A Medical Myth

A common medical myth is that Testosterone is somehow causative of prostate cancer. This has been found to be completely incorrect, as we will see below. Rather than elevated Testosterone being associated with prostate cancer, it is **LOWER** levels that are associated with aggressive prostate cancer with poor outcome. Indeed, lower testosterone has been found to be associated with increased all cause mortality in males in a number of studies.(ZZZ)

PSA and Testosterone Observations (see references 1-16)

(1) Lower Testosterone Levels (**not higher levels**) are associated with increased risk for aggressive prostate cancer. Higher levels within the normal range are associated with less risk for Prostate CA. This is directly opposite to the ingrained urology dogma, and was demonstrated by biopsy studies by Morgentaler and Rhoden. (7)

(2) PSA level will go down when testosterone is withdrawn or given DHT blockade with finasteride.

(3) PSA will rise transiently after starting Testosterone, and then stabilize at new level.

(4) Hypogonadal symptomatic patients following treated prostate cancer having undetectable PSA of zero, may be safely treated with testosterone therapy.(9-14)

Left Image: Anatomy Drawing of Prostate and Seminal Vesicles Courtesy of Wikimedia Commons

Articles with related interest:

This article is part two. Click Here for part ONE.

PSA Screening for Prostate Cancer, the Failed Medical Experiment

Increased Mortality from Androgen Blockade for Prostate Cancer

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http://www.drdach.com
http://www.naturalmedicine101.com
http://www.truemedmd.com

Links and References

Testosterone and PSA

(1) http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1472885
Rev Urol. 2004; 6(Suppl 6): S41–S43. PMCID: PMC1472885

Rising PSA during Testosterone Replacement Therapy, John Gore, MD and Jacob Rajfer, MD Department of Urology, The David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA

As this case clearly demonstrates, a **rising PSA** does not necessarily imply that an undetected prostate cancer is present. Although the hormonal responsiveness of prostate cancer is well established, it is generally accepted that **TRT does not induce the development of prostate cancer**.3 Furthermore, a recent report demonstrated **no increased risk of prostate cancer in men with prostatic intraepithelial neoplasia**, a precursor of prostate cancer, on TRT, although appropriate controls were not included in the study.4

It is not surprising to see PSA changes in men receiving androgen therapy. Hypogonadal men have depressed PSA levels compared to normal age-matched men, and patients on **finasteride treatment experience a 2.2-fold reduction in serum PSA.5,6** Averaging several investigations of the effect of TRT on PSA, men receiving testosterone will have an associated increase of **0.30 ng/mL/y in serum PSA, with older men experiencing a greater increase of 0.43 ng/mL/y**.5 Changes in PSA are expected in patients on TRT, but this expectation should not downplay the need for rigorous follow up in this patient population.

It is our recommendation that clinicians perform a baseline digital rectal examination and PSA before starting TRT, and that the PSA should be checked 6–12 weeks after initiation of androgen therapy, regardless of the route of administration. The PSA should then be monitored semi-annually as long as the patient remains on TRT, in addition to having an annual digital rectal examination. **A PSA velocity greater than 0.75 ng/mL/y, regardless of the baseline PSA, or a nodule on digital rectal examination while on TRT should prompt further investigation with a prostate biopsy.**

(2) http://jcem.endojournals.org/cgi/content/full/92/2/416

The Journal of Clinical Endocrinology & Metabolism Vol. 92, No. 2 416-417

Guideline for Male Testosterone Therapy: A Clinician's Perspective – Abraham Morgentaler Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Myth that Testosterone Causes Prostate Cancer

(3) http://www.urologic.theclinics.com/article/S0302-2838(06)00787-1/abstract

Volume 50, Issue 5, Pages 935-939 (November 2006) Urologic Clinics

Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth? Abraham Morgentaler

To review the historical origins and current evidence for the belief that testosterone (T) causes prostate cancer (pCA) growth.

Methods: Review of the historical literature regarding T administration and pCA, as well as more recent studies investigating the relationship of T and pCA.

