Testosterone Therapy and Prostate Cancer

Emily Davidson, BS, Abraham Morgentaler, MD*

KEYWORDS

• Testosterone • Prostate • Prostate cancer • Androgens • Prostate-specific antigen
• Testosterone deficiency • Hypogonadism

KEY POINTS

- Considerable evidence contradicts the notion that higher testosterone levels are associated with increased risk of developing prostate cancer, or higher grade Gleason score.
- Major changes in prostate-specific antigens are observed when a serum testosterone moves into or out of the castrate range, but are not observed for changes at higher concentrations.
- Testosterone therapy may now be considered for selected men with a history of prostate cancer, provided that informed consent is obtained and close monitoring is performed.

INTRODUCTION

The biological effects of testosterone have been recognized throughout the recorded history of humankind, even before identification of the key biochemical element produced by the testis. With so much debate surrounding the use of testosterone therapy and prostate cancer, the entire background must be clear. The scientific history of testosterone started in 1849 with Arnold Berthold. Through his experiments with rooster castration and subsequent testes transplantation, he linked the physiologic and behavioral changes of castration to a substance secreted by the testes.[1] More interest developed as Dr Charles E. Brown-Séquard made a presentation on the self-administration of *liquid testiculaire* at the Societé de Biologie in June of 1889. He reported that the injection of testicular extracts derived from dogs and guinea pigs resulted in his increased physical strength, mental abilities, and appetite.[2] Scientists around the world continued to experiment with testicular extracts and testicular "transplants" as treatment for the maladies of aging. Finally, testosterone was isolated by David and colleagues[3] in 1935 and synthesized later that year. Both Adolf Butenandt and Leopold Ruzicka were awarded with the Nobel Prize for Chemistry in 1939 for their work.

Initially, there was an early 'honeymoon period' for testosterone therapy after it first became available, shortly after its synthesis.[4] An article from 1940 in the *New England Journal of Medicine* noted improvements in sexual desire and performance, increased strength, and improved sense of well-being in men treated for hypogonadism.[5] This 'honeymoon period' was short lived, as Huggins and Hodges reported in 1941 that castration caused regression of metastatic prostate cancer, and testosterone injections "activated" prostate cancer,[6] based on alterations in the prostate cancer serum marker, acid phosphatase. From that point on, use of testosterone became rare owing to fear of causing prostate cancer in otherwise healthy individuals.

Disclosure Statement: Dr A. Morgentaler has received payments for research, consulting, lecture honoraria, and/or scientific advisory boards for AbbVie, Antares, Bayer, Clarus, Eli Lilly (27705), Endo (201107293), and Pfizer. Ms E. Davidson has no conflicts to declare.
Men's Health Boston, Department of Surgery (Urology), Harvard Medical School, 200 Boylston Street, Suite A309, Chestnut Hill, MA 02467, USA
* Corresponding author.
E-mail address: dr.morgentaler@menshealthboston.com

Urol Clin N Am 43 (2016) 209–216
http://dx.doi.org/10.1016/j.ucl.2016.01.007
0094-0143/16/$ – see front matter

The Modern Era of Testosterone Therapy

Before the early 1990s, the use of testosterone therapy was rare, and was limited almost exclusively to younger men with severe cases of testosterone deficiency (TD) owing to pituitary tumors, anorchia, or genetic abnormalities such as Klinefelter syndrome. Over the past 20 years there has been a remarkable and steady growth in the use of testosterone therapy. This has occurred as a result of increased physician awareness of TD and the benefits of treatment, together with increased convenience of testosterone formulations.[7] Notable benefits include improved sexual desire and performance, improved energy, increased muscle and bone density, and improved metabolic status, similar to benefits reported at the advent of testosterone use in the 1940s.[5,8] The reinvigorated interest in testosterone therapy has led to a reexamination of traditional assumptions concerning prostate cancer and testosterone.[9] Despite important advances in our understanding of this topic, the use of testosterone therapy continues to be controversial because of prostate cancer fears, and this remains the greatest concern among physicians around the world with regard to the use of testosterone therapy.[10]

The Androgen Hypothesis

Stemming from reports in the 1940s, the androgen hypothesis has come to include the following features: prostate cancer is an androgen-dependent cancer, high testosterone levels contribute to the development of prostate cancer, high testosterone causes rapid growth of prostate cancer, and low testosterone is protective against development of prostate cancer and causes prostate cancer to regress.[1,11–13] Ever since, medical students and physicians have been taught that high testosterone promotes prostate cancer development and there seemed to be no reason to doubt this axiomatic concept.[14] The relationship between testosterone and prostate cancer was classified as “fuel for a fire” or “food for a hungry tumor”.[15] In an international survey published in 2007, as many as 70% of health care providers were concerned about the association of testosterone therapy and prostate cancer.[16] It was not until recently that this conventional wisdom was challenged.

