Testosterone Therapy 2016
Indications, Efficacy and Potential Dangers

Larry I. Lipshultz, M.D.
Professor of Urology
Chief, Division of Male Reproductive Medicine and Surgery
Baylor College of Medicine
Houston, Texas
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“The FDA cautions that prescription testosterone products are approved only for men who have low testosterone caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone due to aging.”
Percentage of Men Given TRT

Does this really represent over treatment in 2011?

Prevalence of Androgen Deficiency in United States

Hypogonadism in Males (HIM)¹

- Office-based, primary care
- Age: 45-96 years
- **Definition:** T < 300 ng/dl + **no symptoms**

**Crude Prevalence:** 38.7%

- 55-64 yr: 40.2%
- 65-74 yr: 39.9%

Prevalence of Androgen Deficiency in United States
Boston Area Community Health Survey

- Community-based
- Age: 30-79 years
- Definition: T < 300 ng/dl + 1 specific or 2 less specific symptoms
- Definition of “hypogonadism” closely agrees with End. Soc. Guidelines

Crude Prevalence: 5.6%

Introduction

- Disease state
- Diagnosis
- Treatment options
- Efficacy
- Safety
Prevalence of Low Testosterone: 13.8 Million Men in the US

Overall, 38.7% of men ≥45y have T-levels < 300 ng/dL

Prevalence of Low T in All Enrolled Patients (% ± 95% CI)

- 45 to 54: 43% ± 95% CI
- 55 to 64: 47% ± 95% CI
- 65 to 74: 52% ± 95% CI
- 75 to 84: 58% ± 95% CI
- >85: 63% ± 95% CI

T = testosterone.
The Impact of Testosterone

Skin
Hair growth, balding, sebum production

Liver
Synthesis of serum proteins

Male Sexual Organs
Penile growth, spermatogenesis, prostate growth, and function

Bone
Accelerated linear growth, closure of epiphyses

Brain
Libido, mood

Muscle
Increase in strength and volume

Kidney
Stimulation of erythropoietin production

Bone Marrow
Stimulation of stem cells

Select Causes of Low Testosterone

• Primary (testicular)
  • Congenital—Klinefelter’s and variants
  • Acquired—Mumps and other viruses
  • Trauma
  • Aging
  • HIV/AIDS

• Secondary (pituitary)
  • Aging
  • Chronic illness
  • HIV/AIDS
  • Certain drugs/alcohol

Forms of Serum Testosterone

- SHBG-Bound T: 60%
- Albumin-Bound T: 38%
- FT: 2%

Only 2% is FT; 98% is bound.

FT = free testosterone; SHBG = sex-hormone binding globulin.
Male Hormonal Status
Changes with Age as SHBG Increases

Comorbidities and Low Testosterone
Prevalence of Low Testosterone in Other Conditions

HIV = 30%.
ED = erectile dysfunction.

Low Testosterone Levels and Diabetes/Metabolic Syndrome

Men with low T  

More likely to develop metabolic syndrome or type 2 diabetes

• Three major studies with >2800 patients\textsuperscript{1-3}
• Those in lowest T quartile over 11 y had 2-fold greater risk of metabolic syndrome and type 2 diabetes\textsuperscript{1}

Why are men with these comorbid conditions NOT being screened and diagnosed for low T?
Why Men Aren’t Being Screened for Low Testosterone?
Lack of Consumer Awareness

Harris Interactive Male Survey

<table>
<thead>
<tr>
<th>Online Surveys</th>
<th>N = 522</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaware of low T symptoms</td>
<td>91 (%)</td>
</tr>
</tbody>
</table>

- 33% of men have experienced ≥2 symptoms of hypogonadism in past 12 months
- 95% say doctor never mentioned low T when presented w/ ≥2 symptoms of hypogonadism

Harris Interactive Polls, 2006.
Diagnosis of Low Testosterone:

- Symptoms
- Signs
- Decreased T
Key Symptoms and Signs Associated with Low Testosterone

