Review

The influence of antidiabetic medications on the development and progression of prostate cancer

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ABSTRACT

Background: The development of prostate tumors has been linked to co-morbid diabetes mellitus (DM) in several studies, potentially through the stimulation of insulin-like growth factor receptor (IGFR). This study evaluates the effect of anti-diabetic medication use on the development of high grade tumors and time to tumor progression compared to non-diabetics.
Methods: This retrospective, nested case control study identified patients with prostate cancer (PCa) from the Kentucky Medicaid Database. Cases were diagnosed with PCa and DM and using at least one of the following antidiabetic medications; sulfonylureas, insulin, metformin or TZDs. Cases were further stratified on their insulin exposure resulting from therapy. Controls were those with PCa without DM or any anti-diabetic medications.
Results: The use of metformin or TZDs trended toward decreased odds of high-grade tumors and decreased risk of progression, while sulfonylureas and high-dose insulin tended toward an increased odds of high-grade tumors and increase the risk of progression compared to non-diabetics.
Conclusions: Future studies should be conducted to further evaluate the effects of anti-diabetic medications on tumor grade and time to prostate cancer progression.

1. Background

Prostate cancer (PCa) is the most common cancer of men in the United States, affecting nearly 2.4 million men in 2008 [1]. Currently 11.8% of the adult male population (13 million men) are estimated to have a diagnosis of diabetes, 90–95% of which is considered to be type II (T2DM) [2]. Unlike type I diabetes, which is defined as a pathologic lack of insulin, T2DM is primarily due to

ed a relationship between diabetes, insulin exposure and cancer risk [3–9]. Namely, diabetes has been found to independently correlate with tumor grade, lower prostate specific antigen (PSA) levels, and an overall decreased risk of prostate cancer [3,6,10–17]. While diabetes has been shown to decrease cancer risk, elevated circulating insulin has been associated with increased Gleason scores, tumor growth, and mortality [7,18,19]. Furthermore, the

duration of diabetes diagnosis also appears to affect this relationship, with those with long-standing T2DM (and therefore lower circulating insulin) having a lower risk than newly diagnosed patients [19,20]. One prominent hypothesis to explain this causal relationship focuses on the role of insulin exposure and the insulin-like growth factor receptor (IGF-1R) as a primary non-hormonal driver of tumorgenesis [4,5,7].

IGF-1R is a type 2 tyrosine kinase receptor, expressed on both .... cell lines, including .... lin or IGF, IGF-1R .... pathways such as PI3K/AKT and RAS/RAF/MAPK causing subsequent aberrant cell growth [18,21–23]. Thus, insulin and IGF-1R signaling serves as an important driver of prostate cancer growth and invasion.

Increasing levels of IGFR-1 expression is associated with increased levels of prostate specific antigen (PSA) and higher Gleason score values, both of which indicate increased aggressiveness and poorer prognosis [18,24,25]. Furthermore, IGFR-1 antagonism has been shown to be associated with decreased androgen-dependent and independent growth [26].

Antidiabetic pharmacotherapy can influence the exposure to exogenous and endogenous insulin, potentially impacting tumor development and growth [27]. Epidemiologic studies have demonstrated a greater risk of cancer for those using insulin

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glargine over regular human insulin [28]. Insulin and insulin-secretagogue agents (i.e. sulfonylureas) have been associated with an increased risk of cancer-related mortality, across all tumor types, while non-insulin stimulating agents like metformin and, thiazolidinediones (TZDs) appear to have little effect on tumor-related outcomes [29–31]. Specifically looking at prostate cancer, the effect of oral agents remains unclear; while some studies have reported decreased risk of tumor development for all agents, others cite and increase risk for insulin-stimulating agents over metformin [5,32,33]. From this information it is clear that the interaction of these agents with tumor development and growth is unclear and more investigation is needed to guide prudent medication selection in diabetic men at-risk for prostate tumors.

In addition to these observed relationships, other factors may also impact the complex interactions of prostate cancer and diabetes. Recent research has suggested that obesity, hypertension, hypercholesterolemia, either individually or as metabolic syndrome may also play a role in the development of higher-grade cancer (Gleason score ≥7) as well as increased progression, potentially through their effects on physiologic glucose and insulin [8,34]. Concurrent medication use, such as bisphosphonates, corticosteroids, and androgen-deprivation therapy (ADT) has all been shown to affect tumor progression as well as the development hyperglycemia, diabetes, and metabolic syndrome [35–37]. Social factors such as rurality/access to care may also influence the development and subsequent treatment of prostate cancer and should be accounted for [38–40].

