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Thiazolidinedione and Metformin Use and the Risk of Benign Prostate Hyperplasia in Veterans with Diabetes Mellitus

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Abstract

Background—Chronic inflammation is important in the development of benign prostatic hyperplasia (BPH) and certain oral antidiabetic medications have anti-inflammatory properties. The purpose of this study was to determine if use of thiazolidinediones or metformin was associated with a reduced risk of requiring medical or surgical treatment for BPH compared to sulfonylureas among diabetic men.

Methods—We constructed a retrospective cohort of 192,457 male veterans newly prescribed either rosiglitazone, pioglitazone, metformin, or a sulfonylurea. We used Cox proportional hazard regression to assess the association between thiazolidinedione or metformin use and the risk of requiring medical or surgical treatment for BPH compared to sulfonylurea use. New BPH treatment was defined by either a new prescription for a α -1 blocker or 5 α -reductase inhibitors or a surgical procedure indicated for severe BPH.

Results—In 259,995 person-years of follow up we identified 14,690 new treatments for BPH. After adjusting for covariates including age, HbA1c, and body mass index, we found no association between rosiglitazone (adjusted hazard ratio [aHR] 1.02, 95% CI 0.86, 1.20), pioglitazone (aHR 0.79, 95% CI 0.45, 1.38), or metformin use (aHR 0.99, 95% CI 0.94, 1.03) and risk of new medical or surgical treatment for BPH compared to sulfonylureas. Analyses ignoring prescriptions for non-selective α -1 blockers (terazosin, doxazosin, prazosin) from our BPH case definition (n = 11,079), yielded similar results.

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Conclusions—In this large cohort, we observed no association between the use of thiazolidinediones or metformin and new medical or surgical treatment for BPH compared to sulfonylureas.

Keywords

Benign prostatic hyperplasia; Diabetes mellitus; Thiazolidinediones; Metformin

Introduction

Benign prostatic hyperplasia (BPH) is the most common symptomatic tumor-like condition in humans. The Medical Therapy of Prostate Symptoms study found 43% of men with BPH had chronic inflammation in prostatic tissue and this inflammation appeared to be closely associated with prostate size^{1,2}. Additionally, biomarkers of inflammation such as interleukin (IL)-8 and C-reactive protein have been found to be associated with increased BPH risk^{3,4}. Along with chronic inflammation, it also appears that diabetes mellitus may be associated with an increased risk for developing BPH⁵. Possible mechanisms for such an association include the hyperinsulinemic state observed in type 2 diabetes mellitus, the mitogenic effect of insulin-like growth factor,^{6,7} and chronic obesity-induced inflammation⁸.

Thiazolidinediones (TZDs) such as rosiglitazone and pioglitazone are potent peroxisome proliferator-activator receptor gamma (PPAR γ) ligands and are clinically prescribed for the treatment of type 2 diabetes mellitus⁹. PPAR γ are nuclear receptor proteins which serve as transcription factors for genes that play a pivotal role in carbohydrate and lipid metabolism¹⁰. In the prostate, loss of PPAR γ function results in widespread inflammation and hyperplasia¹¹. Furthermore, animal studies have demonstrated that pioglitazone decreased prostate weight in response to a high-fat diet¹². These observations suggest that PPAR γ signaling is an important factor driving the insulin resistance/diabetes and BPH association⁸.

Metformin is a biguanide indicated for the treatment of type 2 diabetes and for prevention diabetes in high-risk individuals¹³. Metformin inhibits the release of several pro-inflammatory cytokine including IL-6, IL-8, and nuclear factor-kappa β ^{14,15}. These observations are also directly relevant to BPH as IL-6 and IL-8 are potent autocrine growth factors for epithelial and stromal prostate cells^{16,17}. Indeed, IL-8 has been proposed as a potential biomarker of prostatic inflammation¹⁸. The anti-inflammatory, anti-proliferative, and pro-apoptotic actions of metformin have resulted in considerable interests in its use as an anti-neoplastic agent¹⁹.

With several plausible mechanisms to suggest that the use of either TZDs or metformin might influence prostatic inflammation and possibly slow the development of BPH, our aim was to determine if the regular use of metformin or TZD in the treatment of diabetes mellitus reduces the risk of developing BPH compared to a sulfonylurea in a large cohort of veteran men.