The breakdown of the androgen hypothesis evolved throughout the years, beginning in the early 1990s. Morgentaler and colleagues[17] published a study in which testosterone deficient men with normal prostate-specific antigen (PSA; <4.0 ng/mL) and a normal digital rectal examination underwent a sextant prostate biopsy before initiating testosterone therapy. Interestingly, 11 of the first 77 men had prostate cancer. Compared with the 15.2% prostate cancer rate noted by Thompson and colleagues[18] in the placebo arm of the Prostate Cancer Prevention Trial, this 14.3% rate was shockingly similar. This was the first indication that low testosterone may be a risk factor for prostate cancer, and not protective against prostate cancer and its progression.[14]

Since this revelation, more than 20 population-based longitudinal studies have shown no relationship between prostate cancer and serum testosterone or other androgens.[19] The Endogenous Hormones and Prostate Cancer Collaborative Group published high-level evidence from a metaanalysis consisting of 18 studies that included 3886 men with incident prostate cancer and 6438 controls.[20] The results demonstrated no direct association between endogenous serum androgens and the development of prostate cancer. Additionally, Muller and colleagues[21] analyzed 3255 men in the placebo arm of the reduction by Dutasteride of Prostate Cancer Events trial. Men underwent prostate biopsies at 2 years and 4 years and there was no relationship found between testosterone or dihydrotestosterone levels and prostate cancer risk.

Although high testosterone levels were thought to contribute to the development of prostate cancer, there is a complete lack of compelling evidence in the literature.[22] An extensive review found that men with higher endogenous testosterone or who had undergone testosterone therapy were not at increased risk of prostate cancer.[20] Supraphysiologic doses of testosterone for up to 9 months in healthy men failed to demonstrate a significant increase in PSA or prostate volume.[23,24] The notion that “more testosterone is bad, less testosterone is good” was not necessarily true.

The Saturation Model

However, physicians still recognize that initiation of androgen deprivation causes rapid declines in PSA and that cessation of androgen deprivation causes rapid increases in PSA. Revisiting the landmark work of Huggins and Hodges, the traditional view suggests a continuous relationship between serum testosterone and prostate cancer growth.[15] Studies from Prout and Brewer[25] and Fowler and Whitmore[12] present an alternative possibility. Both papers noted no evidence of progression in men with prostate cancer not treated by androgen deprivation or castration.[12,25] The evidence presents a paradox: how can prostate cancer be so sensitive to androgen deprivation, yet seem to be indifferent to variations in serum androgens under other circumstances?

The resolution of this paradox is the saturation model. The saturation model accounts for the key observation that prostate tissue is exquisitely sensitive to changes in serum testosterone at low concentrations, but becomes indifferent to these changes at higher concentrations.[26] Exposure to increasing concentrations of androgen causes prostate tissue growth, but this growth rate plateaus when the concentration reaches a limit.[27] There exists a threshold (saturation point) beyond which there is no further ability to induce androgen-driven changes in prostate tissue growth.[9] Similar relationships are found throughout biology. This explains why dramatic PSA changes are noted when serum testosterone is manipulated into or out of the castration range, but minimal PSA changes occur when supraphysiologic testosterone doses are administered to normal men.[28]

At least 2 mechanisms underlie the model. The first is the finite ability of the androgen receptor to bind androgen.[29,30] Maximal binding of the androgen to the androgen receptor (saturation) in human prostate is achieved in vitro at approximately 4 nmol-1.[28] In vivo, the saturation point is approximately double this value, at 8nmol/L or approximately 250 ng/dl.[9] Because the primary actions of androgen on prostate tissue occur via binding to androgen receptor, once the androgen receptors are saturated the presence of higher androgen concentrations should not elicit further biochemical response.[26] A second mechanism is that intraprostatic androgen concentrations seem to be somewhat independent of serum concentrations.[28] Marks and colleagues[31] demonstrated that intraprostatic concentrations of testosterone and dihydrotestosterone were unchanged after 6 months of testosterone injections, despite large increases in serum testosterone concentrations. This raises the possibility that the prostate maintains a relatively homeostatic microenvironment with regards to androgens, relatively unaffected by changes in serum androgens.[26]

