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Review – Prostate Cancer

Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

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Abstract

Context: The traditional belief that prostate cancer (PCa) growth is dependent on serum testosterone (T) level has been challenged by recent negative studies in noncastrated men.
Objective: To provide an improved framework for understanding the relationship of PCa to serum T level that is consistent with current evidence and is based on established biochemical principles of androgen action within the prostate.
Evidence acquisition: A literature search was performed of publications dating from 1941 to 2008 that addressed experimental and clinical effects of androgens on prostate growth. Review of studies investigating the prostatic effects of manipulation of androgen concentrations in human and animal studies, and in PCa cell lines.
Evidence synthesis: Prostate growth is exquisitely sensitive to variations in androgen concentrations at very low concentrations, but becomes insensitive to changes in androgen concentrations at higher levels. This pattern is consistent with the observation that androgens exert their prostatic effects primarily via binding to the androgen receptor (AR), and that maximal androgen-AR binding is achieved at serum T concentrations well below the physiologic range. A Saturation Model is proposed that accounts for the seemingly contradictory results in human PCa studies. Changes in serum T concentrations below the point of maximal androgen-AR binding will elicit substantial changes in PCa growth, as seen with castration, or with T administration to previously castrated men. In contrast, once maximal androgen-AR binding is reached the presence of additional androgen produces little further effect.
Conclusions: The evidence clearly indicates that there is a limit to the ability of androgens to stimulate PCa growth. A Saturation Model based on androgen-AR binding provides a satisfactory conceptual framework to account for the dramatic effects seen with castration as well as the minor impact of T administration in noncastrated men.

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1. Introduction

For >65 yr, it has been widely accepted that prostate cancer (PCa) growth is dependent on serum testosterone (T) concentrations, based on experiments by Huggins et al [1,2] that castration caused PCa regression, whereas T administration caused more rapid PCa growth. Yet recent studies have shown little or no relationship between serum T concentrations and PCa [3], making the long-held belief in a T-dependent model of PCa problematic, if not untenable [4,5]. We present here a simple yet critical refinement to the traditional view of T and PCa, namely, that there is a limit to the ability of T to stimulate PCa growth. The Saturation Model presented below is founded on basic biochemical principles of androgen action within the prostate, and it provides a robust framework for understanding the seemingly contradictory sets of results seen with T manipulation.

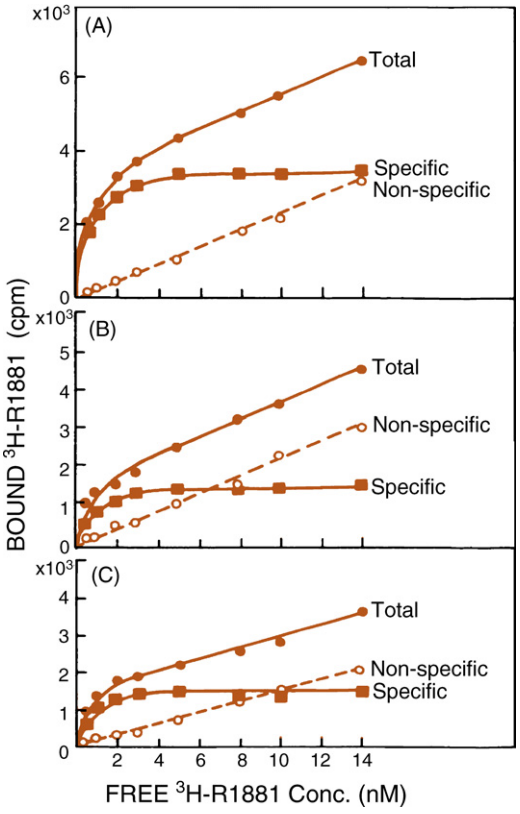

Fig. 1 – Binding of the synthetic androgen [3H]R1881 to the androgen receptor in Noble rat ventral (panel A), dorsolateral (panel B) and anterior (panel C) prostate. Cytosol extracts from castrated Noble rat prostates were incubated at 40 °C for 24 h with increasing concentrations of the synthetic androgen [3H]R1881, in the absence (total binding) or presence (nonspecific binding) of a 100-fold molar excess of unlabeled R1881. Specific binding to androgen receptor (AR; solid squares) is calculated by subtraction of nonspecific binding (open circles) from total binding (solid circles). Note that specific androgen binding to AR reaches a maximum at low androgen concentrations (2–3 nM, roughly 60–90 ng/dl) in all three prostate lobes without further binding over a wide range of increasing concentrations of [3H]R1881. The choice of [3H]R1881 as a ligand for the binding assay for androgen receptor is due to its high affinity for AR and low affinity for nonspecific plasma proteins, including sex hormone–binding globulin.
Reprinted with permission from the American Society of Andrology [45].

Defining the relationship between T and PCa is of considerable importance. Not only is androgen deprivation a mainstay of treatment for advanced PCa, but there is also growing interest in T therapy for hypogonadism. Although T therapy has been shown to improve sexual function, bone density, and body composition [6], none of these benefits might be worthwhile if T therapy increased the risk of PCa.