Materials and Methods

We constructed a retrospective cohort of veterans initiating an oral anti-diabetes drug between October 1, 2001 and September 30, 2008 using national Veterans Health Administration (VHA) databases. Details on this cohort have been published previously^{20, 21}. Briefly, these data include outpatient and inpatient healthcare encounters (coded using International Classification of Disease, Ninth Revision, Clinically Modified [ICD-9-CM] and Current Procedural Terminology [CPT] codes), pharmacy files, vital sign data including weight and height, and laboratory testing values. The VHA pharmacy datasets included data on medication name; date filled, days of medication supply, pills dispensed and prescribed dosage. The institutional review boards of Vanderbilt University and the VA Tennessee Valley Healthcare System approved this study.

Patients were eligible for the cohort if they were aged 18 or older, male, active users of the VHA health system (defined as at least one clinical encounters or prescription fill occurring over the past 730 days), and had a new prescription dispensed for either metformin, a sulfonylurea (glyburide, glipizide), or a TZD (rosiglitazone, pioglitazone). Patients could not have had a prescription filled for any hypoglycemic medication within the 365 days prior to cohort entry and study entry time began at the date of the first prescription. We excluded patients with a prior diagnosis of any cancer (except non-melanoma skin cancer), heart failure, human immunodeficiency virus, end stage renal disease, respiratory failure, liver disease, organ transplant, cocaine use, or a serum creatinine ≥ 1.5 mg/dL identified in the preceding 365 days prior to cohort entry. These exclusion criteria were applied to identify a relatively homogeneous population of individuals suitable for longitudinal follow up. To allow measurements of BPH incidence, we also excluded patients with a prior history of a prescription for either a α -1 blocker or 5 α -reductase inhibitor, prior history of transurethral resection of the prostate, history of prostatectomy, or diagnostic code indicating BPH (Supplemental Table 1).

The primary exposure was persistent use of oral antidiabetic drug. Persistent use of a medication was defined as continuous use with no gaps in medication use greater than 90 days. Study medications included metformin, rosiglitazone, pioglitazone, and sulfonylureas (glyburide, glipizide). Because to our knowledge there was no evidence to suggest that sulfonylureas may have anti-inflammatory properties we chose this drug group as the reference. We used pharmacy information of pills dispensed and prescribed days supply to determine individual patients' drug supply in hand. New oral antidiabetic drug users were followed until either an additional antidiabetic medication was prescribed; the patient went 90 days without any drug in hand; a study outcome; or a censoring event. Patient follow-up was censored at the last day of the study, the ending day of active use of VHA services, death, or a diagnosis of prostate cancer.

The primary composite outcome included: a new prescription for a non-selective α -1 blocker medication, (terazosin, doxazosin, or prazosin); a selective α -1 blocker medication (tamsulosin or alfuzosin); a 5 α -reductase inhibitors (finasteride or dutasteride); or the new occurrence of a transurethral prostatectomy (ICD-9-CM codes 60.21, 60.29, 60.95, 60.96, 60.97 and /or CPT codes 52450, 52601, 52648). Because the non-selective α -1 blockers may

be prescribed for other indications besides BPH, such as hypertension, we conducted a secondary analysis removing these medications from the primary composite outcomes. Because not all diagnoses of BPH require medical or surgical treatment we constructed a secondary outcome which included individuals with a new occurrence of an ICD-9-CM code for hyperplasia of the prostate (ICD-9-CM codes 600.0, 600.2, 600.9) and without a concomitant prescription for a α -1 blockers or 5 α -reductase inhibitors or an incident prescription for α -1 blocker medication or 5 α -reductase inhibitors, or the new occurrence of a transurethral prostatectomy.

The primary analysis was time to the composite outcome. Baseline characteristics between oral diabetic medication users were compared using Pearson test for categorical variables and the Kruskal-Wallis test for continuous variables. We constructed Cox proportional hazard models to estimate the relative hazard ratios and 95% confidence intervals for the association of BPH with metformin, rosiglitazone, or pioglitazone compared to sulfonylureas. The continuous covariates age, body mass index, creatinine, HbA1c, number of medications, and number of outpatient visits were modeled with third degree polynomials to account for non-linearity. We also included use of aspirin (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), race (white, African-American, Hispanic, other, missing), and fiscal year of cohort entry (2004, 2005, 2006, 2007) as covariates. We included the same covariates for our analysis of the secondary study outcome. We conducted additional analyses ignoring non-selective α -1 blockers as a study outcome. Statistical analyses were conducted using R (available at: <http://www.r-project.org>.) and SAS for Windows 9.2 (SAS Institute, Cary, NC).

