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Risk of Diabetes among Patients Receiving Primary Androgen Deprivation Therapy for Clinically Localized Prostate Cancer

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Abstract

Purpose—Androgen deprivation therapy may increase diabetes risk. As the benefits of primary androgen deprivation therapy for localized prostate cancer are controversial, and most prostate cancer survivors are of advanced age with comorbidities, it is important to determine if primary androgen deprivation therapy increases the risk of diabetes and to determine the susceptibility factors.

Materials and Methods—We conducted a retrospective cohort study of 12,191 men diagnosed with incident localized prostate cancer during 1995 to 2008, age 35 to 100 years, and without diabetes or receipt of prostatectomy or radiation 1 year after diagnosis. Patients were enrolled in 1 of 3 managed health plans and followed through 2010. Primary androgen deprivation therapy was defined as androgen deprivation therapy within 1 year after diagnosis. Incident diabetes was ascertained using inpatient and outpatient diagnosis codes, diabetes medications and hemoglobin A1c values. We estimated primary androgen deprivation therapy associated diabetes risk using Cox proportional hazard models in conventional and propensity score analyses.

Results—Diabetes developed in 1,203 (9.9%) patients during followup (median 4.8 years) with incidence rates of 2.5 and 1.6 events per 100 person-years in the primary androgen deprivation therapy and nonprimary androgen deprivation therapy groups, respectively. Primary androgen deprivation therapy was associated with a 1.61-fold increased diabetes risk (95% CI 1.38–1.88). The number needed to harm was 29. The association was stronger in men age 70 or younger than in older men (HR 2.25 vs 1.40, *p* value for interaction = 0.008).

Conclusions—Primary androgen deprivation therapy may increase diabetes risk by 60% and should be used with caution when managing localized prostate cancer. Because of the consistent

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association between androgen deprivation therapy and greater diabetes risk across disease states, we recommend routine screening and lifestyle interventions to reduce the risk of diabetes in men receiving androgen deprivation therapy.

Keywords

prostatic neoplasms; androgens; diabetes mellitus; risk

Prostate cancer is the most common nonskin cancer among U.S. men, with more than 233,000 men estimated diagnosed in 2014.¹ Androgen deprivation therapy has been proven effective as neoadjuvant, concurrent or adjuvant therapy when given with radiation therapy or surgery for locally advanced disease, and is the standard palliative treatment for advanced disease.^{2–4} Since the 1990s ADT has been increasingly used as primary therapy for clinically localized disease. However, PADT for localized PCa is controversial due to the lack of proven survival benefits.^{5,6} Additionally, there is increasing evidence suggesting that ADT has serious effects, including decreased insulin sensitivity,⁷ increased fat mass,⁸ increased low-density lipoprotein cholesterol and triglycerides,⁹ and incident diabetes.^{10–12}

Three large cohort studies have reported a 7% to 44% increased risk of diabetes after ADT for local or regional PCa compared to no ADT.^{10–12} However, these studies did not specifically assess diabetes risk when ADT was used as the primary treatment in patients with localized PCa who had not received radiation or undergone prostatectomy. Because the benefits of PADT remain controversial, and the majority of PCa survivors are older and have comorbidities,¹³ it is important to understand the potential harms of PADT. This may help reduce inappropriate use of ADT in this population.

We investigated PADT associated diabetes risk in 12,191 men with clinically localized PCa. In contrast to previous studies, we studied men older than 35 years,¹⁰ ascertained incident diabetes using laboratory and antidiabetic medication data combined with standard outpatient and inpatient diagnosis codes,^{10–12} and conducted extensive subgroup analyses.

MATERIALS AND METHODS

Data Sources

As reported previously our study cohort included men diagnosed with PCa enrolled in the 3 integrated health care delivery systems within the HMO Cancer Research Network,¹⁴ including Kaiser Permanente Northern California, Kaiser Permanente Southern California and Henry Ford Health System in Detroit.¹⁵ These health plans collect comprehensive information from inpatient and outpatient diagnoses, clinical encounters, laboratory test values, pharmacy dispensaries and tumor registry data.

