

Testosterone Replacement Therapy and Prostate Cancer

Abraham Morgentaler, MD, FACS^{a,b}

^a*Men's Health Boston, Brookline, MA, USA*

^b*Harvard Medical School, Boston, MA, USA*

For the past 65 years, it has been axiomatic that higher serum testosterone (T) levels cause increased prostate cancer (PCa) growth and that T supplementation carries the risk for converting occult PCa into a clinical PCa. This theory originated with the work of Huggins and his coworkers [1,2], who, in 1941, published the landmark papers establishing the androgen dependence of PCa. They reported that reducing serum T to castrate levels caused PCa to regress and that T administration caused enhanced PCa growth.

During this author's training in the 1980s, this relation between T and PCa was unassailable. The arguments supporting the concept that T caused PCa growth were multiple: lowering of T to castrate levels caused PCa to regress (and remains a mainstay of treatment for advanced disease to this day), men castrated early in life never developed PCa, and the occasional new diagnosis of PCa in a patient receiving testosterone replacement therapy (TRT) confirmed the danger of T for men with occult PCa. No wonder, then, that we learned to describe the relation between T and PCa as "fuel for a fire" or "food for a hungry tumor."

This concern regarding PCa and T has led to the lifetime prohibition against TRT for any man diagnosed with PCa, regardless of disease status. It has even been suggested that men at higher risk for development of PCa, such as those with a family history of PCa, be excluded from TRT

trials because of the concern that higher T may cause growth of occult cancer in these men [3].

If T truly caused significant PCa growth, however, there should be observable evidence for it, such as increased PCa rates in men receiving TRT or among men with high endogenous T. Yet, multiple reviews have failed to identify any such supporting evidence [4–7]. A report on T and aging by the Institute of Medicine concluded, "In summary, the influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined..." [3].

This relation between TRT and PCa is important because of the large number of symptomatic hypogonadal men who might potentially benefit from treatment. TRT has been shown to improve erectile dysfunction and diminished libido and to have a wide range of nonsexual benefits as well, including positive effects on mood, fatigue, sense of well-being, muscle strength and mass, bone mineral density, glucose metabolism, and markers of the metabolic syndrome [4,8]. In addition, there is a substantial and growing population of men who have been successfully treated for PCa and who are symptomatic from low serum T and desire TRT. This population, in particular, has caused urologists and oncologists to re-examine the old concern regarding TRT and PCa.

Arguments made to support the belief that testosterone causes prostate cancer growth

Huggins: testosterone administration caused "enhanced growth" of prostate cancer

In 1941, Huggins and his coworkers [1,2] published two articles establishing the hormonal responsiveness of PCa. In the first, it was noted that acid phosphatase declined after lowering of

Dr. Abraham Morgentaler has received lecture honoraria, research funding, or served on clinical advisory boards for the following companies with relevant interests: Solvay, Auxilium, Indevus, and Schering.

E-mail address: amorgent@bidmc.harvard.edu

T by castration or estrogen treatment and that acid phosphatase levels rose with T administration [1]. Although it was reported that T administration was given to three men, results were only provided for two men, and one of these men had been previously castrated. In the second article, T was also administered to three men, and it was reported that acid phosphatase values rose. All men in this study had previously undergone orchiectomy, however [2].

We know today that normalization of T levels after a reduction to castrate levels causes PCa regrowth and also that the serum acid phosphatase test used by Huggins in this study would turn out to perform erratically [9]. The issue at hand, however, is whether T administration causes increased PCa growth in a previously untreated man. In a review 25 years after his original work, Huggins [10] reasserted the concept that T administration in previously untreated men caused enhanced PCa growth, citing only his first article. It is simply astounding to discover that the origin of this long-standing near-universal belief was based on a single patient [11].

