (11.8%)	

^A Pearson's Chi-Square Test

^B Mantel-Haenszel Chi-Square Test

^C Wilcoxon-Mann-Whitney Test

^D Fisher's Exact Test

Table 2
Multivariate analysis of factors associated with biochemical recurrence, systemic progression and all-cause mortality

Risk Factor	Biochemical Recurrence **			Systemic Progression			All-cause mortality		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age at Surgery	1.01	(0.99-1.03)	0.46	0.98	(0.94-1.03)	0.48	1.06	(1.02-1.09)	0.004
BMI at Surgery	1.04	(1.01-1.07)	0.009	1.02	(0.95-1.09)	0.62	1.02	(0.98-1.07)	0.30
Pathological Gleason Score *	1.63	(1.38-1.93)	<0.0001	2.66	(1.84-3.85)	<0.0001	1.21	(0.95-1.53)	0.12
Pathological Stage †	1.66	(1.22-2.27)	0.001	2.37	(1.32-4.25)	0.004	1.57	(1.03-2.38)	0.03
Positive Margin	1.57	(1.13-2.17)	0.006	1.09	(0.52-2.26)	0.83	0.74	(0.47-1.17)	0.20
Log2 PSA (doubling)	1.35	(1.17-1.56)	<.0001	1.17	(0.85-1.61)	0.34	1.14	(0.92-1.42)	0.24
Statin use	1.31	(0.79-2.18)	0.29	2.25	(0.74-6.85)	0.15	1.28	(0.51-3.24)	0.60
Metformin use	0.91	(0.67-1.24)	0.56	0.83	(0.39-1.74)	0.62	1.16	(0.73-1.86)	0.53

* Pathological Gleason score (<6, 7, 8-10) and pathological stage (T2, T3/4, TXN+) analyzed as ordinal factors.

** BCR is also adjusted for use of adjuvant and prior radiation and hormonal therapy.

† According to the 2009 American Joint Committee on Cancer classification system