Androgens & BPH/LUTS/Prostate Cancer: New Knowledge

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Outline

1. Framing the problem
2. Some T Basic Science & Saturation Theory
3. BPH LUTS & T - The Data
4. Prostate Cancer (CAP & T) - The Data
   - Low testosterone as a risk factor for prostate cancer
   - TTh in men with a history of prostate cancer
   - TTh in men with untreated prostate cancer
Physician Concerns About Testosterone Therapy in 2006

- Multinational physician survey on testosterone therapy
  - Most common physician concern is prostate cancer risk

Concerns Rated “Very Important”

BPH, benign prostatic hyperplasia.
"Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms."

"Contraindication: Men with carcinoma of the breast or known or suspected prostate cancer."

The old T & Prostate Theory

- Increases in testosterone make CAP worse. High T increases DHT and thus increase prostate size. Lower testosterone levels decrease CAP risk and LUTS risk (as prostate get smaller).
Finasteride and BPH

- Blocking DHT leads to decreased prostate growth by about 25%*

- The **MTOPS** trial demonstrated this quite well and as a result finasteride and other 5-ARi’s are a mainstay for symptomatic treatment of BPH. It is the only drug to definitively decrease retention and need for prostate surgery.

*Kaplan et al. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostatic sizes in men enrolled in the MTOPS trial. J Urol. 2008;180(3):1030-2
LOH symptom severity increases with increasing LUTS scores. LUTS, lower urinary tract symptoms; SLOH, symptomatic late-onset hypogonadism.

**T and PSA**

- Low T = low PSA
- Little change in PSA with ↑ T
- Saturation point = 8nmol ~ 250ng/dl

T and DHT = Anti-inflammatory

- Hypogonadism can be considered a Pro-inflammatory state

- Chronic inflammation and its effect on LUTS/BPH is seen in conjunction with low testosterone

• *In vitro* cell lines demonstrate increased CD8+ T Cells in finasteride BPH cells
• More than 60% of CD8+ T from blood of health persons migrated to the prostate tissue lysates from the finasteride group - (64.02% versus 10.31%)
• Molt-3 = T lymphocyte cell line

T-Cell Migration in Prostate:

BPH Control Tissue

Finasteride BPH Tissue

Normal T-cell migration capability induced by prostate tissue lysates from no medication group

Normal T-cell migration capability induced by prostate tissue lysates from finasteride group

DHT Effects on Inflammation

Table 1
Outcomes of studies assessing the effect of TRT on the Prostate/LUTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th># of Patients</th>
<th>Follow-up</th>
<th>Design</th>
<th>Data Followed</th>
<th>Therapy</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Emmeloet-Vonk et al, 2008 | Netherlands     | 207           | 6 mo      | RCT, double-blind, placebo-controlled | Prostate volume measured by TRUS, PSA, IPSS | IM Testosterone Undecanoate vs placebo | No increase in TRUS volume with TRT
No change in IPSS or PSA                                                    |
| Kalinchenko et al, 2010 | Russia          | 184           | 30 wk     | RCT, double-blind, placebo-controlled | IPSS                       | IM Testosterone Undecanoate vs placebo | No change in IPSS                                                           |
| Haider et al, 2009     | Multinational   | 122           | 24 mo     | Prospectively Followed cohort | IPSS                       | IM Testosterone Undecanoate vs placebo | Decrease in IPSS with TU treatment (P<.05)                                   |
| Kenny et al, 2010      | United States   | 27            | 3 mo      | Prospective Open-label study  | IPSS                       | Transdermal Testosterone   | No change in IPSS with TRT                                                   |
| Tan et al, 2013        | Malaysia        | 114           | 48 wk     | RCT, double-blind, placebo-controlled | IPSS                       | IM Testosterone Undecanoate vs placebo | No Change in IPSS with TRT                                                   |
| Shigehara et al, 2011  | Japan           | 46            | 12 mo     | RCT with untreated control group | IPSS, Qmax, PVR, Prostate Vol | IM Testosterone Enhanate vs placebo | Decrease in IPSS & Qmax with TRT (P<.05)                                     |
| Saad et al, 2007       | Germany         | 28            | 12 mo     | Prospective Uncontrolled      | IPSS                       | IM Testosterone Undecanoate vs Transdermal Testosterone | Both arms Demonstrated a decrease in IPSS compared to baseline (P = .03) |
| Yassin et al, 2014     | Germany         | 152           | 5.5 y     | Prospective Uncontrolled Registery study | IPSS                       | IM Testosterone Undecanoate | Decrease in IPSS from 10.35 to 6.31 with no statistical analysis             |
| Karazindiyaoğlu et al, 2008 | Turkey        | 25            | 12 mo     | Prospective cohort study      | IPSS, bladder compliance, maximal bladder capacity | Transdermal Testosterone  | Increase in bladder capacity and compliance with TRT (P<.05).             |

Note: There are no trials showing an increasing in IPSS scores.