This saturation model derails the notion that testosterone is "fuel for a fire" or "food for a hungry tumor."[14] An analogy that better fits the available evidence is "testosterone is like water for a thirsty tumor." Once that thirst has been quenched by adequate testosterone concentrations, additional androgens serve as nothing more than excess.[27]

The presentation of the saturation model and the shift in concepts regarding testosterone and prostate cancer have important clinical implications. Approximately 20% to 30% of elderly men over the age of 60 experience TD.[32] Symptoms of TD vary, but include fatigue, weakness, decreased libido and energy, erectile dysfunction, reduced muscle and bone mass, and increased abdominal fat.[33] Testosterone therapy is an effective, commonly used treatment shown to be effective in mitigating the bothersome symptoms of TD.[34]

As physicians gain a better understanding of TD and its consequences, there has been a reevaluation of the risks of testosterone therapy, particularly with regard to prostate cancer. Some clinicians still fear that testosterone therapy may unmask occult prostate cancer in otherwise healthy men with TD, but more evidence is mounting in favor of the benefits of testosterone therapy.[34] Whereas prior history of prostate cancer was considered an absolute contraindication to the use of testosterone therapy, physicians are recognizing the benefits of testosterone treatment in certain populations.[33]

Although no randomized, controlled trials have been performed to assess testosterone therapy and prostate cancer risk, evidence to date fails to suggest increased risk.[9] Calof and colleagues[35] conducted a metaanalysis of 19 placebo-controlled testosterone therapy trials and found no significant increase in prostate cancer or development of PSA levels greater than 4.0 ng/ml in men treated with testosterone therapy versus placebo. A systematic review of 11 placebo-controlled studies by Shabsigh and colleagues[36] showed that men who received testosterone therapy had neither increased risk of prostate cancer nor greater Gleason grade among those who developed prostate cancer. In the UK Androgen study, Feneley and Carruthers[37] followed 1365 British men 28 to 87 years of age and found the risk of prostate cancer diagnosis to be similar to age-matched controls. Only 1 of 20 patients with high-grade prostatic intraepithelial neoplasia developed prostate cancer during 12 months of testosterone therapy.[38] Combined with the studies cited previously reporting no increased risk of prostate cancer based on endogenous androgen concentrations, these data can reliably ease the fear that higher testosterone concentrations increase the risk of prostate cancer.

Association of Low Serum Testosterone with Prostate Cancer

Clouded by the long-held fear that high serum testosterone is a risk for prostate cancer, there has been little appreciation for a literature that strongly shows a relationship between low serum testosterone concentrations and high-risk prostate cancer.[15] Men with the lowest tertile of serum testosterone had nearly double the risk of being diagnosed with prostate cancer on biopsy compared with men with less severe TD, in a study

of 345 men with TD and PSA levels of less than 4.0 ng/mL.[18] Among men with prostate cancer, a high Gleason score has been reported with lower serum testosterone concentrations.[39,40] In an open clinical study conducted by Mearini and colleagues,[41] 37% of the 65 patients with prostate cancer had testosterone levels of less than 2.5 ng/mL. One study from García-Cruz and colleagues[42] including 137 men undergoing biopsy for suspicion of prostate cancer found an inverse relationship between serum testosterone and prostate cancer. Salonia and colleagues[43] measured serum testosterone on the day before radical prostatectomy (RP), and found that the risk of seminal vesicle invasion, a markedly poor prognostic indicator, was increased significantly in men with low testosterone levels, including a 3-fold increased risk in men with severely reduced serum testosterone.[14]

Low levels of serum testosterone have also been reported in association with poor prognosis from prostate cancer. Yamamoto and colleagues[44] reported increased rates of biochemical recurrence after RP in patients with low testosterone, and low levels of free testosterone were reported as an independent prognostic factor for prostate cancer progression in a study of 154 men undergoing active surveillance for prostate cancer.[45]

These studies are consistent with the epidemiology of prostate cancer, in that there is increased prevalence of high-grade prostate cancer as men age (Thompson and colleagues[18]) and testosterone levels decline.