Results

A total of 364,865 incident prescriptions for an oral diabetes medication were identified. After excluding women, individuals with serious illnesses which might limit long-term follow up, prior use of an α -blocker or 5 α -reductase inhibitor, prior history of a transurethral resection of the prostate, and individuals started on combination diabetic medications (metformin and sulfonylurea combined) the analytic cohort included 192,457 diabetic men (Figure 1).

Metformin use increased over time relative to other oral diabetes medication while use of thiazolidinediones decreased (Table 1). Metformin users tended to be younger and have a greater body mass index when compared to sulfonylureas or TZD users. Compared to other oral antidiabetic drug users, sulfonylureas users entered the cohort with slightly higher HbA1C values.

After 259,995 person-years of follow up there were 14,690 outcome events. The most common event was an incident prescription for terazosin accounting for 56.7% of all events (Table 2). New prescriptions for non-selective α -blockers occurred in 75.4% of the cohort. New prescriptions for either selective α -blockers or 5 α -reductase inhibitors accounted for 4.7% and 10.4% of outcomes, respectively. Approximately 9% of outcomes were urological surgical procedures. The median time to study event was 430 days in the new metformin

users, 367 days in the new sulfonylurea users, 233 days in the new rosiglitazone users, and 139 days in the new pioglitazone users.

In unadjusted analyses, we found that metformin users had a reduced hazard ratio of 0.90 (95% CI 0.86, 0.94) compared to sulfonylurea users for developing BPH that required either medications or surgical intervention (Table 3). We found no association of either rosiglitazone or pioglitazone on risk of medical or surgical treatment for BPH. After adjusting for possible confounders, we found no evidence of an association between metformin (adjusted hazard ratio [aHR] 0.99, 95% CI 0.94, 1.03), rosiglitazone (aHR 1.02, 95% CI 0.86, 1.20) or pioglitazone (aHR 0.79, 95% CI 0.45, 1.38) and risk of BPH treatment compared to sulfonylureas.

After ignoring non-selective α -1 blockers from our analysis results remained consistent with no evidence of an association between metformin (aHR 0.98, 95% CI 0.89, 1.08), rosiglitazone (aHR 1.00, 95% CI 0.72, 1.39) or pioglitazone (aHR 1.09, 95% CI 0.40, 2.91) and risk for medical or surgical treatment for BPH compared to sulfonylureas use (Table 3).

In secondary analyses that expanded our outcome definition to include any new diagnosis of BPH defined by the new occurrence of a study ICD-9-CM code, the total number of study outcomes increased to 19,556. Nevertheless, we found no evidence of a statistically significant association between use of metformin, rosiglitazone, or pioglitazone and BPH risk compared to sulfonylureas whether or not we ignored non-selective α -1 blockers from our analysis (Table 3).

Because of the 10% difference seen in the hazards ratio between the unadjusted and adjusted models in metformin users when compared to sulfonylureas users, we evaluated the effect of each individual model covariate on the metformin hazards using stepwise selection methods. We found that in the age-only adjusted model metformin users had a HR of 0.97 (95% CI 0.92, 1.01) compared to sulfonylureas users suggesting that the differences in age between patients prescribed metformin and those prescribed sulfonylureas users likely accounted for our unadjusted analysis findings.

Discussion

In this large retrospective cohort, we found no association between PPAR γ ligands, (rosiglitazone or pioglitazone), or metformin and the risk of BPH requiring medical or surgical treatment compared to sulfonylureas. We had hypothesized that the anti-inflammatory and insulin sensitizing actions of these medications might delay the progression of BPH; however, our study findings did not lend support to this hypothesis. Additionally, we conducted a secondary analysis ignoring medications that may have been prescribed for other indications, such as the non-selective α -1 blockers, and our overall results remained largely unchanged.