“Testosterone is a growth factor for prostate cancer”

This statement has generally been used to imply that there exists a concentration-dependent rate of growth of PCa for T, without an upper limit. A more accurate statement is that the presence of androgens is necessary for the growth of most but not all human prostate cancer and under many but not all laboratory conditions [12,13].

There is strong evidence that a saturation level exists for prostate tissue with regard to T, with T levels greater than this saturation point not associated with additional growth. For example, TRT in hypogonadal men caused prostate volume to increase to the size of age-matched eugonadal controls but no higher [14]. Further, administration of supraphysiologic doses of T to a group of healthy men resulted in no change in prostate-specific antigen (PSA) or prostate volume [15].

The saturation for T in prostate tissue likely occurs at relatively low serum concentrations, because TRT in hypogonadal men causes only a minor increase in PSA and prostate volume of approximately 15% [16]. This compares with a 13% increase in PSA at 48 weeks among men aged 50 to 60 years in the placebo arm of an unrelated clinical trial [17]. In contrast, these parameters

increase several fold in healthy volunteers when castrate T levels are allowed to normalize after discontinuation of luteinizing hormone-releasing hormone (LHRH) agonists [18]. Finally, there is recent evidence that the effects of dutasteride, a 5 α -reductase inhibitor, on PSA, prostate volume, and voiding symptoms were no different for men even with substantially reduced endogenous serum T levels [19]. These results suggest that maximal or near-maximal prostate growth (and its potential for reversal with 5 α -reductase inhibitors) occurs at low circulating levels of T.

“Prostate cancer does not occur in eunuchs”

Although often mistakenly attributed to Huggins, the source for this statement is a 1948 article by Hovenian and Deming [20], in which they report on growth characteristics of human PCa tumors transferred to guinea pigs. In an unreferenced comment, they wrote, “...human clinical experiences have revealed that cancer of the prostate has not been found in eunuchs” [20].

The assertion was made during a time when prostate examinations were not routinely performed, there was no accurate blood test for PCa, and there was no existing large population of men castrated early in life who had been followed for 40 to 50 years to determine whether or not they ever developed PCa. Moreover, PCa has indeed been reported in anorchic men [21], and one series reported 25 men with PCa and testicular atrophy at the time of therapeutic orchiectomy [22].

Testosterone administration caused high rate of unfavorable responses among men with metastatic prostate cancer

In 1981, Fowler and Whitmore [23] reported on the experience at Memorial Sloan Kettering Cancer Center, in which 67 men with a history of PCa with bony metastases received T injections. In this review of cases accumulated from 1949 through 1967, T administration had been attempted as a possible therapeutic measure because of a lack of additional treatment options in advanced cases. Of 52 evaluable cases, 45 men had an “unfavorable response,” defined broadly to include subjective symptoms, such as worsening of bone pain, and objective measures, such as an increase in acid phosphatase or clinical progression.

This high rate of unfavorable responses has been offered as proof that T causes rapid PCa

growth and progression. However, all but four of these men had previously been castrated or treated with estrogen, however. Within this small untreated group, one man had an unspecified unfavorable response within 30 days of beginning daily T injections, another had a subjective “beneficial response,” and the remaining two eventually developed unfavorable responses at 56 and 310 days. Given the advanced stage of PCa in these men, and the lack of a control group, it must be considered that the unfavorable responses seen in this population may have been attributable entirely to the natural history of their disease and were unrelated to T administration.

Intrigued by the apparent lack of T-related clinical progression in this previously untreated group, Fowler and Whitmore [23] postulated that “near maximal stimulation of prostate cancer occurred at physiologic T levels.” This statement represents an early and prescient articulation of the saturation model for PCa and T.

Testosterone flare

LHRH agonists are known to increase T levels substantially for 7 to 10 days before they decline to castrate levels [24]. This “testosterone flare” has been associated with adverse events, such as increased bone pain, urinary retention, and vertebral collapse with paraplegia, and it has been assumed that these adverse events occurred because of T-driven PCa growth [24]. Several clinical strategies have thus been developed to prevent the consequences of this flare phenomenon, such as the addition of antiandrogens or the use of LHRH antagonists that do not cause a transient increase in T levels.