Testosterone Therapy in Men with a History of Prostate Cancer

Testosterone therapy for men with a history of prostate cancer remains controversial, particularly because prostate cancer has been considered a contraindication for testosterone therapy for several decades, and testosterone product labels carry this warning as well. However, with the emergence of the saturation model and evidence mounting against the traditional androgen hypothesis, the paradigm has shifted. Multiple investigators have now reported on the use of testosterone therapy in men with prostate cancer, with published case series beginning in the mid-2000s. Overall, these studies have provided reassuring results regarding the risk of testosterone therapy in men with prostate cancer. In a study by Kaplan and Hu,[46] Surveillance, Epidemiology, and End Results data were linked to Medicare data to identify 149,354 men diagnosed with prostate cancer between 1992 and 2007. Of these, 1181 (0.79%) received testosterone therapy after diagnosis. No differences were reported in overall survival, cancer-specific survival, or in the use of salvage androgen deprivation therapy in men with or without use of testosterone after diagnosis.

In 2004, Kaufman and Graydon[47] reported no prostate cancer recurrences in 7 men treated with testosterone therapy after RP. Median follow-up in the study was 2 years, with the longest follow-up of 12 years. Agarwal and Oefelein[48] reported no recurrences in 10 testosterone deficient men with history of RP who received testosterone therapy for up to 19 months. In a larger case series of 57 men with predominantly low and intermediate risk prostate cancer, Khera and colleagues[49] reported no biochemical recurrences after a median follow-up time of 13 months. Men were treated with testosterone therapy for an average of 36 months after RP. In the largest series to date, Pastuszak and colleagues[50] examined the records of 103 hypogonadal men after RP. In this study there were also 49 eugonadal men who underwent RP but did not receive testosterone therapy, included as a comparison group. Approximately one-quarter of these men in each group were considered high risk based on Gleason score 8 to 10, positive margins, or the presence of positive lymph nodes at surgery. With a median follow-up of 27 months, biochemical recurrence rates were 4% in the testosterone-treated group and 16% in the untreated, eugonadal group.

In 2007, Sarosdy[51] published a case series evaluating 31 men with TD receiving testosterone therapy after brachytherapy treatment for prostate cancer. The median time for initiation of testosterone therapy was 2 years after treatment and median follow-up was 5 years (range, 1.5–9). There was no evidence of biochemical recurrence and none of the men halted testosterone therapy owing to prostate cancer recurrence. Morales and colleagues[52] reported a prospective case series consisting of 5 men that had been previously treated with external beam radiation therapy for prostate cancer. After reaching nadir PSA levels, these men received testosterone therapy. Median follow-up was 14.5 months (range, 6–27). The PSA level did increase transiently in 1 patient, but none exceeded 1.5 ng/mL to raise any concern of biochemical recurrence.

A small number of reports also describe testosterone therapy in men who underwent radiation therapy for prostate cancer. In 2013, Pastuszak and colleagues[53] evaluated 13 men with low and intermediate risk prostate cancer treated with testosterone therapy after radiation (brachytherapy or external beam radiation therapy). After median follow-up of 29.7 months, no biochemical recurrences were reported. More recently,

Balbontin and colleagues[54] reported no biochemical recurrence in a case series of 20 men with low-risk prostate cancer treated with brachytherapy. Testosterone treatment lasted for a median of 14 months and median follow-up was 31 months (range, 12–48). Notably, PSA level declined from 0.7 to 0.1 ng/mL. More recently, Pastuszak and colleagues[55] also present a multiinstitutional cohort of 98 men who received testosterone therapy after radiation treatment for prostate cancer. Of these men, 76.6% had low or intermediate risk prostate cancer and the median follow-up was 40.8 months. A small but statistically significant increase in PSA levels was noted with testosterone therapy, from 0.8 to 0.9 mg/mL, and 6 men (6.1%) experienced biochemical recurrence. This recurrence rate is lower than previously reported rates of biochemical recurrence after radiation therapy. However, one must be cautious in drawing conclusions owing to the limited sample size of this and other studies, their retrospective study design, and single-arm methodology.