The Saturation Model has been introduced previously [7]; in this paper, we present the model in full, together with supporting evidence from human and laboratory studies. In brief, the Saturation Model accounts for the key observation that PCa growth is exquisitely sensitive to variation in serum T concentrations at or below the near-castrate range and is insensitive to T variations above this concentration. This model postulates that physiologic concentrations of T provide an excess of T and its intracellular prostatic metabolite, 5α-dihydrotestosterone (DHT), for optimal prostatic growth requirements. However, reducing T concentration below a critical concentration threshold (the Saturation Point) creates an intracellular milieu in which the availability of androgen becomes the rate-limiting step governing prostate tissue growth. This model is based on evidence that binding of androgen to the androgen receptor (AR) follows a similar saturation curve. We believe this simple model has important ramifications for clinical medicine and basic science research.

2. Evidence acquisition

2.1. *Androgen receptor binding*

It is well-recognized that prostate tissue growth and function are modulated by androgens via specific interactions with the androgen receptor (AR). Metabolic transformation of T into DHT and subsequent interaction with AR initiates a cascade of signaling pathways, which involves recruitment of AR coactivators, leading to increased gene expres-

sion and regulation of cellular metabolism and cell growth.

The binding of DHT to AR is characterized by high degree of stereospecificity, high affinity, and limited capacity due to the presence of a finite number of binding sites per cell. Data from binding studies in rat, dog, and human prostate tissues have demonstrated that AR binds its ligand with Kd approximating 0.3–0.5 nM, as assessed by Scatchard plot analyses [8,9]. Binding of androgen to AR demonstrates a saturation curve, with a steep increase in binding seen with increasing androgen concentration up to a plateau, representing maximal binding due to filling of all binding sites. Further increases in androgen concentration do not result in any further binding to AR (Fig. 1).

Since the primary actions of androgen on prostate tissue occur via binding to AR, it follows that once AR is saturated the presence of higher androgen concentrations should not elicit any further biochemical response. This saturation phenomenon appears to be common to other systems in which steroid hormones exert a trophic or proliferative influence via binding to specific receptors, such as estrogen receptors in the uterus [10] and aldosterone receptors in the bladder [11].

2.2. *Studies in animal models*

A number of animal models have been used to investigate the effects of androgen action in the prostate. A common finding in most of these studies is demonstration of a T-dependent phase of cellular proliferation at low T concentrations or DHT concentrations followed by a lack of further cellular proliferation at higher androgen concentrations (quiescence). This biphasic curve is consistent with the saturation of AR at relatively low androgen concentrations.

2.2.1. *Effects of testosterone administration on prostate growth in castrated animals*

Wright et al [12] examined the effects of varying doses of T on prostate regrowth in the castrated 55-d-old Sprague-Dawley rat. After castration, prostates were allowed to regress for 14 d, followed by T administration at various doses that produced serum T concentrations ranging from castrate (6.4 ng/dl) to the supraphysiologic range for the rat (500 ng/dl). Mean serum T was 286 ng/dl in intact animals. Total prostate wet weight, DNA content, and secretory activity all increased steeply with increasing serum T concentration for the lowest T doses, and then reached a plateau at higher T doses. The half-maximal response for all three measures occurred at serum T concentrations in the near-castrate range of $\leq$36 ng/dl, corresponding to a human concentration of approximately 50 ng/dl (Fig. 2).

2.2.2. *Effects of testosterone administration on prostate growth in intact animals*

Varying doses of T were administered to intact Sprague-Dawley rats (250–300 g body weight), and