The relationship between insulin, diabetes and prostate cancer is complex with multiple modifying factors. An improved characterization of this association on the development and progression of prostate tumors could potentially impact thousands of patients. Based upon previous epidemiologic, animal and in vitro studies we hypothesize that increased insulin exposure will increase the initial tumor invasiveness as measured by Gleason score and shorten the time to disease progression.

2. Methods

2.1. Study design

This retrospective nested case-control study used the Kentucky Medicaid (KM) population, with additional data and validation provided by the Kentucky Cancer Registry (KCR). The KM database contains billing information, identified through International Disease Classification 9th revision (ICD-9) and Current Procedural Terminology (CPT) codes on healthcare utilization including procedures, medication use and diagnoses of low-income patients. The KCR is a mandatory state cancer reporting system that is part of the National Cancer Institute's Surveillance Epidemiology End Results (SEER) program [41]. The protocol was approved by the IRB at the University of Kentucky, the Kentucky Cabinet for Health and Family Services and the Kentucky Cancer Registry.

2.2. Study population

All male patients >18 years with a diagnosis of prostate cancer between July 1, 2000 and December 31, 2005 were identified. In the event that diagnosis dates differed between the KM and KCR databases, information was used from the KCR database due to the independent validation of this dataset in accordance with SEER program. Patients were followed until the last date of contact or August 31, 2009, whichever came first. Patients must have had Medicaid enrollment for >11 months to allow for medication use analysis.

Prostate cancer diagnosis was determined through the ICD-9 diagnosis codes for primary prostate gland cancer (ICD9 185.x) and primary prostate utricle cancer (ICD9 189.3). Patients with benign lesions or carcinoma in situ were excluded. Patients must have reported at least two cancer-related visits to a healthcare provider within 1 year.

Cases were patients with T2DM at risk for increased insulin exposure due to injectable and oral antidiabetic agents. Cases were further stratified into cases with (a) T2DM and elevated serum insulin exposure and (b) T2DM without elevated serum insulin exposure. T2DM were defined in accordance with the Healthcare Effectiveness Data and Information Set (HEDIS) definition; (a) two T2DM related healthcare visits (ICD 250.x2 or 250.x0) and (b) prescription for an antidiabetic medication filled within 1 year after the visit. The presence of type I diabetes was not eligible for study inclusion due to the inefficacy of oral agents in these patients.

Cases subclassification was based on insulin exposure due to antidiabetic medication use. The definition of physiologic doses of exogenous insulin was based on standard replacement therapy guidelines used in type 1 DM:

- Elevated insulin exposure: Patients using agents known to cause increase in endogenous insulin production, or utilizing supra-physiologic doses of exogenous insulin. Includes sulfonylureas, insulin at doses >0.8 units/kg/day (high-dose; utilized an average weight of 85 kg determined from internal data on the weight of prostate cancer patients in Kentucky) or combination therapy with either of these agents for >2/3 the entire study period.
- Physiologic insulin exposure: Patients using agents with no known effect on endogenous insulin production or utilizing physiologic doses of exogenous insulin. Includes metformin, TZDs, insulin at doses ≤0.8 units/kg/day, or combination therapy for >2/3 of the study period, without high-dose insulin or sulfonylureas use.

Those with unclear combination therapy for >2/3 the study period, one-time medication use or poor diabetes medication compliance were classified as indeterminate insulin exposure. Cases were age-matched to controls in randomized blocks of 2, allowing for up to 2 controls for every case.

Controls were chosen to compare not only the effect of extracellular insulin on progression of disease, but also the effect of T2DM on progression of disease. Controls were patients without the risk of elevated insulin exposure; they lacked a diagnosis of types I or II diabetes, or the receipt of an antidiabetic medication at any time during the study observation.

Patients with an ICD-9 diagnosis of diabetes, but no prescriptions for diabetes treatment were excluded. Patients using repaglinde, nateglindine, α-glucosidase inhibitors were not included due to variable insulin exposure. Agents such as exenatide, pramlintide or sitagliptin were not present in the Medicaid population during the study period.

