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European Association of Urology

Collaborative Review – Andrology

A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

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Article info

Article history:
Accepted August 7, 2013
Published online ahead of print on August 16, 2013

Keywords:
Testosterone
Androgens
Prostate cancer
Saturation
Prostate-specific antigen

Abstract

Context: Decades-old beliefs regarding androgens and prostate cancer (PCa) have undergone dramatic shifts in light of modern evidence and new theoretical constructs, but considerable confusion remains on this topic, particularly with regard to the use of testosterone therapy in men with any history of PCa.
Objective: To review current literature regarding the relationship of serum testosterone on PCa and in particular the effect of testosterone therapy on PCa progression and recurrence.
Evidence acquisition: A Medline search was conducted to identify all original and review articles assessing the effect of androgens on the prostate and the use of testosterone in men with a history of treated and untreated PCa.
Evidence synthesis: Contrary to traditional teaching, high endogenous serum testosterone does not increase the risk of developing PCa, and low serum testosterone does not protect against PCa. Although limited in size and duration, current studies similarly fail to indicate any increased risk of PCa in men receiving testosterone therapy. These results indicate a finite ability of androgens to stimulate PCa growth (the saturation model). A majority of studies demonstrate an association between low serum testosterone and poor prognostic features of PCa, including high-grade disease, advanced pathologic stage, and increased risk of biochemical recurrence following radical prostatectomy. The prostate-specific antigen-to-testosterone ratio predicted PCa risk in several biopsy studies. Multiple reports of testosterone therapy in men after treatment for localized PCa have shown low or absent recurrence rates. Some men with untreated PCa have received testosterone therapy without evidence for PCa progression.
Conclusions: The long-held belief that PCa risk is related to high serum androgen concentrations can no longer be supported. Current evidence indicates that maximal androgen-stimulated PCa growth is achieved at relatively low serum testosterone concentrations. It may therefore be reasonable to consider testosterone therapy in selected men with PCa and symptomatic hypogonadism.

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1. Introduction

Over the past 15 yr, there has been growing recognition of the benefits of testosterone therapy for men with testosterone deficiency, also termed *hypogonadism*. These benefits include improved sexual interest and performance, improved mood and energy, increased muscle and bone density, decreased fat, and possibly improved longevity [1]. The new interest in

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2013.08.015

testosterone therapy has precipitated reexamination of traditional assumptions regarding the relationship between testosterone and prostate cancer (PCa) [2], leading to a fundamental paradigm shift. This shift is at odds with longstanding beliefs and has resulted in controversial new practices, such as offering testosterone therapy to men with PCa.

The belief that androgens cause de novo PCa or accelerate its growth has been called the *androgen hypothesis*. The androgen hypothesis arose from reports beginning in the 1940s in which men with metastatic PCa demonstrated clinical and biochemical improvement with androgen deprivation via castration or estrogen treatment and conversely demonstrated rapid PCa progression with testosterone administration [3,4]. Medical students and physicians have been taught for years that high testosterone promotes the development of PCa, low testosterone is protective, and the administration of testosterone to a man with existing PCa is like "feeding a hungry tumor" or "pouring gasoline on a fire." An international survey revealed that the most common concern about testosterone therapy among physicians is the risk of PCa [5].

Today, the androgen hypothesis has been seriously challenged, as overwhelming evidence contradicts its basic principles [6]. Men with high serum testosterone are not at increased risk of developing PCa, low serum testosterone provides no protection against the development of PCa, and some men with untreated PCa have received testosterone therapy without evidence of PCa progression [7–9]. The androgen hypothesis has therefore been replaced by the saturation model [10] to accommodate the dual observations that PCa is (1) exquisitely sensitive to variations in androgens at low concentrations and (2) indifferent to variations at normal and high concentrations. The simple yet profound paradigm change is that androgens appear to have a finite ability to stimulate PCa growth. This creates opportunities for new clinical uses of testosterone therapy.