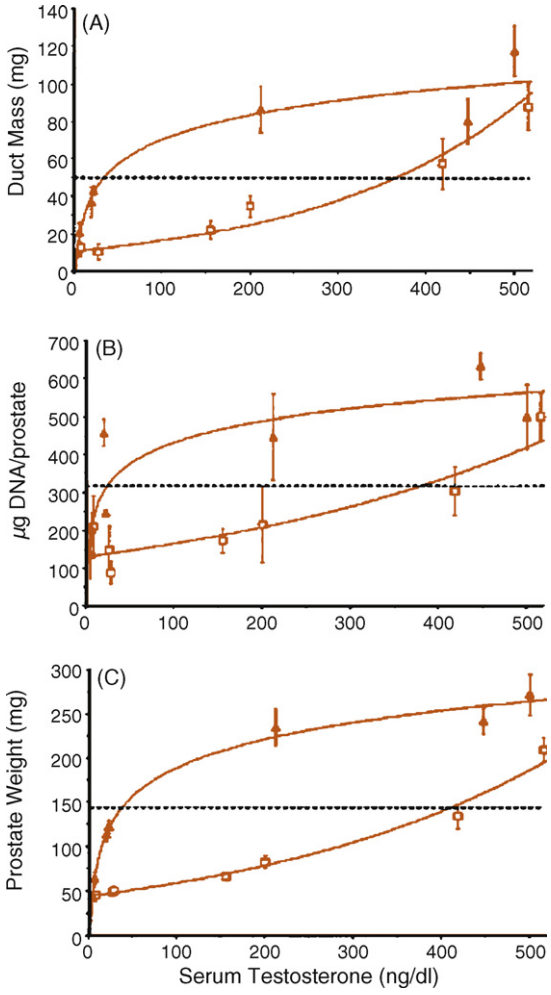

Fig. 2 – Prostate regrowth following castration as a function of serum testosterone (T) in the rat. The upper curves (solid triangles) represent prostate growth in animals implanted with T. A steep initial rise is seen at very low T concentrations, followed by minimal further rise over a wide range of increasing T concentrations. Note that a straight, horizontal line can be drawn through most T values >50 ng/dl, suggesting saturation with regard to serum T. The lower curve, marked by open squares, represents animals treated additionally with finasteride. No saturation is noted, as prostate growth correlates with T concentration when intracellular 5α-dihydrotestosterone (DHT) is at castrate levels.
Reprinted with permission from the Endocrine Society [12].

the animals were sacrificed 3 mo later. Prostate weight rose with increasing serum T concentration at lower T doses, but then reached a plateau at higher doses, without additional growth noted [13].

Banerjee et al [14] found similar results in Brown Norway intact male rats. Rats of different ages were implanted with T at varying doses. A growth response was observed for rats of all ages; growth increased with rising T concentrations until a plateau was reached, with no additional difference in growth observed with increasing T concentrations beyond that point.

Analogous results were obtained with DHT administration in intact animals. Berry and Isaacs [15] showed that prostate size in rats treated with exogenous DHT for as long as 650 d did not increase beyond the maximal size reached in untreated control rats at 365 d of age.

2.3. *Effects of androgen concentrations on in vitro prostate cancer models*

In vitro experiments with the androgen-responsive PCa tumor cell line, LnCaP, demonstrated saturation kinetics or even inhibitory responses to increasing concentrations of T or of DHT. In one set of experiments by Bologna et al [16], the growth rate and cell doubling time were enhanced only at the lowest tested concentrations of T and of DHT (0.001 μM), with higher concentrations resulting in nonsignificant growth inhibition.

Arnold et al [17] found similar results in vitro with the LnCaP model. Cell proliferation increased progressively with rising T concentrations at low concentrations, and then reached a plateau with no greater response despite logarithmically increased T concentrations. A dose response curve for prostate-specific antigen (PSA) expression revealed T-dependent expression at low concentrations followed by a T-independent portion of the curve at T concentrations ranging from 0.1 nM to 10 000 nM.

2.4. *Human studies*

Below, we review human studies to determine whether previously contradictory results may now be better understood via the prism of androgen-AR binding and the Saturation Model. This model predicts that a steep T concentration–dependent relationship will be seen at the lower end of the T concentration range, whereas at higher T concentrations there will be little or no further effect. Note that values of 300–1000 ng/dl, or approximately 10–35 nM (nmol/l), are commonly used reference values for normal serum T in humans [18].

2.4.1. *Effect of reducing testosterone to castrate levels in men without prostate cancer*

Weber et al treated seven patients with a mean age of 67 yr with the luteinizing hormone-releasing hormone (LHRH) agonist nafarelin for 6 mo, followed by a 6-mo recovery period [19]. Serum T concentration decreased from a mean of 435 ng/dl to < 50 ng/dl for all patients, and then recovered to 482 ng/dl at 12 mo. PSA level declined in all men, from a baseline mean of 2.95 ng/ml to a nadir of 0.5 ng/ml at 6 mo, followed by recovery at 12 mo to 2.98 ng/ml. PSA level correlated significantly with T concentration during both treatment and follow-up. Prostate volume decreased from 50 cm^3 to 37 cm^3 at 6 mo, followed by recovery to 47 cm^3. The rise in PSA level from a T-deficient to a T-replete state represented an increase of approximately 600%.

Page et al treated a small group of men with the short-acting LHRH antagonist acyline [20]. At day 28 mean T concentrations were in the castrate range and mean PSA level had declined from a baseline of 0.8 ng/ml to 0.3 ng/ml. PSA level recovered to 0.8 ng/ml upon recovery 28 d later, representing an increase of 267% from T-deficient to T-replete states. Prostate volume did not change in this short study.

The 5α-reductase inhibitors finasteride and dutasteride are used clinically to treat symptoms of benign prostatic hyperplasia (BPH). These medications provide a selective form of androgen deprivation by severely reducing intracellular concentrations of DHT. Review of multiple studies reveals a median decrease in PSA level of approximately 50%, and a decline in prostate volume by one-third with 5α-reductase inhibitors used for 3–12 mo [21]. Discontinuation of treatment results in restoration of baseline PSA, representing an increase of approximately 100%.

These results demonstrate that in men without PCa, reducing serum T concentration or intraprostatic DHT concentration to castrate levels produces substantial, consistent, and rapid decreases in PSA levels and, to a lesser degree, prostate volume. Conversely, the change from castrate to normal androgen concentrations is associated with similar substantial changes, with PSA-level increases of several hundred percent. Effects on PSA level are milder but still substantial with drug treatment that lowers intracellular DHT but not T. These results indicate a powerful effect of androgen concentrations on prostate tissue within the castrate or near-castrate range.

