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TESTOSTERONE REPLACEMENT in Hypogonadal Men with Treated and Untreated Prostate Cancer? *Where's the Meat? - A Collection of Studies Supporting the Safety of Its Use*

The claimed safety of raising serum testosterone (T) levels into the normal range in men with prostate cancer symptomatic from T deficiency rests on the correctness of the underlying biology posited by Abraham Morgentaler in his "saturation theory."

The goal of safe testosterone supplementation, i.e. therapy that does not reawaken or promote progression of prostate cancer, is ameliorating the many well recognized undesirable consequences of diminished testosterone.

If the safety of testosterone replacement therapy (TRT) were clearly established, clinicians would then feel comfortable in prescribing T to the many older patients with prostate cancer who are experiencing symptoms from T inadequacy.

Testosterone replacement is actively researched and many studies have been reported, with the overwhelming majority supporting the safety of TRT in the short- and medium-term. This article will review some of those of studies: one relating to basic science; a recent study of TRT in men with ***untreated*** cancer; and finally a summary of many studies establishing safety of TRT in men already treated "curatively" for the disease.

1. BASIC SCIENCE:

Strong support for the "saturation theory" is presented in a technically elegant study conducted by Drs. Elahe Mostagel and Peter Nelson from the Fred Hutchinson Cancer Research Center aided by Jonathan Epstein, David Bostwick, Alan Partin and others: "Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism," JAMA, 2006.

Forty-one volunteers with no biopsy evidence of cancer at entry were randomized to "receive 150 mg of testosterone enanthate or matching placebo intramuscularly

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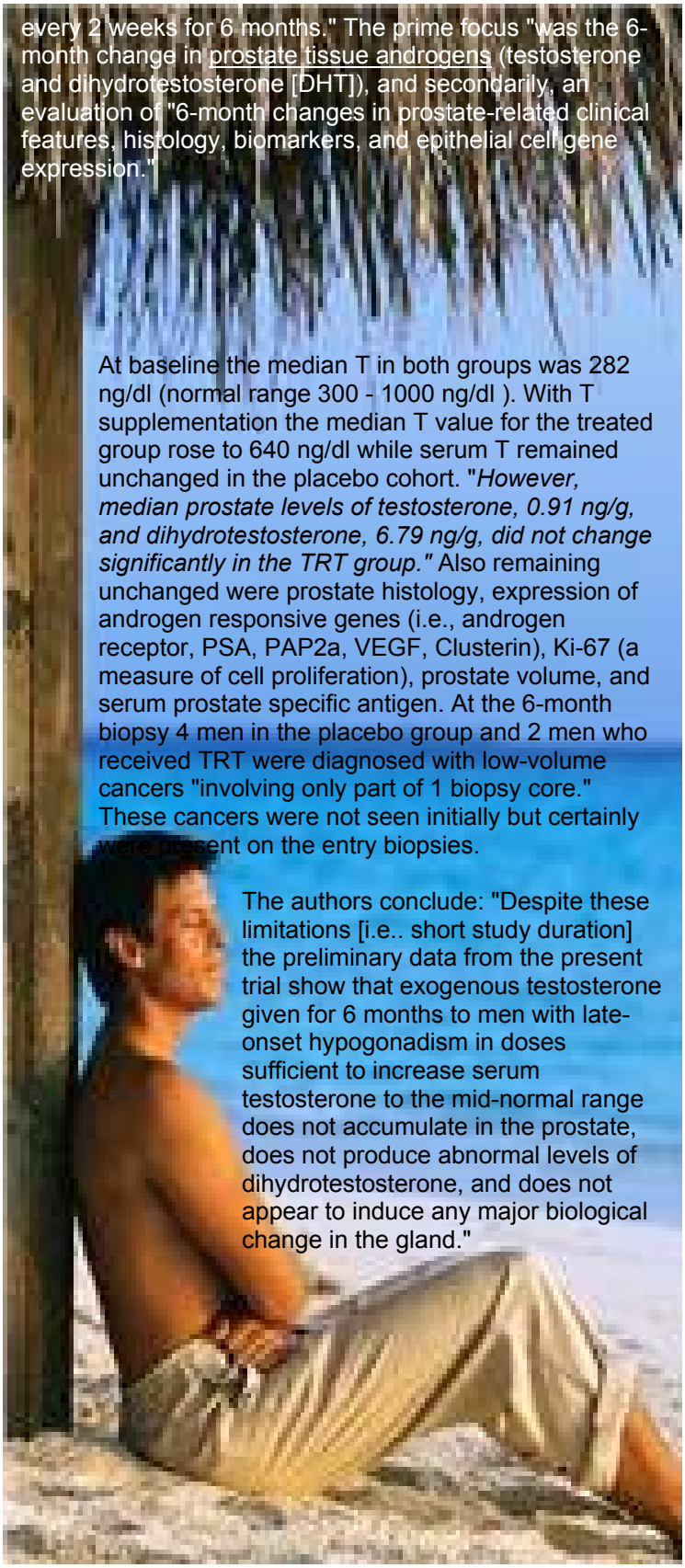