Results: In **1941 Huggins and Hodges** reported that marked reductions in T by castration or estrogen treatment caused metastatic pCA to regress, and administration of exogenous T caused pCA to grow. Remarkably, this latter conclusion was based on results from only one patient. Multiple subsequent reports revealed no pCA progression with T administration, and some men even experienced subjective improvement, such as resolution of bone pain. More recent data have shown no apparent increase in pCA

rates in clinical trials of T supplementation in normal men or men at increased risk for pCA, no relationship of pCA risk with serum T levels in multiple longitudinal studies, and no reduced risk of pCA in men with low T. The apparent paradox in which castration causes pCA to regress yet higher T fails to cause pCA to grow is resolved by a saturation model, in which maximal stimulation of pCA is reached at relatively low levels of T.

Conclusions. This historical perspective reveals that there is not now—nor has there ever been—a scientific basis for the belief that T causes pCA to grow. Discarding this modern myth will allow exploration of alternative hypotheses regarding the relationship of T and pCA that may be clinically and scientifically rewarding.

Take Home Message . **It has long been believed that higher testosterone levels cause greater prostate cancer growth. However, review of the original literature and current data reveal that this once-plausible hypothesis has become a modern myth that interferes with critical assessment of the topic.**

Effect of Tesosterone on PSA level

(4) http://www.andrologyjournal.org/cgi/content/full/24/3/299

Journal of Andrology, Vol. 24, No. 3, May/June 2003

Managing the Risks of Prostate Disease During Testosterone Replacement Therapy in Older Men: Recommendations for a Standardized Monitoring Plan. SHALENDER BHASIN et al

Lowering of serum testosterone concentrations by withdrawal of androgen therapy in young men with hypogonadism is associated with a **decrease in serum PSA levels** (Meikle, 1997). Similarly, treatment of men with BPH with a 5-alpha reductase inhibitor, **finasteride, is associated with a significant lowering of serum and prostatic PSA levels** (Gormley et al, 1992). Testosterone replacement in healthy young men with hypogonadism have demonstrated a significant **increase in serum PSA levels** after testosterone administration (Table 1),

This means that the average effect of testosterone replacement therapy is to increase PSA levels by about 0.68 standard deviations over baseline. Because the average standard deviation was 0.47 in this systematic analysis, the standard deviation score of 0.68 translates into an average increase in **serum PSA levels of about 0.30 ng/mL**.

Monitoring PSA Levels in Older Men Receiving Testosterone Replacement—

Older men considering testosterone supplementation should undergo digital examination of the prostate, evaluation of risk factors for prostate cancer, and symptom scores for BPH using either the AUA or the IPSS questionnaire, and a baseline PSA measurement (Table 3). As a general rule, men with a previous history of prostate cancer should not be given androgen supplementation, and those with **palpable abnormalities** of the prostate **or PSA levels >4 ng/mL** should undergo urological evaluation (Table 4). We recognize that some men with hypogonadism who have had a radical prostatectomy for prostate cancer and undetectable PSA levels for several years may be “cured” and **may be candidates for testosterone replacement therapy**. Because testosterone administration could potentially promote the growth of residual cancer, replacement therapy in this setting should only be considered after urological consultation and after a thorough discussion of the potential risks. If replacement therapy is provided to such men, PSA levels must be monitored more frequently. Men

with **BPH** and mild to moderate symptoms of (AUA symptom score less than 21) can be safely treated with testosterone replacement with careful follow-up.
After initiation of testosterone replacement therapy, PSA levels and digital examination of the prostate should be repeated at 3, 6, and 12 months, and annually thereafter (Andropause Consensus Panel, 2001). Clinical experience and data from controlled clinical trials have established that the increments in PSA levels after testosterone administration in men with hypogonadism **occur in the first 3–6 months,** at which point new steady state PSA levels are achieved. Continued treatment beyond 12–24-weeks would be expected to be associated only with predictable, age-related changes in PSA levels. Therefore, **excessive increases in serum PSA levels after 3–6 months of initiating testosterone replacement therapy should be investigated.** Our recommendations for requesting a urological consultation are provided in Table 5.
Thus, on average, **older men experience a greater increase** in serum PSA concentrations than populations of predominantly younger men. The average effect of testosterone replacement in older men is to increase PSA levels by almost 1.5 standard deviations over baseline. There is, however, significant variability in the results among these 6 studies ($P < .0001$), and the average standard deviation was skewed by 1 study, which had a very high standard deviation (Kenny et al, 2001). After excluding this study, the average change in serum PSA levels after testosterone replacement in studies of older men was **0.43 ng/mL**
These data taken together suggest that the administration of replacement doses of testosterone in men with androgen deficiency can be expected to produce a modest increment in serum PSA levels. Increments in PSA levels after testosterone supplementation **in men with androgen deficiency are generally less than 0.5 ng/mL, and increments in excess of 1.0 ng/mL over a 3–6 month period are unusual**. **Nevertheless, administration of testosterone to men with baseline PSA levels between 2.5 and 4.0 ng/mL will cause PSA levels to exceed 4.0 ng/mL in some men**. Increments in PSA levels above 4 ng/mL will trigger a urological consultation and many of these men will be asked to undergo prostate biopsies.

