

Null Results in Brief

Use of Thiazolidinediones Does Not Affect Prostate-Specific Antigen Levels in Men with Diabetes

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Abstract

Thiazolidinediones (TZD) have been shown to down-regulate prostate-specific antigen (PSA) levels in prostate cancer cell lines and decrease PSA velocity among prostate cancer patients; however, the effect of TZDs on serum PSA levels among men with diabetes at risk for prostate cancer is unknown. We conducted a retrospective cohort study of veterans receiving care for diabetes between 1999 and 2005 to determine if TZD use affects PSA levels in veterans at risk for prostate cancer. Eligible patients were male, ≥ 45 years old, taking at least one

oral antidiabetic medication, and with two or more recorded PSA values. Patients with a prior history of prostate cancer or prostatectomy were excluded. Of the 13,791 patients included in the adjusted analysis, 2,016 (14.6%) were prescribed a TZD. No effect of cumulative TZD dose on change in PSA was detected ($P = 0.26$). Increased TZD exposure was not associated with a change in PSA, suggesting that TZD treatment for diabetes is unlikely to affect prostate cancer detection. (Cancer Epidemiol Biomarkers Prev 2009;18(6):1937–8)

Introduction

In the United States, prostate cancer is the most common malignancy in men (1). Previous studies have reported lower prostate cancer risks among men diagnosed with diabetes (2–4); however, this association may be related to detection bias as diabetic men who use antihyperglycemic medications have a lower predicted mean prostate-specific antigen (PSA) level compared with nondiabetic men [change in predicted geometric mean, -29.4% (95% confidence interval -41.7 to -14.4); $P = 0.002$; ref. 5].

Thiazolidinediones (TZD) are widely prescribed for the treatment of diabetes and target peroxisome proliferator-activated receptor- γ (6). *In vitro* studies have found that TZDs down-regulate PSA expression in human prostate cancer cells (7). A phase II trial of troglitazone in patients with prostate cancer with no symptomatic metastatic disease showed a prolongation in the stabilization of PSA levels (8). The purpose of this study was to investigate if TZD exposure changes serum PSA levels in a population of diabetic men with no known diagnosis of prostate cancer.

Materials and Methods

We conducted a retrospective cohort study of veterans with diabetes who received care in the Mid-South Veterans Integrated Service Network, which includes six healthcare systems comprised of seven medical centers and multiple community-based clinics. The Tennessee Valley Healthcare System, Veterans Affairs Medical Center Institutional Review Board approved the study.

We identified 62,510 patients who had an active prescription for any diabetes medication between October 1, 1999 and June 30, 2005. Patients were eligible for the PSA cohort if they were male, ages 45 years or older, and had at least one PSA measurement. Patients were excluded if they had a prior history of prostate cancer or prostatectomy or a PSA of ≥ 10 ng/dL. Diagnoses of prostate cancer and prostatectomy were identified through ICD-9 codes (prostate cancer codes: V10.46, 185, 233.4, 236.5; prostatectomy codes: 602.3, 60.2, 60.21, 60.29, 60.3, 60.4, 60.5, 60.6, 60.62, 60.97). Patients were censored on the date of development of prostate cancer, prostatectomy, PSA ≥ 10 ng/dL, PSA = 0 ng/dL, death, or the end of the study on December 31, 2004.

Daily TZD dose as milligrams per day was determined by multiplying the number of pills dispensed by the dose prescribed divided by the recorded days supply. Cumulative TZD dose in milligrams was calculated by summing the daily dose from the time of baseline PSA to the time of follow-up PSA. Because pioglitazone and rosiglitazone come in different tablet sizes, pioglitazone doses per day were converted to rosiglitazone equivalents in order to calculate cumulative TZD dose (9). Serum PSA measurements

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were obtained from the Veterans Affairs Medical Center laboratory files. The primary outcome was change in PSA (Δ PSA) and was calculated as the difference between the last available PSA prior to censoring (follow-up PSA) and the first available PSA (baseline PSA). Cumulative finasteride dose was calculated using the same procedures as for the calculation of cumulative TZD dose.