The purpose of this review is to synthesize historical and modern evidence to provide an objective and up-to-date basis for clinical decision making. Indications for testosterone therapy in men include low testosterone levels in combination with signs and symptoms of testosterone deficiency, such as fatigue, erectile dysfunction, depression, decreased libido, and decreased muscle mass. Although any history of PCa has been a longstanding contraindication for testosterone therapy, there may now be circumstances where this is a reasonable therapeutic choice, as we discuss below.

2. Evidence acquisition

A Medline search from 1940 to 2013 was conducted to identify all original and review articles assessing the effect of androgens on the prostate and the use of testosterone in men with a history of treated and untreated PCa. Key words used were *testosterone, androgens, prostate cancer, saturation*, and *prostate specific antigen*.

3. Evidence synthesis

3.1. Physiology of androgens and the prostate

Testosterone is the principal circulating androgen in males. Approximately 90% of testosterone is synthesized from testicular Leydig cells and 10% from the adrenals. Androgens induce differentiation of the Wolffian ducts, prostate, and male genitalia. Within the prostate, the primary androgen is 5α-dihydrotestosterone (DHT), metabolized intracellularly from testosterone by the 5α-reductase (5-AR) enzyme. The androgen receptor (AR) binds both testosterone and DHT but has greater affinity for DHT. The androgen–AR complex then enters the nucleus and stimulates transcription of androgen-regulated genes via binding to androgen response elements [11].

The importance of DHT to the prostate is demonstrated by poorly developed prostates in men with congenital 5-AR deficiency and by the well-known effect of 5-AR inhibitors (5-ARIs) to reduce prostate volume and prostate-specific antigen (PSA) production. Testosterone also contributes to prostate function independently of DHT, as luteinizing hormone-releasing hormone agonists (LHRHa) produce greater reductions in prostate volume and PSA than 5-ARIs [12], which produces castration levels of DHT without lowering serum testosterone. The relative importance of testosterone versus DHT appears to be tissue specific: DHT plays a primary role in prostate, scalp, genital differentiation, and corpora cavernosa, and testosterone appears to be the dominant androgen in spermatogenesis, muscle, and bone.

3.1.1. Historical basis for concerns regarding testosterone and prostate cancer

The longstanding concerns regarding testosterone and PCa stem from several observations, including dependence of the prostate on androgens for normal development and function; the near-universal presence of AR in PCa specimens; beneficial responses to androgen-deprivation therapy (ADT) in men with advanced or metastatic PCa; historical reports of rapid PCa progression in men who received testosterone administration; dramatic PSA declines in men with PCa who undergo ADT; reduction in PSA and prostate volume in men with benign prostatic hyperplasia treated with 5-ARI medications; and the parallel rise in PSA and serum testosterone upon cessation of LHRHa treatment.

These observations are consistent with a picture of the prostate, malignant and benign, as an androgen-dependent organ. Huggins and Hodges in 1941 asserted that testosterone "activated" PCa and caused it to undergo an "enhanced rate of growth." This concept has led to a general concern that higher serum testosterone concentrations pose a risk for PCa. Although the dramatic effects of ADT in PCa are indisputable, a wealth of current evidence fails to support the concept that increasingly high serum testosterone or DHT leads to ever-greater growth of benign or malignant prostate tissue. For example, multiple studies have shown no correlation between endogenous testosterone and PSA or prostate volume [13–15]. Administration of supraphysiologic doses of testosterone to healthy volunteers for up to 20 wk resulted

in no increase in PSA or prostate volume [13,15], and large prospective studies have almost universally revealed no relationship between endogenous serum androgen concentrations and PCa risk. These results indicate little or no relationship between serum testosterone and prostate biology through the moderately low to supraphysiologic range.