Additional data collected include: medication use (including steroid and bisphosphonate use), geography, comorbidity index, tumor grade, tumor stage, metastatic sites, surgical information, time with diagnosis of diabetes within the study period and compliance. Medication use was defined as use prior to cancer diagnosis (for primary analysis) or recurrence (for secondary analysis); steroid use was limited to those with use for ≥30 days. Geography was determined through the use of the United States Department of Agriculture (USDA) Rural-Urban continuum codes [42]. The co-morbidity index was calculated using the Charlson score. The Charlson score is a weighted composite score that evaluates the presence of 22 conditions, including cancer [43]. The Charlson score was calculated prior to the diagnosis of cancer to reduce falsely elevated comorbid disease. Medication Possession Ratio (MPR) was used to evaluate medication compliance of

diabetes medications and determine study inclusion. MPR is calculated as the sum of the days supply medication over a time period divided by the time period of evaluation [44]. An MPR of <80% was used to determine poor diabetes medication compliance and led to study exclusion.

2.3. Determination of endpoints

Gleason score information is available as part of the KCR database from pathology reports at the time of diagnosis. Patients with a Gleason score ≥7 were considered to have high grade, more aggressive tumors.

Time to progression was a composite endpoint classified through ICD-9 and CPT codes in the KM database. Patients experiencing any of the following events ≥60 days after the diagnosis of prostate cancer were considered to have progressed:

- Recorded elevation of PSA ICD-9 code (790.93) at any point after the index date of PSA normalization.
- Initiation of chemotherapy (CPT codes 96401–96549) or the presence of chemotherapy within the KM prescription database (low dose oral methotrexate was excluded).
- Recorded secondary cancer diagnosis, not diagnosed as metastatic. This was based on ICD9 codes and sites of metastatic spread including bone/spine, regional lymph nodes, bladder, kidney, liver, lung, colon/rectum and other pelvic/genital structures [45].

2.4. Statistical analysis

Demographic variables were evaluated using descriptive statistics. Simple comparisons of continuous variables between the study groups used ANOVA testing for normally distributed data and Kruskal–Wallis testing for non-parametric variables. Categorical variables were evaluated using chi-square testing of independence; however, when low cell counts were found, Fisher's exact testing was utilized. All tests were 2 sided with $\alpha = 0.05$ where appropriate.

The primary endpoint was the presence of high Gleason score at diagnosis. An odds ratio of the presence of high Gleason score between cases and controls was evaluated through bivariate and multivariate conditional logistic regression to control for confounders. Confounders included in the analysis were geography, comorbidity measure and steroid use prior to diagnosis regardless of the results of the bivariate model. The secondary endpoint was the time to progression as defined above. Kaplan–Meier survival curves and log-rank testing evaluated the differences in time to progression between insulin exposure groups. Cox proportional hazard regression was used to evaluate the overall hazard ratios, accounting for confounders of geography, comorbidity, stage/metastatic spread, and steroid and bisphosphonate use prior to recurrence. Statistical analysis was performed using STATA v.10 (StataCorp LP, College Station, TX, USA).

3. Results

Out of 1272 patients initially identified, 722 patients were eligible for inclusion. A diagram of exclusion is provided in Fig. 1. Of these patients, 50 were found to have physiologic insulin exposure, 103 had elevated insulin exposure, and 16 had indeterminate exposure. The remaining 569 patients had no evidence of diabetes. From this, 338 were randomly age-matched and selected as controls. Those with indeterminate exposure were excluded from the final analysis due to low numbers, leading to a total of 491 patients evaluated. Demographic information is listed in Table 1.