Application of the PSA Velocity Criterion to Prostate Monitoring During Testosterone Administration

Carter et al (1995) demonstrated that if the baseline PSA were between 4 and 10 ng/mL, a rate of change of **>0.75 ng/mL/y in PSA was unusual in men with benign prostatic disease.**
In another study a PSA velocity cutoff of 0.75 ng/mL or more per year provided a sensitivity of 79% and a specificity of 66% in predicting prostate cancer (Smith and Catalona 1994). These observations came from a prostate cancer detection study that involved 312 men with baseline PSA levels of <4.0 ng/mL and who subsequently developed PSA values >4.0 ng/mL

Effects of Testosterone Supplementation on Prostate Volume and Course of BPH

Lowering of serum testosterone concentrations by administration of a GnRH agonist, or blocking androgen effects by administration of an antiandrogen is associated with a **reduction in prostate volume**. These treatments are typically associated with a 20%–30% reduction in prostate volume. Inhibition of steroid 5-alpha-reductase enzyme by finasteride decreases serum and intraprostatic DHT concentration, and was associated

with an average **16% reduction in prostate volume** in a large multicenter study (Gormley et al, 1992). Thus, once established, androgen deprivation is moderately effective in reducing prostate volume.
Therefore, we do not know whether testosterone replacement therapy will increase the need for invasive treatment of BPH.
Because androgen replacement in men with androgen deficiency increases prostate volumes only modestly (Sasagawa, 1990; Behre, 1994; Cooper et al, 1996; Meikle, 1997), there is typically little or no change in prostate symptom scores in most men treated with replacement doses of testosterone. However, it is possible that in patients with pre-existing, **severe symptoms of BPH, even small increases in prostate volume during testosterone administration may exacerbate obstructive symptoms**. In these men, testosterone should either not be administered or it should be administered with careful monitoring of their obstructive symptoms and only after their prostatic enlargement has been effectively treated urologically.
(5) http://www.testosteroneupdate.org/podcasts_d.php
Presentations held at the 2008 American Urological Association Annual Meeting
May 17-20, 2008, Orlando, Florida
(6)http://www.ncbi.nlm.nih.gov/pubmed/17113983
J Steroid Biochem Mol Biol. 2006 Dec;102(1-5):261-6.
Prostate cancer risk in testosterone-treated men. Raynaud JP.
In hypogonadal men who were candidates for testosterone therapy, a **14% incidence** of occult cancer was found. A percentage (**15.2%**) of prostate cancer has been found in the placebo group (with normal DRE and PSA) in the prostate cancer prevention study investigating the chemoprevention potential of finasteride.
Data from all published prospective studies on circulating level of total and free testosterone do not support the hypothesis that high levels of circulating androgens are associated with an increased risk of prostate cancer.
A study on a large prospective cohort of 10,049 men, contributes to the gathering evidence that the long standing “androgen hypothesis” of increasing risk with increasing androgen levels can be rejected, suggesting instead that **high levels within the reference range of androgens, estrogens and adrenal androgens decrease aggressive prostate cancer risk. Indeed, high-grade prostate cancer has been associated with low plasma level of testosterone**.
Furthermore, pre-treatment total testosterone was an independent predictor of extraprostatic disease in patients with localized prostate cancer; **as testosterone decreases, patients have an increased likelihood of non-organ confined disease and low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy.** A clinical implication of these results concerns androgen supplementation which has become easier to administer with the advent of transdermal preparations (patch or gel) that achieve physiological testosterone serum levels without supra physiological escape levels. During the clinical development of a new testosterone patch in more than 200 primary or secondary hypogonadal patients, no prostate cancer was diagnosed.
Higher Testosterone and DHEA levels reduces risk of Aggressive prostate cancer.
(6) http://www.ncbi.nlm.nih.gov/pubmed/16434592

Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):86-91.
Circulating steroid hormones and the risk of prostate cancer.Severi G, Morris HA, MacInnis RJ, English DR,
Epidemiologic studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk and some recent studies have even suggested that high testosterone levels might be protective particularly against aggressive cancer. We tested this hypothesis by measuring total testosterone, androstanediol glucuronide, androstenedione, DHEA sulfate, estradiol, and sex hormone-binding globulin in plasma collected at baseline in a prospective cohort study of 17,049 men.
The hazard ratio for aggressive cancer almost **halved for a doubling of the concentration of testosterone** (HR, 0.55; 95% CI, 0.32-0.95) and androstenedione (HR, 0.51; 95% CI, 0.31-0.83), and was 37% lower for a doubling of the concentration of DHEA sulfate (HR, 0.63; 95% CI, 0.46-0.87).
High levels of testosterone and adrenal androgens are thus associated with reduced risk of aggressive prostate cancer but not with nonaggressive disease.

Prostate Cancer Associated with Lower Testosterone Levels

(7) http://www.ncbi.nlm.nih.gov/pubmed/17169647
Urology. 2006 Dec;68(6):1263-7.
Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Morgentaler A, Rhoden EL. Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center,
OBJECTIVES: To determine the prevalence of prostate cancer in hypogonadal men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less.
METHODS: A total of 345 consecutive hypogonadal men with a PSA level of 4.0 ng/mL or less underwent evaluation with digital rectal examination and prostate biopsy before initiating a program of testosterone replacement therapy. All men had low serum levels of total or free testosterone, defined as less than 300 and 1.5 ng/dL, respectively.
RESULTS: Cancer was identified in 15.1%. The cancer detection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/mL, respectively ($P < 0.05$).
Cancer was detected in 26 (30.2%) of 86 men with a PSA level of 2.0 to 4.0 ng/mL. Cancer was detected in 21% of men with a testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL ($P = 0.04$). Men with free testosterone levels of 1.0 ng/dL or less had a cancer rate of 20% compared with 12% for men with greater values ($P = 0.04$). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile was 2.15 (95% confidence interval 1.01 to 4.55) for total testosterone and 2.26 (95% confidence interval 1.07 to 4.78) for free testosterone.
CONCLUSIONS: Prostate cancer was present in more than 1 of 7 hypogonadal men with PSA of 4.0 ng/mL or less. **An increased risk of prostate cancer was associated with more severe reductions in testosterone.**
(7A) http://www.ncbi.nlm.nih.gov/pubmed/17627161
Urol Int. 2007;79(1):13-8.Hormonal predictors of prostate cancer. Sofikerim M, Eskicorapci S, Oruç O, Ozen H.