In contrast, the saturation model appears to account for all existing observations in which prostate tissue, malignant and benign, is exposed to changes in serum androgen concentrations. It is critical to note that the androgen hypothesis was accepted prior to the discovery of AR and PSA, and before the availability of reliable serum testosterone assays. It should therefore not be surprising that some predictions of the androgen hypothesis would prove false when submitted to scientific investigation.

3.1.2. *The saturation model*

The saturation model explains the paradoxical observations that prostate tissue is exquisitely sensitive to changes in serum testosterone at low concentrations but becomes indifferent to changes at higher testosterone concentrations. A threshold effect occurs in which increasing androgen concentrations reach a limit (the saturation point) beyond which there is no further ability to induce androgen-driven changes in prostate tissue growth (Fig. 1). This explains why dramatic changes in PSA are noted when serum testosterone is manipulated into or out of the castration range, whereas minimal or absent PSA changes occur when supraphysiologic testosterone doses are administered to normal men.

One important mechanism contributing to the saturation model is the finite ability of androgen to bind AR. Maximal androgen–AR binding (ie, saturation) occurs at fairly low androgen concentrations in rat and human prostate tissue, reported in human prostate in vitro at approximately 4 nmol/l (approximately 125 ng/dl). In clinical practice, the saturation point appears to be approximately 8 nmol/l or 250 ng/dl, subject to interindividual variation. This difference is likely explained by in vivo interactions with other molecules (eg, sex hormone–binding globulin [SHBG]). Other physiologic mechanisms may contribute, as well. For example, intraprostatic concentrations of testosterone and DHT were unchanged after 6 mo of intramuscular testosterone injections despite large changes in serum concentrations, suggesting the presence of local regulatory mechanisms [16]. Different tissues appear to have different saturation points.

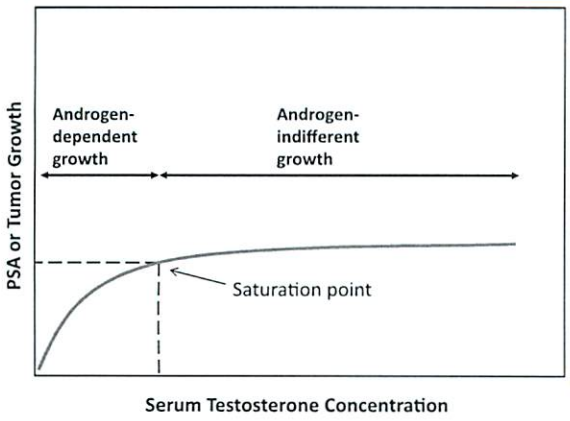

Fig. 1 – The saturation model. Increasing androgen concentrations produce increasing prostate tissue growth or function, as reflected by prostate-specific antigen concentrations, until a limit is reached (the saturation point), beyond which there is no further ability to induce androgen-driven changes. Prostate cancer is exquisitely sensitive to changes in androgen at low concentrations (androgen dependent) but does not respond to changes in androgen concentrations above the saturation point (androgen indifferent). Current evidence suggests that the saturation point for human prostate tissue is approximately 250 ng/dl (approximately 8 nmol/l). The saturation point will differ between individuals and varies considerably between different tissue types. Adapted from Morgentaler and Traish [10], with permission.
PSA = prostate-specific antigen.

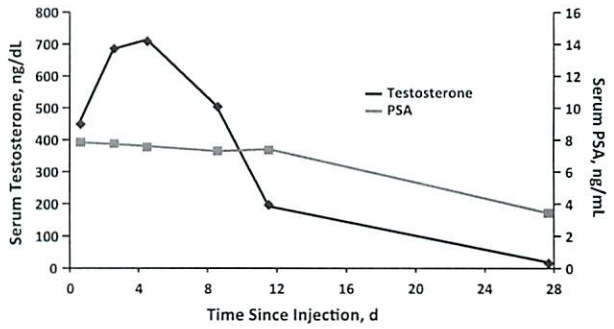

Fig. 2 – Prostate-specific antigen (PSA) response to testosterone flare in 25 men with stage D prostate cancer. Testosterone concentrations rose by approximately 50% in men with metastatic disease who received luteinizing hormone-releasing hormone agonist. PSA was unchanged during flare, and then fell rapidly when serum testosterone declined toward the castration range. These results provide support for the saturation model by revealing no change in PSA while androgen concentrations vary within the androgen-indifferent range, and then dramatic changes after androgen concentrations move into the androgen-dependent range, which occurs at low concentrations. Data from Tomera et al. [17], figure adapted from Morgentaler and Traish [10], with permission.
PSA = prostate-specific antigen.