2.4.2. *Effect of endogenous testosterone concentration on prostate-specific antigen*

Monath et al investigated the relationship of endogenous T concentration on PSA level in a study of 150 men without prostate cancer [22]. The mean age was 60.1 yr, with a range of 41–79 yr. Mean PSA level was 2.0 ng/ml, and mean serum T concentration was 458 ng/dl, with 96% reported to have T concentrations within the normal range. The results revealed no correlation between T concentration and PSA level ($r = 0.054$, $p = 0.515$). A much larger sample of men ($n = 1576$) from the Massachusetts Male Aging Study also found no correlation between PSA level and T concentration [23]. Variation in endogenous T concentrations within the physiologic range does not appear to influence PSA levels.

2.4.3. *Effect of testosterone administration in eugonadal men*

Cooper et al [24] randomized 31 healthy men with an average age of 28 yr to weekly T injections of 100 mg, 250 mg, or 500 mg. Supraphysiologic T concentrations of 1138 ng/dl and 1994 ng/dl were noted for the 250-mg and 500-mg groups, respectively. No significant changes in PSA level or prostate volume were noted in any group over the 40-wk study period. In another study, Bhasin et al [25] administered 600 mg T or placebo weekly for 10 wk to men ranging in age from 19 yr to 40 yr. Treated men developed supraphysiologic T concentrations greater than 2800 ng/dl. However, PSA levels did not change from baseline.

Nair et al [26] treated 27 men with a T patch, and 31 men received placebo. No difference in PSA values were noted between the treated group and the placebo group at the end of 24 mo. Recently, Emmelot-Vonk et al [27] reported results of a 6-mo clinical trial in 207 older eugonadal men randomized to oral T undecanoate or placebo. End-of-study changes in PSA levels were not different between the treated and placebo groups.

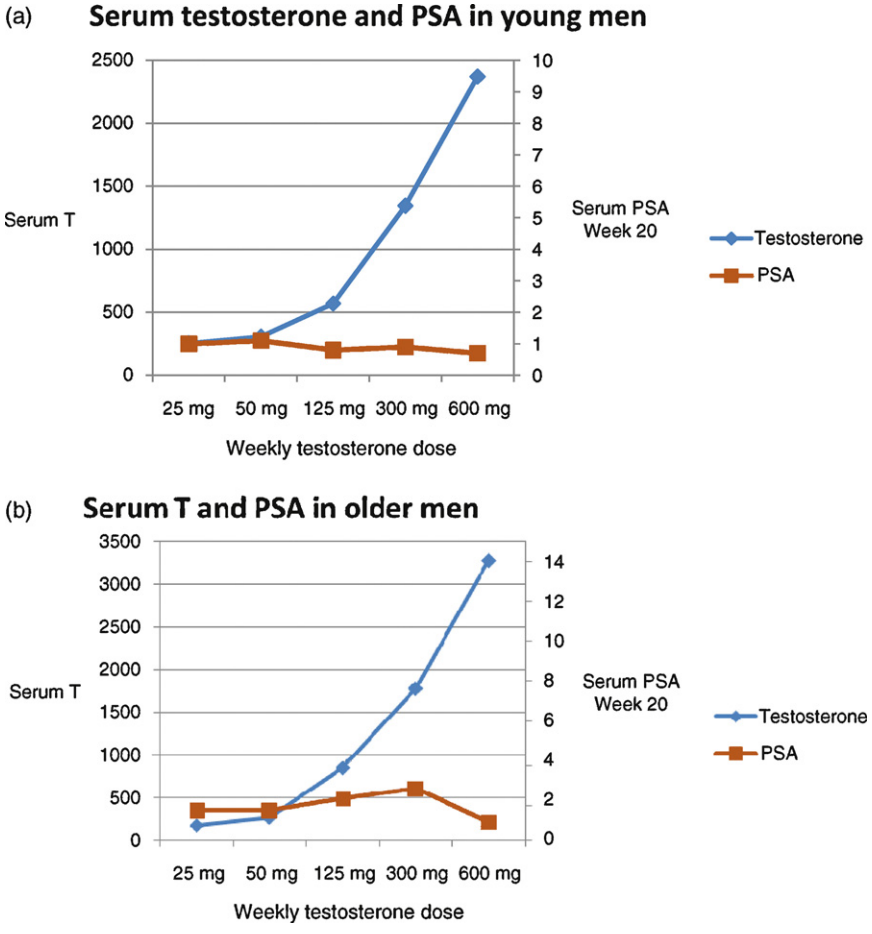

Fig. 3 – Effect of serum testosterone (T) on serum prostate-specific antigen (PSA) level in (a) young men and (b) older healthy men. Men underwent suppression of endogenous T via luteinizing hormone-releasing hormone (LHRH) agonist followed by weekly T injections for 20 wk at doses ranging from 25 mg to 600 mg. Serum T values were measured at week 16, and serum PSA values were measured at week 20. No significant increase in serum PSA level was seen, even among men exposed to supraphysiologic T concentrations for >4 mo.
Adapted from Bhasin et al [28] and Bhasin et al [29].