INTRODUCTION: we evaluated the role of serum testosterone, free testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in predicting prostate cancer risk in patients who had transrectal ultrasonography-guided prostate biopsy with the suspicion of prostate cancer.
MATERIAL AND METHODS: A total of 211 patients who were selected to undergo prostatic biopsy due to abnormal digital rectal examination and/or a serum prostate-specific antigen (PSA) level >2.5 ng/ml were included in the study. The patient characteristics of total PSA, free/total PSA ratio, serum total testosterone, free testosterone, free/total testosterone ratio, FSH and LH levels were compared according to the pathological diagnosis.
RESULTS: The mean age was 63.91 years (range 44-83) and the mean PSA level was 9.23 ng/ml (range 0.13-50.41) in the whole group. Of 211 patients, 69 (32.7%) were positive for prostate cancer. The patients who were positive for prostate cancer had statistically **lower levels of serum total testosterone** compared with the patients who were diagnosed as having benign prostatic hyperplasia (BPH; 405 vs. 450.5 ng/dl, respectively; p = 0.013). **The serum FSH level was significantly higher** in men with prostatic cancer than in men with BPH (7.56 vs. 6.06 mIU/ml, respectively; p = 0.029). No significant differences between men with prostatic cancer and those with BPH were found for serum LH levels. When normal ranges for serum free and total testosterone levels were defined as 9 pg/ml and 300 ng/dl, respectively, patients who had low free testosterone and total testosterone levels had significantly higher cancer detection rates than patients with high serum androgen levels: 40.8% (40/98) versus 25.6% (29/113) (p = 0.021), and 48.6% (18/37) versus 29.3% (51/174), respectively (p = 0.023). After logistic regression analysis, none of the hormones showed a significant difference in predicting the risk of prostate cancer in patients undergoing prostate biopsy with suspicion of the disease.
CONCLUSION: Our data suggest that patients diagnosed with prostate cancer have **low levels of serum testosterone and high levels of serum FSH** compared with the patients with BPH. No support was found for the theory that high levels of testosterone increase prostate cancer risk.

Increasing PSA detects Prostate Cancer in 5% of pts on Testosterone

(7 http://www.ncbi.nlm.nih.gov/pubmed/19154450
BJU Int. 2009 May;103(9):1179-83. Epub 2008 Dec 23.
Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. Coward RM, Simhan J, Carson CC 3rd.
OBJECTIVES: To retrospectively review hypogonadal men receiving testosterone replacement therapy (TRT), and evaluate the changes in prostate-specific antigen (PSA) levels over an extended period, and thus evaluate the occurrence of prostate cancer, as a primary concern in treating late-onset hypogonadism (LOH) is the potential increased risk of prostate cancer; we also recorded the cardiovascular effects of TRT.
PATIENTS AND METHODS: In all, 81 hypogonadal men (mean age 56.8 years) were followed for a mean (range) of 33.8 (6-144) months after starting TRT. All men had a normal baseline PSA level before TRT and had routine laboratory investigations, including measurements of body mass index (BMI), haematocrit, lipid profile, and liver function tests (LFTs). Testosterone and PSA levels were assessed every 6-12 months.

Patients with a biopsy-confirmed or recent history of prostatitis before treatment were excluded. TRT was discontinued in men who developed prostate cancer.
RESULTS: Before and 36 months after treatment the total testosterone levels were 241.1 and 379.8 ng/dL (P < 0.05), respectively. Four men (4.9%) developed prostate cancer at a mean (range) of 32.5 (22-41) months after starting TRT.
In men without prostate cancer (95.1%), PSA levels did not increase significantly at 1-year intervals for 5 years. There was no statistical difference in PSA level change from baseline to 36 months when patients without prostate cancer were stratified into groups according to age (< or =50, 55-65 and > or =70 years).
In men with prostate cancer there was an increase in mean PSA level from baseline to 18 months of 1.8 ng/mL, and to 36 months of 3.2 ng/mL (P < 0.05).
Total cholesterol improved from 203.8 to 166.6 mg/dL (P < 0.05) after 36 months of TRT; the BMI, haematocrit and LFTs did not change significantly.
CONCLUSIONS: LOH is an increasingly prevalent disease characterized by a symptomatically low testosterone level, and TRT is effective in normalizing serum testosterone levels, providing a beneficial cardiovascular effect, and improving sexual function and overall quality of life. PSA levels remain stable after normalization of testosterone for > or =5 years, prostate cancer can be effectively diagnosed and treated in men taking TRT, and **the incidence of prostate cancer among men with LOH on TRT is no greater than that in the general population.**