The link between chronic inflammation and BPH has led to several studies investigating the impact of anti-inflammatory agents on BPH development. Observational studies have yielded inconsistent results. The Olmsted County Study of Urinary Symptoms and Health Status among Men reported an inverse association between daily NSAID use and incident

BPH. In a secondary analysis of the Prostate, Lung, Colorectal and Ovarian Cancer Screening randomized trial no association between NSAIDs and BPH was seen^{22, 23}. In a small single arm clinical trial of patients with a diagnosis of BPH treated with an α -1 blocker but with residual nocturia, the NSAID loxoprofen sodium significantly improved residual symptoms of nocturia²⁴. This study however was limited by the lack of a control arm.

PPAR γ has a critical role in the regulation of lipid metabolism and additionally appears to have anti-inflammatory actions⁸. PPAR γ ligands reduce the recruitment of inflammatory cells and limit induction of pro-inflammatory cytokines such as IL-6 and TNF α ^{25, 26}. Vikram et al found that Sprague-Dawley rats fed a high fat diet developed prostatic enlargement and that pioglitazone mitigated the impact of a high-fat diet on prostate enlargement²⁷. In our study we found no evidence to suggest that diabetic patients taking PPAR γ ligands had a reduced risk of BPH relative to sulfonylureas use. However we did not have data regarding dietary intake or measures of insulin sensitivity.

Few studies have investigated the impact of metformin on BPH in humans. There has been considerable interest regarding metformin use and prostate cancer risk with some studies suggesting a protective effect²⁸⁻³⁰. Nevertheless, despite the beneficial effects of metformin on insulin sensitivity as well as its effects on inflammatory cytokines production, we found no evidence of a metformin protective effect on BPH risk after adjustment for potential confounders including age, HbA1c, and BMI. One explanation for the null effects could be the short duration of follow-up for the cohort. BPH can take years to develop and our cohort follow-up time might not have been long enough to see an effect in metformin users. Future work with this cohort should be aimed at investigate the effects of metformin on BPH when more follow-up time have been accrued.

One possibility for the studies null findings observed for PPAR γ ligands could be related to limited power to detect an event. Because of the smaller sample size for rosiglitazone users we had 80% power to detect an effect size (i.e. hazard ratio) as small as 1.05. Nevertheless, if we had committed a Type II error and erroneously determined no association between rosiglitazone use and BPH risk, any true effect would likely be clinically insignificant. The sample size for pioglitazone was much smaller and our power was limited in this group. This could be relevant if the potential effects of rosiglitazone and pioglitazone on prostatic inflammation differ.

Our study has several strengths. By constructing a national cohort we had adequate power to detect even small differences between metformin and sulfonylureas use. VHA databases include detailed information regarding the amount of medication dispensed allowing us to better classify drug exposure status. There are however several limitation. First, we could have misclassified some outcomes if our surgical procedure codes were associated with a diagnosis that was not BPH. Additionally, despite the large overall sample size, the number of rosiglitazone and pioglitazone users was small. Finally, the median time to event ranged from 139 days in the pioglitazone group to 430 days in the metformin group. This relatively short time from cohort entry to developing BPH may have resulted in too short a time frame to see a possible effect of metformin or TZD use.

Conclusion

In conclusion, despite plausible mechanisms which suggest an anti-inflammatory action and beneficial effect of the thiazolidinediones or metformin on BPH risk, this large retrospective cohort study of diabetic males found no association between thiazolidinediones or metformin and the risk of BPH compared with sulfonylureas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Study Flow Chart