Delay, UCNA 2016
Systematic Review and Meta-analysis

14 trials of 2029pt, with mean age of 64.5 y/o with LOH

Forest Plot of IPSS score with men on TRT vs Placebo

TRT does not worsen LUTS in men with LOH

DHT and T Protection

- 340 men with measurements of Bio-T, E2, DHT, DHEA followed longitudinally for LUTS symptoms to appear
- Higher Mid-life DHT = less LUTS/BPH¹
- Higher T levels inversely proportional to rate of LUTS/BPH²-⁴
- 3-point improvement of IPSS while on T⁵
- After controlling for confounders, data from the CUPID study showed only predictors of low T in cardiac population were age, BMI and irritative symptoms

4. Litman HJ, Bhasin S, O'Leary MP, Link CL, McKinlay JB. An investigation of the relationship between sex-steroid levels and urological symptoms: results from the Boston Area Community Health survey. BJU International. 2007;100(2):321-6
Inflammation Cycle of the Prostate

LUTS/BPH

5αRI
T
DHT

5αRI
T

Obesity
MetS
Atherosclerosis
Hypogonadism
Age

Hyperplasia

Hypertrophy

TNFa
IL6
IL8

Fibrosis

Micro-ischemia

HIF
TGF

Hypoxia

Improved
LUTS/BPH

Inflammation

CD8 T-Cells

Apoptosis
CCL5

Improved
LUTS/BPH
Number of articles showing testosterone therapy causes prostate cancer in PSA era

None!
Effect of TTh on Normal Prostate Tissue?
Effects of TTh on Prostate Tissue of Aging Men with Low Serum T

- R, DB, PC trial of 44 men (44-78 years)

- Inclusion criteria:
  - T < 300 ng/dl
  - Symptoms of hypogonadism

- Randomly assigned to receive 150 mg TE or placebo q 2 weeks X 6 months

- 12-core TRUS prostate biopsies were performed at baseline and 6 months

- Primary outcomes: 6-month change in prostate T & DHT

Effects of TTh on Prostate Tissue of Aging Men with Low Serum T

**Graph:**
- **Prostatic Tissue**
  - **Y-axis:** ng/g
  - **X-axis:** Baseline, 6 Months
  - **Legend:**
    - Orange: Testosterone
    - Yellow: DHT
  - **Comparisons:**
    - **TRT (n=21):**
      - Baseline: 6 ng/g
      - 6 Months: 8 ng/g
    - **Placebo (n=19):**
      - Baseline: 4 ng/g
      - 6 Months: 5 ng/g
If one assumes that higher testosterone levels increase the risk for prostate cancer, then are lower testosterone levels considered protective against the development of prostate cancer?
Low Testosterone Associated with Increased Risk of Prostate Cancer

  • Lower testosterone correlated with higher:
    • Pathological stage
    • Clinical stage
    • Biopsy Gleason grade

  • Lower testosterone correlated with:
    • Increased positive surgical margins
      • 39% in low TT vs 14.6% in normal TT

  • Lower testosterone correlated with:
    • Higher tumor density
    • Higher Gleason score
Global Pooled Longitudinal Study of Hormones and PCa Risk

- 3886 men with PCa
- 6448 age-matched controls
- No significant relationship between androgens and PCa

No History of Prostate Cancer -> TTh and Risk for Prostate Cancer

High Risk (High Grade P.I.N.) -> TTh and Risk for Prostate Cancer

Treated Prostate Cancer
- Radiation
- Radical Prostatectomy
High Risk (HGPIN)

• 75 hypogonadal men treated with TTh for 12 months

• All men underwent prostate biopsy prior to TTh
  • 55 men had benign biopsies (-PIN)
  • 20 men with PIN (+PIN)

• Results
  • No significant change in PSA in either group
  • One patient in +PIN group found to have prostate cancer on biopsy after abnormal DRE

• Conclusion: After 1 year of TTh, men with PIN did not have a greater increase in PSA or a significant increased risk of cancer than men without PIN

No History of Prostate Cancer

High Risk (High Grade P.I.N.)

TTh and Risk for Prostate Cancer

Treated Prostate Cancer
  - Radiation
  - Radical Prostatectomy
98 hypogonadal men treated with TTh after XRT or brachytherapy

Among high risk patients, PSA increased from 0.10ng/dl to 0.36ng/dl
Six (6.1%) men met criteria for biochemical recurrence
Retrospective review of 103 hypogonadal men treated with TTh after RP between 2003-2011 and 49 eugonadal controls having undergone RP treated during this time

- **High Risk CaP** - post-surgical pathology with one or more of the following: 1) Gleason score ≥8, 2) positive surgical margins, or 3) positive lymph nodes
- **TTh Group** - 77 men with low/intermediate risk CaP (non-high risk) and 26 with high-risk CaP
- **Control Group** – 34 men non-high risk and 15 men high-risk CaP

**Results:**

- 12 biochemical recurrences ONLY in high risk patients after 36 months
  - 4 biochemical recurrence in TTh group (15.3%)
  - 8 biochemical recurrences in control (non-TTh group) (53.3%)

TTh after Prostate Cancer

• A total of 9 published studies thus far have provided information on TTh after treatment for prostate cancer (RP, brachytherapy, EBRT)
  • Total of 346 patients given TTh after treatment for their prostate cancer
• Only 10 men, or 2.8% of men, were noted to have a biochemical recurrence
• Recurrence rate is less than published series in favorable groups²
• TTh protective?

