Chapter 7
Testosterone and Prostate Effects

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7.1 Introduction

Historically, testosterone (T) was thought to be involved in negative prostate events such as the growth of benign or malignant prostate tissue. This notion stems from the seminal 1941 article by Huggins and Hodges, which demonstrated that in men with metastatic prostate cancer (CaP), surgical castration led to a reduction in acid phosphatase levels, while administration of exogenous T led to an increase in these levels [1]. Our understanding has been further expanded with the concept of the saturation model, which suggests that above a certain T threshold, the androgen receptors are maximally stimulated and, thus, further increases in T levels have no additional effects on prostate cells [2]. However, at lower levels of T, prostate cells do respond to increased T levels, and changes in prostate tissue may occur. While the exact T saturation threshold in humans is not known, animal studies suggest that this is near-castrate levels and is at sub-physiologic levels in humans [2]. More recent data suggests that this total testosterone (TT) threshold is <250 ng/dL (8.67 nmol/L), although there is interindividual variability [3]. This chapter focuses on the effects of T on prostate tissues.

7.2 Prostate-Specific Antigen (PSA) Changes

Data from the Testim Registry in the US (TRiUS) nicely demonstrates the effect of T on PSA levels. This registry contains data of 451 men with testosterone deficiency (TD). These men were separated into two groups: those with TT < 250 ng/dL

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(8.67 nmol/L) ($n = 197$) and those with TT ≥ 250 ng/dL (8.67 nmol/L) ($n = 254$) [4]. At lower levels of TT, i.e., TT < 250 ng/dL (8.67 nmol/L), TT was loosely correlated with PSA ($r = 0.20$, $p = 0.005$) as was free T (FT), $r = 0.22$, $p = 0.03$. In contrast, this correlation was not seen in men with TT ≥ 250 ng/dL (8.67 nmol/L) [4]. These men were then evaluated after 12 months of T therapy (TTH). Results showed statistically significant PSA changes in men with TT < 250 ng/dL (8.67 nmol/L), with a mean increase in PSA of 0.19 ± 0.61 ng/mL (21.9%, $p = 0.02$). Those with baseline TT ≥250 ng/dL (8.67 nmol/L) experienced similar increases, although these were not statistically significant (0.28 ± 1.18 ng/mL, or 14.1%, $p = 0.06$). The highest observed PSA was within the first month of TTH followed by subsequent decline [4].

Marks et al. [5], evaluated 40 men with TD, as defined by symptoms and TT < 300 ng/dL (10.40 nmol/L). Men were randomized to intramuscular T (IMT) or placebo and were evaluated (to include prostate biopsies) at baseline and at 6 months [5]. The primary endpoint was intraprostatic T or dihydrotestosterone (DHT) levels, which were unchanged in the TTH group between baseline and 6 months ($p = 0.29$ and 0.51, respectively). However, PSA was higher after 6 months of TTH: 2.29 ng/mL (IQR 0.40–7.19) versus 1.55 ng/mL (IQR 0.30–5.80), $p < 0.001$ [5]. Similarly, when comparing the change in PSA between TTH and placebo, results were higher among TTH men at 0.90 ± 0.89 ng/mL versus 0.60 ± 1.55 ng/mL, $p = 0.008$.

Snyder et al. [6] evaluated 790 men ≥65 years old with TD, defined as TT < 275 ng/dL (9.53 nmol/L). Men were randomized 1:1 to T gel versus placebo for 1 year. At the completion of therapy, 23 TTH men were found to have PSA rises of >1 ng/ml compared to 8 in placebo (no *p*-value; study not specifically designed to compare adverse events between cohorts) [6].

Calof et al. [7] conducted a meta-analysis of 19 double-blinded placebo-controlled TTH trials with a total of 651 men on TTH and 433 on placebo. All studies included men ≥45 years old who were on TTH ≥ 90 days [7]. Results showed that "prostate events" as a whole were higher in the TTH group (OR 1.78, 95% CI 1.07–2.95). However, differences with individual prostate events, including PSA changes, were not statistically significant between the two groups. Specifically, PSA increases of >1.5 ng/mL or total PSA > 4 ng/dL occurred in 41.6 per 1000 patient-years in the placebo group versus 57.1 in the TTH group, OR 1.19 (95% CI 0.67–2.09) [7].

