Update on Late Onset Male Hypogonadism

Mohit Khera, M.D., M.B.A., M.P.H.
Assistant Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, TX
Testosterone: Ancient History

- **1000 B.C.**: the Ayurveda of Susrata, an ancient medical manuscript, records the ingestion of testicular tissue as a treatment for impotence
- **Ancient Egyptians**: medicinal powers to the testes
Testosterone: The Early 20th Century

- **1939**: Butenandt and Ruzicka win the Nobel Prize for discovery and synthesis of testosterone

- **1939**: Researchers report that testosterone improved female sexual dysfunction
TESTOSTERONE

It restores sex drive. It boosts muscle mass. And soon you can get it as a gel. But it also can be dangerous. Is the edge worth it?
Growth of Testosterone Market

- Aging population
- Increased link of Low T with poor general health
- Reduced concern of TRT and PCa
- New entries with increased promotion
- Direct to consumer advertising
Discussion

• Prevalence of androgen deficiency and late onset hypogonadism
• Diagnosis of low testosterone in men
• Testosterone treatment options
• Testosterone and prostate cancer
• Adverse medical conditions associated with androgen deficiency
• Beneficial effects of TRT
Diagnosis of Androgen Deficiency and Late Onset Hypogonadism

Biochemical + Signs and Symptoms
Prevalence of Androgen Deficiency

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

T = testosterone.
Prevalence of Symptomatic Androgen Deficiency in Men

Andre B. Araujo, Gretchen R. Esche, Varant Kupelian, Amy B. O'Donnell, Thomas G. Travison, Rachel E. Williams, Richard V. Clark, and John B. McKinlay

The Impact of Testosterone

**Skin**
Hair growth, balding, sebum production

**Liver**
Synthesis of serum proteins

**Bone**
Accelerated linear growth, closure of epiphyses

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

**Brain**
Libido, mood

**Muscle**
Increase in strength and volume

**Kidney**
Stimulation of erythropoietin production

**Bone Marrow**
Stimulation of stem cells

Physical Signs of Low Testosterone

**Physical Signs**

- Increased body fat, BMI
- Reduced muscle bulk and strength
- Low bone mineral density
- Loss of body hair (axillary and pubic)

Adapted from The Endocrine Society Guidelines, 2006.
Symptoms of Low Testosterone

**Symptoms**

- Decreased energy or motivation
- Diminished libido, erectile dysfunction
- Diminished work performance
- Poor concentration and memory
- Sleep disturbance
- Depression
Multicenter, 12-month observational registry ($N = 849$) of hypogonadal men prescribed testosterone gel

Depression symptoms were measured using PHQ-9

Before treatment with TRT, 92.4% demonstrated some level of depressive symptoms, with 17.3% having severe depressive symptoms

After 12 months of TRT, patients with severe depressive symptoms decreased from 17.3% to 2.1%

Patients already on anti-depressants also experienced a significant improvement in PHQ-9 at 12 months
Prevalence of Low Testosterone in Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Opioid Use</td>
<td>74</td>
</tr>
<tr>
<td>Obesity</td>
<td>52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50</td>
</tr>
<tr>
<td>AIDS</td>
<td>50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40</td>
</tr>
<tr>
<td>ED</td>
<td>19</td>
</tr>
</tbody>
</table>

HIV = 30%.
ED = erectile dysfunction.
Why are men with low testosterone conditions NOT being screened and diagnosed for low testosterone?
Low Testosterone Treatment Patterns

95% receive no medical treatment

Only 5% of men with low testosterone are currently treated

US Food and Drug Administration Updates. Available at: http://www.verity.fda.gov/search97cgi
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 low testosterone in past 12 months
- 95% say doctor never mentioned low testosterone when presented with ≥2 symptoms of low testosterone

Harris Interactive Polls, 2006; Funded by Auxilium Pharmaceuticals, Inc.
Diagnosis of Low Testosterone
Production of Testosterone