Table 1

Selected Baseline Characteristics by Diabetes Medication

	Metformin (n = 113,860)	Sulfonylurea (n = 72,108)	Rosiglitazone (n = 5734)	Pioglitazone (n = 755)	P-value
Age, (yrs)	61 (55, 70) [†]	65 (57, 75)	67 (58, 76)	63 (56, 73)	<0.001
Race					
White (%)	60	59	56	61	
African-American (%)	11	12	9	8	<0.001
Missing (%)	26	24	27	26	
BMI, (mg/kg ²)	31.9 (28.5, 36.1)	30.3 (27.0, 34.2)	30.5 (27.3, 34.4)	30.9 (27.6, 35.1)	<0.001
HgA1c (%)	7.1 (6.5, 7.9)	7.3 (6.6, 8.4)	6.9 (6.3, 7.7)	6.7 (6.1, 7.5)	<0.001
Creatinine (mg/dL)	1.00 (0.9, 1.10)	1.10 (0.90, 1.30)	1.10 (0.90, 1.30)	1.10 (0.90, 1.20)	<0.001
Number of outpatient medications (prior 90 days)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0, 6.0)	<0.001
Outpatient Visits (annually)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)	<0.001
Hospitalized in prior 365 days (%)	6	6	5	4	<0.001
Aspirin use (% prescription in past 1 year)	17	17	14	15	<0.001
Thiazide diuretic use (% prescription in past 1 year)	32	30	27	24	<0.001
Loop diuretic use (% prescription in past 1 year)	8	13	14	14	<0.001
Fiscal Year of Cohort Entry (%)					
2003	14	21	10	35	
2004	18	23	23	37	
2005	21	21	28	16	<0.001
2006	23	20	23	7	
2007	23	15	16	5	

[†] median (lower quartile, upper quartile)

Table 2
Overall Distribution of Benign Prostatic Hyperplasia Events in the Primary Outcome (N events = 14,690)

Event	n	Percent
α -blocker medication (non-selective)		
terazosin	8326	56.7%
doxazosin	1711	11.6%
prazosin	1042	7.1%
α -blocker medication (selective)		
tamsulosin or alfuzosin	687	4.7%
5 α -reductase inhibitors medication		
finasteride or dutasteride	1529	10.4%
Surgical procedure code	1395	9.5%

Table 3
Association of Oral Antidiabetic Drug Use and the Risk of Benign Prostatic Hyperplasia

Primary outcome definition [†] , all study events included (N event = 14,690)					
Events/N	Person-Years	Unadjusted HR	95% CI	Adjusted HR [§]	95% CI
Sulfonylurea	5433/72,108	reference	--	reference	--
Metformin	8911/113,860	0.90	0.86, 0.94	0.99	0.94, 1.03
Rosiglitazone	324/5734	1.07	0.90, 1.26	1.02	0.86, 1.20
Pioglitazone	22/755	0.79	0.45, 1.38	0.79	0.45, 1.38
Primary outcome definition, study events ignoring non-selective α -blockers [‡] (N event = 3,611)					
Sulfonylurea	1511/72,108	reference	--	reference	--
Metformin	2001/113,860	0.73	0.67, 0.80	0.98	0.89, 1.08
Rosiglitazone	94/5,734	1.05	0.75, 1.46	1.00	0.72, 1.39
Pioglitazone	5/755	0.99	0.38, 2.63	1.09	0.40, 2.91
Secondary outcome definition [†] , all study events included (N event = 19,556)					
Sulfonylurea	7256/72,108	reference	--	reference	--
Metformin	11810/113,860	0.88	0.85, 0.92	0.97	0.93, 1.01
Rosiglitazone	455/5,734	1.13	0.98, 1.30	1.07	0.93, 1.23
Pioglitazone	35/755	0.93	0.60, 1.43	0.92	0.60, 1.42
Secondary outcome definition, study events ignoring non-selective α -blockers (N event = 12,008)					
Sulfonylurea	4509/72,108	reference	--	reference	--
Metformin	7177/113,860	0.85	0.81, 0.90	0.97	0.92, 1.02
Rosiglitazone	298/5,734	1.25	1.06, 1.48	1.16	0.98, 1.38
Pioglitazone	24/755	1.09	0.66, 1.80	1.13	0.68, 1.85

[†] Primary outcome definition includes new prescription for any α -blockers or 5- α reductase inhibitor or study urologic surgical procedure code

[‡] Secondary outcome definition includes new prescription for any α -blockers or 5- α reductase inhibitor or study urologic surgical procedure code and any new appearance of an ICD-9-CM code indicating benign prostatic hyperplasia

[§] Adjusted for age, race, hemoglobin A1c, serum creatinine, body mass index, number of outpatient medications prescribed within the prior 90 days, number of outpatient visits within the prior 365 days, use of aspirin, use of loop diuretics, use of thiazide diuretics, and fiscal year of cohort entry

Non-selective α -blockers include terazosin, doxazosin, and prazosin.

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