No Testosterone related adverse effects on Prostate Tissue Determined by Biopsy

(8) http://www.ncbi.nlm.nih.gov/pubmed/17105798
JAMA. 2006 Nov 15;296(19):2351-61.
Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. Marks LS, Mazer NA,
OBJECTIVE: To determine the effects of TRT on prostate tissue of aging men with low serum testosterone levels.
DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled trial of 44 men, aged 44 to 78 years, with screening serum testosterone levels lower than 300 ng/dL (<10.4 nmol/L) and related symptoms, conducted at a US community-based research center between February 2003 and November 2004.
INTERVENTION: Participants were randomly assigned to receive 150 mg of testosterone enanthate or matching placebo intramuscularly every 2 weeks for 6 months.
MAIN OUTCOME MEASURES: The primary outcome measure was the 6-month change in prostate tissue androgen levels (testosterone and dihydrotestosterone). Secondary outcome measures included 6-month changes in prostate-related clinical features, histology, biomarkers, and epithelial cell gene expression.
RESULTS: Of the 44 men randomized, 40 had prostate biopsies performed both at baseline and at 6 months and qualified for per-protocol analysis (TRT, n = 21; placebo, n = 19). Testosterone replacement therapy increased serum testosterone levels to the mid-normal range (median at baseline, 282 ng/dL [9.8 nmol/L]; median at 6 months, 640 ng/dL [22.2 nmol/L]) with no significant change in serum testosterone levels in matched, placebo-treated men.

However, median prostate tissue levels of testosterone (0.91 ng/g) and dihydrotestosterone (6.79 ng/g) did not change significantly in the TRT group. No treatment-related change was observed in prostate histology, tissue biomarkers (androgen receptor, Ki-67, CD34), gene expression (including AR, PSA, PAP2A, VEGF, NXK3, CLU [Clusterin]), or cancer incidence or severity. Treatment-related changes in prostate volume, serum prostate-specific antigen, voiding symptoms, and urinary flow were minor.
CONCLUSIONS: These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels **but appears to have little effect on prostate tissue androgen levels and cellular functions.**

Testosterone Given After Treatment for Prostate CA

(9) http://www.ncbi.nlm.nih.gov/pubmed/17183557
Cancer. 2007 Feb 1;109(3):536-41.
Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Sarosdy MF.South Texas Urology and Urologic Oncology, San Antonio, Texas 78229, USA.
BACKGROUND: Controversy and a notable paucity of published clinical data best characterize the current knowledge of testosterone-replacement therapy (TRT) for hypogonadism after treatment for early, localized prostate cancer.
The objective of this study was to assess the risk of biochemical failure with TRT after treatment of early prostate cancer with permanent transperineal brachytherapy with or without external beam therapy in patients with low serum levels of testosterone and clinical symptoms of hypogonadism.
METHODS: Patients who underwent prostate brachytherapy from 1996 to 2004 and received subsequent TRT for symptomatic hypogonadism were reviewed to detail cancer characteristics and treatment as well as pre- and post-TRT serum testosterone and prostate-specific antigen (PSA) values.
RESULTS: Thirty-one men received TRT after prostate brachytherapy for 0.5 to 8.5 years (median, 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median, 5.0 years) postbrachytherapy. TRT was started from 0.5 years to 4.5 years (median, 2.0 years) after brachytherapy. Serum total testosterone levels ranged from 30 ng/dL to 255 ng/dL (median, 188 ng/dL) before TRT and rose to 365 ng/dL to 1373 ng/dL (median, 498 ng/dL) on TRT. Transient rises in PSA were observed in 1 patient. The most recent PSA level was <0.1 ng/mL in 23 patients (74.2%), <0.5 ng/mL in 30 patients (96.7%), and <1 ng/mL in 31 patients (100%). No patients stopped TRT because of cancer recurrence or documented cancer progression.
CONCLUSIONS: For patients with low serum testosterone levels and symptoms of hypogonadism, **TRT may be used with caution** and close follow-up after prostate brachytherapy.

(10) http://www.ncbi.nlm.nih.gov/pubmed/15643240
J Urol. 2005 Feb;173(2):533-6.
Testosterone replacement therapy after primary treatment for prostate cancer.

