Testosterone Therapy and the Prostate

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TRT - Risks

- Prostate (Cancer, BPH)?
- Cardiac? Lipids?
- Polycythemia
- Sleep apnea
- Gynecomastia
- Edema
Testosterone Replacement Therapy: A Caution

“Recognizing the dependency of prostate cancer on testosterone, I am not convinced there is enough evidence on the safety of testosterone to justify its widespread use.”

Andrew von Eschenbach, M.D.
Director, National Cancer Inst.
New York Times; March 11, 2003
The prostate increases in size after the onset of puberty as testosterone levels increase.

The prostate does not increase in size in genetic males who have complete androgen insensitivity. (Corbetta S, et al. Fertil Steril. 2011;95:1119)

The prostate is rudimentary in males with 5-\(\alpha\) reductase deficiency, indicating that DHT is the major androgen in the prostate. (Imperato-McGinley J, et al. J Clin Endocrinol Metab. 1992; 75:1022-6)

The prostate was non-palpable (20/26) or very small (6/26) in Chinese eunuchs 41-65 years post-castration. (Chinese Med J. 1987;100:271–272)
Anatomic Progression of BPH

**Autopsy Studies**

**PROSTATE WEIGHT**

- Graph showing the increase in prostate weight with age, from 5 to 85 years.

**PATHOLOGICALLY DEFINED BPH**

- Graph showing the increase in percent of men with pathologically defined BPH with age, from 5 to 85 years.

*Berry et al., J. Urology 1984; 132:474-479*
Potential Effects of Testosterone Replacement Therapy on the Prostate

- Increase in prostate volume
- Increased risk of LUTS and BPH
- Increase in PSA levels
- Stimulate growth of an occult tumor
Prostate Volume in 16 Hypogonadal Men before and after Testosterone Treatment for 36 months


![Graphs showing changes in testosterone and prostate volume over 36 months.](image)
Mean Prostate Volume +/- Treatment with Testosterone Enanthate or Transdermal Patch


![Graph showing prostate volume changes](image)

*P<0.001 decrease, -T vs. +TE
**p<0.001 increase, +TTD vs. -T

TE = testosterone enanthate
TTD = transdermal patch
Risk of Developing Lower Urinary Tract Symptoms (LUTS) or BPH with TRT
AUA Symptom Index Changes During Study Period

N=120; Mean duration of followup therapy: 692 +/- 773 days
Risk of Developing a Clinical Prostate Cancer with TRT
Relationship of Prostate Cancer and Testosterone Levels

Slide courtesy of E. David Crawford, MD.
Prostate Cancer In US: Estimated Incidence and Mortality Rates in 2014

- Estimated new cases of prostate cancer in 2014 = 233,000 (27% of new cancer cases in males)
- Estimated deaths due to prostate cancer in 2014 = 29,480 (10% of cancer deaths in males)
Prevalence of Occult Prostate Cancer

Sakr et al, In Vivo 8:430-443, 1994

Percent vs. Age (yrs) for Prostate Cancer and HGPIN.
Why is the relationship between T and PCa under great scrutiny?

- Treatment of hypogonadism with TRT has been progressively expanding

- The number of PCa survivors who are symptomatically hypogonadal and who request treatment is increasing
Huggins’ heritage from a 1967 review article:

“Orchiectomy or the administration of estrogens resulted in regression of PCa whereas, in untreated prostates, Testosterone enhanced the rate of growth of cancer”

There is no dispute that castration causes PCa to regress.

However

Proof for the second part of Huggins’ assertion: “T causes PCa to grow”, has been elusive!!
Huggins and Hodges reported that daily injections of testosterone propionate caused acid phosphatase levels to increase.

Although 3 men were injected, results were provided for only 2 of them.

One of these two had already been castrated.

In the remaining patient, acid phosphatase levels rose during 18 days of T treatment, but fluctuated widely before and afterwards, reaching the same peak levels 3 weeks after T discontinuation.

Huggins & Hodges, Cancer Research, 1941.
The original assertion that Testosterone caused Prostate Cancer in untreated patients was thus based on equivocal acid phosphatase results in a single individual!!
Articles demonstrating T Therapy causes PCa progression

None!
Global Pooled Longitudinal Study of Hormones and PCa Risk

- 3886 men with PCa
- 6448 age-matched controls
- No significant relationship between androgens and PCa
- Highest 20% T vs lowest 20% - no difference

Roddam et al, JNCI 2008;100(3):170-183

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<th>Hormone</th>
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T AND PROSTATE CANCER IN PLACEBO ARM OF REDUCE TRIAL

- 3255 men
- Prostate biopsies at 2y and 4y
- PCa risk NOT associated with serum T or DHT
- Men with high T no greater PCa risk

Muller et al, European Urology, 2012
T THERAPY IN MEN WITH PCa

If there is limited ability of T therapy to stimulate additional PCa growth in most men, can we then offer T therapy to symptomatic men with PCa?
Testosterone following PCa treatment

T therapy after RRP
- 3 published retrospective studies
- N=74 men
- No PSA recurrence
- Follow-up as long as 12 yr

T therapy after brachytherapy
- 31 men, median 4.5 y TRT
- No PSA recurrences

T THERAPY AFTER RADICAL PROSTATECTOMY

- T therapy in 103 men after RP
  - 26 high risk (Gleason 8-10, +margins, +nodes)
- No T therapy in 49 eugonadal controls after RP
  - 15 high risk
- Mean followup 27 mo
- Biochemical recurrence in 4 (4%) T group and 8 (16%) in control group

Pastuszak et al, J Urol 2013
T replacement after brachyRx

- 31 men treated with TRT after brachytherapy
- Followed median 4.5 years (0.5-9)
- T increased from 188 to 498 ng/dL on Rx
- Only one patient with transient PSA increase
- 97% with PSA<0.5 ng/mL (74% <0.1 ng/mL)
  - Close monitoring advised
  - Appears “safe”

Sarosdy et al., Cancer 109:536, 2006
THERAPY IN MEN WITH UNTREATED PCa

Abstract AUA 2013 Hult and Morgentaler

- TTh in 33 men on active surveillance
- Gleason 6 in 31, Gleason (3+4) in 2
- Mean f/u: 2.5y (longest f/u 6y)
- Progression (increase of >2 cores) in 2 men
- No progression based on Gleason score
- PSA unchanged at all time points
A thought experiment…

Imagine

- 2 brothers, identical twins, age 60
- Both s/p radical prostatectomy for Gleason 6
- PSA <0.1 ng/ml at 12 months
- Brother #1 happy, sexually active, T 600 (20nmol/L)
- Brother #2 tired, absent libido, T 250 (8nmol/L)
- Brother #2 requests T therapy
A thought experiment…

Physician:
- I can’t treat you. It’s dangerous.

Brother #2:
- “Why is it alright for my brother to have a T of 600 (20nmol/L), but not me?”
- “If T of 600 is unsafe, why don’t you lower my brother’s T?”
A thought experiment...

Our traditional unwillingness to offer T therapy to Brother #2 is illogical and unreasonable.
Tetosterone Treatment Summary

- TRT: beneficial effects for multiple systems
- Safe, with appropriate medical monitoring
- Need for more evidenced based studies
TRT REGISTRY
Mick Jagger, 72 years