Hypothalamus

Pituitary

Testis

Testosterone

FSH

LH

GnRH

Sperm

Testosterone

# Classification of Hypogonadism

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular Causes</td>
<td>Hypothalamic Causes</td>
<td>Dual HPG Axis Defects</td>
</tr>
<tr>
<td>▪ Klinefelter syndrome</td>
<td>▪ Kallman syndrome</td>
<td>▪ Hemochromatosis</td>
</tr>
<tr>
<td>▪ Orchitis</td>
<td>▪ Constitutional delay in growth</td>
<td>▪ Sickle cell disease</td>
</tr>
<tr>
<td></td>
<td>and development</td>
<td>▪ Glucocorticoid treatment</td>
</tr>
<tr>
<td></td>
<td>▪ Chronic illness</td>
<td>▪ Alcoholism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Aging</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diurnal Variation in Serum Total Testosterone Levels

Diagnosing Low Testosterone

• **Signs and Symptoms**
  - ADAM questionnaire

• **Clinical laboratory blood test**
  - Testosterone (<300ng/dl)
  - Other hormones related to low testosterone

ADAM = Androgen deficiency in aging male
ADAM Questionnaire
(Androgen Deficiency in the Aging Male)

Validated screening tool for males ≥40 years of age

Check if you have any of the following:

- 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 noticed 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?

If you checked question 1 or 7 or any 3 other questions, you may have low testosterone. A simple blood test can determine your testosterone level. **Talk with your doctor to see if you should be tested.**

Testosterone Distribution

- 68% ALBUMIN Weakly Bound
- 30% SHBG Tightly Bound
- 2% FREE

Male Hormonal Status Changes With Age as SHBG Increases

- Low testosterone is increasingly common as men age
- Levels of free testosterone *decrease* and levels of SHBG *increase* with age

## Factors Affecting SHBG Levels

<table>
<thead>
<tr>
<th>Increases SHBG</th>
<th>Decreases SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Opioids</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Androgens</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Nephrotic Syndrome</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Low testosterone</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Age (1%/yr of age)</td>
<td>Obesity</td>
</tr>
</tbody>
</table>

Adapted from Bhasin S, et al J Clin Endocrinol Metab 2006;91:1995-2010
Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%), bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>4.3</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>50</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>13.1</td>
</tr>
</tbody>
</table>

**Free Testosterone**

\[
0.202 \text{ nmol/L } = 1.54\% 
\]

**Bioavailable Testosterone**

\[
4.74 \text{ nmol/L } = 36.2\% 
\]

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/circumstances without the prior consultation of experts or professional persons. No responsibility whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

This calculator was developed at the Hormonology department, University Hospital of Ghent, Belgium. If you have suggestions to improve this calculator, or for further questions or help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman

www.issam.ch
Treatment of Low Testosterone
TRT Treatment Options
Most Commonly Prescribed Form of Testosterone Replacement

- Gels: 70%
- Injectables: 17%
- Patches: 10%
- Other: 3%

IMS NPA; 2006.
Buccal

• April 2011: Actient Pharmaceuticals LLC Acquires U.S. Rights to STRIANT from Columbia Laboratories

• Applied: upper gum just above the incisor tooth

• Starting dose: 30mg q12 hours

• Max dose: 30mg q12 hours
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Percent (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum or Mouth Irritation</td>
<td>9.2%</td>
</tr>
<tr>
<td>Bitter Taste</td>
<td>4.1%</td>
</tr>
<tr>
<td>Gum Pain</td>
<td>3.1%</td>
</tr>
<tr>
<td>Gum Tenderness</td>
<td>3.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.1%</td>
</tr>
<tr>
<td>Gum Edema</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
Androderm

- Applied: back, abdomen, upper arms, or thighs
- Available doses: 2.5 grams and 5 grams
- Starting dose: 24.3 mg (5 grams) daily
- Max dose: 48.6 mg (10 grams) daily
## Androderm Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritis at application site</td>
<td>37%</td>
</tr>
<tr>
<td>Burn-like blister reaction</td>
<td>12%</td>
</tr>
<tr>
<td>Erythema at application site</td>
<td>7%</td>
</tr>
<tr>
<td>Vesicles at application site</td>
<td>6%</td>
</tr>
<tr>
<td>Prostate abnormalities</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>4%</td>
</tr>
</tbody>
</table>
Testosterone Injections