2. "TESTOSTERONE REPLACEMENT in Men with Untreated Prostate Cancer" - a seminal study reported by Abraham Morgentaler et al., *J Urol. April, 2011.*

This report presents the outcome of 13 symptomatic testosterone deficient men diagnosed with prostate cancer who were intent on relieving distressing symptoms - erectile dysfunction, decreased libido, fatigue/low energy, and depressed mood. They had sufficient confidence in the "saturation theory" to receive TRT for a median of 2.5 years (range 1.0 to 8.1) during a period of active surveillance. Surveillance follow-up included measurement of PSA and DRE at 3 month intervals and a yearly prostate biopsy (mean number of biopsies was 2). Mean age was 58.8; initial biopsy Gleason score, 6 in 12 men, and 7 (3+4) in one. With TRT the mean total T rose to 664 ng/dl from 238 ng/dl.

Results: "Mean prostate specific antigen *did not change* with testosterone therapy" - baseline 5.5 +/- 6.4 ng/ml vs. 3.6 +/- 2.6 ng/ml at 24 months. "No cancer was found in 54% of follow-up biopsies," despite positive biopsies on entry. One man in a subsequent biopsy was upgraded due to finding Gleason 3+4 in 5% of one core. Another man showed Gleason 4+3 in a follow-up biopsy after 8 years of TRT and underwent a radical prostatectomy. "The final pathology revealed Gleason score 6 disease involving 5% of the prostate, with negative margins and nodes."

The author's conclusion: Testosterone therapy in men with *untreated* prostate cancer was not associated with prostate cancer progression in the short and medium term."

3. **TESTOSTERONE REPLACEMENT in Men Having Had Prior "Curative" Treatment**.

The "meat" supporting TRT use in this group has been served up in small, but relevant, portions, i.e., in a handful favorable studies. An excellent review of the entire subject is presented by Morgentaler, "Testosterone Therapy in Men with Prostate Cancer: Scientific and Ethical Considerations," *J Urol. March 2009,* in which some of the following studies were cited.

a) Seven hypogonadal and symptomatic men received TRT following curative radical prostatectomy. "After variable follow-up periods [as long as 12 years] no biochemical or clinical evidence of cancer recurrence was found in any of the group." (*Kaufman. J Urol 2004 Sep*)

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EDITORIAL: Testosterone Replacement Therapy in Men with Treated Prostate Cancer- *the Paradigm is shifting*

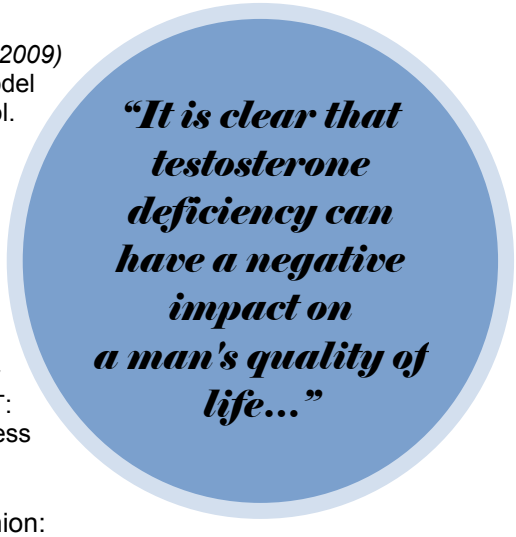
Testosterone replacement therapy (TRT) in testosterone deficient men with a history of treated prostate cancer understandably has been and continues to be a controversial issue. This reticence to prescribe T stems from clinicians' primary concern - "do no harm." Quality of life issues have therefore been assigned a lower priority than safety. However, the standard paradigm may be shifting. (Of course, an absolute contraindication for TRT is ongoing androgen suppression therapy.)