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased body fat, BMI</td>
<td>• Decreased energy or motivation</td>
</tr>
<tr>
<td>• Reduced muscle bulk and strength</td>
<td>• Depressed mood</td>
</tr>
<tr>
<td>• Low BMD</td>
<td>• Diminished libido, ED</td>
</tr>
<tr>
<td>• Loss of body hair (axillary and pubic)</td>
<td>• Diminished work performance</td>
</tr>
<tr>
<td></td>
<td>• Poor concentration and memory</td>
</tr>
<tr>
<td></td>
<td>• Sleep disturbance</td>
</tr>
</tbody>
</table>

Adapted from The Endocrine Society Guidelines, 2006.
Androgen Deficiency in the Aging Male
ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased “enjoyment of life”?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Positive result is defined as “yes” answer to questions 1 or 7, or any other 3 questions.
What Is Considered a Low Serum T-Level?

- Total Testosterone < 300 ng/dL*
- FT < 50 pg/mL
- Bioavailable Testosterone < 70 ng/dL

*Most frequently used lab test for the diagnosis of hypogonadism.
Testosterone Replacement Therapy: Treatment Options
TRT Treatment Options

- Oral Tablets: Not in U.S.
- Intramuscular Injections
- Pellet Implants
- Transdermal Patches
- Transdermal Gels
TRT Formulation-Specific Adverse Effects

Oral tablets
- Effects on liver and cholesterol (methyltestosterone)

Intramuscular injections of testosterone enanthate or cypionate
- Fluctuation in mood or libido
- Pain at injection site
- Excessive erythrocytosis (especially in older patients)

Transdermal patches
- Skin reactions at application site

Transdermal gel
- Potential risk for testosterone transference to partner

Pellet implants
- Infection, expulsion of pellet

Transdermal Gels are the Most Commonly Prescribed Form of TRT.

- Gels: 70%
- Injectables: 17%
- Patches: 10%
- Other: 3%
Testosterone Levels After Replacement With Gel, Patch, or Injection

Testosterone gel (AndroGel 1%) Unimed Pharmaceuticals and Solvay Pharmaceuticals, 2002.
Improved Sexual Symptoms in Low T Patients

Improved Sexual Desire

- Mean Daily Score
- Change (%)

Time (mo)

Significant Improvement From Baseline

- 60.4%

Dean Study

Steidle Study

Improved Sexual Performance

- Mean Weekly Score
- Change (%)

Time (mo)

Significant Improvement From Baseline

- 76.6%

Testosterone Replacement Improves Sexual Function

Objective Assessment Rigiscan® Erectile Index
(N = 20)

Hypogonadal Baseline
Testosterone Replacement

Erectile Index (%)

Base
Tip

Improved Non-Sexual Symptoms in Low T Patients

Increased Lean Body Mass

Mean Change from Baseline

0.5

1.0

1.5

2.0

2.5

+4.8 lb

Decreased Fat Mass

Mean Change from Baseline

-0.5

-1.0

-1.5

-2.0

-2.5

-4.0 lb

0

3

6

9

12

0

3

6

9

12

Dean Study

Steidle Study

Significant Improvement From Baseline

Significant Improvement From Baseline

Testosterone \(\rightarrow\) Changes in Bone Mineral Density (BMD)

Changes in Lumbar Spine BMD

Mean ± SEM

- \(T\)
- \(T+F\)

Placebo

\(P < .001\)

Testosterone Replacement Therapy: Understanding the Benefit/Risk Ratio
March 3, 2015

“The FDA is investigating the risk of stroke, heart attack and death in men taking FDA-approved testosterone products. We...decided to reassess this safety issue based on the recent publication of two separate studies\(^1,2\) that suggested an increased risk of CV events among groups of men prescribed testosterone therapy.”