- Main advantage: cost
- Testosterone cypionate
  - Cottonseed oil
  - T1/2 = 12 days
  - Greater fluid retention
- Testosterone enanthate
  - Sesame oil
  - T1/2 = 10.5 days
- Dosage
  - 200mg IM every 2 weeks
  - 100mg IM every week
  - 60 mg IM twice a week
Different Testosterone Levels After Replacement Therapy

Adapted from Bhasin and Bremner. *J Clin Endocrinol Metab.* 1997;82:3-8
Testosterone gel (AndroGel® 1%) Unimed Pharmaceuticals and Solvay Pharmaceuticals, 2002
Testim

- Applied: shoulders/upper arms
- Starting dose: 50 mg (1 tube)
- Max dose: 100mg (2 tubes)
- Follow up: 14 days after initiation of therapy
- Swim or shower: 2 hours
## Testim Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Testim 50mg</th>
<th>Testim 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Reaction</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>BPH</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>HTN</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Taste Disorder</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
New TRT Gels in the Market
Fortesta

- Applied: Inner thighs
- Starting dose: 40 mg (4 pumps)
- Max dose: 70 mg (7 pumps)
- Swim or shower 2 hours after application
- Follow up: blood draw 2 hours after applying gel at approximately 14 days and 35 days after starting treatment or after making a dose adjustment
**Suggested Titration Schedule**

<table>
<thead>
<tr>
<th>Total Serum Testosterone Concentration 2 hours Post FORTESTA Application</th>
<th>Dose Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equal to or greater than 2,500 ng/dL</td>
<td>Decrease daily dose by 20 mg (2 pump actuations)</td>
</tr>
<tr>
<td>Equal to or greater than 1,250 and less than 2,500 ng/dL</td>
<td>Decrease daily dose by 10 mg (1 pump actuation)</td>
</tr>
<tr>
<td>Equal to or greater than 500 and less than 1,250 ng/dL</td>
<td>No change: continue on current dose</td>
</tr>
<tr>
<td>Less than 500 ng/dL</td>
<td>Increase daily dose by 10 mg (1 pump actuation)</td>
</tr>
</tbody>
</table>
# Fortesta Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin reaction</td>
<td>24 (16.1%)</td>
</tr>
<tr>
<td>Prostatic specific antigen increased</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>2 (1.3%)</td>
</tr>
</tbody>
</table>
Axiron

- **Applied:** axilla
- **Starting dose:** 60 mg (2 pumps)
- **Max dose:** 120mg (4 pumps)
- **Follow up:** blood draw 2 – 8 hours after applying and at least 14 days after starting treatment
Axiron Application Instructions

• Apply deodorant BEFORE applying Axiron
• Swim or shower after 2 hours
## Axiron Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent at 180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Irritation</td>
<td>8%</td>
</tr>
<tr>
<td>Application Site Erythema</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
</tr>
<tr>
<td>PSA increase</td>
<td>4%</td>
</tr>
</tbody>
</table>
Androgel 1.62%

- Applied: shoulders and upper arms
- Starting dose: 40.5 mg (2 pumps)
- Max dose: 81mg (4 pumps)
- Follow up: a single blood draw at approximately 14 days and 28 days after starting treatment
- Swim or Shower after 2 hours
## Androge1 Comparison

<table>
<thead>
<tr>
<th></th>
<th>Androge1 1%</th>
<th>Androge1 1.62%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site</td>
<td>Shoulders, upper arms, abdomen</td>
<td>Shoulders, upper arms</td>
</tr>
<tr>
<td>Starting pumps</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Starting dose</td>
<td>50mg</td>
<td>40.5mg</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>100mg</td>
<td>81mg</td>
</tr>
<tr>
<td>Time to swim or shower</td>
<td>6 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>
Testopel®