Arguably the strongest data on the role of TTH in PSA changes comes from the supporting text of the American Urological Association (AUA) Testosterone Deficiency guidelines [8]. A meta-analysis was performed on nine randomized control trials with a total of 2601 men. All trials compared TTH versus placebo in men with baseline TT < 350 ng/dL (12.14 nmol/L). The meta-analysis demonstrated findings that were borderline (but not statistically) significant for a mildly elevated PSA (OR 1.71, 95% CI 0.98–3.00; note that CI >1.00 is required for significance) [8].

In summary, the above data are inconclusive and somewhat contradictory. Results seem to suggest a possible effect of TTH on increasing PSA, although the overall effect is likely minor and appears to be more prominent among men with lower baseline TT levels. Larger, adequately powered series dedicated to specifically evaluating changes in PSA are required to definitively address whether TTH truly increases PSA, particularly in men with normal baseline TT levels.

7.3 Prostate Volume Changes

In Marks et al.'s [5] study of men on TTH versus placebo for 6 months, there was no change in prostate volume as measured by MRI (magnetic resonance imaging). This held true for total prostate volume [43.8 (15.5–112.0) versus 42.0 (19.8–117.9) mL; $p = 0.16$] and for the volume of the transition zone [21.8 (4.8–76.5) versus 15.4 (4.1–47.8) mL; $p = 0.58$] [5].

Liu et al. [9] also evaluated the effect of T levels on prostate volume. They evaluated 148 men aged ≥45 years old as part of a free health screening. The men underwent a transrectal ultrasound, completed the International Prostate Symptom Score (IPSS), and had PSA and T labs completed [9]. Their mean age was 59.8 years with a mean TT of 488 ± 170 ng/dL (16.64 ± 5.89 nmol/L) and FT of 8.4 ± 2.8 ng/dL (0.29 ± 0.10 nmol/L) . Results demonstrated that T did not correlate with prostate volume ($p = 0.35$ for TT and 0.45 for FT, respectively). On multivariable analysis (MVA) of predictors of prostate volume, only age was a significant predictor ($p < 0.001$) [9]. This provides further evidence that T levels do not influence prostate volume. However, it is important to note that these men had normal T levels and only a minority of patients had T levels close to the previously described saturation point.

In contrast to the above studies, Behre et al. [10] performed a study evaluating prostate volumes among men with much lower TT levels. Specifically, the authors compared 47 men with untreated TD, 78 men with TD on TTH for ≥6 months, and 75 men with normal TT levels [10]. The mean TT level for the TD group was 150 ng/dL (5.2 nmol/L) (95% CI 127–173) compared to 554 ng/dL (19.21 nmol/L) (95% CI 494–611) and 577 ng/dL (20.01 nmol/L) (95% CI 539–614) for TD on TTH and normal TT groups, respectively. Baseline prostate volumes were much lower in the TD groups at 12.2 mL (95% CI 11.0–13.5) compared to 21.3 mL (95% CI 19.9–22.8) in the TD on TTH and 22.9 mL (95% CI 21.4–24.4) in the normal T group, $p < 0.05$ [10]. A multivariable analysis of predictors of prostate volume was performed separately for each of the three patient groups. Interestingly, TT levels were only significantly associated with prostate volume in the TD group ($p = 0.006$) [10]. These findings are consistent with the previously described saturation model, in that, at lower baseline TT levels (i.e., below the saturation point), increases in TT result in concomitant increases in prostate volume.

7.4 Lower Urinary Tract Symptoms (LUTS)

LUTS can be measured subjectively, usually using a validated questionnaire called the IPSS (International Prostate Symptom Score), or objectively using a uroflow rate, which measures the strength of the urinary stream. The IPSS is adapted from the AUA Symptom Index for Benign Prostatic Hyperplasia [11] and includes seven questions for symptoms such as weak or intermittent urinary stream, frequency, urgency, and straining to urinate as well as a question on quality of life. Higher scores denote more severe symptoms. Marks et al. [5] evaluated LUTS in men after 6 months of TTH or placebo. After 6 months of TTH, when compared to baseline values, there was no change in IPSS score (13.0 [IQR 0–26.0] to 12.5 [0–30], $p = 0.43$ or with uroflow rates (14.0 [IQR 4.0–31.0] to 10.6 [IQR 4.8 to 18.9] mL/sec, $p = 0.09$ [5]. Similarly, when compared to the placebo group, there were no differences in IPSS score (+1.43 ± 8.14 versus −1.21 ± 7.74, $p = 0.30$) or uroflow rates (−3.66 ± 7.48 versus −3.44 ± 7.27 mL/sec, $p = 0.94$) among the men treated with TTH [5].