Surprisingly, in the two studies that measured PSA during the period of elevated T, PSA values never rose to greater than baseline [25,26]. Because PSA levels have been shown to correlate with PCa progression [27], the failure of PSA to increase during the T flare suggests that higher serum T levels do not cause increased PCa growth even in men with stage D disease.

Case reports

Several anecdotal reports have described development of PCa some time after initiation of TRT [28,29]. Because the diagnoses of PCa and TRT are common occurrences in urology practices, however, it is to be expected that some men receiving TRT are eventually likely to be diagnosed with PCa. This is no different

than reporting cases of PCa in men with blue eyes. Because association does not equal causality, these types of reports are of value only if they bring to light an unrecognized relation. In this case, if TRT truly increased PCa rates in the short term, there should be an observable increased rate of PCa in men receiving TRT, an effect that has not been demonstrated. These reports and their cautions regarding TRT are examples of confirmation bias, in which an observation seems to confirm a previously held belief without being subject to standard scientific rigor.

Racial variation in prostate cancer prevalence corresponds with serum testosterone levels

It has been argued in the past that the greater prevalence of PCa in African-American men can be explained by higher serum T levels in African-American men compared with US men of European descent [30]. Multiple studies have shown the magnitude of this difference to be nonexistent or small (<10%) for men older than 30 years of age, however [30]. Moreover, several studies have also shown higher serum T levels in low-risk Asian populations compared with white men [31,32]. Ethnic or racial variation in serum T levels thus seems to be highly unlikely to account for observed racial differences in PCa prevalence.

Prostate Cancer Prevention Trial

The Prostate Cancer Prevention Trial (PCPT) trial was a placebo-controlled study of the effects of finasteride on the risk for PCa development [33]. Finasteride is a 5 α -reductase inhibitor that markedly reduces the conversion of T to dihydrotestosterone (DHT) the primary androgen for the prostate. A 25% reduction in PCa risk was observed for men taking finasteride, suggesting that androgens are indeed involved in the development or growth of PCa [33].

It is important to emphasize here that there is no dispute that the presence of androgens is important for PCa growth or that severe reduction of androgens causes PCa regression. The question at hand is whether higher concentrations of T cause increasingly greater PCa growth, especially beyond the near-castrate range. The PCPT did not address this question.

Review of historical and current evidence regarding the relation of testosterone and prostate cancer

Historical experience with testosterone administration in men with prostate cancer

Several reports before 1980 described the results of T administration in previously untreated men with advanced PCa, most of whom had bony metastases. The largest of these was by Prout and Brewer [9], who described daily T injections in 26 men, 20 of whom were previously untreated, and other investigators reported smaller experiences [34,35]. The behavior of acid phosphatase in response to T administration was highly variable. Pearson [36], noting that Huggins and Hodges had described only one hormonally intact patient who developed an increase in acid phosphatase with T administration, offered a case report of another individual with metastatic PCa who received daily T injections without an appreciable increase in acid phosphatase until he developed clinical progression 9 months later.

Although these reports were not controlled, it is noteworthy that none of the investigators described clinical progression attributable to T administration. On the contrary, several men treated with T experienced subjective improvement, including prompt resolution of bone pain, increased appetite, weight gain, and improved sense of well-being [10]. Some of these men with metastatic disease were treated with daily T injections for as long as 1 year without adverse results.

These reports, largely lost to history, suggest a lack of apparent clinical progression with T administration, even in men with far-advanced disease.

Testosterone replacement therapy trials

Although no large-scale long-term studies of TRT have been performed, several smaller TRT trials of greater than 6 months' duration have revealed an annual cancer detection rate of approximately 1% [4]. The longest of these trials was 42 months [8]. This 1% cancer rate is similar to cancer detection rates in prostate screening trials [4].