Study Participants

Using the TNM system of the American Joint Committee on Cancer¹⁶ we identified 53,353 men older than 35 years diagnosed from January 1, 1995 to December 31, 2008 with clinically localized PCa (no lymph node involvement or metastasis detected). We excluded men who 1) received radiation, radical prostatectomy or chemotherapy within 1 year after

PCa diagnosis (37,808); 2) underwent orchiectomy within 1 year after PCa diagnosis (as this group was too small to analyze at 117); 3) received neoadjuvant ADT at least 9 months before surgery or radiation that occurred a year after PCa diagnosis (240); 4) were missing cause and date of death or had other record errors (18); or 5) had evidence of diabetes any time from 1995 to PCa diagnosis (2,893) or 30 days after PCa diagnosis (86) to rule out men diagnosed with diabetes as part of the PCa diagnostic evaluation. The final cohort included 12,191 men (fig. 1). Patients were followed through December 31, 2010 until diabetes diagnosis or censoring due to death or disenrollment (median followup 59 months).

Primary Androgen Deprivation Therapy

ADT use was defined as any use of a gonadotropin-releasing hormone analog (eg leuprolide, goserelin or triptorelin) or gonadotropin-releasing hormone antagonist (eg abarelix or degarelix), with or without an oral antiandrogen (flutamide, bicalutamide or nilutamide) for combined androgen blockade. PADT was defined as receipt of medical ADT for localized PCa within the first 12 months of diagnosis and without receipt of radiation or radical prostatectomy. Among the 12,191 men in our cohort 2,648 (22%) received PADT and 9,543 (78%) did not receive PADT.

Diabetes

The outcome was incident diabetes, defined as the first diabetes diagnosis at least 90 days after the initial PCa diagnosis. We ascertained diabetes among men who met at least 1 of the criteria of 1) 1 inpatient primary diagnosis, 2) 2 outpatient diagnoses at least 30 days apart, 3) antidiabetic medication prescriptions and 4) at least 1 HbA1c test result greater than 7%.¹⁷ If men met more than one of these conditions, we chose the earliest recorded diagnosis date. Overall 113 diabetes events (9.4%) were ascertained from antidiabetic medications or HbA1c data. These events were not considered in previous studies that used only diagnosis codes to ascertain incident diabetes.^{10–12}

Independent Variables

We obtained patient characteristics using health plan tumor registries that operate in accordance with national registry standards and are the primary sources for data transmitted to the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) program. Covariates included age at diagnosis, race/ethnicity, year of PCa diagnosis and prior or subsequent primary cancers diagnosed other than PCa. Clinical variables included tumor stage, serum prostate specific antigen at baseline defined as the closest value within 6 months before diagnosis, and Gleason grade expressed as a summary score from the first biopsy leading to PCa diagnosis. Based on patient T-stage, prostate specific antigen and Gleason sum, we computed risk groups as low, intermediate or high based on AUA definitions.¹⁸

We also ascertained the presence of hypertension, hyperlipidemia and obesity, 3 individual health conditions strongly related to the risk of diabetes,^{19,20} between 2 years before PCa diagnosis and up to 90 days after PCa diagnosis. We required an inpatient diagnosis and/or at least 2 outpatient diagnosis codes at least 30 days apart to minimize false-positive diagnoses. Obesity was ascertained using BMI greater than 30 kg/m² when available in 32%

of the study population, or ICD-9 diagnosis within 2 years before PCa diagnosis. We also explored different models that adjusted for the presence of at least 2 or 3 of these diabetes related comorbidities.

Statistical Analysis

We compared population characteristics according to PADT use. We then plotted product-limit failure curves of diabetes incidence to assess the risk of the disease as a function of time after PCa diagnosis among men with vs without PADT use. We calculated the number of diabetes events per 100 person-years of followup (incidence rate) to compare the absolute risk of diabetes events in the PADT vs nonPADT groups. We also calculated the adjusted number needed to harm for 1 additional diabetes event in PADT vs nonPADT by obtaining the probability of diabetes in the PADT and nonPADT groups using a logistic regression with inclusion of other covariates for adjustment.