Snyder et al. [6] also demonstrated no change in LUTS based on IPSS score in men on TTH versus placebo. After 1 year of treatment, the rate of men with moderately severe LUTS (as determined by an IPSS score > 19) was similar in TTH and placebo groups (27 versus 26 men, respectively; no p-value provided) [6]. Similarly, Liu et al. [9] in their evaluation of the impact of T levels on prostate parameters found that neither TT nor FT was correlated with IPSS scores ($p = 0.26$ for TT and 0.74 for FT) [9]. In Behre et al.'s [10] study that compared prostate volume in men with untreated TD, TD on TTH for ≥6 months, and normal T, uroflow was also compared, with no differences observed among cohorts [10]. Thus, these studies all suggest no role of T in LUTS.

While the Calof et al.'s meta-analysis noted a higher rate of prostate events in the TTH men overall (OR 1.78, 95% CI 1.07–2.95), this did not hold true when evaluating specific prostate events [7]. For example, IPSS increases were similar (2.8 per 1000 patient-years in placebo versus 5.5 in TTH, OR 1.08 (95% CI 0.46–2.52). Episodes of acute urinary retention were also equivalent (0 in placebo versus 2.2 per 1000 patient-years in TTH group, OR 0.99, 95% CI 0.40–2.44) [7]. It is thought that this can be explained by the fact that statistically these calculations assume that there is only one prosate event (if any) per each individual man and not that one man has multiple prostate events. In actuality, each prostate event probably occurs in the same men. For example, a man with acute retention is likely to have an increase in IPSS score as well. This explains why individual prostate events are not higher but prostate events as a whole are [7].

7.5 Prostate Cancer (CaP) Development

Arguably the biggest historical concern regarding TTH is the risk of CaP development or progression. This notion is based on the observations that CaP is a testosterone-dependent event, with data from eunuchs and men with congenital

5-alpha reductase deficiency demonstrating no or reduced development of prostate cancer compared to the general population [12, 13]. In relation to hypogonadal men with existing prostate cancer, data from Huggins and Hodges suggested that TTH may exacerbate progression of the disease, while castration improved symptoms [1]. These findings are further supported by numerous studies which have confirmed a role for chemical/surgical castration in the management of advanced CaP. However, current data suggests that TTH does not increase CaP risk in men with low T and without an existing diagnosis of prostate cancer. Snyder et al. [6] evaluated almost 800 men randomized to placebo versus TTH for 1 year. During the study period, only one man in the TTH group and no one in the placebo group were diagnosed with CaP. In the year after the study, only two TTH men and one placebo patient were diagnosed, suggesting low rates in both patient populations and highlighting a need for longer-term follow-up to truly evaluate the risks for prostate cancer development and progression [6].

Muller et al. [14] analyzed the placebo arm of the REDUCE trial, wherein all participants underwent a prostate biopsy regardless of PSA levels [14]. All men were 50–75 years old with a prior negative biopsy and a baseline PSA between 2.5 and 10 ng/mL. A total of 3255 men in the placebo arm had a repeat biopsy during the trial and were included in this current study. TD was defined as <288 ng/dL (10 nmol/L). Overall, 25.2% of men were diagnosed with CaP, and these rates were similar in men with TD (25.5%) compared to normal T (25.1%), $p = 0.831$ [14]. On secondary analysis, results showed that higher T levels were associated with higher CaP rates only in men with TD (OR 1.23, 95% CI 1.06–1.43; $p = 0.006$). In men with normal baseline T levels, there was no association between T levels and CaP risk ($p = 0.33$) [14]. This supports the saturation model, as once the androgen receptors are maximally stimulated, there is no additional risk of prostate cancer with further addition of T.