Within the 491 patients, 236 were found to have evaluable pathologic information, including Gleason score. One-hundred forty-nine (59.36%) were found to have a Gleason score <7, while 102 (40.64%) were diagnosed with high-grade disease. A breakdown of this by insulin exposure group is in Fig. 2. Overall diabetic patients, regardless of insulin exposure, presented with lower Gleason scores, although this was not statistically significant. Compared to those without diabetes, patients with elevated exposure had a 5% lower odds (95% CI: 0.47–1.91; $p = 0.887$) of developing high-grade disease, while those with physiologic exposure had a 45% lower odds (95% CI: 0.21–1.46; $p = 0.233$). When adjusted for geography, co-morbidity, and corticosteroid use prior to prostate cancer diagnosis, elevated insulin exposure appeared to slightly increase the odds of presenting with high-grade disease (OR = 1.04 (0.44–2.44); $p = 0.685$), while physiologic insulin exposure decreased the odds (OR = 0.62 (0.22–1.70); $p = 0.929$) compared to controls (Table 2), although neither of these findings were statistically significant.
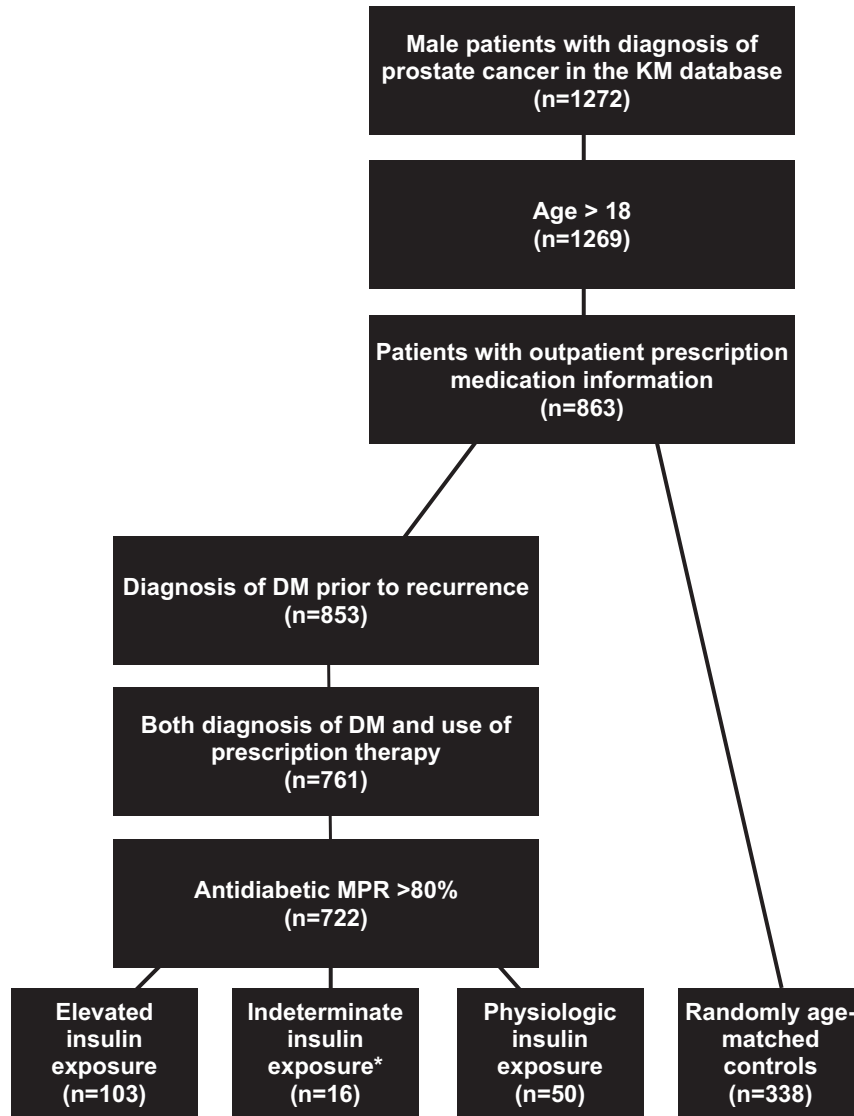
Evaluating the secondary endpoint (Fig. 3), 122 patients were found to have recurrence. Median time to recurrence was 31.4 (0.03–98.1) months for those with physiologic exposure compared to 27.6 (1.38–92.7) months for those with elevated insulin exposure and 26.6 (0.92–96.2) for those without diabetes ($p = 0.8623$). Adjusting for potential confounders, there was no significant effect of insulin exposure on the time to tumor progression, although it appeared that elevated insulin exposure may increase the risk of progression, while physiologic exposure decreases the risk of progression compared to non-diabetics (Table 3). Only the use of steroids prior to recurrence was found to have a statistically significant impact on the time to tumor progression. A 68% decrease ($p = 0.019$) in the risk of progression over the five years studied was found in patients that used corticosteroids when controlling for other factors.