• Applied: subcutaneously in side of hip or abdomen
• Dose: 1 pellet = 75 mg of testosterone
• Starting dose: 10-12 pellets
• Duration: 3-6 months
• Follow up: serum testosterone at 1 and 4 months after insertion
Subcutaneous Testosterone Pellets

Injection of local anesthetic with 27 gauge 1 1/2" needle

Skin wheal

Epidermis
Dermis
1-2 mm thickness
Subcutaneous tissue
Gluteus maximus muscle

Mark skin along line of femur halfway between and 3 cm below iliac crest and sacroiliac joint

Application of sterile drape to create sterile field

Prep with Hibiclens, alcohol, and betadine
Subcutaneous Testosterone Pellets

A  Pellet is placed into slot in trocar

C  Pellets are then advanced forward into trocar with forceps

Advance pellets into subcutaneous tissue by pushing in stylet while simultaneously withdrawing trocar

Pellet 3 mm x 8 mm
What About Prostate Cancer?

• Testosterone replacement is contraindicated for men with known or suspected prostate cancer

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

• Rate of prostate cancer in those men being treated with testosterone is identical in those men not being treated with testosterone

Historical Basis for Concern that Testosterone Causes Prostate Cancer

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 that Testosterone Causes Prostate Cancer

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)
Number of published articles showing testosterone therapy causes prostate cancer progression in PSA era... None!
Prostate Saturation Model

Saturation Model of Physiologic Testosterone Replacement

“Normal Physiologic Range”

Saturation Effect

Saturation:

T for PCa is like “water for a thirsty tumor”

Once the “thirst” has been quenched, additional T has no further effect.
Supraphysiologic Levels of Testosterone

- 600mg of testosterone or placebo weekly for 10 weeks
- PSA did not change significantly from baseline despite supraphysiological testosterone levels (>2500 ng/dl)

Bhasin et al. NEJM 1996; 335:1
451 hypogonadal men started on TRT for 12 months

Divided into 2 groups

- **Group A**: Testosterone < 250ng/dl
- **Group B**: Testosterone > 250ng/dl

**ONLY in group A (Testosterone < 250ng/dl):**

- PSA correlates with testosterone and free testosterone
- Significant rise in PSA after 12 months of TRT
# Testosterone After Radical Prostatectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>Pre TRT PSA</th>
<th>Post TRT PSA</th>
<th>Pre T</th>
<th>Post T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al</td>
<td>10</td>
<td>19</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>197</td>
<td>591</td>
</tr>
<tr>
<td>Kaufman et al</td>
<td>7</td>
<td>24</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>97</td>
<td>434</td>
</tr>
<tr>
<td>Khera et al</td>
<td>57</td>
<td>17</td>
<td>0.005</td>
<td>0.005</td>
<td>275</td>
<td>440</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>74</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kaufman et al J Urol 2004
Khera et al JSM 2009
Current Clinical Trial: NCT00848497

- FDA approved
- Randomized placebo controlled trial
- TRT in hypogonadal men starting 3 months after radical prostatectomy
- **Inclusion Criteria:**
  - Must have undergone a bilateral nerve sparing radical prostatectomy.
  - Nadir PSA values should be less than 0.01 ng/ml on two consecutive occasions separated by 4 weeks at the start of treatment.
- **Exclusion Criteria:**
  - Testosterone level greater than 300 ng/dl
  - Pre-operative SHIM score less than 17.
  - Positive surgical margins or evidence of residual prostate cancer.
  - Clinically suspected advanced disease or actual evidence of metastatic prostate cancer.
  - Primary Gleason Grade greater than 3 or secondary Gleason Grade greater than 4 in the final pathologic specimen will be excluded.

http://clinicaltrials.gov/ct2/show/NCT00848497
Risk of Occult Prostate Cancer?
• Retrospective study of 14 men who elected surveillance for PCa and who received TRT for a minimum of six months

• Thirteen men had Gleason score 6 at initial biopsy and one man had Gleason score 7 (3+4)