In the 2005 meta-analysis by Calof et al., a higher rate of prostate biopsies and prostate cancer was noted among TTH men compared to placebo; however, these were not statistically significant. Specifically, prostate biopsies during the study period occurred in 2.8 per 1000 patient-years in placebo compared to 38.7 in the TTH group. The overall odds ratio was 1.87 (95% CI 0.84–4.15) [7]. Similarly, prostate cancer diagnosis was in 8.3 per 1000 patient-years in placebo and 9.2 in TTH, OR 1.09 (95% CI 0.48–2.49) [7].

The AUA Testosterone Deficiency guidelines also addressed the risk of CaP in men on TTH. A meta-analysis of 10 randomized control trials (RCT) with 2508 men was conducted. All trials compared men with TD (defined as T < 350 ng/dL or 12.14 nmol/L) who were on TTH ($n = 1372$) versus placebo ($n = 1136$). Results demonstrated that 10 TTH patients and 9 placebo patients developed CaP, demonstrating an insignificant increased risk in CaP in men on TTH (OR 1.0, 95% CI 0.36–2.8) [8].

In addition to the lack of evidence that TTH increases the risk for prostate cancer (among men with T levels above the saturation level), there are also data that indicate that increased T levels are not associated with higher grades of prostate cancer. In a series of 431 men who had TT levels obtained pre-radical prostatectomy (RP),

men with Gleason 4 predominant cancer had lower overall TT levels compared to those with Gleason 3 predominance (400 versus 450 ng/dL or 12.87 versus 15.60 nmol/L, $p = 0.001$) [15]. Similarly, TD (defined as TT < 300 ng/dL or 10.40 nmol/L) was higher in Gleason 4 predominant men compared to Gleason 3 (22.9 versus 11.4%, $p = 0.002$). The inverse was also true. When comparing men with TD ($n = 62$) to normal T ($n = 369$), Gleason 4 patterns were more common in the TD group (47% versus 28%, $p = 0.003$). On multivariable analysis (MVA), TD was a predictor of Gleason 4 predominant CaP (OR 1.87, 95% CI 1.105–3.169, $p = 0.02$) [15]. Overall results suggest that TTH is not a risk factor for CaP, and T deficiency is associated with more aggressive cancer.

A smaller study found a correlation between low FT and more aggressive CaP. Hoffman et al. evaluated 117 men with CaP. TD was defined as a TT ≤ 300 ng/dL (10.40 nmol/L) or FT ≤ 1.5 ng/dL (0.05 nmol/L) [16]. Men with low FT (but not low TT) had a greater percentage of positive biopsy cores (43% in men with low FT versus 22% in men with normal FT, $p = 0.013$). Interestingly, all men in the study with Gleason ≥8 had low FT. Of the men with low FT, 11% had Gleason ≥8 disease compared to 0% in the men with normal T, $p = 0.025$ [16].

Similar findings were seen in a larger series of 937 men post-RP. In this study, they compared Gleason scores in biopsy versus RP specimen. TD was defined as TT < 300 ng/dL (10.40 nmol/L). On RP, Gleason 4 predominance was higher in the TD group at 41.7% versus 29.1% in the normal T group, $p = 0.0029$ [17]. Men with TD were also more likely to have an upgrade in Gleason score between biopsy and RP. Nearly 20.1% of men with TD were upgraded from Gleason 3 to 4 predominance compared to 11.6% of men in the normal T group, $p = 0.002$. Interestingly, the PSA levels were the same in men with TD versus normal T (PSA 8.5 ± 5.3 ng/mL versus 8.5 ± 5.5, $p = 0.72$) [17]. This is an important point, as the conventional thinking is that more aggressive CaP is seen in men with TD as their PSA is lower and falsely reassuring, which leads to a delay in diagnosis. However, this data demonstrating similar PSA levels in men with and without TD suggests an alternative mechanism for more aggressive CaP in these men.