A sophisticated study design to create relatively defined T concentrations was used by Bhasin et al [28]. Fifty-four healthy young men, aged 18–35 yr, were randomized to five treatment groups at various T doses after suppression of endogenous T production with a long-acting LHRH agonist. Serum T concentrations ranged from the hypogonadal to the supraphysiologic range, yet there was no difference in PSA values at week 20 between groups (Fig. 3a). A similar study [29] in older eugonadal men aged 60–75 yr also showed no difference in PSA levels despite T concentrations rising well into the supraphysiologic range for men receiving the highest T doses (Fig. 3b). These results convincingly demonstrate that variation of serum T concentrations changes in the near-physiologic to supraphysiologic range appears to have no effect on the prostate, as measured by prostate volume or the androgen-dependent protein marker, PSA.

2.4.4. *Effect of testosterone administration in hypogonadal men*

One of the largest controlled studies of T therapy in hypogonadal men [30] involved 406 men randomized to 90 d of treatment with either placebo, one of two doses of T gel, or T patch. Mean PSA level increased in the treated groups by 17%, but was not significantly different from placebo. A meta-analysis of 19 controlled studies by Calof et al [31] found no greater proportion of adverse prostate outcomes, such as elevations in PSA level or development of PCa, in men treated with T compared with placebo.

Dean et al studied 371 hypogonadal men with a mean age of 58.5 yr who received T gel for 12 mo. PSA levels increased 30% at 3 mo from a baseline of 1.26 ng/ml, without any further changes over the remaining 9 mo of the study [32]. Wang et al reported results from a long-term study of T therapy in 163 hypogonadal men (mean age, 51 yr) treated with T gel for 42 mo [6]. Mean PSA increased from 0.85 ng/ml at baseline to 1.11 ng/ml at the first assessment at 6 mo (30% increase), without further increase over the remaining 3 yr. These uncontrolled studies compare with a 12-mo increase in PSA level of 13% found in the control arm of an unrelated study of men aged 50–60 yr [33].

In a retrospective review of 58 men who underwent 12 mo of T therapy, the mean increase in PSA level was 17% over baseline (1.83 ng/ml to 2.14 ng/ml). However, the response of PSA level to T therapy was quite variable, since 43% of the group failed to demonstrate any increase in PSA level at all, including 20% whose PSA level declined [34].

Several studies of T therapy in hypogonadal men have shown no changes in measures related to BPH, such as symptom scores, urinary flow, or residual urine volumes [35]. T therapy in hypogonadal men appears to produce limited or no change in prostate measures. When present, the magnitude of the changes in measures such as PSA level is a fraction of what is seen with T repletion from castrate T concentrations.

2.4.5. *Effect of lowering testosterone in men with prostate cancer*

Kuhn et al randomized 36 men with disseminated PCa to the LHRH agonist buserelin with or without an antiandrogen [36]. Baseline mean PSA levels were >500 ng/ml in both groups. By day 29 PSA levels had declined by over 70% in both groups. A study of the

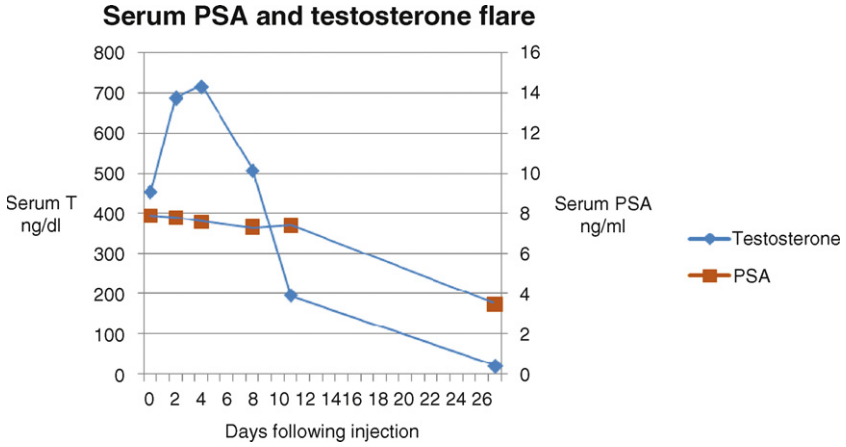

Fig. 4 – Serum prostate-specific antigen (PSA) level is unchanged during testosterone (T) flare. Men with stage D prostate cancer were treated with luteinizing hormone-releasing hormone (LHRH) agonists and T, and PSA levels were determined on selected days following injection. Despite an increase in serum T of approximately 50% over baseline, no increase in PSA level was seen.
Adapted from Tomera et al [38].

LHRH antagonist abarelix in men with Stage D PCa [37] resulted in a 90% reduction in PSA. Reducing T to castrate levels in men with PCa produces large changes in PSA levels within 1 mo.

2.4.6. *Effect of testosterone flare on prostate-specific antigen in men with prostate cancer*

Two studies [36,38] that reported PSA results during the T flare in men with Stage D PCa revealed no increase in PSA level above baseline (Fig. 4). In both studies, LHRH agonists produced a transient T-concentration increase of approximately 50–80%, lasting 5–8 d. The effect of a longer duration of increased T concentration on PSA level in this population is unknown.

