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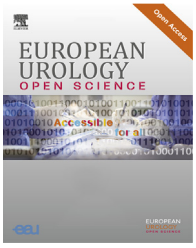

European Association of Urology

Brief Correspondence

Implications of Delayed Testosterone Recovery in Patients with Prostate Cancer

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Abstract

To assess the clinical impact of delayed testosterone recovery (TR) following the discontinuation of medical androgen deprivation therapy (ADT), a retrospective, longitudinal analysis was conducted in adult males with prostate cancer using the Optum® de-identified Electronic Health Record data set and Optum® Enriched Oncology Data (2010–2021). Of 3875 patients who initiated and discontinued ADT, 1553 received one or more testosterone-level tests within the 12 mo following discontinuation and were included in this study. These 1553 patients were categorized into two cohorts: 25% as TR (testosterone levels >280 ng/dl at any test within 12 mo following ADT discontinuation) and 75% as non-TR. At baseline, non-TR patients were older, had lower testosterone levels, and were more likely to have diabetes, hyperlipidemia, and hypertension, but less likely to have sexual dysfunction. After adjustment for baseline characteristics, the TR cohort had a lower risk of new-onset diabetes (hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.27–0.79), trended toward a lower risk of new-onset depression (HR 0.58; 95% CI 0.33–1.02), and had a higher likelihood of seeking treatment for sexual dysfunction (HR 1.33; 95% CI 0.99–1.78) versus the non-TR cohort. These findings support monitoring testosterone levels after ADT discontinuation to manage potential long-term comorbidities in patients with prostate cancer.

Patient summary: This real-world analysis of males with prostate cancer who were treated with medical androgen deprivation therapy (ADT) found that most patients did not have their testosterone level checked in the 12 mo after stopping ADT. Of those who did, 75% did not achieve normal testosterone levels (>280 ng/dl), and these patients were more likely to experience new-onset diabetes than those who achieved normal testosterone levels. These results suggest that to ensure effective clinical decision-making, physicians should check patients' testosterone levels after stopping ADT.

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Androgen deprivation therapy (ADT), the backbone of treatment for patients with advanced prostate cancer (PCa), can be achieved surgically or chemically using gonadotropin-releasing hormone (GnRH) agonists or antagonists [1]. While generally well tolerated, GnRH agonists are associated with delayed testosterone recovery (TR) after treatment cessation, prolonging the side effects of androgen deprivation and negatively impacting patients' quality of life [2]. GnRH antagonists have more frequent dosing and a different TR profile than agonists, with a median time to TR of ≤7 versus 12 mo after discontinuation of short-term (4 mo) ADT [3–5]. Given the limited data on the clinical impact of delayed TR, there is a need to compare the rates of clinical adverse event (AE) outcomes among patients with PCa who achieve or those who do not achieve TR after ADT discontinuation.

To fill this gap, a retrospective, longitudinal cohort analysis was conducted using the Optum® de-identified Electronic Health Record data set and Optum® Enriched Oncology Data between January 2010 and June 2021 for patients from the USA. Eligible males had a PCa diagnosis, initiated ADT between January 2011 and June 2020, and had one or more testosterone-level tests during ADT and another within 12 mo of ADT discontinuation. Patients with prescriptions for two or more types of ADT on the initiation date were excluded. For each patient, the baseline period was defined as the 12 mo prior to ADT initiation and the study period as the 12 mo following ADT discontinuation (Supplementary Fig. 1). Patients were categorized as having reached TR if their testosterone level was >280 ng/dl at any test during the study period (TR cohort).

Baseline characteristics were analyzed using descriptive statistics and standardized mean differences for comparisons between TR and non-TR cohorts, with differences of ≥10% indicating imbalance [6]. Differences in the median follow-up, number of testosterone-level tests, and median duration on ADT were assessed by cohort to evaluate their potential influence on surveillance-based outcomes.