In addition, there are now several reports of testosterone therapy in men undergoing active surveillance for prostate cancer. Morgentaler and colleagues[56] performed a retrospective study of 13 hypogonadal men receiving testosterone therapy for at least 12 months while undergoing active surveillance for prostate cancer. Median follow-up was 2.5 years (range, 1–8.1). At initial biopsy, 12 men had low-risk prostate cancer and 1 man had intermediate risk prostate cancer (Gleason 3 + 4). No prostate cancer progression was noted, and no cancer was found in 54% of biopsies. Recently, Kacker and colleagues[57] retrospectively reviewed a larger series of men on active surveillance, comparing progression rates in 28 men with TD who underwent testosterone therapy with 96 men with TD who did not receive testosterone therapy. Median follow-up was 38.9 months and 42.4 months for the testosterone group and the no-testosterone groups, respectively. Progression rates were similar between the 2 groups.

A cautionary note was struck by Morales,[58] who reported erratic PSA responses to testosterone therapy in 6 men with untreated prostate cancer and one man without documented prostate cancer. However, no follow-up biopsy results were reported, making it difficult to interpret these results.[58]

Discussion

Given the proven benefits of testosterone therapy for testosterone-deficient men, clinicians are faced with a dilemma. Large numbers of men around the world, including younger men aged 40 to 50 years, have been treated and cured of prostate cancer. With some of these men having long life expectancies, is it reasonable to deprive these men of a treatment that may provide important benefits and enhanced quality of life based on a historical concern that does not seem to be supported by current scientific evidence?

When evidence contradicts theory, it is useful to try to understand how the theory came into being. From the early 1940s when Huggins first reported that castration lowered serum acid phosphatase in men and that testosterone injections increased it, there was extremely limited clinical experience with testosterone therapy. This situation changed with introduction of the first branded topical testosterone products in the late 1990s and early 2000s. Before that time, the only experience physicians had with manipulation of testosterone levels, particularly urologists, was to lower serum testosterone into the castrate range as treatment for prostate cancer. This effectively lowered PSA. There was no reason, therefore, to question the axiom that high testosterone contributed to prostate cancer development and growth, and that low testosterone protected against it. It was therefore stunning to discover in 2006 that the original conclusion by Huggins—that testosterone injections "activated" prostate cancer—was based on only a single hormonally intact patient. The reliable, albeit temporary, results observed by all urologists with lowering androgen concentrations, and the lack of experience with raising testosterone contributed to the belief that higher testosterone concentrations were risky.

Today, it must be recognized that there exists no evidence that testosterone therapy increases prostate cancer risk in testosterone-deficient men. Although the fear of aggravating prostate cancer with testosterone therapy among physicians is understandable given our training, it should be clear that the theoretic underpinning of this concept has been shown to be unsound, and there are now numerous clinical experiences and publications that demonstrate that the risk of worsening prostate cancer outcomes with testosterone therapy seems to be small, if present at all.

The leading controversy today is whether testosterone therapy can be safely offered to men with a history of prostate cancer. Recommendations for this have been provided in a recent review by a group of experts in the field.[9] Our own recommendations are similar. Candidates should be those with symptomatic TD who stand to benefit from treatment. Informed consent should be provided to patients, specifically including information that safety data are limited, no controlled prospective studies have yet been

performed, and there is thus an unknown degree of risk of cancer progression or recurrence with testosterone therapy. We require a signed consent form stating these points in our practice. In addition, patients should be informed of the standard risks associated with testosterone therapy, including acne, erythrocytosis, fluid retention, peripheral edema, infertility, testicular atrophy, and gynecomastia.

It is useful to remember that prostate cancer recurrence occurs at a significant rate in men treated for prostate cancer, even if no testosterone therapy is offered. This baseline risk of approximately 15% must be considered when offering testosterone therapy. This means that some men will experience prostate cancer recurrence or progression whether or not they receive testosterone therapy. However, there will be a reflex presumption on the part of patients and other physicians that it was the increase in serum androgens that triggered the recurrence or progression. Adequate counseling of patients before beginning testosterone therapy is of great help in countering this eventuality, and we repeat this conversation regularly during the course of treatment.