2.4.7. *Effect of testosterone administration in men with untreated prostate cancer*

A number of older studies investigated the effect of T administration in men with advanced, untreated PCa, including the original reports by Huggins et al in 1941 [1,2]. Although these authors reported that daily T injections for 11 d to 18 d ''activated'' PCa [2] based on clinical deterioration or a rise in acid phosphatase, it has not been widely recognized that all but one of these men had already been castrated [4].

This distinction between prior castration and no prior hormonal treatment is critical. Data from a 1981 review from the Memorial Sloan-Kettering Cancer Center [39] revealed that 44 of 48 men with castrate T concentrations developed a rapid ''unfavorable response'' to daily T injections, most within 1 mo. In contrast, three of four previously untreated men had no early negative response to T administration, and continued to receive daily T injections for 52 d, 55 d, and 310 d. This difference in response to T administration among hormonally intact men prompted the authors to propose an early version of the Saturation hypothesis: ''Normal endogenous testosterone levels may be sufficient to cause near maximal stimulation of prostatic tumors'' [39].

Similarly, Prout and Brewer in 1967 reported that 5 of 10 previously castrated men with advanced PCa demonstrated clinical progression or death within weeks of receiving daily T injections, whereas none of 26 men who were hormonally intact or had just undergone orchiectomy demonstrated any negative clinical or biochemical consequences [40].

2.4.8. *Relationship of endogenous serum testosterone to prostate cancer*

At least 21 longitudinal studies have investigated the possibility that endogenous serum androgens or other hormones are associated with subsequent risk of developing PCa. None has shown any direct association between total T concentration and PCa risk, but several have reported weak associations that were not confirmed in subsequent studies. Recently, a collaborative analysis of pooled worldwide data from 18 of these studies, involving 3886 men with PCa and 6438 controls, found no relationship between endogenous androgen concentrations and PCa [3].

A variety of studies have investigated the effect of endogenous T concentrations in men with known PCa. These studies have shown either no relationship to high T concentration [4], or an association of worrisome features with *low* T concentration, such as high Gleason grade, risk of capsular penetration at surgery, and worse survival [41]. T deficiency has even been correlated with increased risk of positive biopsy in hypogonadal men with normal PSA levels [42,43].

3. Evidence synthesis

3.1. *The Saturation Model*

We propose here a Saturation Model (Fig. 5a) to replace the traditional T-dependent model. This model posits that T and its intracellular metabolite 5α-DHT serve as critical factors for prostate tissue growth, but are present in excess at physiologic serum T concentrations. Below some critical serum T concentration, termed the Saturation Point, there is relative scarcity of T or DHT, causing androgen concentration to serve as the rate-limiting step in prostate tissue proliferation. Above this Saturation Point, variation in serum T concentration has little or no effect on prostate growth, malignant or benign.

This Saturation Model accounts for the dramatic prostatic effects seen with reducing T concentration to castrate levels or raising T concentration out of the castrate range in men with metastatic PCa, and also for the lack of discernable negative clinical outcomes when T was administered to untreated men with advanced PCa. The Saturation Model further explains why raising T concentration several times higher than the physiologic range produces no measurable change in PSA level or prostate volume among men without cancer.

The Saturation Model derives its name from the similarity of response seen in other systems in which a receptor or other biochemical modulator becomes saturated with regard to its ligand, as seen with other steroid hormones [10,11] or even simple nutrients, such as glucose or calcium (Fig. 5b).