¹Morgentaler J Urol 2009; 181:972
²van Oort et al. Urol Oncol 2008 Epub
TTh and Prostate Cancer Cell Suppression

- Hatzoglou et al. - membrane androgen receptor activation induced apoptotic regression of human prostate cancer cells in vitro and in vivo¹

- Sonnenschein et al. - androgens were able to trigger an inhibition of prostate cancer cell proliferation at higher concentration²

- Chuu et al. - androgens caused growth suppression and then reversion of androgen independent tumors to an androgen dependent tumors³

¹ Hatzoglou et al J Clin Endocrinol Metab 2005, 90:893-903
³Chuu et al Cancer Res 2005, 65:2082-4
The Patrick C. Walsh Prostate Cancer Research Fund

A New Way to Treat Recurrent Prostate Cancer: More Testosterone?

Volume 9, Winter 2013
14 patients with CRPC

TE 400mg IM q month for 3 months

Castrating therapy continued to suppress endogenous testosterone production, allowing for rapid cycling from supraphysiologic to near-castrate serum testosterone levels = bipolar androgen therapy (BAT)

BAT was well tolerated and resulted in high rates of PSA (7 of 14 evaluable patients) and radiographic responses (5 of 10 evaluable patients)
What about Active Surveillance?
Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results

Ravi Kacker¹, Mariam Hult¹, Ignacio F San Francisco², William P Conners¹, Pablo A Rojas², William C Dewolf³, Abraham Morgentaler¹

- 28 hypogonadal men on AS and TTh for at least 6 months
- Control: 96 hypogonadal men on AS and not receiving TTh
- Follow-up 38.9 and 42.4 months T and non-T group, respectively
- Non-T group (n=96): All men with GL 3+3
  - 43 (44.7%) developed biopsy progression, including 9 men (9.38%) with upgrading to Gleason 7 (3 + 4)
- T group (n=28): 22 men with GL 3+3 and 6 men with GL 3+4
  - GL 3+3: 7 (31.8%) men developed biopsy progression including 3 men (13.6%) who developed Gleason 3 + 4 PCa
  - GL 3+4: 2 (33.3%) men developed an increase in tumor volume, and none developed upgrading beyond Gleason 3 + 4

Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance

Ignacio F. San Francisco, Pablo A. Rojas, William C. DeWolf* and Abraham Morgentaler*

- 154 men were followed with AS for prostate cancer
- 54 (35%) progressed to active treatment
- Men who progressed had significantly lower free testosterone levels than those who remained on AS (0.75 vs 1.02 ng/dL, P = 0.03)
- Free testosterone levels <0.45 ng/dL were associated with a seven-fold increase in the risk of disease progression (OR 4.3, 95% CI 1.25-14.73)
- Multivariate analysis demonstrated that free testosterone and family history of PCa were independent predictors of disease progression

San Francisco et al. BJU Int. 2014 Aug;114(2):229-35.
A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

Mohit Khera\textsuperscript{a,}\textsuperscript{*}, David Crawford\textsuperscript{b}, Alvaro Morales\textsuperscript{c}, Andrea Salonia\textsuperscript{d}, Abraham Morgentaler\textsuperscript{e}

Table 2 – Criteria to consider before initiating testosterone therapy in men with history of treated prostate cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>The clinical picture is consistent with a diagnosis of testosterone deficiency.</td>
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<tr>
<td>The patient must understand that safety data are limited and that there is an unknown degree of risk of PCa progression or recurrence.</td>
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<tr>
<td>The patient must be willing and able to provide informed consent.</td>
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<tr>
<td>No medical contraindications to testosterone therapy (eg, erythrocytosis) exist.</td>
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<tr>
<td>There is an undetectable or stable PSA level.</td>
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<tr>
<td>Clinicians must be prepared for the possibility of PCa recurrence or progression, which will occur in some men regardless of testosterone therapy but may be attributed to testosterone therapy by patients, family, or other clinicians.</td>
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</tr>
<tr>
<td>Use testosterone therapy with extreme caution in men at high risk for PCa recurrence or progression.</td>
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<tr>
<td>Do not recommend testosterone therapy for men currently receiving any form of ADT.</td>
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</tbody>
</table>

PCa = prostate cancer; PSA = prostate-specific antigen; ADT = androgen-deprivation therapy.
Conclusion

• While TTh does significantly impact PSA levels and size in hypotrophic prostates (levels of serum testosterone below saturation point), TTh does not appear to affect prostate size, or intra-prostatic testosterone levels in T saturated prostates.

• There is currently no evidence that TTh promotes the initiation of BPH/LUTS or prostate cancer in hypogonadal men.

• Hypogonadal men receiving TTh after history of prostate cancer appear to have low recurrence rates of prostate cancer. Some hypogonadal men who are given TTh have improvement in LUTS.