1. Vigen et al., LAMA 2013
2. Finkle et al., PLoS One, 2014
FDA-Cited Studies Showing CV Risk

- Complex, retrospective study with poorly defined data set
- The authors write “…the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no TRT group vs. 25.7% in the TRT group at 3 years following coronary angiography”
- The raw rate of events (without statistical manipulation) was 10.1% in the TRT group vs. 21.2% in the no TRT group
- Adjustment for 50 variables with 10% of the data found to be from women!
- 29 medical societies have called for retraction of the article; *JAMA* has refused
FDA-Cited Studies Showing CV Risk

- Analysis of health insurance claims (53,593)
- Control group: men receiving Rx for PDE5i
- Reported a 36% increase in nonfatal MI in 90 days post TRT RX vs. 12 months prior
- No CV risk factor information or serum T levels
- MI rate before TRT (3.48/1000 person-years) vs. after TRT (4.75/1000) both lower than NIH expected risk for man 54 YO (13/1000)
Aging Males and Mortality
Men with Low T May Not Live As Long

- 800 Men, 50-91 y, followed for 18 y
- 1/3 had low T
- Men with low T versus those with higher T had:

- Increased levels of inflammatory cytokines
- Increased waist girth
- 3x more likely to have metabolic syndrome
- 40% greater risk of death

Aging Males and Mortality
Low Serum T and Mortality in Male Veterans

Mortality (%)

<table>
<thead>
<tr>
<th>T-Level</th>
<th>Normal</th>
<th>20.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td>34.9</td>
</tr>
</tbody>
</table>

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

Low Plasma Testosterone Is Associated With Elevated Cardiovascular Disease Biomarkers

Alexander W. Pastuszak M.D., Ph.D.,
Joel Estes MSc., Larry I. Lipshultz M.D.
All results were mined from the Singulex database 1/2013-9/2014
Median age 58 (range 18-97); majority of patients were > 40 YO
Median (IQR) BMI was 28 (25,320); BMI data available for 53% of the study population
Biomarkers Tested

- IL-6
- cTnl
- TNF-α
- IL-17A
- ET
- NTproBNP
- Leptin
- HDL
- hs-CRP
- HbA1C

High sensitivity biomarkers

Routine biomarkers
## Cardiovascular Risk as a Function of Plasma Biomarkers

To examine the relationship between T and CV risk, patients were divided into 4 groups by T concentrations.

- The % of patients above reference limit (RL) was determined for 10 biomarkers.
- 9/10 biomarkers demonstrated increasing CV risk with decreasing NOT INCREASING T levels.

<table>
<thead>
<tr>
<th>All Patients</th>
<th>High Sensitivity (SMCTM) Biomarkers (% Patients &gt; RL)</th>
<th>Standard Biomarkers (% Patients &gt; RL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL-6</td>
<td>cTnI</td>
</tr>
<tr>
<td>&lt;200</td>
<td>4.8</td>
<td>6.7</td>
</tr>
<tr>
<td>500-599</td>
<td>10.9</td>
<td>9.7</td>
</tr>
<tr>
<td>900-999</td>
<td>4.2</td>
<td>6.2</td>
</tr>
<tr>
<td>&gt;999</td>
<td>4.3</td>
<td>8.5</td>
</tr>
</tbody>
</table>

- **p-value for trend**: <0.0001 0.0261 <0.0001 0.1229 0.0013 <0.0001 <0.0001 <0.0001 <0.0001 <0.0001

- **Reference Limit**: >7.2 pg/mL 5.8 or 6.1 pg/mL* >4.2 pg/mL >3.3 pg/mL >3.7 pg/mL >124 or >494 pg/mL* >25.2 ng/mL <35 mg/dL >0.9 µU/mL 5.9%
Cardiovascular Risk Decreases With Normalization of Plasma Testosterone Levels

- Each line represents a different biomarker
- The number of men with increased CV risk decreases as T levels increase to normal

% of Patients Above Biomarker Ref. Range

Testosterone ng/dL

- IL-6
- TNF-a
- ET-1
- IL-17A
- Leptin
- HDL
- CRP
- HbA1C
- NTproBNP

<200 200-299 300-399 400-499 500-599 600-699 700-799 800-899 900-999 >999
Elevated CV Risk is Observed at Both Low and High Plasma Testosterone Levels for cTnI, HDL, and hsCRP

There may be CV risk at both low and very high T levels. This phenomenon is seen here for cTnI, HDL and hsCRP. May help explain increased early CV deaths among performance athletes taking super-physiologic T1

Our findings do not support the FDA conclusion that men with higher T have an increased risk for CV disease.
Testosterone and Male Fertility
Testosterone Replacement Therapy