4. Discussion

This study found that management of diabetes with medications which create supra-physiologic serum insulin exposure does not lead to more aggressive prostate cancers at diagnosis or shorter time to progression, although due to limited power needs to be investigated further. Previous analyses have demonstrated a link between diabetes and developing cancer, an effect which is potentially modified by the choice of antidiabetic treatment [29–33]. In vitro studies clearly demonstrate that extra-cellular insulin can stimulate IGFR-1 receptors in prostate cancer cell lines, activating mitogenic and angiogenesis pathways. These findings suggest that this is not a disease–disease interaction, but rather a disease treatment–disease interaction. While several others have evaluated the association of diabetes and cancer, none have focused on the impact of serum insulin exposure from disease management.

Recent data released by the Health Professionals Study suggest that tumors with Gleason score <7 are associated with higher levels of insulin-like growth factor and binding protein (IGF-1 and IGFBP-3) [46]. The data in the Health Professionals Study suggests that increasing insulin levels may actually lead to lower-grade tumors in patients with high serum insulin who develop cancer. This proposed mechanism is counter to what has been seen in previous in vitro, in vivo, and epidemiologic analyses, and those used in the development of the hypothesis evaluated in this study [13,47,48]. In further evaluating this, alternate hypotheses for increased high-grade tumors in patients with elevated insulin exposure should be further investigated.

One potential rationale for the differences in effect seen between this study, the Health Professionals Study and previous investigation may be from the effect of DM on testosterone.

Male patients with diagnosis of prostate cancer in the KM database (n=1272)

Age > 18 (n=1269)

Patients with outpatient prescription medication information (n=863)

Diagnosis of DM prior to recurrence (n=853)

Both diagnosis of DM and use of prescription therapy (n=761)

Antidiabetic MPR >80% (n=722)

Elevated insulin exposure (n=103)

Indeterminate insulin exposure* (n=16)

Physiologic insulin exposure (n=50)

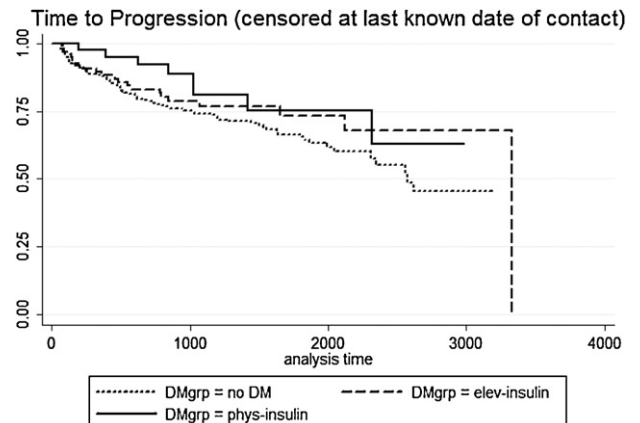**Randomly age-matched controls (n=338)**

* Patients with indeterminate exposure were excluded from the final analysis

Fig. 1. Patient selection for cases and randomly selected controls. *Patients with indeterminate exposure were excluded from the final analysis.
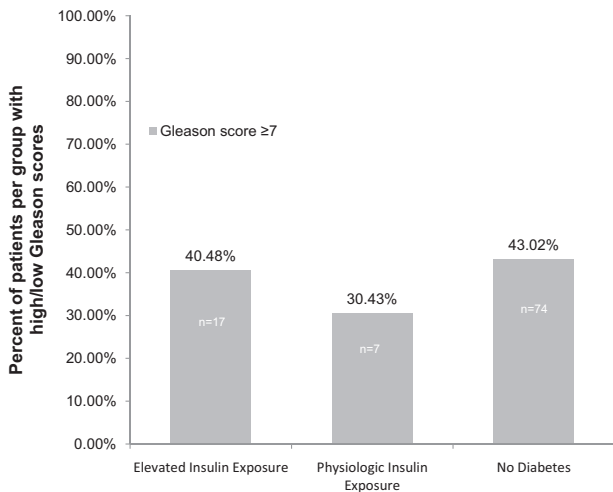
Fig. 2. Gleason score based on insulin exposure.

Fig. 3. Kaplan–Meier analysis of time to progression by insulin exposure.

Table 1
Patient demographic information.