Data also suggests higher positive margin status in men with TD. Teloken et al. [18] noted that men with TD are more likely to have positive surgical margins after RP [18]. In their study of 64 men who underwent RP, TD was defined as TT < 270 ng/dL (9.36 nmol/L). Men with TD had higher rates of positive margins (39% versus 14.6%, $p = 0.026$). When comparing T levels of men with positive versus negative margins, they found lower T levels in the men with positive margins: 284.7 ± 145.1 ng/dL (9.87 ± 5.03 nmol/L) versus 385.7 ± 205.2 (13.37 ± 7.11 nmol/L); no p-value provided [18]. However, there was no difference between men with TD and normal T in the other pathological variables such as extracapsular extension (20.3% versus 26.6%, $p = 0.25$) or seminal vesicle involvement (3.1% versus 4.7%, $p = 0.84$). The rates of men with low (≤6) versus high (≥7) Gleason scores were also similar between men with TD and normal T ($p = 0.56$ at biopsy and 0.88 on RP specimen). Similarly, distribution of pathologic stages (pT1 and pT2 versus pT3 and pT4) was the same between men with TD and normal T ($p = 0.14$) (Table 7.1) [18].

In contrast, Kim et al. [19] noted an increased risk of extracapsular extension (ECE) and biochemical recurrence (BCR) in men with TD [19]. They evaluated 60

Table 7.1 Prostate events and recommendations

Prostate events	Synthesis of available evidence	Recommendations
PSA changes	Small PSA increases can be expected after starting TTH, especially for men with lower T levels below the saturation point	Assess PSA 2–4 weeks after starting TTH. Counsel patients to expect a PSA increase initially, especially when their T is below saturation threshold
Prostate volume changes	T levels are not correlated with prostate volume unless T is below the saturation threshold. TTH does not appear to increase prostate volume overall	Counsel patients that TTH should not impact prostate volume unless they have very low baseline T levels
LUTS	There is no evidence that TTH increase LUTS as measured by IPSS or uroflow	Reassure patients that TTH should not impact their urinary function
CaP development	Current data suggests that men receiving TTH do not have an increased risk of CaP development. Data suggests that men with TD can have more aggressive CaP	Discuss with patients that while TTH is not associated with increased risk of CaP, some evidence suggests that TD is associated with more aggressive CaP

men post-RP; 21 had TD, defined as <300 ng/dL (10.4 nmol/L) and 39 had normal T. ECE was higher in the TD group at 61.9% versus 28.2% in men with normal T ($p = 0.011$). BCR was also higher in the TD group at 23.8% compared to 5.1% in men with normal T ($p = 0.032$). On MVA of ECE, TD was a significant risk factor (OR 4.96, 95% CI 1.41–17.38, $p = 0.012$). Similarly, TD was also identified as a predictor of BCR on MVA (OR 13.64, 95% CI 1.66–2.43, $p = 0.015$) [19].

In the analysis by Muller et al. [14] of the placebo arm of the REDUCE trial, the authors did not find a link between T levels and CaP aggressiveness. The men in this study who were diagnosed with CaP were categorized into three Gleason categories: ≤6, 7, and ≥8. The median T levels in each group were similar ($p = 0.72$), suggesting that TD is not associated with higher Gleason scores [14]. On MVA of high-risk CaP, there was no association between T levels (as quintiles) and high risk CaP ($p \geq 0.1$ for all) [14]. While these findings seem to contradict the consensus in the literature, the study design may explain this. In this trial, these men were only included if they had a negative biopsy at baseline. They then underwent repeat biopsies at years 2 and 4 of the study regardless of PSA levels [14]. In contrast, most of the other studies specifically look at men diagnosed with CaP and then evaluate their T levels.

7.6 Conclusion

In summary, the role of T and prostate events, such as increased PSA, prostate volume, LUTS, or CaP, is variably defined, with relatively limited, short-term studies with small patient numbers available. Overall, there is a minor association with PSA

levels and T in most men. As explained by the saturation model, PSA and T levels are most strongly correlated at T levels below the saturation threshold. Beyond the saturation point, the correlation between T and PSA is less pronounced and remains debatable. Similarly, prostate volume does not correlate with T levels beyond the saturation point, and there are no data to suggest an association with LUTS and T levels. With regard to CaP, the literature does not support a link between TTH and CaP risk, particularly among men with baseline levels beyond the saturation point. In contrast, TD seems to be associated with higher risk of CaP and higher grade and/or pathologic features compared to men with normal T. Thus, the currently available data suggests that TTH does not increase the risk for prostate cancer among men who do not have any evidence for existing prostate cancer.

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