Testosterone replacement therapy in a high-risk population

Men with high-grade prostatic intraepithelial neoplasia (PIN) have been reported to develop

frank PCa at a rate 25% or greater over 3 years [37]. In one study, TRT was provided to 20 hypogonadal men with PIN and 55 hypogonadal men with benign biopsies [38]. At the end of 12 months, PCa was identified in 1 man in the PIN group and none in the benign group. This represents a 5% cancer rate in the PIN group and a 1.3% cancer rate for the entire group. These results do not suggest a precipitous increase in the risk for PCa in this high-risk population.

Longitudinal studies

The relation of T and other sex hormones to subsequent development of PCa has been extensively studied in at least 16 population-based longitudinal studies [39–44]. In these studies, a health history is obtained and blood samples at baseline are then frozen for the duration of the study, up to 20 years or longer in some cases. At the end of the study, men who have developed PCa are identified, and a matched set of men without PCa serves as a control group.

A total of greater than 430,000 men have been included in these studies, including 1400 men with PCa and 4400 men identified as controls. Not one study has shown a direct correlation between total T levels and PCa. Isolated associations have been reported with some measures and PCa: minor androgens [42] in one study, calculated free T [43] in another study, and with quartile analysis of hormone ratios or controlling for multiple variables in a third study [44]. None of these positive associations have been supported by later studies. It is worth noting that the largest study of this type actually noted reduced PCa risk in men with higher T levels [41].

The importance of these studies is that they provide a sophisticated method of investigation to determine the long-term effects of hormone levels, especially T, on the subsequent risk for development of PCa. Although such studies cannot entirely replace the value of a prospective, long-term, controlled study of TRT, they do address the question as to whether high levels of T (or other hormones) predispose men to a greater risk for later development of PCa. On this question, these prospective longitudinal studies provide two uniform and convincing answers: first, that men who develop PCa do not have higher baseline T levels and, second, that men with higher T levels are at no greater risk for developing PCa than men with lower T concentrations.

Prostate cancer rates in men with low testosterone

If high T is believed to be associated with an increased risk for PCa, it follows that low T should be associated with a reduced risk. Sextant prostate biopsy in 77 hypogonadal men with normal digital rectal examination results and PSA of 4.0 ng/mL or less revealed cancer in 11 men, however [45]. A more recent study in 345 hypogonadal men found a similar overall cancer rate of 15.1% in men with PSA of 4.0 ng/mL or less, with an odds risk that was doubled for men with the lowest tertile of serum T compared with the upper tertile [46]. The overall cancer rate was similar to the 15.2% PCa rate noted by Thompson and colleagues [47] in the placebo arm of the PCPT but in a population that was a decade younger.

Other work has shown that low T is associated with high-grade Gleason scores, advanced stage at presentation, and worse survival [48–52]. These associations between low T and PCa risk constitute a new and emerging area of interest in oncology research [53].

Epidemiology of prostate cancer and testosterone

A major shortcoming of the theory that T causes enhanced PCa growth is the natural history of PCa. Clinical PCa almost never occurs when men are in their 20s, when T levels are at their lifetime peak. Conversely, it becomes highly prevalent when men are older and T levels have declined. If T truly behaved as fuel for a fire for PCa, one should expect to see a substantial number of PCa cases in extremely young men, especially because autopsy studies have identified the presence of PCa microfoci in as many as 2% of men in their 20s and 29% in their 30s [54]. In addition, because one in seven hypogonadal men has biopsy-detectable PCa [45,46], why is it that the cancer rate in clinical TRT trials is only 1% [4]?

Resolving the paradox: saturation

Because castration causes PCa to regress, how is it possible that T administration would fail to cause PCa to grow? The resolution of this apparent paradox was recognized at least a quarter of century ago by Fowler and Whitmore [23], who suggested that near-maximal stimulation of PCa occurred at physiologic T levels. This suggests a model of saturation in which existing PCa tumors have access to all the androgens they can use at fairly low serum concentrations, with

higher amounts representing a surfeit without impact on further growth.