The rates of AEs reported over the study period were stratified by the TR versus non-TR cohort. Outcomes were based on clinical relevance and were categorized as chronic (diabetes and depression) or acute (sexual dysfunction, hot flashes, myocardial infarction, and cerebrovascular accident). New-onset chronic conditions were defined as conditions that were not reported in the data during the baseline period and were reported in the 12 mo following ADT discontinuation. Adjusted multivariate Cox proportional hazard models estimated hazard ratios (HRs) for clinical outcomes for TR versus non-TR cohorts. Cox models were adjusted for baseline characteristics, including age category, individual comorbidities, Charlson Comorbidity Index, ADT index year, geographic region, insurance coverage, ADT type (agonist [goserelin, histrelin, leuprolide, and triptorelin] vs antagonist [degarelix]), and ADT duration.

Of 3875 patients who initiated and discontinued ADT (without switching to another ADT), 1553 (40%) had one or more testosterone-level tests available during the study period (Supplementary Fig. 1). Of the 1553 patients, 25% were categorized as TR and 75% as non-TR patients (Table 1 and Supplementary Table 1). At baseline, non-TR patients were older, had lower baseline testosterone levels, and were more likely to have diabetes, hyperlipidemia, and hypertension, but less likely to have sexual dysfunction compared with TR patients.

In the 12 mo following ADT discontinuation, the non-TR cohort had a lower median number of testosterone-level tests (1.0 vs 2.0), a shorter median time from discontinuation to last testosterone-level test (4.7 vs 7.6 mo), and lower median testosterone levels (26.0 vs 294.8 ng/dl), after being treated with ADT for a longer median duration (0.8 vs 0.5

Table 1 – Baseline[a] patient characteristics stratified by TR

	TR[b] (*n* = 390)	Non-TR[b] (*n* = 1163)
Age at initiation of ADT (yr), mean ± SD	66.8 ± 8.5[c]	70.6 ± 8.6[c]
Type of ADT, *n* (%)		
GnRH agonist[d]	370 (94.9)	1102 (94.8)
GnRH antagonist[d]	20 (5.1)	61 (5.2)
Use of concomitant therapies, *n* (%)		
First-generation nonsteroidal antiandrogen therapy[e]	172 (44.1)	543 (46.7)
Sexual dysfunction therapy[f]	55 (14.1)[c]	83 (7.1)[c]
Clinical characteristics, *n* (%)		
Cerebrovascular accident	6 (1.5)[c]	45 (3.9)[c]
Depression	23 (5.9)	77 (6.6)
Diabetes	40 (10.3)[c]	218 (18.7)[c]
Fractures	11 (2.8)	41 (3.5)
Hot flashes	<5 (<1.3)	22 (1.9)
Myocardial infarction	15 (3.8)	39 (3.4)
Osteopenia	26 (6.7)	83 (7.1)
Osteoporosis	12 (3.1)	35 (3.0)
Sexual dysfunction[g]	70 (17.9)[c]	117 (10.1)[c]
Comorbid conditions, *n* (%)		
Angina pectoris	5 (1.3)	20 (1.7)
Arrhythmia	5 (1.3)	19 (1.6)
Hyperlipidemia	146 (37.4)[c]	529 (45.5)[c]
Hypertension	165 (42.3)[c]	582 (50.0)[c]
Inflammatory bowel disease	<5 (<1.3)	8 (0.7)
Peripheral arterial disease	18 (4.6)	61 (5.2)
Modified CCI,[h] mean ± SD	0.4 ± 0.9[c]	0.6 ± 1.0[c]
Patients with available baseline testosterone test values,[i] *n* (%)	189 (48.5)	572 (49.2)
Baseline serum testosterone level (ng/dl), median (IQR)	413.0 (276.0–539.0)[c]	208.0 (26.0–341.5)[c]

ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; GnRH = gonadotropin releasing hormone; IQR = interquartile range; PCa = prostate cancer; SD = standard deviation; TR = testosterone recovery.

[a] Baseline was defined as the 365-d period prior to ADT initiation (ie, the day after the first administration of ADT on or after the first recorded PCa histology or PCa diagnosis code).