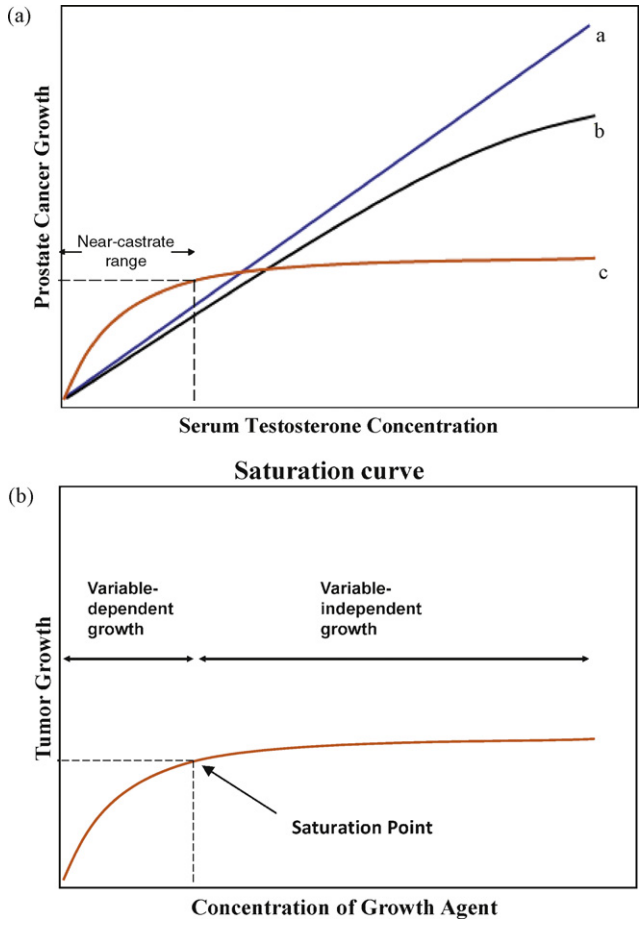

Fig. 5 – (a) The traditional model of testosterone (T)-dependent prostate cancer (PCa) growth suggested that greater serum T concentrations would lead to some degree of greater PCa growth (curves a, b). The Saturation Model (curve c) describes a steep T-dependent curve at T concentrations at or below the near-castrate range, with a plateau representing little or no further growth above this concentration. (b) The relationship between testosterone (T) and prostate cancer (PCa) appears to follow a saturation curve, present in many biological systems, in which growth corresponds with concentration of a key nutrient until a concentration is reached in which an excess of the nutrient is achieved. This type of curve is seen with hormones acting via binding to specific receptors, which have a finite number of binding sites. Once full binding is achieved (saturation), further increases in concentration of the hormone (or other nutrient) produce no further growth.

A simple analogy is the shriveled, dehydrated house plant that grows lushly when it finally receives water; yet once adequately watered any further growth will depend on factors other than the relative abundance of water.

Animal data suggest the Saturation Point occurs in the near-castrate range, and this appears to apply to humans as well. Among 1162 men, no difference in PSA level or prostate volume was noted, with varying degrees of T-deficiency ranging from 300 ng/dl to <150 ng/dl [44] (Fig. 6).

3.2. *Analysis of the Saturation Model*

We have here attempted to refine the traditional model of PCa growth based on current knowledge of the biochemistry of androgen action on the prostate. The critical observation is simple but has profound implications—there is a limit to the ability of serum T concentration to stimulate prostate growth.

The Saturation Model follows directly from considerable evidence in animals, cell lines, and humans—that there is exquisite prostate sensitivity to androgen concentrations at or below the near-castrate range (a T-dependent phase) and little if any effect above this level (T-independent phase). It is based on the long-established observation that maximal binding of androgen to AR occurs at low androgen concentrations. In rats, half-maximal prostate growth occurred in the near-castrate range at 36 ng/dl (approximately 1 nM) [12], whereas saturation of AR binding occurred at concentrations of 2–3 nM (60–90 ng/dl) [45,46]. The concept of saturation is not unique to androgens and the prostate: saturation has been demonstrated in other systems in which steroid hormones bind to specific receptors, such as estrogen in the uterus [10] and aldosterone in the bladder [11].

Additional mechanisms may also contribute. In a 6-mo study of T therapy in hypogonadal men, no increase in intraprostatic T or DHT concentrations were noted despite substantial increases in serum T level [47], suggesting that the intraprostatic milieu may be relatively protected from large changes in serum androgens.

The Saturation Model explains why young men, with peak lifetime T concentrations, do not develop massive benign enlargement of the prostate, and do not regularly develop clinical PCa despite the presence of PCa microfoci [48]. Similarly, the Saturation Model provides a reasonable explanation for the failure to observe a high rate of PCa in T therapy trials despite biopsy-detectable PCa in one of seven hypogonadal men [42,43]. Counter-intuitive support for the saturation model comes from the Prostate Cancer Prevention Trial (PCPT), which compared PCa rates in men whose prostates were androgen-deprived with regard to DHT (finasteride group) versus men with presumably normal androgens (placebo group) [49]. The observed 25% reduction in PCa rates in the finasteride-treated group is consistent with a reduction in androgen concentration below the saturation point. It is important to

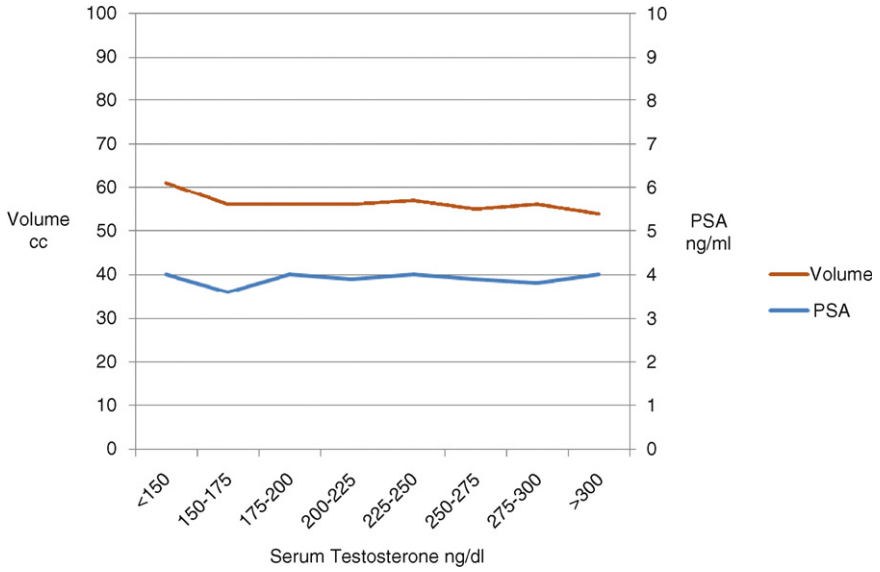

Fig. 6 – Serum prostate-specific antigen (PSA) and prostate volume as a function of serum testosterone (T) in 4254 men with benign prostatic hyperplasia (BPH). Note that the curves for PSA level and prostate volume are flat, even for men with severe T deficiency, and are no different than those for men with T concentrations in the normal range (>300 ng/dl). Adapted from Marberger et al [44].

note that the PCPT did not address the question as to whether *raising* androgens in a non–androgen-deprived group would increase PCa rates.