	Elevated insulin exposure	Physiologic insulin exposure	No evidence of DM	Total	p-Value
N	103 (20.98%)	50 (10.18%)	338 (68.84%)	491	
Age (years) (mean, SD)	70.8 (±9.78)	71.2 (±9.32)	70.6 (±10.18)	70.7 (±9.99)	0.9250
Geography					0.651
Urban	32 (31.07%)	10 (20.00%)	96 (28.40%)	138 (28.11%)	
Suburban	16 (15.53%)	11 (22.00%)	61 (18.05%)	88 (17.92%)	
Rural	55 (53.40%)	29 (58.00%)	181 (53.55%)	265 (53.97%)	
Stage[*]	n = 62	n = 30	n = 202	n = 294	0.281
Localized	46 (74.19%)	26 (86.67%)	142 (70.30%)	214 (72.79%)	
Regional	4 (6.45%)	0 (0%)	11 (5.45%)	15 (5.10%)	
Distant metastases	7 (11.29%)	2 (6.67%)	39 (19.31%)	48 (16.33%)	
Unknown/unstageable	5 (8.06%)	2 (6.67%)	10 (4.95%)	17 (5.78%)	
Presence of metastases at diagnosis					0.159
No	96 (93.20%)	48 (96.00%)	299 (88.46%)	443 (90.22%)	
Yes	7 (6.80%)	2 (4.00%)	39 (11.54%)	48 (9.78%)	
Metastatic sites					0.119
No metastatic sites	96 (93.20%)	48 (96.00%)	299 (88.46%)	443 (90.22%)	
Bone/spine	1 (0.97%)	2 (4.00%)	15 (4.44%)	18 (3.67%)	
Other sites	6 (5.83%)	0 (0%)	24 (7.10%)	30 (6.11%)	
Comorbidity information					
Charlson scores (median, range)[*]	2 (1–7)	2 (1–5)	1 (1–12)	2 (1–12)	0.0351
	n = 86	n = 40	n = 173	n = 299	
Medication use					
Chemotherapy use					0.088
No	90 (87.38%)	49 (98.00%)	308 (91.12%)	447 (91.04%)	
Yes	13 (12.62%)	1 (2.00%)	30 (8.88%)	44 (8.96%)	
Antiandrogen/GNRH agonist use					0.869
No	82 (79.61%)	38 (76.00%)	266 (78.70%)	386 (78.62%)	
Yes	21 (20.39%)	12 (24.00%)	72 (21.30%)	105 (21.38%)	
Bisphosphonate use					0.706
No	96 (93.20%)	48 (96.00%)	311 (92.01%)	455 (92.67%)	
Yes	7 (6.80%)	2 (4.00%)	27 (7.99%)	36 (7.33%)	
Corticosteroid use[a]					0.118
No	82 (79.61%)	45 (90.00%)	262 (77.51%)	389 (79.23%)	
Before diagnosis	5 (4.85%)	1 (2.00%)	8 (2.37%)	14 (2.85%)	0.346
Spanning diagnosis	12 (11.65%)	4 (8.00%)	43 (12.72%)	59 (12.02%)	0.722
After diagnosis	4 (3.88%)	0 (0.00%)	25 (7.40%)	29 (5.91%)	0.068
Diabetes information					
Time diagnosed with DM (years) (median, range)	4.2 (0.16–9.61)	3.9 (0.16–9.59)	0 (0)	4.1 (0.16–9.61)	0.515
Time from diagnosis of DM to diagnosis of PCa (years) (mean, SD)	1.8 (±1.89)	1.8 (±2.01)	0 (0)	1.8 (±1.93)	0.851
Antidiabetic medication use					
Sulfonylurea use					
No sulfonylurea use	10 (9.71%)	38 (76.00%)	338 (100%)	386 (78.62%)	
Sulfonlyurea + other DM	69 (66.99%)	12 (24.00%)	0 (0%)	81 (16.50%)	<0.001
Exclusive sulfonylurea	24 (23.30%)	0 (0%)	0 (0%)	24 (4.89%)	<0.001
Thiazolendione use (TZD)					
No TZD use	69 (66.99%)	26 (52.00%)	338 (100%)	433 (88.19%)	
TZD + other DM med	34 (33.01%)	18 (36.00%)	0 (0%)	52 (10.59%)	<0.001
Exclusive TZD	0 (0%)	6 (12.00%)	0 (0%)	6 (1.22%)	<0.001
Metformin use					
No metformin use	48 (46.60%)	19 (38.00%)	338 (100%)	405 (82.48%)	
Metformin + other DM	55 (53.40%)	17 (34.00%)	0 (0%)	72 (14.66%)	<0.001
Exclusive metformin	0 (0%)	14 (28.00%)	0 (0%)	14 (2.85%)	<0.001
Insulin use					
No insulin use	60 (58.25%)	31 (62.00%)	338 (100%)	429 (87.37%)	
Insulin + other DM	37 (35.92%)	14 (28.00%)	0 (0%)	51 (11.88%)	<0.001
Exclusive insulin	6 (5.83%)	5 (10.00%)	0 (0%)	11 (2.24%)	<0.001
Average medication possession ratio (MPR) of diabetic meds (median, range)	1.00 (0.80–4.72)	0.99 (0.82–3.53)	0 (0)	1.00 (0.80–4.72)	0.797
Use of antidiabetic medications after PCa dx (as percent of total DMgrp)	14 (13.59%)	11 (22.00%)	0 (0%)	25 (5.09%)	