[b] TR was defined as serum testosterone levels ≥280 ng/dl in the year following ADT discontinuation.

[c] Indicates a percent standardized difference of >10%, which was considered a significant imbalance.

[d] GnRH agonists included goserelin, histrelin, leuprolide, and triptorelin; GnRH antagonists included degarelix. Relugolix was not included in the analysis because the study identification period ended in June 2020, before relugolix was approved for the treatment of advanced PCa by the U.S. Food and Drug Administration.

[e] First-generation nonsteroidal antiandrogen therapies include bicalutamide, finasteride, flutamide, and nilutamide.

[f] Sexual dysfunction therapies include avanafil, sildenafil, tadalafil, and vardenafil.

[g] Sexual dysfunction was defined as one or more diagnosis codes for sexual dysfunction or one or more documented treatments for sexual dysfunction.

[h] A version of the CCI adjusted to exclude malignancies was reported.

[i] The testosterone test value closest to the start of the baseline period was reported. Testosterone values were summarized among patients with available laboratory data.

yr), than the TR cohort (Supplementary Table 2). Most patients across both cohorts had their first testosterone-level test within 4 mo of ADT discontinuation (Supplementary Fig. 2).

Based on the adjusted Cox models, the TR cohort had a lower risk of new-onset diabetes (HR: 0.47; 95% confidence interval [CI] 0.27–0.79; Fig. 1), trended toward a lower risk of new-onset depression (HR: 0.58; 95% CI 0.33–1.02), and had a higher likelihood of seeking treatment for sexual dysfunction (HR: 1.33; 95% CI 0.99–1.78) versus the non-TR cohort. Other AE outcomes showed no evidence of differences between cohorts. Cox models adjusted for a set of demographic and clinical characteristics, including ADT duration. Each additional year of ADT duration was significantly associated with an increased risk of depression (HR: 1.47 95% CI 1.22–1.77) and a lower likelihood of seeking care for sexual dysfunction (HR: 0.76; 95% CI 0.61–0.93)

As a retrospective, longitudinal cohort analysis, study limitations included the risk of bias from unmeasured or residual confounding and the inability to assess the potential for reverse causation in patients with comorbidities that may affect TR. Additionally, missing prognostic variables, such as disease stage and baseline testosterone values, could not be adjusted for in the multivariable assessment. Not all patients had recorded testosterone values prior to ADT initiation, and among those who did, some had castrate testosterone levels ($\leq$50 ng/dl), potentially limiting the likelihood of TR [2]. Of note, the time from discontinuation to the last testosterone-level test was approximately 3 mo shorter in the non-TR cohort, indicating fewer tests later in the year than the TR cohort. Misclassification in this direction potentially yields conservative estimates of differences in clinical outcome rates. Overall, a lack of frequent testosterone testing led to the inability to precisely pinpoint TR timing.

In conclusion, the TR cohort was less likely to experience new-onset diabetes and displayed trends toward a lower rate of new-onset depression than the non-TR cohort. The TR cohort had a higher rate of seeking care for sexual dysfunction. Although this may seem counterintuitive, TR patients were younger and more likely to be on sexual dysfunction therapies at baseline than non-TR patients, which may reflect greater sexual activity and recovery of libido after TR. Additionally, most patients did not have recorded TR during the study period and those who recorded TR had few tests, with inconsistent timing. While currently available guidelines do not emphasize measuring testosterone levels after ADT discontinuation [7], these findings suggest a need for such an assessment to facilitate the identification and management of long-term comorbidities associated with hypogonadism. Effective counseling among patients with PCa includes discussion of the potential for prolonged testosterone suppression after treatment cessation.

With the expansion of ADT treatment options, including the approval of the oral GnRH antagonist relugolix [8], providers can consider clinical efficacy data such as TR during their clinical decision-making process. As testosterone deficiency may be associated with metabolic AEs and other clinical sequelae [9], further research is warranted on the factors associated with delayed TR, including the duration or type of ADT and benefits of rapid TR. This study reinforces the need for regular monitoring of testosterone levels and further exploration into how the length of ADT duration affects TR once patients with PCa have discontinued treatment.