Several additional observations provide broad support for the saturation model. In animal studies, testosterone or DHT replacement in castrated males causes restoration of prostate mass to its precastration size but not greater. Laboratory experiments with androgen-sensitive PCa cell lines demonstrate dose-response curves with increased growth and cell numbers as androgen concentrations are increased, but then reach a maximum where no additional growth is observed despite logarithmic increases in androgen concentration [10]. Remarkably, some studies of men with metastatic PCa who received LHRHa medications failed to demonstrate any PSA increase during the interval of testosterone flare [17] (Fig. 2).

3.2. *Clinical implications*

3.2.1. *Endogenous serum testosterone and prostate cancer risk*

More than 20 population-based longitudinal studies have shown no relationship between PCa and serum testosterone or other androgens [2]. An analysis of pooled data from 18 of these studies, comprising a study population of 3886 men with PCa and 6438 age-matched controls, found no

relationship between PCa risk and serum concentrations of testosterone, DHT, or free testosterone (FT) [18]. Muller et al. reported on 3255 men in the placebo arm of the reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial who underwent planned prostate biopsies at 2 yr and 4 yr and found no association between PCa risk and baseline serum testosterone or DHT [19]. These various studies conclusively demonstrate that PCa risk is unrelated to endogenous serum androgen concentrations. Specifically, men with higher endogenous testosterone are at no greater risk than men with lower serum testosterone.

3.2.2. *Testosterone therapy and risk of prostate cancer*

No prospective, controlled studies have yet been performed with adequate population sizes and durations to definitively assess PCa risk with testosterone therapy, but evidence to date fails to suggest increased risk. A meta-analysis of 19 placebo-controlled testosterone therapy cases found no significant increase in PCa or development of PSA >4.0 ng/ml in men treated with testosterone therapy versus placebo [7]. Shabsigh et al. conducted a systematic review of 11 placebo-controlled studies and found that men who received testosterone therapy had neither increased PCa risk nor greater Gleason grade among those who developed PCa [20].

Longer uncontrolled series reveal similar results. In the UK Androgen Study, 1365 men 28–87 yr of age (mean: 55) received testosterone therapy for up to 20 yr, with PSA and digital rectal examination (DRE) performed every 6 mo [21]. Fourteen new cases of PCa, all localized, were detected at 1–12 yr. The cancer rate of one case per 212 yr of treatment is no greater than for the general population. Raynaud et al. reported on an initial population of 200 men treated with a transdermal testosterone patch, 161 who finished 1 yr of treatment, and 51 who completed a 5-yr extension [22]. PSA increased at 3 mo from 0.47 to 0.60 ng/ml, followed by negligible change in PSA (0.03 ng/ml per year) over the remaining 5 yr. No PCa was identified in this trial. In a 12-mo trial of testosterone therapy in men at increased risk for PCa because of high-grade prostatic intraepithelial neoplasia, only 1 of 20 men developed PCa [23].