[*] Not available for all patients; number evaluated listed.
[a] Differences between the steroid group overall listed first; differences listed with each point of steroid use (before, during, after) are listed at the point of use–these were determined from dichotomous values (e.g. used/did not use steroid before diagnosis)

Diabetes is linked with lower levels of circulating testosterone, a known stimulatory agent of prostate cancer growth. Further, testosterone has been associated with higher-grade tumors [49–51], a finding that supports what was seen in the studies by Hong and DeNuzio [13,34]. As demonstrated there are conflicting reports, and potentially conflicting underlying biochemical mechanisms regarding the effect of diabetes on prostate tumor grade.

This highlights the importance of further study in this area with clear measurement of the effect of serum insulin, insulin/IGFR-1 receptors and testosterone on tumor grade.

Another potential factor leading to the disparities seen within studies may be due to the effect of obesity and other components of metabolic syndrome on tumor development. Increased BMI, weight, and hypercholesterolemia have been associated with

Table 2
Multivariate analysis of odds of developing high Gleason score based on insulin exposure ($n = 133$).

	Odds Ratio	95% Confidence Interval	p-value
Rurality			
Urban	Reference		
Suburban	0.50	(0.17–1.52)	0.222
Rural	0.74	(0.30–1.80)	0.500
Charlson score	1.07	(0.79–1.44)	0.670
Corticosteroid use (before dx)			
No	Reference		
Yes	1.47	(0.23–9.46)	0.685
Diabetes group			
No diabetes	Reference		
Elevated insulin exposure	1.04	(0.44–2.44)	0.929
Physiologic insulin exposure	0.61	(0.22–1.70)	0.350
Physiologic compared to elevated	0.61	(0.23–1.62)	0.320

Table 3
Multivariate analysis of hazard of prostate cancer progression ($n = 168$).

	Hazard ratio	95% Confidence interval	p-Value
Rurality			
Urban	Reference		
Suburban	0.82	(0.31–2.15)	0.684
Rural	0.68	(0.30–1.53)	0.351
Charlson score	0.85	(0.62–1.16)	0.313
Stage			
Localized	Reference		
Regional	0.96	(0.28–3.30)	0.945
Distant Metastases	0.96	(0.36–2.53)	0.926
Unknown/unstageable	1.83	(0.42–8.01)	0.421
Corticosteroid use (prior to recurrence)			
No	Reference		
Yes	0.32	(0.13–0.83)	0.019
Bisphosphonate use (prior to recurrence)			
No	Reference		
Yes	2.01	(0.64–6.35)	0.232
Antiandrogen/GNRH agonist use (prior to recurrence)			
No	Reference		
Yes	0.91	(0.43–1.93)	0.814
Diabetes group			
No Diabetes	Reference		
Elevated insulin exposure	1.18	(0.57–2.44)	0.649
Physiologic insulin exposure	0.62	(0.22–1.73)	0.363
Physiologic compared to elevated	0.58	(0.22–1.53)	0.272

increased risk of high-grade tumor development, independent of the effect of DM or insulin exposure [6,34,52,53]. It is thought that alterations in lipid and androgen metabolism may lead to these effects. Due to the limitations of the KM database, BMI and weight information was not available. The interaction between DM, other factors in metabolic syndrome, serum insulin and tumor growth is complex and should be continue to be evaluated in the future.