If there is one article that clinicians treating men with prostate cancer can read to bring them up to speed on this issue it is, "Androgen Replacement Therapy after Prostate Cancer Treatment". (*Mohit Khera, Current Urological Report 2010).* To liberally quote from the introduction:

> *"It is clear that testosterone deficiency can have a negative impact on a man's quality of life, including decreased energy and libido, erectile dysfunction, depression, increased body fat, decreased bone mineral density, and decreased muscle mass ... One could argue that men with hypogonadism who have undergone a radical prostatectomy (RP) are much more likely to need testosterone supplementation than other men with hypogonadism without a history of prostate cancer. After prostate cancer surgery [and brachytherapy], men are more likely to suffer from depression, erectile dysfunction, decreased sexual performance, and decreased libido. These are also [symptoms] seen in men with low serum testosterone."*

PREVALENCE: Late onset testosterone deficiency (T <300 mg/dl, sometimes set at <250 ng/dl) is more common than might be suspected. A community based survey of 2162 men found deficiency in 40.2% in the age range 55-64; in 39.9% of men between ages 65-74; and in 45.5 % between 75-84 years old. The percent of men with deficiency when based on circulating bio-available T (free T index) is even higher in each age bracket. Low T occurred more frequently in men with hypertension, diabetes, obesity, prostate disease, and chronic obstructive pulmonary disease. (*Mulligan Int J Clin Pract, 2006*)

THE SATURATION THEORY was set forth by Morgentaler and Traish (*Eur Urol 55(2009)* in *"*Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth" (Reviewed in PCa Commentary, Vol. 62, Mar/April 2010, "Basic Science & Biology: About Testosterone") The saturation theory is based on animal studies that suggest that the extent of T and DHT binding to the androgen receptor in *prostate tissue* is limited by a finite availability of these receptors, the net amount being the result of the rate of androgen receptor gene expression and the functional life of each receptor in the cytoplasm before degradation. The theory postulates that serum T levels above 120 ng/ml are "excess". "Once maximal AR androgen binding has been achieved ("saturation") the addition of more T appears unable to influence PCa growth." *(Morgentaler and Morales. J UROL Oct 2010: Should Hypogonadal Men With Prostate Cancer Receive Testosterone?)* Morgentaler gives a bit of leeway in the prescription of T: "However, special concern exists for the man with severely depressed serum T (less than 150 ng/ml) who may still have capacity for androgen mediated growth."



THE PARADOX: In a summary comment in his article, Khera (ibid) offers his opinion:

> *"*There appears to be an inconsistency in the way we currently manage our patients after treatment of prostate cancer. While we are reluctant to raise serum testosterone levels to normal ranges in hypogonadal men, we are comfortable in not lowering serum testosterone in eugonadal men. We do not castrate all eugonadal men after RP. We should be consistent in how we approach patients with eugonadism or hypogonadism after prostate treatment."

Editorial Comment: It is difficult after considerations of the findings and arguments in these studies not to sense an erosion of the old paradigm that proscribes testosterone replacement in symptomatic, testosterone deficient men after "curative" treatment. More data will be needed to establish long-term outcomes, but the safety of a trial of TRT in appropriately chosen men seems to have been established◆◆◆

SERUM TESTOSTERONE AND PROSTATE CANCER:

Observations in relation to prostate cancer diagnosis, disease aggressiveness, and disease progression after treatment

Pooled data involving 3886 men with and without PCa were presented by the Baltimore Longitudinal Study of Aging *(Roddam. JNCI 2008):*

"The results revealed no association between any serum androgen measurement and PCa including total and free T. ...The primary conclusion of this study was that variations in serum T within the naturally occurring range have no impact on PCa."

