Testosterone and Prostate Cancer

Dr. Ilan Z. Kafka
“Prostate cancer is the most common of concerns among physicians recommending T therapy”

Introduction

- **Testosterone**
  - 90%-- Leydig Cells of Testes
  - 10%-- Adrenal Glands
Testosterone Deficiency in Men
Testosterone Deficiency in Men

- Hypogonadism-
  - AKA-
    - Androgen decline in the aging male (ADAM)
    - Late-onset hypogonadism (LOH)
    - Andropause
    - Testosterone deficiency syndrome (TDS)

- Annual incidence of TDS in the United States is as high as 500,000 new cases in men aged 40–69 /yr

- Low serum testosterone <300 ng/ml in men <50; <200 ng/ml in older men

<table>
<thead>
<tr>
<th>System/Function</th>
<th>Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile function</td>
<td>↓</td>
</tr>
<tr>
<td>Sexual desire</td>
<td>↓</td>
</tr>
<tr>
<td>Mood/cognition</td>
<td>↓/→</td>
</tr>
<tr>
<td>Tiredness/lack of motivation</td>
<td>↓</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>↑/→</td>
</tr>
<tr>
<td>Spatial cognition</td>
<td>↓</td>
</tr>
<tr>
<td>Vasomotor (hot flushes)</td>
<td>↑</td>
</tr>
<tr>
<td>Quality of life</td>
<td>↓</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>↓</td>
</tr>
<tr>
<td>Leptin production</td>
<td>↑</td>
</tr>
<tr>
<td>LDL and HDL cholesterol</td>
<td>→</td>
</tr>
<tr>
<td>Fat mass</td>
<td>↑</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>↓</td>
</tr>
<tr>
<td>Bone mass</td>
<td>↓</td>
</tr>
<tr>
<td>Hair and skin changes</td>
<td>↓</td>
</tr>
</tbody>
</table>
Serum Testosterone and Prostate Cancer incidence

Do circulating sex hormones influence the risk of PCa?
- Collaborative analysis of 18 longitudinal studies
- 3886 men with PCa, 6438 controls
- No association of PCa with serum androgens
- Men with PCa have similar intraptostatic androgen concentrations as men without PCa
- Men with highest T at no greater risk of PCa than men with lowest T

Roddam AW et al, JNCI 2008; 100:170-83
PCa in men receiving TT

- TT does not exert a deleterious effect on prostate
  - 44 men, 44-78 years
  - testosterone levels <300 ng/dL and related symptoms
  - 150 mg of testosterone or placebo intramuscularly every 2 weeks for 6 months.
- TT increased serum testosterone levels to the midnormal with no significant change in serum testosterone levels in matched, placebo-treated men
- Median prostate tissue levels of testosterone did not change significantly in the TT group.
- No treatment-related change was observed in prostate histology, tissue biomarkers, gene expression, or cancer incidence or severity.
- 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 and Prostate Cancer

• HOW IT ALL STARTED...
Introduction

- Huggins and Hodges-

Huggins C, Hodges CV. *Studies on prostatic cancer, I: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate.*

*Cancer Res* 1941;1:293–7.

Regression of metastatic Pca in 3 men after reduction in serum testosterone levels

Progression of metastatic disease and symptoms in 1 man who received exogenous testosterone.

Charles B. Huggins, M.D

*Won Nobel Prize 1966*
Is it justifiable to withhold TT, which is known to provide many benefits for symptomatic hypogonadal men, because of a “risk” that is unproven?
Age, Serum T and pCA
Effects of testosterone on prostate cancer growth

- **TT in hypogonadal men**
  - ↑ in PSA, ↑ prostate volume

- **TT in eugonadal men**
  - No changes


- **In men w/ low testosterone receiving TT**
  - ↑ PGV- age matched eugonadal men

Serum testosterone and PSA in young men

From Bhasin et al. J Physiol Endocrin Metab. 281:e1172, 2001

- n=54
- 18-35 yo
- Long acting GnRH agonist

Serum T and PSA in older men


- n=60
- 60-75 yo
- Long acting GnRH agonist
Effects of testosterone on prostate cancer growth

- Testosterone Administration to px with bone mets from PCa.
  - Previously untreated – beneficial response
  - Prior orchiectomy or estrogen exposure- unfavorable response
  - Response largely related to pre- tx testosterone levels

Testosterone increases risk of PCa

- Serum Testosterone associated w/ aggressive Pca in older men.
  - 781 men in the BLSA – no cancer= 636
    - cancer not high risk= 109; cancer high risk=36
  - >65yo likelihood of high risk PCa w/ increase in free testosterone
  - <= 65yo likelihood inversely related to free testotsterone
- CONCLUSION -Higher levels of serum free testosterone are associated with an increased risk of aggressive prostate cancer among older men.

*Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging*
Phillip M. Pierorazio, Luigi Ferrucci, Anna Kettermann, Dan L. Longo, E. Jeffrey Metter, H. Ballentine Carter
• Low Testosterone and PCa?
Association between low serum testosterone and PCa
- 345 hypogonadal men
- PSA level of 4.0 ng/mL or less
- Testosterone 300 ng/dL or <
- DRE and prostate biopsy before TRT

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

Morgentaler A, Rhoden EL. Urology 2006
Serum Testosterone and Prostate Cancer incidence

- **Low testosterone levels associated with:**
  - Advanced Pathological State
  - High Gleason score
  - Biochemical recurrence after RP
  - \% positive-core rate at Bx.