Although epidemiologic evidence exists suggesting that the use of antidiabetic therapy may alter the development of prostate tumors, again, no evidence exists that these agents alter tumor grade. In this evaluation, the use of insulin stimulating agents was associated with a slight increase in high grade tumors while non-stimulating agents were associated with a lower grade tumor compared to those without diabetes. While this is not statistically significant, this does provide evidence that perhaps the increase in serum insulin seen may lead to increased mitogenic effects. This study was only able to access data from the Kentucky Medicaid database over a 5-year period, leading to low study power. In addition to the small sample size gained from this database, the Kentucky Medicaid population is limited to low-income patients. Although efforts were taken to ensure that the demographics of this population was representative of the larger American population, Medicaid patients inherently have different access to care that may have limited the ability to determine statistically significant differences. Evaluation in a larger nation-wide database, such as the Veteran's Administration or private insurance databases may provide further clarity on the effect of diabetic medication use on the development of high-grade prostate tumors.

Similarly, the difference in the time to tumor progression based on the use of antidiabetic medications has not been previously evaluated in the literature. Overall, this study found a potentially lower risk of tumor progression in those using TZDs, metformin or low-dose insulin compared to non-diabetics and a higher risk of progression in those using sulfonylureas or high-dose insulin compared to non-diabetics. Although this was not statistically significant, this observed decrease in tumor progression may not be due to the effects of these agents on insulin production and serum mobilization, but rather from non-insulin dependent anti-tumor effects of metformin and TZDs. Metformin has been shown inhibit in vitro growth of prostate cell lines through AMPK activation and mTOR inhibition [54]. Thiazolidinediones have also been shown to have independent anti-tumor activity in vitro. This effect is thought to be primarily through the activation of PPAR-γ, although PPAR-γ independent mechanisms have also been suggested [55]. Although sulfonylureas have not yet been shown to have antitumor effects, it is thought that the effects on increased tumor risk and mortality seen with sulfonylureas may be a statistical abnormality due to the comparison to those with known anti-tumor activity [56]. In this study metformin and TZDs were associated with a potentially decreased time to progression, while sulfonylureas had a slight increase in progression. Since the anti-tumor effects were unable to be accounted for it is difficult to ascertain if the effects seen were a result of the effect on insulin, or a modification of alternate tumorgenic cellular pathways by diabetic medications. Further evaluation in larger datasets should be continued to elucidate the effects of medication-induced insulin stimulation on the development and progression of prostate tumors.

Comparing the impact of patients both case groups vs. controls with T2DM, an overall decrease in tumor progression in patients with elevated and physiologic insulin exposure compared to those without DM. Similar to the results of the primary evaluation, this was not statistically significant, but leads to interesting observations on the effect of DM on tumor progression. In addition to potential anti-tumor effects of diabetic medications, the decrease in progression risk in those with elevated exposure may indicated a protective effect of physiologic changes in diabetic patients. Vascular changes are common in diabetics, often leading to numerous complications on end-organs. Post hoc analysis demonstrated that overall case patients in both groups had a lower incidence of metastatic disease than non-diabetics, indicating that despite potentially higher grade at diagnosis, diabetics may have less metastatic spread due to poor vascularization. This hypothesis could not be evaluated in this analysis, but should continue to be investigated in future studies.

5. Conclusion

The use of antidiabetic medications that cause high insulin exposure did not increase the grade of prostate tumor upon diagnosis or decrease the time to tumor progression in this analysis. Although the results were inconclusive this data provides needed insight into the interactions between diabetes treatments and the development and progression of prostate tumors. While

this study was underpowered to provide any conclusive results, the hypothesis remains credible and should continue to be investigated through larger database analyses, as well as potential prospective studies. As seen, there is a multitude of factors that interplay within the proposed mechanism to lead to tumor development and progression. Future analysis should consider an evaluation of serum insulin, weight, BMI, lipids (cholesterol, HDL, LDL, TG), testosterone, and IGFR-1 expression on pathologic samples, along with robust medical histories (including complete antidiabetic and lipid-lowering agents, bisphosphonate use, hormone therapy, and steroid medications histories) in order to fully evaluate the effect of medications on prostate tumors. Through a better characterization of these interactions, future treatment of patients with diabetes and prostate cancer may be optimized and overall health outcomes improved.

Conflict of interest statement

The authors have no direct financial or personal relationships pertaining to the subject matter described in this manuscript that may have introduced bias or affected the integrity of this work in any way.

Disclosure

Drs. Hitron, Adams, Talbert and Steinke have no financial disclosures to report.

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