Agarwal PK, Oefelein MG. Department of Urology, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio 44106, USA.
PURPOSE: **A history of prostate cancer has been an absolute contraindication for testosterone supplementation**. We studied a cohort of hypogonadal patients treated with radical retropubic prostatectomy (RRP) for organ confined prostate cancer to determine if testosterone replacement therapy (TRT) could be efficacious and administered safely without causing recurrent prostate tumor.
MATERIALS AND METHODS: Ten hypogonadal patients previously treated with RRP for organ confined prostate cancer were identified. They presented with low serum total testosterone (TT) and symptoms of hypogonadism after RRP.
RESULTS: At a median followup of 19 months no patient had detectable (greater than 0.1 ng/ml) PSA. TT increased significantly after starting TRT from a mean +/- SD of 197 +/- 67 to 591 +/- 180 ng/dl (p = 0.0002). There was decrease in hot flashes and an increase in energy level.
CONCLUSIONS: At a median of 19 months of TRT hypogonadal patients with a history of prostate cancer had **no PSA recurrence** and had statistically significant improvements in TT and hypogonadal symptoms. **In highly select patients after RRP TRT can be administered carefully and with benefit to hypogonadal patients with prostate cancer.**
Testo causes Minor PSA elevation, but no increased CA risk

(11) http://www.ncbi.nlm.nih.gov/pubmed/12399540
J Androl. 2002 Nov-Dec;23(6):922-6.
Prostate-specific antigen changes in hypogonadal men treated with testosterone replacement. Gerstenbluth RE, Maniam PN, Corty EW, Seftel AD.
We assessed the effect of this treatment on serum prostate-specific antigen (PSA) levels and risk of prostate cancer in hypogonadal men with erectile dysfunction. Criteria for inclusion were a normal pre-treatment PSA (<4.0 ng/mL) in conjunction with a normal digital rectal examination (DRE) or a negative pretreatment prostate biopsy for men with either an abnormal DRE or an elevated PSA. Patients received intramuscular injections every 2 to 4 weeks, allowing for dose titration. In this retrospective analysis, 54 hypogonadal men with erectile dysfunction were included, with a mean age of 60.4 years (range 42.0-76.0) and a mean follow-up of 30.2 months (range 2.0-82.0) on testosterone therapy. Mean pretreatment total testosterone level was 1.89 ng/mL (range 0.2-2.92), which increased during treatment to a mean of 9.74 ng/mL (range 1.50-26.30, P <.001). Mean pretreatment PSA was 1.86 ng/mL (median 1.01 ng/mL, range 0.0-15.80), which increased to a mean PSA level of 2.82 ng/mL (median 1.56 ng/mL, range 0.0-32.36, P <.01) with testosterone treatment. Of the 54 men included in this study, 6 (11.1%) required prostate biopsy while on testosterone therapy because of a rise in serum PSA above 4.0 ng/mL. One patient (1.9%) was diagnosed with prostate cancer.
In conclusion, testosterone replacement therapy in men with erectile dysfunction and hypogonadism is associated with a **minor PSA elevation**, but there does not appear to be a short-term increase in risk for the development of prostate cancer.
No Reason to Withhold Testosterone for Men with Treated Prostate CA

(12) http://www.ncbi.nlm.nih.gov/pubmed/16904053
Curr Treat Options Oncol. 2006 Sep;7(5):363-9.
Testosterone therapy for men at risk for or with history of prostate cancer. Morgentaler A.
Since the early 1940s when Huggins showed that severe reductions in serum testosterone by castration or estrogen therapy caused regression of prostate cancer (PCa), it has been assumed that higher testosterone levels cause enhanced growth of PCa. For this reason, it has been considered taboo to offer testosterone replacement therapy (TRT) to any man with a prior history of PCa, even if all objective evidence suggests he has been cured. The fear has been that higher testosterone levels would "awaken" dormant cells and cause a recurrence. Thus, US Food and Drug Administration-mandated language in all testosterone package inserts states that testosterone is contraindicated in men with a history of, or suspected of having, PCa. Although there is little modern experience with administration of testosterone in men with known history of PCa, there is a varied and extensive literature indicating that TRT does not pose any increased risk of PCa growth in men with or without prior treatment. For instance, the cancer rate in TRT trials is only approximately 1%, similar to detection rates in screening programs, yet biopsy-detectable PCa is found in one of seven hypogonadal men. Moreover, PCa is almost never seen in the peak testosterone years of the early 20s, despite autopsy evidence that men in this age group already harbor microfoci of PCa in substantial numbers. The growing number of PCa survivors who happen to be hypogonadal and request treatment has spurred a change in attitude toward this topic, with increasing numbers of physicians now offering TRT to men who appear cured of their disease. **Publications have now reported no prostate-specific antigen (PSA) recurrence with TRT in small numbers of men who had undetectable PSA values after radical prostatectomy. Although still controversial, there appears to be little reason to withhold TRT from men with favorable outcomes after definitive treatment for PCa.** Monitoring with PSA and digital rectal examination at regular intervals is recommended