3.2.3. *Serum testosterone and risk of prostate cancer at prostate biopsy*

Several studies have suggested that low testosterone increases the risk of a positive prostate biopsy. Morgentaler et al. in 1996 reported a PCa rate of 14% in 77 men with testosterone deficiency with normal PSA levels (<4.0 ng/ml) and DRE, a rate similar to PCa rates with sextant biopsies in contemporaneous series in men with elevated PSA levels [24]. In a larger study of 345 men with testosterone deficiency and PSA levels <4.0 ng/ml, men with the lowest tertile of serum testosterone had double the risk of PCa compared with men with less severe testosterone deficiency. The cancer rate was 30% for these men with a PSA value of 2.0–4.0 ng/ml [25]. Hoffman and colleagues reported a 47% PCa rate in men with testosterone <300 ng/dl versus 28% in men with normal testosterone levels [26]. García-Cruz et al. likewise found an inverse relationship between serum testosterone and PCa risk in 137 men undergoing biopsy for suspicion of PCa. Low testosterone was also associated with increased D'Amico risk categories, high Gleason scores, risk of bilateral disease, and overall tumor burden [27].

A high ratio of PSA to testosterone was associated with increased PCa risk in men with moderate elevation of PSA (3–10 ng/ml) [28] and in testosterone deficiency men with PSA values <4.0 ng/ml [29]. These results suggest that reduced testosterone increases the risk of PCa for any given PSA value.

Svatek et al. investigated whether the PSA response to a single intramuscular injection of 400 mg testosterone cypionate 1 mo prior to biopsy predicted PCa in 40 men with a PSA value of 2.5–4.0 ng/ml [30]. A larger PSA increase was seen in men with PCa versus those without PCa, but these results must be viewed cautiously, as they are inconsistent with extensive literature indicating minimal PSA response to increases in serum testosterone, including men with metastatic PCa during testosterone flare [17].

3.2.4. *Serum testosterone and prostate cancer grade, stage, and survival*

Multiple studies have reported the association of lower serum testosterone concentrations with high-grade PCa and higher stage at presentation [9,31–36]. Univariate analysis of hormone parameters in 724 men prior to radical prostatectomy (RP) revealed that total testosterone, estradiol (E2), and the testosterone-to-E2 ratio values were significantly associated with high-risk PCa [37]. The association between serum sex steroids and PCa aggressiveness depicted a nonlinear U-shaped behavior, with the lowest and highest levels associated with high-risk PCa. Pathologic assessment from RP in 673 men revealed a >50% increased risk of high Gleason score in men with testosterone <300 ng/dl (10 nmol/l) compared with men with normal testosterone (33% vs 19.8%; $p = 0.0009$), and seminal vesicle invasion (SVI) nearly doubled (21% vs 11%; $p = 0.003$). For men with severe testosterone deficiency, the risk of SVI trebled (59.5% vs 19.8%; $p < 0.0001$). Low serum testosterone has also been associated with increased rates of biochemical recurrence (BCR) [31,34]. In one study involving 227 men who underwent RP with a median follow-up of 7.7 yr, reduced risk of biochemical failure was noted for men with serum testosterone >11 nmol/l [9].

Contradictory evidence was reported by Pierorazio et al., who stated that men >65 yr of age with aggressive PCa had higher serum testosterone than men with less aggressive PCa or no cancer [38]. However, the significance of this finding is questionable, because the results were based not on testosterone but on the FT index (a ratio of testosterone to SHBG); baseline serum testosterone was numerically lower in the aggressive PCa group, and findings were based on <18 men.

3.2.5. *Testosterone therapy in men with prostate cancer*

In light of evidence that testosterone therapy may not be as harmful to men with a history of PCa as once believed, several investigators have reported the use of testosterone therapy in men after curative treatment for PCa (Table 1).