This saturation model is supported by the landmark article by Marks and colleagues [55], in which intraprostatic levels of T and DHT were determined before and after 6 months of TRT. Although serum levels of both hormones increased substantially in the treatment arm, intraprostatic T and DHT did not change significantly and were no different from intraprostatic T and DHT in the placebo arm. Moreover, markers of cellular proliferation also did not change with therapy. These results indicate that changes in serum androgen levels in hypogonadal men are not reflected within the prostate itself. Another implication of the study is that the prostate seems able to create for itself a homeostatic environment with regard to androgens, at least within the range of serum T included in the study.

The traditional model regarding the relation of T and PCa is that PCa growth is tied to serum T concentration, such that low levels cause low rates of growth (or even negative growth in the case of castration) and higher levels cause enhanced growth, as originally described by Huggins. A graphic representation of this traditional model is shown in Fig. 1 and is represented by curves a and b, with an unquantified positive correlation between T and PCa growth, without apparent

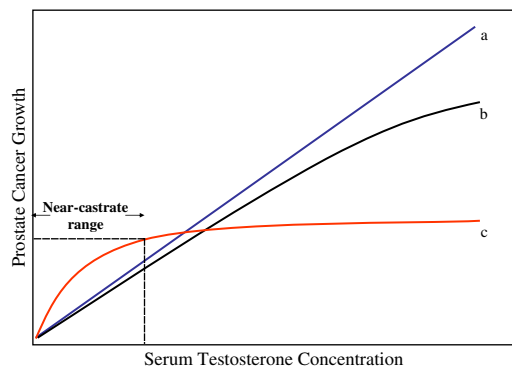


Fig. 1. Proposed saturation model for the relation of PCa growth and serum T concentration. The traditional belief has been that higher T concentrations caused increasing rates of PCa growth, as represented by curves a and b. All available evidence demonstrates a powerful effect of T on PCa growth at low T concentrations, however, but little or no effect beyond the near-castrate range. The proposed model for the relation between T and PCa is thus shown as curve c and is consistent with a saturation model, as seen in many other biologic systems.

limit. This approach can be summarized as “more T, more PCa growth.”

Yet, all available evidence fails to demonstrate any significant relationship between T and PCa beyond the castrate or near-castrate range. Without question, there is a powerful effect of T concentration on PCa at the low extreme of serum T concentration. However, this effect clearly plateaus at some low concentration of T. This saturation model is represented by curve c in the Fig. 1.

This type of saturation curve is common in biology and oncology. A similar curve c would apply to nearly any tumor and glucose or calcium. Both chemicals are metabolically required for growth; however, at some concentration, the cellular requirement for these agents is satisfied and higher concentrations do not have an impact on tumor growth.

This saturation model for T and PCa suggests that our old analogy of T being like food for a hungry tumor is false and misleading. An analogy that fits the available evidence far better is that “T is like water for a thirsty tumor.” Once the thirst has been quenched by adequate (and relatively low) T concentrations, additional amounts serve as nothing more than an excess.

Testosterone replacement therapy after treatment for prostate cancer

There are now several publications reporting no ill effects from administration of TRT in hypogonadal men previously treated for PCa. These included two small series in men with an undetectable PSA level after radical prostatectomy, with no recurrences noted in the 17 men followed for up to 12 years [56,57]. A more recent study of 31 hypogonadal men receiving TRT after brachytherapy for a mean of 4.5 years revealed that 100% maintained PSA levels less than 1.0 ng/mL, with a mean follow-up of 5 years [58]. No biochemical or clinical recurrences occurred. These results are consistent with the previously mentioned historical studies before 1980 in which T was administered to men with metastatic and advanced local disease without clinical evidence of harmful effects.