Spermatogenesis

- TRT leads to atrophy of germinal epithelium in normal men
- TRT suppresses spermatogenesis leading to azoospermia after 10 weeks
- Sperm concentrations may rebound to pre-treatment levels but may take 18 months
- 4%-10% may remain azoospermic
Higher Centers

GnRH

Hypothalamus

Anterior Pituitary

GnRH

Hypothalamus

FSH

LH

Inhibin

Testosterone

Germinal Epithelium

Sertoli Cells

Leydig Cell

4*
Higher Centers

Hypothalamus

GnRH

FSH

LH

Testosterone

Inhibin

Anterior Pituitary

Germinal Epithelium

Sertoli Cells

Leydig Cell

+ +

- -

4*
Studies in Male Contraception: Testosterone

• 271 men received 200 mg TE weekly
• 157 (65%) azoospermic at 6 months
  • Mean time to azoospermia 120 days
  • Entered 6 month efficacy phase: 1 pregnancy
• Recovery Follow-up (n=230: 85%)
  • 84% to ≥ 20 million/mL (median 3.7 months)
  • Only 46% to baseline

Recovery of Spermatogenesis in Steroid Suppressed Patients
Recovery of Spermatogenesis After Exogenous Testosterone Administration: Methods

• Retrospective study, 26 men ages 25-54
• Presenting for fertility evaluation and recent history of T usage
• Men with history of transdermal (TD) use received testosterone from physician
• Men with history of IM-T were either “self-prescribed” or prescribed by outside physician
• Duration of testosterone use, delivery method, and initial hormone profile were recorded
• Time to recovery of sperm in ejaculate and post-treatment hormone profiles documented

Treatment

• All men had detailed history, physical examination and laboratory assessment

• Treatment:
  • **Discontinue exogenous testosterone**
  • **Initiate 3000 units of hCG IM qod**
    • Aromatase inhibitor (anastrozole) or selective estrogen receptor modulator (tamoxifen)
    • All meds continued ≥ 3 months

• Semen analyses and hormone assays checked at 4 weeks and monthly thereafter until semen analysis stable
Results
Study Population

- Intramuscular (12 patients)
- Transdermal (14 patients)
Recovery of T-Induced Azoospermia with HCG

Results (n = 26)

<table>
<thead>
<tr>
<th>T Delivery</th>
<th>Pre-treatment T IM or TD</th>
<th>Post-treatment T hCG</th>
<th>Time to sperm recovery (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular (12)</td>
<td>426 ± 320</td>
<td>547 ± 226</td>
<td>3.1 ± 1.6</td>
</tr>
<tr>
<td>Transdermal (14)</td>
<td>352 ± 182</td>
<td>507 ± 179</td>
<td>7.4 ± 5.5</td>
</tr>
</tbody>
</table>

P-value

Recovery of Spermatogenesis in Steroid Suppressed Patients
Use of HCG-Based Combination Therapy for Recovery of Spermatogenesis

Regardless of type of testosterone, time to recovery = ~ 4 months

Infertility Prevention

Can we protect the hypogonadal male who must use T from becoming sterile?
“Low dose human chorionic gonadotropin appears to maintain semen parameters in hypogonadal men on testosterone replacement therapy”
Basis of hCG Therapy

**hCG and Intratesticular T**

- **29 normal volunteers**
- **Testosterone enanthate 200mg/week**
  - AND
  - 0, 125, 250 or 500 IU hCG qod
- • Measure serum and intratesticular testosterone (ITT) day 0 and 21
- • Measure serum gonadotropins

Basis of hCG Therapy

hCG and Intratesticular T

Testosterone (nmol/L)

Baseline ITT

Day 21 ITT

Basis of hCG Therapy

hCG and Intratesticular T

Despite supraphysiologic doses of AAS, high levels of intratesticular T are maintained with administration of low-dose hCG.