Finally, we performed Cox proportional hazard models to estimate the risk, presented as a hazard ratio, of diabetes associated with PADT use up to a maximum of 16 years after cancer diagnosis (median followup 4.9 years). Followup began with PCa diagnosis and concluded with diabetes diagnosis or censoring due to disenrollment from health plans, death or end of the study period, whichever came first. In Cox proportional hazard models a man's followup would end once diabetes developed so PADT after diabetes diagnosis would not be counted toward PADT associated diabetes risk.

We modeled PADT use as a time dependent variable (considering patients nonexposed until the start of the first prescription, and then exposed afterwards until event occurrence or 12 months after last ADT, whichever came first). Because 1,599 (17%) patients in the nonPADT group received ADT after 12 months, we adjusted for late ADT by treating it as another time dependent variable in the model to account for its effect on diabetes risk among the nonPADT group. We adjusted for patient age, race/ethnicity, year of diagnosis, cancer sequence, presence of comorbidities and health plan to account for potential confounding effects. Covariates that did not show an association with diabetes ($p > 0.05$) were removed from the final main model.

We also performed propensity score analysis using the 3 different approaches of SMR weighting, matching and inverse probability treatment effect weighting to assess the robustness of our results from conventional models.²¹ The propensity score (probability of receiving PADT) was computed using a multiple logistic regression model with patient characteristics and clinical factors as independent variables. We examined the balance of each covariate between both treatment groups after propensity score adjustment by assessing whether the standardized differences in proportions (for binary variables) or means (for continuous variables) by PADT and nonPADT groups for all covariates were less than 10%. Results of the balance check were previously reported in detail.¹⁵

We also assessed PADT associated diabetes risk in patient subgroups according to patient age at PCa diagnosis (70 or less, greater than 70, median 70), race/ethnicity (nonHispanic white, others), AUA risk groups (low, intermediate and high), and the presence of hypertension, hyperlipidemia or obesity.

RESULTS

Population Characteristics and PADT

Among 12,191 eligible patients with incident localized PCa (median age 70 years), the majority were nonHispanic white (68%), had PCa as their first cancer (92%) and were classified as having a low risk of recurrence (66%). A total of 3,741 (31%) men died during the followup period. PADT was used in 2,648 patients (22%) with a median duration of 357 days (supplementary table 1, <http://jurology.com/>). Median followup was 4.2 and 5.0 years for the PADT and nonPADT groups, respectively. Median age of patients in the PADT and nonPADT groups was 76 and 69 years, respectively. Compared with the nonPADT group, men receiving PADT tended to be older, had disease diagnosed in earlier years and had a higher risk of PCa recurrence according to AUA criteria.

Risk of Diabetes

Overall 1,203 (9.9%) patients were diagnosed with incident diabetes during the followup period of 67,647 person-years (incidence rate 1.78 per 100 person-years). We found a steadily increasing risk of diabetes during followup, with the PADT group having a consistently higher risk of diabetes than the nonPADT group (fig. 2). The incidence rate of diabetes was 2.48 and 1.61 events per 100 person-years of followup in men receiving PADT and those not receiving PADT, respectively. In adjusted analyses PADT was associated with a 1.61-fold increased risk of diabetes (HR 1.61, 95% CI 1.38–1.88, supplementary table 2, <http://jurology.com/>). The adjusted number needed to harm was 29. Other factors significantly associated with incident diabetes included ADT after 12 months from diagnosis (HR 1.79, 95% CI 1.44–2.24), hypertension (HR 1.61, 95% CI 1.43–1.82) and obesity (HR 2.10, 95% CI 1.69–2.61). When we adjusted for 2 or 3 diabetes related comorbidities, PADT associated diabetes risk estimates remained similar. We obtained similar estimates of PADT associated risk in our sensitivity analysis using 3 different methods in propensity score analysis (table 1).

In subgroup analyses we found that age at PCa diagnosis may modify PADT associated diabetes risk (HR 2.25 and 1.40 for men diagnosed with PCa at age 70 years or less vs greater than 70 years, respectively, $p = 0.008$, table 2). Although nonwhite patients and patients with hypertension, hyperlipidemia or obesity had a higher risk of diabetes, there were no statistically significant interactions between PADT and these factors when assessing the risk of diabetes after PADT ($p > 0.1$, supplementary table 2, <http://jurology.com/>). PADT associated diabetes risk remained increased regardless of risk disease group.