Discussion

The theory that higher T leads to enhanced PCa growth has been widely held for more than two thirds of a century and continues to inform

current medical behavior and recommendations. As reviewed previously, however, arguments offered over the years to support this theory lack substance, scientific rigor, or relevance. It is critical to acknowledge that the original assertion by Huggins that T causes greater PCa growth in untreated men was based on a single patient [1].

The persistence of this unsupported theory seems to owe its appeal and longevity to the confounding of three concepts regarding the relationship of T and PCa:

1. T is important for PCa growth (True).
2. Reducing androgens to castrate levels causes PCa regression (True).
3. Raising T in noncastrated men leads to enhanced PCa growth (Alleged, despite all evidence to the contrary).

The indisputable evidence supporting the first two does not necessarily make the third true. Yet, there has been little attempt in the past to tease apart these various points, and they have thus been accepted together as a general “truth” regarding the relation of T and PCa.

Evidence for a lack of a growth-enhancing effect of T beyond the near-castrate level includes the following: longitudinal studies show no correlation of PCa risk with serum T levels, no precipitous increase in PCa is seen in high-risk men receiving TRT, PCa risk does not seem to be reduced in men with low T, and the natural history of PCa is that clinical disease is almost nonexistent when T levels are at their lifetime peak and only becomes highly prevalent when T levels have declined. In addition, among men with known PCa, studies have failed to show any correlation between higher T levels and tumor grade, stage of presentation, or survival.

The assumption that T causes enhanced growth of PCa in otherwise untreated men represents the persistence of an unexamined historical belief [11]. This historical model is overly simplistic, suggesting that T provides a stimulus to PCa growth as a continuous variable (ie, more T, more growth). Available evidence supports a different model in which PCa growth is stimulated at near-castrate serum T concentrations but then soon reaches a saturation point greater than which higher T concentrations provide no increased stimulus to growth. This saturation model would explain why PCa occurs rarely in young men despite the simultaneous presence of PCa microfoci and high T levels and also why PCa

behavior and characteristics do not seem to correlate with T levels within the physiologic range. Although this saturation model accounts for much of what is known regarding T and PCa, its validity remains to be confirmed. If confirmed, might it be possible that TRT could be offered to men with untreated or even metastatic PCa?

At a minimum, it is time to acknowledge that our behavior regarding T and PCa is inconsistent and illogical. For example, we allow serum T levels to increase within the normal range after discontinuation of LHRH agonist treatment with radiation therapy, yet we generally withhold TRT from those who are symptomatic from failure of T levels to normalize, citing concerns of PCa progression. Some have suggested that TRT should not be offered to hypogonadal men at risk for PCa, yet there is no serious discussion of reducing T as prophylaxis for these men.

Although there is yet to be a large, long-term, controlled study on the effect of TRT on PCa risk, it should be abundantly clear that raising T in hypogonadal men has little, if any, impact on PCa risk or growth in the short to medium term. The withholding of TRT in men because of the fear of PCa risk or progression is no longer tenable in an age of evidence-based medicine, because neither evidence nor theory supports this position. It is time for a more sophisticated rethinking of the relation between T and PCa, one that is internally consistent, scientifically based, and accounts for all the rich and varied set of clinical and research data regarding PCa and hormones. Most importantly, physicians should be freed of antiquated and unscientific restrictions that inhibit optimal treatment of their patients.

Summary

The long-standing belief that higher T leads to greater PCa growth in noncastrated men is contrary to all accumulated evidence and should be discarded. The relation of T and PCa seems most consistent with a saturation model in which there is a powerful impact of serum T on PCa growth at castrate or near-castrate concentrations but little or no effect at higher T concentrations. Although there are no large long-term studies on the safety of TRT with regard to PCa, there does exist a wealth of evidence suggesting that TRT does not increase PCa risk. With proper medical monitoring, TRT can be safely offered to men with T deficiency.

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