Among men with a history of prostate cancer, the safest candidates for testosterone therapy are those with low-risk disease who have an undetectable PSA after RP. A relatively low-risk group also includes those with excellent PSA responses to radiation therapy. Until more data are available, testosterone therapy in men on active surveillance should be undertaken only with great caution. And testosterone therapy should be avoided in men with advanced or metastatic disease, and in men currently treated with androgen deprivation.

Another point to consider is that any man, with or without a history of prostate cancer, is likely to experience an increase in PSA if their baseline serum testosterone is below the saturation point. This varies from one individual to another, but the saturation point seems to be approximately 250 ng/dL. Thus, if a man begins treatment with a serum testosterone of 150 ng/dL it can be expected that his PSA will increase for the first 3 to 6 months, whereas this is less likely in a man with a baseline serum testosterone of 290 ng/dL.

For all men receiving testosterone therapy with treated or untreated prostate cancer, follow-up should be rigorous, especially in the first year of treatment. Physicians must be prepared for prostate cancer recurrence and the possibility that it may be interpreted as a result of testosterone therapy. Hematocrit and hemoglobin should be measured 2 to 4 times in the first year, then annually. PSA levels should be measured every 3 to 4 months in the first year, then biannually. Digital rectal examination should be performed 1 to 2 times in the first year, then annually. It should also be noted that for those men undergoing active surveillance, an annual prostate biopsy should be performed to ensure cancer stability. After stability has been determined, longer intervals may be suitable.

SUMMARY

There has been a revolution in thought and practice over the last 20 years regarding the relationship of testosterone and prostate cancer. The increase in the use of testosterone therapy has coincided with a growing awareness that the historical fear regarding testosterone and prostate cancer can no longer be accepted as true. Considerable evidence contradicts the notion that higher testosterone levels are associated with increased risk of developing prostate cancer, or higher grade Gleason score. The saturation model provides a satisfying explanation for why major changes in PSA are observed when a man's serum testosterone moves into or out of the castrate range. Indeed, there is now ample evidence that investigators should be more concerned about the risks of low testosterone concentrations rather than high testosterone with regard to prostate cancer. The use of testosterone therapy among men with a history of prostate cancer should no longer be considered an absolute contraindication. Scientific thought has been turned upside down over the last 20 years on the issue of testosterone therapy and prostate cancer.

REFERENCES

1. Morales A. The long and tortuous history of the discovery of testosterone and its clinical application. J Sex Med 2013;10(4):1178–83.
2. Freeman ER, Bloom DA, McGuire EJ. A brief history of testosterone. J Urol 2001;165:371–3.
3. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. Clin Endocrinol 2006;65:275–81.
4. Morgentaler A, Feibus A, Baum N. Testosterone and cardiovascular disease–the controversy and the facts. Postgrad Med 2014;127:159–65.
5. Aub JC. Endocrines: the use of testosterone. N Engl J Med 1940;222:877–81.
6. Huggins C, Hodges CV. The effect of castration, of estrogen and of androgen injection on serum phosphatase on metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.
7. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. JAMA Intern Med 2013;173:1465–6.