β -Coefficients summarizing the effect of TZD exposure on Δ PSA were calculated from a multivariate linear regression model which included adjustments for elapsed time from baseline to follow-up PSA, baseline age, body mass index, glycosylated hemoglobin A1C (A1C), race, site of clinical care, and finasteride use. We used Huber-White sandwich estimates of SE to address observed heteroscedasticity. Statistical analyses were done using STATA/SE 9.2 (Stata Corporation).

Results

Of the 62,510 diabetes patients in the source population, we identified 35,255 active male VA enrollees over the age of 45 years, without a prior prostate cancer diagnosis or participation in a TZD trial, and with an eligible baseline PSA. We further excluded 21,465 patients without an eligible follow-up PSA measurement or missing covariate data. Thus, this analysis included 13,791 patients with complete baseline characteristics, and is summarized in Table 1.

A total of 2,016 (14.6%) patients were prescribed a TZD between baseline and follow-up PSA. The median cumulative TZD dose was 1,996 mg (interquartile range, 840-3,848) and the average follow-up time was 923 days (SD \pm 378). Four hundred and fifty-eight (3.3%) men were prescribed finasteride between their baseline and follow-up PSA, with a median cumulative finasteride dose of 1,407.5 mg (IQR, 600-2,700) and average follow-up time of 978 (SD \pm 385) days. In the fully adjusted model, differences in PSA levels from baseline to follow-up were not significantly associated with daily TZD dose or cumulative TZD dose ($P = 0.25$; Table 2). In contrast, each milligram of increase in cumulative finasteride dose was associated with a significant 0.0002 ng/dL decrease in PSA levels ($P < 0.0001$). After removing patients who were ever on finasteride from the analysis, cumulative TZD dose did not have a significant effect on PSA levels ($P = 0.34$).

Discussion

In this study of men with diabetes, cumulative TZD dose was not associated with changes in PSA levels. In contrast, our study identified a significant decrease in PSA associated with finasteride use. With 2,016 TZD users, our 99% confidence interval for the effect of TZDs on

Table 1. Baseline characteristics of participants included in the cohort

	Cohort ($n = 13,791$)
PSA, ng/dL median (IQR)	0.90 (0.50-1.70)
Age, y mean (\pm SD)	63.2 (8.95)
Race, black, n (%)	1,605 (11.6)
BMI, mean (\pm SD)	31.2 (\pm 5.81)
A1C, mean percentage (\pm SD)	7.5 (\pm 1.69)

Abbreviations: BMI, body mass index in kg/m^2 ; A1C, percentage of hemoglobin A1C.

Table 2. Effect of TZD and finasteride use on change in PSA from baseline to follow-up period (mean follow-up time, 923 d)

Variable	No. of users	β -Coefficient (99% confidence interval)	P
Cumulative TZD dose	2,016	-0.000007 (-0.000022, 0.0000085)	0.26
Cumulative finasteride dose	458	-0.00021 (-0.00029, -0.00013)	<0.0001

NOTE: Model adjusted for baseline age, body mass index, race, site of clinical care, and body mass index. TZD model further adjusted for finasteride use.

PSA was very narrow (-0.000022 to 0.0000085). As such, the range of plausible values for an effect of TZD is similarly quite small. The largest plausible value, -0.000022 , is approximately one-tenth the size of the observed effect of finasteride. These confidence intervals suggest that any true effect of TZD use on PSA levels is unlikely to be larger than one-tenth that of the observed finasteride effect.

In our cohort, we found a finasteride dose of 5 mg daily for 1 year, or a cumulative dose of 1,800 mg, would result in a 0.385 ng/mL decrease in PSA. Given a baseline median PSA of 0.9 ng/dL in this cohort, this corresponds to a 43% decrease, which is consistent with the effects of finasteride on PSA levels reported in the Prostate Cancer Prevention Trial, and in other studies (10, 11). This consistency between our study and prior data regarding the effects of finasteride on PSA lends support to our conclusion that TZD use has little effect on PSA levels and is unlikely to affect prostate cancer detection.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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