Table 1 – Results of testosterone therapy in men with prostate cancer

Study	No. of patients	Intervention	Follow-up, mo	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment testosterone, ng/dl	Post-treatment testosterone, ng/dl	Comments
Agarwal et al. [39]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591	No PSA recurrences
Kaufman et al. [38]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434	No PSA recurrences; longest follow-up = 12 yr
Khera et al. [40]	57	RP	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459	No PSA recurrences
Pastuszak et al. [41]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004	0.007	261	460	Included 26 men with high-risk PCa and positive margins or nodes or Gleason score >8; comparison group of 49 men with RP without testosterone therapy; four PSA recurrences in the testosterone therapy group (4%), eight recurrences in the comparison group (16%)
Sarosdy [42]	31	Brachytherapy	60	5 (3) 6 (19) 7 (6) 8/9 (3)	NA	<1	188	489	No PSA recurrences
Morales et al. [43]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150 (5.2 nmol/l)	507 (17.6 nmol/l)	One patient had a transitory increase in PSA; none had PSA increase >1.5 ng/ml
Pastuszak et al. [44]	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30	0.66	178	368	No PSA recurrences
Morgentaler et al. [8]	13	AS	30	6 (12) 7 (1)	5.5	3.6	238	664	Follow-up biopsies in all men; no definite PCa progression in any patient; no increase in mean PSA or prostate volume; no cancer in 54% of follow-up biopsies
Morales et al. [45]	6	AS	NA	6 (5) 8 (1)	5.66	NA	259 (9 nmol/l)	NA	Variable PSA response in several men; no follow-up biopsies reported; one man subsequently underwent RP

PSA = prostate-specific antigen; RP = radical prostatectomy; PCa = prostate cancer; NA = not available; EBRT = external-beam radiation therapy; AS = active surveillance.

Kaufman and Graydon reported no recurrences in seven men who received testosterone therapy after RP, with the longest follow-up 12 yr [37]. Agarwal et al. reported no cancer recurrences in 10 men treated with testosterone therapy for symptoms of testosterone deficiency after RP for localized PCa [39]. Khera et al. reported no PCa recurrence in 57 men following RP, with a mean testosterone therapy duration of 13 mo [40]. In the largest series to date, Pastuszak et al. evaluated 103 hypogonadal men (77 low to intermediate risk and 26 high risk) who received testosterone therapy after RP and compared BCR to 49 eugonadal controls (35 low to intermediate risk and 15 high risk) [41]. High risk was defined as Gleason score ≥8, positive surgical margins, and positive lymph nodes. After a median of 27.5 mo of follow-up, there were four BCRs (4%) in the testosterone therapy group versus eight (16%) in the non–testosterone therapy group.

Sarosdy et al. reported no BCR among 31 men treated with testosterone therapy after brachytherapy, with a median duration of treatment of 4.5 yr [42]. Two published studies have reported results in which testosterone therapy was offered after external-beam radiation therapy (EBRT) for PCa. Morales et al. reported no BCR in five men with up to 27 mo of follow-up [43]. Pastuszak et al. reported no recurrences in 13 additional men with a median follow-up of 29.7 mo [44] (Table 1).

The small size and limited duration of these case series make it impossible to assess the overall safety of testosterone therapy after definitive treatment for PCa, but so far, these results are reassuring. Large, randomized prospective studies will be needed to provide reliable safety information. We are aware of a single controlled prospective study to date following RP (Baylor College of Medicine, ClinicalTrials.gov identifier NCT00848497).

One possible explanation for the lack of PCa recurrence noted in the previous studies is that these men may not have had any residual PCa cells to be stimulated by androgens. A more provocative study, therefore, is to assess the response to testosterone therapy in men with untreated PCa. Morgentaler et al. treated 13 men on active surveillance with testosterone therapy for a median of 2.5 yr (range: 1.0–8.1) [8]. All men underwent follow-up prostate biopsies, with a mean of two sets of biopsies per patient. At initial biopsy, 12 men had Gleason score 6 and one had Gleason 7 (3 + 4). Mean serum testosterone increased from 238 to 664 ng/dl. Mean PSA and prostate volume did not change with testosterone therapy. No definite PCa progression was noted in any man, and no cancer was found in 54% of follow-up biopsies. These were the first results to directly assess the effect of raising testosterone in men with untreated PCa.