DISCUSSION

In this population based study we showed that PADT may increase the risk of diabetes 1.61-fold in men with clinically localized PCa and no prior diabetes who did not receive radiation or undergo radical prostatectomy. The benefits of PADT in managing clinically localized PCa remain controversial, and our findings caution against using PADT as an alternative to observational strategies or active treatment (radiation or radical prostatectomy) for localized PCa.

Physiologically ADT can change fat composition (increased fat mass, decreased lean mass) and lipid profiles (increased low-density lipoprotein, high-density lipoprotein and triglycerides) as well as increase insulin resistance.^{7,9,22} Insulin resistance, often occurring during the first few months of ADT,^{9,23} can increase the rate of hyperglycemia and result in diabetes. ADT related body changes can also exacerbate insulin resistance, resulting in diabetes.²⁴

Our findings are consistent with previous studies. A study of Medicare enrollees age 66 years or older with incident local or regional PCa reported a 1.44-fold (95% CI 1.34–1.55) increased ADT associated diabetes risk.¹⁰ Another study of veterans with local or regional PCa showed ADT to be associated with a 1.48-fold (95% CI 1.31–1.67) increased risk of diabetes.^{12,25} A cohort study of a Canadian population using administrative data showed a 1.36-fold (95% CI 1.07–1.74) increased ADT associated diabetes risk.¹¹ Our study estimate was slightly higher (HR 1.61, 95% CI 1.38–1.88) but consistent with previous studies confirming diabetes risk with ADT use across disease status.

Our finding that men diagnosed with PCa at a younger age may be more susceptible to PADT associated diabetes than men diagnosed with PCa after age 70 is consistent with another report on men older than age 65.²⁶ The observed age effect could be due to a lower baseline diabetes rate in young men, which would make the PADT associated diabetes risk appear stronger than in an older population. Additionally, it may take months or even years for ADT to induce those metabolic changes and for diabetes to develop. The observed age effect on PADT associated diabetes risk could also be because the older group had a higher mortality rate than the younger group so that followup in the older group was shorter, leading to a weaker PADT associated diabetes risk than observed in the younger group.

Our findings reinforce the need to closely monitor patient blood glucose during ADT. According to recent diabetes care guidelines published by the American Diabetes Association, screening with hemoglobin A1c, fasting blood sugars and 2-hour postprandial blood sugars should be performed at 3-year intervals among adults of any age who are overweight (BMI greater than 25 kg/m²), obese (BMI greater than 30) or older than 45 years.²⁷ Men with PCa receiving ADT may benefit from monitoring hemoglobin A1c values at baseline and at least yearly.²⁸ Additional strategies for preventing and controlling diabetes in the general population, such as exercise, healthy diet and weight loss, should be considered for men receiving ADT. Additionally, recent evidence suggests that ADT is associated with worsening diabetes control among patients with existing diabetes.²⁹ The weight of the evidence on diabetes and ADT use in patients with PCa underscores the importance of preventing and controlling diabetes in patients with PCa receiving ADT.

Some limitations in our study should be noted. This is an observational study and the results may be affected by potential selection bias of PADT use. Although selection bias cannot be completely removed from observational studies, we obtained consistent results using different propensity score analyses. Nevertheless, we could not adjust for unobserved confounders. In addition, despite using BMI data and ICD-9 codes, we likely underestimated the prevalence of obesity, which is a strong risk factor for diabetes. Due to data limitations we used 7% instead of 6.5% as the HbA1c cutoff for diabetes diagnosis, which may result in

some unclassified patients with early diabetes. Such misclassification of diabetes would likely bias toward the null, implying that the actual risk may be greater than the risk we obtained. Finally, our results may have limited generalizability to non-HMO health systems as HMO systems may promote the early prevention and detection of diabetes, reducing the occurrence of diabetes in both the PADT and nonPADT groups and, therefore, attenuating PADT associated diabetes risk.