Serum Testosterone and Prostate Cancer

- **Saturation Theory**

- **Suppression Theory**
Saturation Theory


AR is maximally bound with androgen (saturated) at 60-90 ng/dl (2-3 nmol/L)
**Suppression Theory**

- **63 healthy men 43 - 67 years**- clinically confined prostatic adenocarcinoma
- Blood for- testosterone, % free testosterone, DHT, estradiol, LH, FSH, sex hormone binding, globulin and prolactin.
- Following radical prostatectomy -increase in serum testosterone, free testosterone, estradiol, LH and
  - decrease in serum
- Does the normal prostate and/or prostate neoplasm could secrete a substance **or substances that give** negative feedback control to pituitary gonadotropin secretion?

_Influence of Radical Prostatectomy in Serum Hormone Levels_
Leslie R Miller, Alan W Partin, et al
_Journal of Urology_
August 1998
Prostatic changes in hypogonadal men with and without high grade prostatic intraepithelial neoplasia (PIN) after 1 year of TRT.

75 hypogonadal men - 12 months of TRT
55 negative Bx. 20 PIN

Prostate specific antigen (PSA), and total and free testosterone were determined prior to treatment and at 1 year. Repeat biopsy was performed for a change noted on digital rectal examination or for a PSA increase of 1 ng/l or greater.

No significant differences in PSA responses were noted between these two groups, and in follow-up only a single PCa was detected (in the PIN group).

## TT after definitive therapy for localized PCa

### Table 1 – Reports addressing the effect of testosterone therapy in symptomatic hypogonadal men after definitive prostate cancer treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size, n</th>
<th>PCa treatment</th>
<th>Start of TRT after PCa treatment</th>
<th>Follow-up</th>
<th>Cases of BCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman and Graydon [29]</td>
<td>7</td>
<td>RP</td>
<td>Mean: 2.7 yr</td>
<td>Mean: NR</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 0–108 mo</td>
<td>Range: 1–12 years</td>
<td></td>
</tr>
<tr>
<td>Agarwal and Oefelein [28]</td>
<td>10</td>
<td>RP</td>
<td>Not reported</td>
<td>Mean: 19 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 9–29 mo</td>
<td>Range: 1–60 mo</td>
<td></td>
</tr>
<tr>
<td>Khera et al [25]</td>
<td>21</td>
<td>RP</td>
<td>Mean: 54 mo</td>
<td>Median: 12 mo</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 1–181 mo</td>
<td>Range: 1–60 mo</td>
<td></td>
</tr>
<tr>
<td>Nabulsi et al [27]</td>
<td>22</td>
<td>RP</td>
<td>Mean: 26 mo</td>
<td>Mean: 24 mo</td>
<td>1/22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 2.5–11.8 mo</td>
<td>Range: 14–30 mo</td>
<td></td>
</tr>
<tr>
<td>Davilla et al [24]</td>
<td>20</td>
<td>RP: 14</td>
<td>Mean: 74 after RP</td>
<td>Mean: 12 mo after EBRT</td>
<td>None after RP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RP: 57 mo after EBRT</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Range: NR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(according to ASTRO criteria)</td>
<td>None</td>
</tr>
<tr>
<td>Morales et al [69]</td>
<td>5</td>
<td>EBRT</td>
<td>Not reported</td>
<td>Mean 14.6 mo</td>
<td>None (according to ASTRO criteria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range: 6–27 mo</td>
<td>PSA &lt; 0.1 in 74%</td>
</tr>
<tr>
<td>Sarosdy [26]</td>
<td>31</td>
<td>Brachytherapy (with or without EBRT)</td>
<td>Median: 24 mo</td>
<td>Median: 60 mo</td>
<td>PSA &lt; 1.0 in 100%</td>
</tr>
</tbody>
</table>

ASTRO = American Society for Therapeutic Radiation Oncology; BCR = biochemical recurrence; EBRT = external beam radiotherapy; NR = not reported; PCa = prostate cancer; RP = radical prostatectomy; TT = testosterone therapy.
Current GL on TT

Current GL on TT

- All: No evidence that TT↑ risk of developing PCa, or converts subclinical PCa into clinically significant disease.
- EAU- TT relative contraindicated in men at high risk of dev. Pca – no def. of high risk Px.
- All: Literature on TT and PCa too sparse to draw a definitive conclusion on safety of TT.
- All: TT contraindicated in men w/ Dx. PCa.—Risk of PCa assessment
  - DRE+ PSA-----Bx.
Current GL on TT

- EAU- TT may be considered in symptomatic hypogonadal men s/p successful PCa Tx.
  - After a prudent interval - No clinical or laboratory evidence of recurrence
- Endocrine Society- no recommendation
Conclusions...

- Do men with PCa have higher T than men without PCa?
- Do men with higher T have greater risk of developing PCa than men with lower T?
- No evidence that TRT increases the risk of developing clinical prostate cancer
Future...

- Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer
  - Eur Urol. 2009 Aug

- A Randomized Phase 1 Study of Testosterone Replacement for Patients with Low-Risk Castration-Resistant Prostate Cancer.
  - Eur Urol. 2009 Feb
Thank You...