(13) http://www.ncbi.nlm.nih.gov/pubmed/19296069
Urologe A. 2009 May;48(5):516-22. Testosterone replacement therapy and prostate cancer. The current position 67 years after the Huggins myth] [Article in German]
Rinnab L et al.
There are compelling data showing that testosterone replacement therapy (TRT) does not increase the risk of prostate cancer. The literature (four published studies) concerning men treated with TRT after definitive therapy for prostate cancer reports only one biochemical recurrence. Based on these data, **physicians cannot really justify withholding TRT from symptomatic patients after they have been successful treated for prostate cancer.**

(14) http://www.ncbi.nlm.nih.gov/pubmed/17983894
Urol Clin North Am. 2007 Nov;34(4):549-53, vi.
The role of testosterone replacement therapy following radical prostatectomy.
Khera M et al.

There are compelling data to suggest that testosterone replacement therapy (TRT) in normal and high-risk men does not increase the risk for prostate cancer. In the few studies of men treated with TRT after a radical prostatectomy, there have been no biochemical recurrences. Based on these data, **it is difficult to justify withholding TRT following a radical prostatectomy.** If we do not lower the testosterone levels of eugonadal men after a radical prostatectomy, how can we justify not replacing testosterone levels in hypogonadal men to make them eugonadal following a radical prostatectomy?
Case Report: Untreated Prostate CA, PSA declines after Testosterone Rx

(15) http://www.ncbi.nlm.nih.gov/pubmed/19215619
J Sex Med. 2009 Feb;6(2):574-7
Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. Morgentaler A. Harvard Medical School, Urology, CONCLUSION: A decline in PSA was noted in a man with untreated PCa who received T therapy for 2 years. This case provides support for the notion that PCa growth may not be adversely affected by changes in serum T beyond the castrate or near-castrate range.

(16) http://www.ncbi.nlm.nih.gov/pubmed/19429438
J Steroid Biochem Mol Biol. 2009 Mar;114(1-2):96-105. Epub 2009 Jan 30.
Testosterone deficiency syndrome: treatment and cancer risk. Raynaud JP.
Testosterone deficiency syndrome (TDS) can be linked to **premature mortality** and to a number of co-morbidities (such as **sexual disorders, diabetes, metabolic syndrome,** …). Testosterone deficiency occurs mainly in ageing men, at a time when prostate disease (benign or malign) start to emerge. New testosterone preparations via different route of administration appeared during the last decade allowing optimized treatment to these patients. One potential complication of this treatment is the increased risk of prostate and breast cancer. Consequently, the guidelines from the agencies and the institutions, the recommendations of the scientific expert committees and the attitude of the clinicians to who, when and how to treat hypogonadal patients, is very conservative, not to say, highly restrictive.
To date, as documented in many reviews on the subject, nothing has been found to support the evidence that restoring testosterone levels within normal range increases the incidence of prostate cancer.
In our experience, during a long-term clinical study including 200 hypogonadal patients receiving a patch of testosterone, **50 patients ended 5 years of treatment and no prostate cancer have been reported. In fact, the incidence of prostate cancer in primary or secondary testosterone treated hypogonadal men is lower than the incidence observed in the untreated eugonadal population.**
Furthermore, it has been advocated that, under a rigorous surveillance, patients cured of prostate cancer can be treated with testosterone supplementation with beneficial results.

17) Low Testosterone Associated with Increased Mortality
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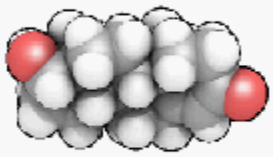
Summary



Article Name

PSA and Testosterone Observations - Part Two

Description

The PSA May Be Affected by Testoterone Treatment.

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