These results in men with untreated PCa must be regarded cautiously given the severely limited global experience, and a report by Morales of erratic PSA responses to testosterone therapy in several men on active surveillance [45].

3.2.6. *New clinical concepts*

With abandonment of the androgen hypothesis, two new, related issues must now be contemplated. One is whether there is a rationale to perform serum testosterone testing in men at risk for PCa or with known PCa because of evidence that low testosterone concentrations predict higher PCa risk and aggressiveness. Low testosterone concentrations have also been demonstrated to predict PCa recurrence in men following RP. The second is whether testosterone therapy may actually protect against PCa development or recurrence. This second issue stems from the relatively low risk of PCa recurrence in men treated with testosterone therapy after PCa treatment and emerging data demonstrating decreased PCa growth and progression with increasing testosterone levels. These results suggest a clinically useful prognostic role for serum testosterone in men at risk for PCa or for men with known PCa. We are not aware of any published risk calculators that currently incorporate serum testosterone, but current evidence suggest that this addition may prove rewarding.

A second issue to be considered is whether testosterone therapy may have beneficial effects with regard to PCa, as suggested by low rates of PCa recurrence in men treated with testosterone therapy after definitive local PCa treatment. This concept is supported by laboratory data demonstrating that androgens promote less aggressive phenotypes and inhibit dedifferentiation in some PCa cell lines. These include the findings that activation of membrane androgen receptors induced apoptotic regression of human PCa cells in vitro and in vivo [46], androgens triggered inhibition of cell proliferation at higher concentration in LNCaP cells [47], and androgens caused growth suppression and reversion of androgen-independent tumors to an androgen-stimulated phenotype [48].

3.3. *Discussion*

For seven decades, it was assumed that higher testosterone produced more rapid PCa growth across the entire range of possible serum testosterone concentrations, leading to the belief that high testosterone was risky for PCa, low testosterone was protective, and that testosterone therapy was absolutely contraindicated in any man with a history of PCa. Today, none of those beliefs can be accepted at face value. The evidence is now clear that PCa growth is androgen dependent only at the lowest end of testosterone concentrations, reaches a saturation point at a relatively low serum testosterone concentration, and becomes indifferent to changes in serum androgens at higher concentrations. This fundamental shift in our understanding of the relationship of PCa and androgens brought about by the saturation model has important clinical implications.

The most important and controversial implications are with regard to the use of testosterone therapy in men with symptomatic testosterone deficiency and a history of PCa. Current evidence does not fully support the prohibition against the use of testosterone therapy in these men. Rapid growth of PCa during testosterone therapy is far from universal and appears to occur exclusively in men with severely depressed testosterone concentrations. This idea was an extrapolation from the special case of men who were androgen deprived. Even in the 1960s there were reports that some men with metastatic PCa did well with testosterone

Table 2 – Criteria to consider before initiating testosterone therapy in men with history of treated prostate cancer

The clinical picture is consistent with a diagnosis of testosterone deficiency.
The patient must understand that safety data are limited and that there is an unknown degree of risk of PCa progression or recurrence.
The patient must be willing and able to provide informed consent.
No medical contraindications to testosterone therapy (eg, erythrocytosis) exist.
There is an undetectable or stable PSA level.
Clinicians must be prepared for the possibility of PCa recurrence or progression, which will occur in some men regardless of testosterone therapy but may be attributed to testosterone therapy by patients, family, or other clinicians.
Use testosterone therapy with extreme caution in men at high risk for PCa recurrence or progression.
Do not recommend testosterone therapy for men currently receiving any form of ADT.

PCa = prostate cancer; PSA = prostate-specific antigen; ADT = androgen-deprivation therapy.

administration, particularly if they had not undergone castration, but "the response to testosterone was extremely variable" [50] or occurred only in a minority of patients [51].

