Controversies with Testosterone Therapy

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Controversies with TTh

Diagnosis

BPH

Prostate Cancer

CVD
Diagnosis of Androgen Deficiency and Late Onset Hypogonadism (LOH)

Biochemical + Signs and Symptoms
FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.
1 INDICATIONS AND USAGE

AndroGel 1% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.
Specific Medical Conditions Associated with Hypogonadism

- Unknown: 89.1%
- Specific medical conditions: 10.9%
- Genetic: 3.4%
- Empty sella: 1.7%
- Drugs: 1.1%
- PRL-adenomas: 2.4%
- Trauma: 1.1%
- Radiotherapy: 0.1%

Laboratory Diagnosis

• Problems with testosterone and free testosterone testing
  • Variations between total testosterone assay methods
  • Variation in reference ranges for total testosterone
    • Study of 25 different testosterone reference labs\(^2\)
    • Lower reference value: 130 to 450 ng/dL (350% difference)
    • Upper reference value: 486 to 1,593 ng/dL (325% difference)

At What Levels Should We Treat?: Free Testosterone

• Currently, there is no accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism.

• “Free testosterone level below 225 pmol/l (65 pg/ml) can provide supportive evidence for testosterone treatment.” (Level 3)
At What Levels Should We Treat?: Total Testosterone

• For most symptoms, the average testosterone threshold corresponds to the lower limit of the normal (approximately 300 ng/dl), with a greater likelihood of having symptoms below this threshold than above it.¹²

• Threshold of testosterone levels vary for various symptoms of androgen deficiency and target organs, and among individuals.¹²

² Zitzmann et al J Clin Endocrinol Metab 2006 91:4335–4343
Testosterone and BPH

--------------------- WARNINGS AND PRECAUTIONS ---------------------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to Testim. Secondary exposure to testosterone can produce signs of virilization. Testim should be discontinued until the cause of virilization is identified. (5.2)
- Exogenous administration of androgens may lead to azoospermia. (5.5)
- Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.7, 6.2)
- Sleep apnea may occur in those with risk factors (5.9)
- Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.1, 5.3, 5.10)
Testosterone and LUTS

• 95 hypogonadal men treated with long-acting IM testosterone undecanoate every 3 months for 12 months

• Results
  • No significant change in prostate volume
  • Significant improvement in PVR
  • Significant improvement in IPSS
  • Significant improvement in CRP

International Prostate Symptom Score (IPSS) in 255 Middle-Aged to Elderly Men Treated with TU up to 60 mo

p<0.0001 vs baseline  #p<0.0001 vs previous year

Testosterone and Cardiovascular Disease

Millions of Men at Potential Risk for Fatal Harm Due to Unnecessary ‘Low T’ Therapy

If you, or a loved one, have been prescribed any of the following low testosterone drugs, you may be entitled to compensation, and should speak to an attorney about your legal rights.

McLaughlin & Lauricella P.C.
Low-T Testosterone Lawsuit Lawyers
Aging Males and Mortality
Low Serum T and Mortality in Male Veterans

Survival (y)

Men With a Normal T-Level (n = 452)
Men With a Low T-Level (n = 166)

Survival
79.9%
65.1%

Low Testosterone and Increased Mortality (N >500)

<table>
<thead>
<tr>
<th>Recent Studies</th>
<th>HR (95% CI)</th>
<th>Nature</th>
<th>Men, n</th>
<th>Follow-Up, y</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Shores, 2006</td>
<td>1.88 (1.34–2.63)</td>
<td>Retrospective</td>
<td>858</td>
<td>8</td>
<td>All-cause</td>
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<td>Laughlin, 2008</td>
<td>1.38 (1.02–1.85)</td>
<td>Prospective</td>
<td>794</td>
<td>20</td>
<td>CVD</td>
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<td>Khaw, 2007</td>
<td>2.29 (1.60–3.26)</td>
<td>Prospective</td>
<td>2314 of 11,606</td>
<td>10</td>
<td>All-cause and CVD</td>
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<tr>
<td>Haring, 2010</td>
<td>2.32 (1.38–3.89)</td>
<td>Prospective</td>
<td>1954</td>
<td>7.2</td>
<td>All-cause</td>
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<td></td>
<td>2.56 (1.15-6.52)</td>
<td></td>
<td></td>
<td></td>
<td>CVD</td>
</tr>
<tr>
<td>Malkin, 2010</td>
<td>2.27 (1.45–3.60)</td>
<td>Prospective</td>
<td>930</td>
<td>6.9</td>
<td>All-cause in men with coronary disease</td>
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<tr>
<td>Tivesten, 2009</td>
<td>1.65 (1.29–2.12)</td>
<td>Prospective</td>
<td>3014</td>
<td>4.5</td>
<td>All-cause</td>
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<td>Menke, 2010</td>
<td>1.43 (1.09–1.87)</td>
<td>Prospective</td>
<td>1114</td>
<td>9</td>
<td>All-cause</td>
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<tr>
<td>Vikan, 2009</td>
<td>1.24 (1.01–1.54)</td>
<td>Prospective</td>
<td>1568</td>
<td>11.2</td>
<td>All-cause</td>
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<tr>
<td>Corona, 2010</td>
<td>7.1 (1.8–28.6)</td>
<td>Prospective</td>
<td>1687</td>
<td>4.3</td>
<td>CVD</td>
</tr>
</tbody>
</table>