Low T as a risk factor for more aggressive cancer: Morgentaler states, "*In men with known PCa worrisome prognostic features have been associated with low T rather than high T, including evidence that PCa risk is associated with the severity of T deficiency*." (*Morgentaler. J Urol Mar 2009)*

Because low T is a risk factor for aggressive disease, Morgentaler is more likely to biopsy a man with low T than a man of comparable risk whose T is normal. Hoffman *(J Urol 2000)* reported that in 117 men being evaluated for cancer, biopsies were positive in 43% of men with low T (<300 ng/dl) compared to 22% whose T levels were normal. Additionally, in the low T group 7 of 64 men had a Gleason score 8 or greater compared to 0 of 48 with normal T levels. (P=0.025).

In his excellent review (*Eur Urol. 2009, "Testosterone and Prostate Cancer: Revisiting Old Paradigms",* Morgentaler reported on 77 men with PSA values <4ng/ml. Prostate cancer was diagnosed in 14%, a percent similar to data from the Prostate Cancer Prevention Trial. "In men with serum testosterone levels greater than 250 ng/ml, the PCa rate was 12%; in men with testosterone levels less than 250 ng/ml it increased to 21%."

Yamamoto *(Eur Urol 2007)* studied 272 men with clinically localized PCa, 49 with T <300 and 223 with normal values, who underwent surgery and reported: "Preoperative serum testosterone levels were an independent and significant predictor of subsequent PSA recurrence along with Gleason score (P=0.006), surgical margin status (0.0001)... After 5 years, the PSA failure-free survival rate was significantly worse in men with low pre-operative values than that of men with normal testosterone (67.8% vs. 84.9%)."

BOTTOM LINE: Evaluations of relationship of testosterone deficiency to the risk of a diagnosis of prostate cancer, the aggressiveness of cancer and its association with PSA recurrence after treatment suggest that low levels of testosterone can adversely affect prostate cancer in all phases of the disease ◆◆◆

"Evaluations of relationship of testosterone deficiency to the risk of a diagnosis of prostate cancer, the aggressiveness of cancer and its association with PSA recurrence after treatment suggest that low levels of testosterone can adversely affect prostate cancer in all phases of the disease."

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b) Ten men following surgery underwent TRT. At a "median follow-up of 19 months no patient had detectable (greater than 0.1 ng/ml) PSA." TRT raised T levels from a mean of 197 to 591 ng/dl resulting in a significant decrease in hot flashes and increase in energy levels. *(Agarwal. J Urol 2005 Feb)*

c) "Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy," (*Sarosdy. Cancer 2007 Feb*) reported on "Thirty-one men [who] received TRT after prostate brachytherapy for 0.5 - 8.5 years (median 4.5 years), with a follow-up that ranged from 1.5 years to 9.0 years (median 5 years) post brachytherapy." The most recent PSA level was <0.1 ng/ml in 74.2%, <0.5 in 96.7%, and all 31 were under 1 ng/ml.

d) Khera (*J Sex Med. 2009 Apr*) followed 57 men on TRT after surgery for an average of 36 months (range 1-136 months). Eligibility required undetectable post-op PSA levels and negative surgical margins. Average follow-up after starting TRT was 13 months (range 1-99 months). TRT raised the T levels from a mean of 288 ng/dl to 459 ng/dl. "No patient had a biochemical recurrence."

Morgentaler, in a meta-analysis including the cases cited above and others, summarized, "Altogether biochemical recurrence was noted in 2 of 111 men (1.8%) who received T therapy after various forms of localized PCa therapy (ibid). Khera reported: "When including all abstracts and publications, to date, there have been a total of 292 patients treated with testosterone after prostate cancer, and the risk of recurrence is less an 1%." *(Khera.Curr Urol Report 2010)*

BOTTOM LINE: Basic science and clinical studies support the safely of short- to medium-term TRT in hypogonadal men following definitive therapy for localized prostate cancer. Safety of TRT is also reported in a small group of men with diagnosed prostate cancer managed by active surveillance. Although longer term studies will be needed to establish long-term safety data, the data to date would seem to support the safety of a short trial period of TRT in symptomatic hypogonadal men to evaluate its effectiveness in relieving symptoms. If a significant improvement in quality of life follows then a careful discussion of the risks versus benefits would be in order◆◆◆

Your comments and requests for information on a specific topic are welcome at **ecweber@nwlink.com**

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