Can low-dose hCG maintain ITT and spermatogenesis during TRT?
Maintaining Spermatogenesis
TRT and hCG

• **Design:**
  - 10 men prospectively studied
  - TRT: IM (n=8) or transdermal (n=2)
  - 500 U hCG IM qod
  - SA performed routinely throughout study

• **Results:**
  - Mean followup 4.5 months (range 2-11)
  - Mean density: 19 M/mL at most recent followup

Maintaining Spermatogenesis

TRT and hCG

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th>TRT</th>
<th>Months on hCG + T</th>
<th>Sperm Density before therapy</th>
<th>Sperm Density after therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>TC</td>
<td>2</td>
<td>80.0</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>TE</td>
<td>5</td>
<td>42.8</td>
<td>29.0</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>TC</td>
<td>3</td>
<td>25.6</td>
<td>55.2</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>TC</td>
<td></td>
<td></td>
<td>25.6</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>Testim</td>
<td></td>
<td></td>
<td>36.0</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>TC</td>
<td>11</td>
<td>24.8</td>
<td>18.8</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>TC</td>
<td>5</td>
<td>*</td>
<td>10.8</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>TC</td>
<td>3</td>
<td>*</td>
<td>21.0</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>Androgel</td>
<td>3</td>
<td>6.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>

No one became azoospermic!
Maintaining Spermatogenesis
TRT and hCG

Semen density (million/mL)

Time from initiation of HCG + Testosterone therapy (months)

Minimal decline in density
Preserving Spermatogenesis with HCG for Men on TTH

$N = 26$

### Type of Testosterone

<table>
<thead>
<tr>
<th></th>
<th>Total Sperm Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before</strong></td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>35.5</td>
</tr>
<tr>
<td>Injectable</td>
<td>33.7</td>
</tr>
<tr>
<td>$p$ Value</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>After</strong></td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>30.8</td>
</tr>
<tr>
<td>Injectable</td>
<td>30.6</td>
</tr>
<tr>
<td>$p$ Value</td>
<td>0.99</td>
</tr>
</tbody>
</table>

High Risks Conditions for TRT

Very high risk of serious adverse outcomes

• Metastatic prostate cancer
• Breast cancer

Moderate-to-high risk of adverse outcomes

• Prostate nodule or induration
• Unexplained PSA elevation
• Erythrocytosis (hematocrit >50%)
• Unstable severe congestive heart failure (class III or IV)

Adapted from The Endocrine Society Guidelines, 2006.
What About Prostate Cancer?

• TRT is contraindicated for men with known or suspected prostate cancer

• To date, there is no conclusive evidence that TRT causes prostate cancer

• PSA values do not significantly increase after TRT\textsuperscript{1-3}

• Prostate cancer rate in seven published TRT trials:
  • Similar to screening trials of general population\textsuperscript{4}
  • 1\% of 461 TRT men had a positive biopsy within 6 to 36 months’ follow-up\textsuperscript{4}

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

- R, DB, PC trial of 44 men (44-78 years)
- Screening 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-P Bx baseline and 6 months
- Primary outcome measure: 6-month change in prostate T, DHT and serum PSA

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

Serum Levels

* p < .001
** p < .002

TRT (n=21)
Placebo (n=19)
Effects of TRT on Prostate Tissue of Aging Men with Low Serum T

These preliminary data suggest that while 6 months of TRT normalizes serum androgen levels, it appears to have little effect on prostate tissue androgen levels and androgen dependent cellular functions.
Number of published articles showing testosterone therapy causes prostate cancer progression in PSA era...
TRT for Hypogonadism After Treatment of Prostate Cancer with Brachytherapy

- 31 men started TRT 0.5 to 4.5 years (median 2 years) after brachytherapy
- Patients received TRT for 0.5 to 8.5 years (median, 4.5 years)
- Follow-up 1.5 to 9.0 years (median, 5 years)
- Testosterone rose from 188 ng/dl to 498 ng/dl
- No patient stopped TRT because of cancer recurrence or demonstrated cancer progression

Conclusions

• Low-T in adult men is often underdiagnosed and undertreated

• T-levels gradually diminish with age, often to hypogonadal levels (<300 ng/dL)

• Hypogonadism may cause decreased energy, BMD, libido, ED

• TRT can increase T-levels to normal ranges, significantly improving symptoms, and is safe with proper monitoring
Thank You

Texas Medical Center, Houston