8. Zarotsky V, Huang MY, Carman W, et al. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. Andrology 2014;2:819–34.
9. Khera M, Crawford D, Morales A, et al. A new era of testosterone and prostate cancer: from physiology to clinical implications. Eur Urol 2014;65:115–23.
10. Morgentaler A. Testosterone and prostate cancer: what are the risks for middle-aged men? Urol Clin North Am 2011;38:119–24.
11. Huggins C, Stevens RE, Hodges CV. Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209–23.
12. Fowler JE Jr, Whitmore WF Jr. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. J Urol 1981;126:372–5.
13. Morgentaler A. Goodbye androgen hypothesis, hello saturation model. Eur Urol 2012;62:765–7.
14. Morgentaler A. Turning conventional wisdom upside-down. Cancer 2011;117:3885–8.
15. Morgentaler A. Rapidly shifting concepts regarding androgens and prostate cancer. ScientificWorldJournal 2009;9:685–90.
16. Carson CC 3rd, Kirby R. Prostate cancer and testosterone replacement therapy-what is the risk? J Urol 2015;194(6):1527–8.
17. Morgentaler A, Bruning CO, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996;276:1904–6.
18. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level≤ 4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.
19. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. Eur Urol 2006;50:935–9.
20. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, et al. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170–83.
21. Muller RL, Gerber L, Moreira DM, et al. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. Eur Urol 2012;62:757–64.
22. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92.
23. Cooper CS, Perry PJ, Sparks AE, et al. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. J Urol 1998;159:441–3.
24. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001;281:1172–81.
25. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. Cancer 1967;20:1871–8.
26. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009;55:310–21.
27. Morgentaler A. Testosterone replacement therapy and prostate cancer. Urol Clin North Am 2007;34:555–63.
28. Morgentaler A, Conners WP. Testosterone therapy in men with prostate cancer: literature review, clinical experience, and recommendations. Asian J Androl 2015;17:206.
29. Ho SM, Damassa D, Kwan PW, et al. Androgen receptor levels and androgen contents in the prostate lobes of intact and testosterone-treated noble rats. J Androl 1985;6:279–90.
30. Traish AM, Williams DF, Hoffman ND, et al. Validation of the exchange assay for the measurement of androgen receptors in human and dog prostates. Prog Clin Biol Res 1988;262:145–60.
31. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA 2006;296:2351–61.
32. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore longitudinal study of aging. J Clin Endocrinol Metab 2001;86:724–31.
33. Kava BR. To treat or not to treat with testosterone replacement therapy: a contemporary review of management of late-onset hypogonadism and critical issues related to prostate cancer. Curr Urol Rep 2014;15:1–10.
34. Traish AM, Miner MM, Morgentaler A, et al. Testosterone deficiency. Am J Med 2011;124:578–87.
35. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005;60:1451–7.
36. Shabsigh R, Crawford ED, Nehra A, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. Int J Impot Res 2009;21:9–23.
37. Feneley MR, Carruthers M. Is testosterone treatment good for the prostate? Study of safety during long-term treatment. J Sex Med 2012;9:2138–49.
38. Morgentaler A. Testosterone deficiency and prostate cancer: emerging recognition of an important and troubling relationship. Eur Urol 2007;52:623–5.
39. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol 2000;163:8247.

40. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate 2001;47:52–8.
41. Mearini L, Costantini E, Zucchi A, et al. Testosterone levels in benign prostatic hypertrophy and prostate cancer. Urol Int 2008;80:134–40.
42. García-Cruz E, Piqueras M, Huguet J, et al. Low testosterone levels are related to poor prognosis factors in men with prostate cancer prior to treatment. BJU Int 2012;110:E541–6.
43. Salonia A, Gallina A, Briganti A, et al. Preoperative hypogonadism is not an independent predictor of high-risk disease in patients undergoing radical prostatectomy. Cancer 2011;117:3953–62.
44. Yamamoto S, Yonese J, Kawakami S, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol 2007;52:696–701.
45. San Francisco IF, Rojas PA, DeWolf WC, et al. Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance. BJU Int 2014;114:229–35.
46. Kaplan AL, Hu JC. Use of testosterone replacement therapy in the United States and its effect on subsequent prostate cancer outcomes. Urology 2013;82:321–6.
47. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol 2004;172:920–2.
48. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. J Urol 2005;173:533–6.
49. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. J Sex Med 2009;6:1165–70.
50. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol 2013;190:639–44.
51. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer 2007;109:536–41.
52. Morales A, Black AM, Emerson LE. Testosterone administration to men with testosterone deficiency syndrome after external beam radiotherapy for localized prostate cancer: preliminary observations. BJU Int 2009;103:62–4.
53. Pastuszak AW, Pearlman AM, Godoy G, et al. Testosterone replacement therapy in the setting of prostate cancer treated with radiation. Int J Impot Res 2013;25:24–8.
54. Balbontin FG, Moreno SA, Bley E, et al. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. BJU Int 2014;114:125–30.
55. Pastuszak AW, Khanna A, Badhiwala N, et al. Testosterone therapy after radiation therapy for low, intermediate, and high risk prostate cancer. J Urol 2015;194(5):1271–6.
56. Morgentaler A, Lipshultz LI, Bennett R, et al. Testosterone therapy in men with untreated prostate cancer. J Urol 2011;185:1256–60.
57. Kacker R, Mariam H, San Francisco IF, et al. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. Asian J Androl 2016;18(1):16–20.
58. Morales A. Effect of testosterone administration to men with prostate cancer is unpredictable: a word of caution and suggestions for a registry. BJU Int 2011;107:1369–73.