CONCLUSIONS

PADT was associated with a higher risk of incident diabetes in patients with clinically localized PCa and should be used with caution when managing localized PCa. Although established guidelines for screening for diabetes among men on ADT do not exist, men treated with long-term ADT may benefit from diabetes monitoring at baseline and after initiating ADT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
AUA	American Urological Association
BMI	body mass index
HbA1c	hemoglobin A1c
HMO	health maintenance organization
PADT	primary androgen deprivation therapy
PCa	prostate cancer
SMR	standard mortality ratio

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Figure 1.

Flowchart of study population identification. *RP*, radical prostatectomy. *RT*, radiotherapy.

Figure 2.
Time from PCa diagnosis to incident diabetes curves by use of primary ADT within 12 months after diagnosis among 12,191 men with localized PCa without diabetes at diagnosis.

Table 1

Adjusted risk of type 2 diabetes with PADT using different analytical approaches

	HR	95% CI
Unadjusted risk estimates	1.76	1.54–2.01
Adjusted risk estimates:		
Time dependent analysis	1.61	1.38–1.88
Propensity score adjusted estimates:		
SMR weighted approach	1.59	1.34–1.90
Matching approach	1.70	1.32–2.18
Inverse probability treatment weighted approach	1.71	1.58–1.86

All values p <0.0001.

Multivariable analysis adjusted for age and year at PCa diagnosis, race/ethnicity, order of PCa diagnosis in relation to other cancer, health plan, and presence of hypertension, hyperlipidemia and obesity comorbidity up to 2 years before diagnosis.

Table 2

Stratified risk of type 2 diabetes event with PADT use

	Event No.	Event Rate (per 100 person-yrs)	HR (95% CI) *	p Value for Interaction
Age at diagnosis:				
70 or Less (6,129):				0.008
PADT	101	2.33	2.25 (1.71, 2.95)	
NonPADT	423	1.31	1.0	
Greater than 70 (6,062):				
PADT	230	2.56	1.40 (1.16, 1.70)	
NonPADT	449	2.04	1.0	
Race:				0.32
NonHispanic white (8,322):				
PADT	210	2.26	1.69 (1.39, 2.06)	
NonPADT	517	1.39	1.0	
Other race (3,869):				
PADT	121	2.98	1.49 (1.15, 1.92)	
NonPADT	355	2.08	1.0	
Hypertension:				0.17
No history (6,440):				
PADT	149	1.99	1.80 (1.42, 2.29)	
NonPADT	355	1.12	1.0	
With history (5,751):				
PADT	182	3.11	1.49 (1.21, 1.83)	
NonPADT	517	2.29	1.0	
Hyperlipidemia:				0.78
No history (8,971):				
PADT	233	2.21	1.60 (1.33, 1.93)	
NonPADT	613	1.46	1.0	
With history (3,220):				
PADT	98	3.49	1.68 (1.26, 2.25)	
NonPADT	259	2.10	1.0	
Obesity:				0.10
No history (11,063):				
PADT	298	2.40	1.71 (1.45, 2.01)	
NonPADT	791	1.55	1.0	
With history (1,128):				
PADT	33	3.60	0.93 (0.54, 1.60)	
NonPADT	81	2.50	1.0	
AUA risk:				
Low (5,466):				0.412
PADT	47	2.44	1.54 (1.00, 2.38)	

	Event No.	Event Rate (per 100 person-yrs)	HR (95% CI)*	p Value for Interaction
NonPADT	436	1.47	1.0	
Median (3,368):				
PADT	99	2.58	1.86 (1.41, 2.45)	
NonPADT	256	1.61	1.0	
High (3,357):				
PADT	185	2.44	1.47 (1.18, 1.84)	
NonPADT	180	2.04	1.0	

* Cox proportional hazard models estimating hazard ratio. Covariates adjusted included age and year at PCa diagnosis, race/ethnicity, order of PCa diagnosis in relation to other cancer, health plan, and presence of hypertension, hyperlipidemia and obesity comorbidity up to 2 years before diagnosis. Each stratified factor was not excluded from adjustment in subgroup model.