This analysis is subject to several important limitations. The most important is the absence to date of large, long-term controlled trials of T therapy to definitively assess whether or not an increase in serum T concentration raises the risk of PCa. Another is that reports indicating a lack of worrisome clinical effects of T administration in noncastrated men with metastatic PCa were published in the pre-PSA era, when there were no accurate serum markers to identify possible subclinical disease progression. In addition, the relationship of serum T concentrations to intraprostatic concentrations of DHT has not been clearly elucidated in humans. Finally, it should be recognized that PCa progression may not always be reflected by changes in PSA.

4. Conclusions

The idea that there may be a limit to the ability of androgens to stimulate PCa growth represents a refinement of the traditional, T-dependent view of PCa first postulated in the 1940 s, at a time when there was no reliable serum marker for PCa and little experience with T therapy. Shifting the paradigm of T and PCa in this way unifies theory with a substantial body of evidence from human, animal, and cell lines that had been inconsistent with a T-dependent model of PCa growth. It may be time to reevaluate the longstanding concern that T therapy in hypogonadal men will precipitate PCa growth.

Author contributions: Abraham Morgentaler and Abdulmaged Traish had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Morgentaler, Traish.
Acquisition of data: Morgentaler, Traish.
Analysis and interpretation of data: Morgentaler, Traish.
Drafting of the manuscript: Morgentaler, Traish.
Critical revision of the manuscript for important intellectual content: Morgentaler, Traish.
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Editorial Comment on: Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

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For >65 yr, it has been accepted that prostate cancer (PC) growth is modulated by androgens and that castration causes PC regression. Recently, several studies [1–3] have shown controversial data on the relationship between serum testosterone (T) concentrations and PC. An increased risk of PC was associated with low serum T levels [1], and tumors arising in a low-T environment appeared to be more aggressive [2]. The clinical hypothesis is that low serum T levels may be a potential predictor of PC risk and PC aggressiveness in a screening program [4]. These data conflict with the long-standing concern that an increase in serum T level can increase the risk of PC.

Morgentaler and Traish [5] present a critical revision of the traditional view of T and PC. They use a saturation model that is consistent with regression of cancer when T is reduced to castrate levels but lacks observed growth when serum T is increased [5]. The saturation model starts from the observation that PC growth is sensitive to variation in serum T concentrations at or below the castrate range and is insensitive to T variation above this concentration.

Considering the actual interest in using T replacement therapies in men, a new definition of the relationship between T and PC is of considerable importance. Evidence supports the hypothesis that T administration in hypogonadal men without PC does not increase the risk for PC growth if T levels are normalized [1–3]. The dangerous message that could develop from this saturation model [5] is that continuous T administration associated with elevated T serum

levels cannot produce a risk for PC growth, with or without PC disease. This hypothesis may produce clinical applications not supported by significant scientific evidence.

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Editorial Comment on: Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

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In Roman mythology, Janus was the god of gates and doors. He was usually depicted with two heads looking in opposite directions and was frequently used to symbolize changes and transitions, such as the progression from one vision to another. This idea perfectly illustrates the saturation model proposed by Morgentaler and Traish in the current issue of *European Urology* [1].

Indeed, many of us still regard testosterone through Charles Huggins's eyes and consider it to be a key promoter of prostate cancer progression only because its abrupt suppression induces metastatic prostate cancer to shrink. But is this view enough to sustain our common-sense understanding that testosterone promotes or even causes prostate cancer?

Although urologists still diabolize testosterone, endocrinologists, rheumatologists, and cardiologists attract more and more of our attention to its virtues, especially with regard to metabolic and cardiovascular health [2].

This paradigm is an interesting one for the physician counseling a man who was successfully treated for localized prostate cancer and who suffers from late-onset hypogonadism. What puts him more at risk: a high-testosterone-promoting cancer or a low-testosterone-promoting cardiovascular disease? Considering the extensive use of hormone therapy in early prostate cancer, it seems that urologists have some difficulties seeing the man around the prostate, although they should be aware of the lack of efficacy in that setting [3,4].

Morgentaler and Traish's saturation model provides a nice rational background in which to move away from our unwarranted fear of testosterone in prostate cancer [1]. This article should help urologists to understand that treating middle-age men with localized disease requires getting rid of those fears and developing a holistic view of men's health that encompasses balancing the risks and benefits of adjusting testosterone to normal values.

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