Large numbers of men around the world have been treated and cured of PCa. Some of these men have long life expectancies, experience reduced quality of life because of testosterone deficiency, and desire testosterone therapy. The challenging question is how to address this issue in light of our new understanding of androgens and PCa but with extremely limited clinical experience and no controlled studies. A complicating factor is the medico-legal consequences of such treatment, as some men with PCa will inevitably experience recurrences. If this occurs, physicians and patients may well believe that higher testosterone was the cause, even if the events were unrelated.

While we await more formal safety data, some physicians have begun offering testosterone therapy to selected men with PCa, balancing patient well-being against a theoretical concern that lacks evidentiary support. For those physicians inclined to treat, we recommend doing so only after obtaining informed consent and beginning with the lowest-risk individuals, such as those with undetectable PSA >1 yr following RP. Informed consent should include the information that no long-term safety data are available and there is therefore an unknown degree of risk that PCa may recur or progress. Some clinicians may also wish to offer testosterone therapy to men following EBRT, brachytherapy, or other treatment modalities, despite an even more limited body of supporting literature and the compounding difficulty that some of these patients frequently do not reach undetectable levels of PSA. More controversial still is the use of testosterone therapy in men on active surveillance. Clinicians should be aware that safety data regarding testosterone therapy in men with PCa are extremely limited.

We support the creation of an international registry for men treated with testosterone therapy after diagnosis with PCa. We believe certain minimum criteria should be considered before offering testosterone therapy to men with PCa (see Table 2), and follow-up should be rigorous, particularly in the first year of treatment.

It should be reassuring to clinicians to learn that there is no compelling evidence that testosterone therapy increases PCa risk in otherwise healthy individuals. Long-term data indicate that PSA values change little with testosterone therapy after an initial increase that occurs within the first 3 mo, but men with severe testosterone deficiency will likely demonstrate a substantial initial increase because of having serum testosterone concentrations below the saturation point. PSA values stabilize after 3–6 mo after full androgenic stimulation has been achieved. Changes in PSA that occur beyond 6 mo should be managed the same way as if the patient were not on testosterone therapy. In addition, testosterone therapy does not appear to worsen lower urinary tract symptoms [49].

New concepts that merit investigation include the use of low serum testosterone to help predict prostate biopsy outcomes as well as its use as a prognostic indicator for men with known PCa. We encourage investigators to explore this possibility via nomograms and other instruments. Finally, the association of low testosterone as a risk factor for higher PCa grade, stage, and BCR raises the provocative possibility that testosterone therapy may one day have a role in PCa prophylaxis or treatment.

4. Conclusions

New scientific evidence over the past 15 yr has resulted in a revolutionary shift in understanding regarding the relationship of androgens and PCa, with important clinical implications. The key conceptual change is that there appears to be a limit to the ability of androgens to stimulate PCa growth, termed the *saturation model*. In addition, accumulating data indicate an important association between low testosterone concentrations and worrisome aspects of PCa. Given the established benefits of testosterone therapy for symptomatic men with testosterone deficiency, it appears reasonable to offer testosterone therapy in selected individuals with a history of PCa despite the limited safety information in this population.

It is to be expected that the revolutionary changes in fundamental biological concepts developed over the past 15 yr may take time to percolate through the medical community into changes in clinical practice. We are heartened by the changes we have already seen thus far, particularly in the benefits seen in our patients, and we are excited by what the next 15 yr will bring.

Author contributions: Mohit Khera 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: Khera, Crawford, Morales, Salonia, Morgentaler.
Acquisition of data: Khera.

Analysis and interpretation of data: Khera, Crawford, Morales, Salonia, Morgentaler.
Drafting of the manuscript: Khera, Morgentaler.
Critical revision of the manuscript for important intellectual content: Khera, Crawford, Morales, Salonia, Morgentaler.
Statistical analysis: Khera.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Morgentaler.
Other (specify): None.

Financial disclosures: Mohit Khera certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Dr Khera is a consultant for Merck, a speaker for Lilly, and a speaker and consultant for Auxilium and Slate.

Funding/Support and role of the sponsor: None.

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