HR=hazard ratio; CI=confidence interval.
Prior to 2010 Articles Demonstrating Beneficial Effects of T Against CVD

<table>
<thead>
<tr>
<th>Type of Article</th>
<th>Number of Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low levels of endogenous testosterone and increased mortality</td>
<td>8</td>
</tr>
<tr>
<td>Low testosterone levels and increased incidence of coronary artery disease</td>
<td>6</td>
</tr>
<tr>
<td>Low testosterone level correlates with increased severity of coronary artery disease</td>
<td>4</td>
</tr>
<tr>
<td>Low endogenous testosterone level and increased carotid intima-media thickness</td>
<td>8</td>
</tr>
<tr>
<td>TRT decreases obesity</td>
<td>6</td>
</tr>
<tr>
<td>TRT improved cholesterol levels (meta-analysis)</td>
<td>3</td>
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<tr>
<td>TRT improves glycemic control</td>
<td>6</td>
</tr>
<tr>
<td>TRT decreases markers of inflammation</td>
<td>8</td>
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</tbody>
</table>
TRT Causes CVD

Basaria et al
NEJM 2010
- RPCT frail elderly men
- 15 grams of testosterone
- CVD not an endpoint
- Treatment arm greater CV risks
- 5 vs 2 major CV events (ie MI)
- No difference if exclude CHF

Vigen et al
JAMA 2013
- No randomization or placebo
- 2 major corrections
  - “Absolute risk” of MI (19.9 vs 25.7%) vs (21 vs 10%)
  - Exclusion of 1132 men
- RETRACTION 29 societies

Finkle et al
PLoS One 2014
- No randomization or placebo
- No control group or clinical info
- Health insurance database
- 90 days after start testosterone
- Pre-prescription MI rate 3.48/1000
  Post-prescription MI rate 4.75/1000

Xu et al
BMC 2013
- Meta-analysis of CV events in 27 PC studies of >12 weeks
- Just 2 studies provided 1/3 of all CV events in T treat arm
- If exclude 2 studies CV events in T and placebo are identical
Follow-up Studies on TTh and CVD

• Retrospective study of 83,010 hypogonadal veterans receiving TTh or no treatment¹
  • TTh was associated with a significant reduction in all-cause mortality, MI and stroke

• 6,355 hypogonadal men undergoing TTh matched to 19,065 testosterone nonusers²
  • Men with highest MI risk= TTh associated with a significant reduction in developing MI (HR = 0.69; 95%CI= 0.53-0.92)

• Meta-analysis of 75 studies of 3016 men treated with TTh and 2446 treated with placebo for 34 weeks³
  • No significant association between TTh and CV events
  • CV protective effect of TTh in men with metabolic disorders

²Baillargeon et al. Ann Pharmacother 2014
³Corona et al Exp Opin Saf Drug. 2014
FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use.

The testosterone product labels have been updated. The revised labels clarify the approved uses of these medications and include information about a possible increased risk of heart attacks and strokes in patients taking testosterone.

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.
• Low levels of Total T, bioavailable T and free T are associated with increased risk of mortality and CVD (LOE IIa)
• Severity of CAD is inversely correlated with serum concentrations of total T, bioavailable T or free T (LOE IIa)
• Testosterone therapy improves time to onset of symptomatic angina (LOE 1b)
• Exercise capacity and peak oxygen consumption in men with symptomatic CHF improved with TTh (LOE Ia)
Physician Concerns About the Prostate in 2006

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

Concerns Rated “Very Important”

- Prostate cancer risk
  - Brazil: 52%
  - Saudi Arabia: 42%
  - Spain: 50%
  - South Korea: 66%
  - Germany: 50%

- BPH risk
  - Brazil: 18%
  - Saudi Arabia: 18%
  - Spain: 10%
  - South Korea: 0%
  - Germany: 12%
  - United Kingdom: 12%

BPH, benign prostatic hyperplasia.
Historical Basis for Concern

In 1941 – Huggins & Hodges reported:

1. Reducing T to castrate levels caused prostate cancer to regress

2. Administration of exogenous T caused prostate cancer to grow
Historical Basis for Concern

In 1941 – Huggins & Hodges reported:

1. Reducing T to castrate levels caused prostate cancer to regress

2. Administration of exogenous T caused prostate cancer to grow (based on a single patient)
## A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Follow-up (months)</th>
<th>Pre TRT PSA</th>
<th>Post TRT PSA</th>
<th>Pre TRT T (ng/dl)</th>
<th>Post TRT T (ng/dl)</th>
<th>Cancer Recurrence</th>
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<tbody>
<tr>
<td>Agarwal et al</td>
<td>10</td>
<td>RP</td>
<td>19</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>197</td>
<td>591</td>
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<td>Kaufman et al</td>
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<td>RP</td>
<td>24</td>
<td>&lt;0.1</td>
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<td>97</td>
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<tr>
<td>Khera et al</td>
<td>57</td>
<td>RP</td>
<td>13</td>
<td>0.005</td>
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<td>255</td>
<td>459</td>
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<tr>
<td>Pastuszak et al</td>
<td>103</td>
<td>RP</td>
<td>27.5</td>
<td>0.004</td>
<td>0.007</td>
<td>261</td>
<td>460</td>
<td>Yes (4)</td>
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<td>Pastuszak et al</td>
<td>98</td>
<td>Brachy and XRT</td>
<td>41</td>
<td>0.08</td>
<td>0.09</td>
<td>209</td>
<td>420</td>
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<td>Sarosdy</td>
<td>31</td>
<td>Brachy</td>
<td>60</td>
<td>n/a</td>
<td>&lt; 1</td>
<td>188</td>
<td>489</td>
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<tr>
<td>Morales et al</td>
<td>5</td>
<td>XRT</td>
<td>14.5</td>
<td>0.1-0.97</td>
<td>&lt; 0.1 – 1.08</td>
<td>150</td>
<td>507</td>
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<td>Pastuszak et al</td>
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<td>Brachy and XRT</td>
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<td>0.66</td>
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<td>368</td>
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<tr>
<td>Balbontin et al</td>
<td>20</td>
<td>Brachy</td>
<td>31</td>
<td>0.7</td>
<td>0.1</td>
<td>343</td>
<td>592</td>
<td>No</td>
</tr>
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</table>
Retrospective review of 103 hypogonadal men treated with TRT 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
- **TRT 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 TRT group (15.3%)
- 8 biochemical recurrences in control (non-TRT group) (53.3%)
TRT after Prostate Cancer

• A total of 8 studies (abstracts + manuscripts) thus far have provided information on TRT after treatment for prostate cancer (RP, brachytherapy, EBRT)
  • Total of 484 patients treated with testosterone after prostate cancer
  • Only 10 men, or roughly 2% of men, were noted to have a biochemical recurrence
  • Recurrence rate is less than published series in favorable groups²
  • TRT protective?

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

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

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

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

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 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)
Bipolar Androgen Therapy for Men With Androgen Ablation Naïve Prostate Cancer: Results From the Phase II BATMAN Study

• 29 asymptomatic hormone sensitive (HS) prostate cancer patients
  • Low metastatic burden
  • Non-metastatic with biochemical recurrence

• 6 mo ADT followed by 400mg TC IM every 4 weeks for 3 months in alternating 3 month cycles

• 59% of men had PSA < 4ng/dl after 18 mo

• Ten patients receiving BAT had RECIST evaluable disease, and eight (80%) objective responses were observed (four complete; four partial)

• Significant improvements noted in SF-36 and IIEF

Schweizer et al Prostate. 2016 Sep;76(13):1218-26
Conclusion

• Diagnosis of hypogonadism can be challenging with majority of men being treated off-label

• TTh has been shown to improve BPH and LUTS

• Low serum testosterone has been associated with an increased risk of MI and CV risk factors

• There is no convincing data to support that TTh causes prostate cancer
Physiological normal levels of androgen inhibit proliferation of prostate cancer cells *in vitro*

Weitao Song, Mohit Khera

- Prostate cancer LNCaP cells were treated with various levels of testosterone (T) (0 to 16ng/ml)
- 8-12K cells were seeded in triplets, T treatment for 10 days
- The growth rate of prostate cancer cells was assessed
LNCaP and MDA Pca 2b Cells Treated with Testosterone
Testosterone and Prostate Cancer: In-vivo Experiments

- Male nude mice divided into 4 categories
  - Normal control (n=45)
  - Orchiectomy (n=44)
  - 2mg testosterone pellet (n=44)
  - 5mg testosterone pellet (n=44)

- 5 million LNCaP cells injected s.c. one week post surgery

- Mice followed for 84 days
- Serum testosterone and tumor size assessed
Tumor Development Rate

**Tumor Incidence Rate**

<table>
<thead>
<tr>
<th>Groups</th>
<th>NC</th>
<th>Orchi</th>
<th>2 mg</th>
<th>5 mg</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>51% 23/45</td>
<td>9% 4/44</td>
<td>48% 21/44</td>
<td>25% 11/44</td>
</tr>
</tbody>
</table>

Significance levels:
- ***: p < 0.001
- *: p < 0.05

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Laboratory for Andrology Research
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