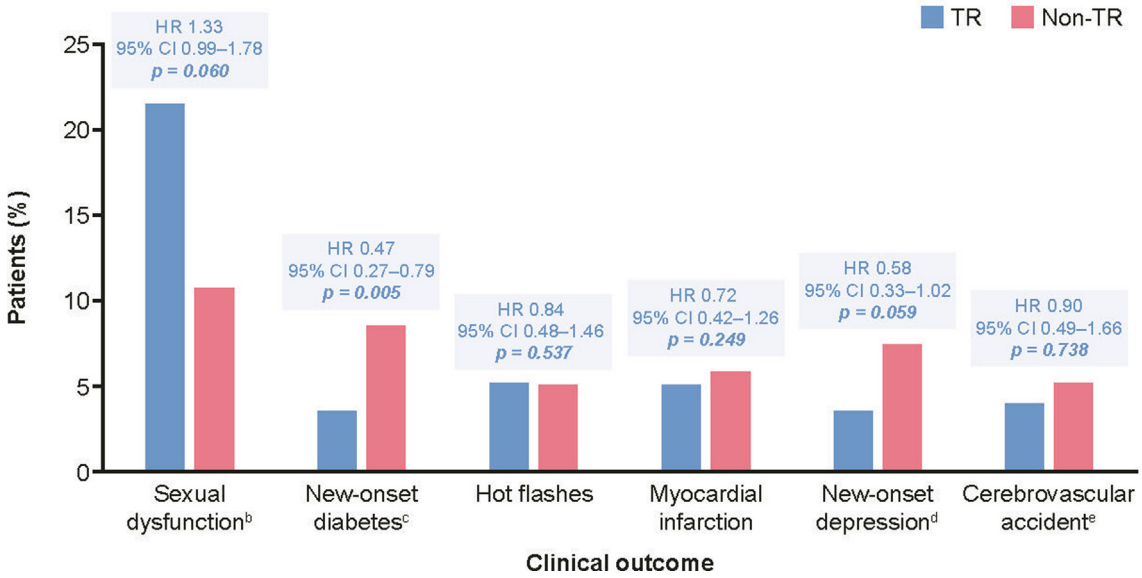

Fig. 1 – Clinical outcomes at 12 mo after ADT discontinuation with adjusted Cox analyses[a] comparing TR and non-TR cohorts. ADT = androgen deprivation therapy; CCI = Charlson Comorbidity Index; CI = confidence interval; HR = hazard ratio; ICD = International Classification of Diseases; TR = testosterone recovery. [a]Cox models adjusted for demographic characteristics including ADT treatment, length of ADT treatment, and baseline clinical characteristics, including treatment use, clinical or comorbid conditions, and CCI. [b]Defined as one or more diagnosis codes for sexual dysfunction or one or more treatments for sexual dysfunction. [c]New-onset diabetes defined based on diagnosis codes: ICD-9: 250.x; ICD-10: E10.x, E11.x, and E13.x. [d]New-onset depression defined based on diagnosis codes: ICD-9: 296.2, 296.3, 296.5, 300.4, 309.x, and 311.x; ICD-10: F20.4, F31.3x, F31.4, F31.5, F32.x, F33.x, F34.1, F42.2, and F43.2. [e]Cerebrovascular accident defined based on diagnosis codes: ICD-9: 362.3, 430.x, 431.x, 433.x1, 434.x1, 435.x, and 436.x; ICD-10: H34.1, I60.x, I61.x, I63.x, I64.x, and G45.x.

Author contributions: Mark A. Preston had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Marden, Kirson, Kongara.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
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Data sharing: As the data supporting the findings of this study were used under license for the current study, restrictions apply to the authors' ability to make data publicly available. The data used were licensed from Optum and are not publicly available. The data utilized for this study was the Optum® de-identified Electronic Health Record data set and Optum® Enriched Oncology Data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.12.003.

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