• The mean duration of TRT following diagnosis of PCa was 23.5 mo (range 9-43)
Results

- No significant change in PSA
  - Initial PSA: 5.5 ± 6.4 ng/ml (range 0.6 to 24.1)
  - Most recent PSA 3.7 ± 2.6 ng/ml (P=0.29)
- No change in prostate volume (45.6 ± 14.5 cc vs 52.4 ± 19.8 cc, respectively; P=0.11)
Results

• Follow-up biopsy in 13 men
• 11/13 men no evidence of progression
  • 8 men had at least one follow-up biopsy that revealed no cancer
• Patient 1:
  • Gleason 7 (3+4) in 5% of one core
  • Initial biopsy revealed low-volume Gleason 6 disease
  • Two subsequent annual biopsies revealed only low-volume Gleason 6 disease
• Patient 2:
  • Elected to undergo radical prostatectomy after biopsy showed Gleason score 7 (4+3) cancer in one of 12 cores with 75% involvement
  • Final Path: Gleason score 6 disease involving 5% of the gland, with negative margins and nodes
Adverse Medical Conditions Associated with Androgen Deficiency
Link Between Low Testosterone and Osteoporosis

MicroMRI of Tibia

Control

Well connected, predominantly plate-like trabecular network of the control

Hypogonadal Man

More disconnected, predominantly rod-like architecture of the hypogonadal man

Hip Fractures in Aging Males

Rate of Hip Fractures in Men with Low Testosterone vs. Controls

- 71% of Men with Hip Fracture
- 32% of Men without Hip Fractures

P = 0.003

HbA$_1c$ (norm value: 4.2-5.8 %) in Diabetic Prostate Cancer Patients under Androgen Deprivation Therapy

Low Testosterone and Cardiovascular Disease

Low testosterone levels were associated with increased risk of arterial plaque formation and cardiovascular disease¹ ²

• Association was independent of age, BMI, total cholesterol, HDL, diabetes mellitus, smoking, and alcohol intake.

• Testosterone may have a “direct” impact on CV health, in the absence of other common risk factors.

¹ Hak et al 2002
² Jones et al 2003
Aging Males and Mortality
Low Serum T and Mortality in Male Veterans

Beneficial Effects of TRT
Increased Testosterone Levels Result in Improvements in...

- REM sleep
- Libido
- Bone mineral density
- Increased muscle mass
- Decreased fat deposition
- Cognitive ability
- Depression
- Erectile function
TRT: Changes in Bone Mineral Density (BMD)

Changes in Lumbar Spine BMD

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Placebo</th>
<th>T</th>
<th>T+F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.001

Waist Circumference in 122 Hypogonadal Patients Presenting with Erectile Dysfunction during 15 months of Treatment with Testosterone Undecanoate (TU)

Significant and Sustained Improvement in Low T Symptoms

Mean Change From Baseline

Increased Lean Body Mass +4.8 lb

Fat Mass −4.0 lb

Placebo Controlled

Open Label

Significant Improvement From Baseline

Mean Change From Baseline

0 3 6 9 12

Months

Role of Testosterone in Erectile Function

- Erections depend on serum testosterone levels
- Viagra depends on serum testosterone levels
  - 23-50% of patients with low testosterone levels are non-responsive to Viagra and Viagra-like drugs
  - Patients failing Viagra and Viagra-like drugs should be screened for low testosterone

Improved Sexual Function with Testosterone Replacement Therapy in Hypogonadal Men: Real-World Data from the Testim Registry in the United States (TRiUS)

Mohit Khera, MD, MBA, MPH,* Rajib K. Bhattacharya, MD,† Gary Blick, MD,‡ Harvey Kushner, PhD,§ Dat Nguyen, PharmD,¶ and Martin M. Miner, MD**

*Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA; †Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA; ‡Circle Medical LLC, Norwalk, CT, USA; §Department of Biometrics, Auxilium Pharmaceuticals, Malvern, PA, USA; ¶Department of Medical Affairs, Auxilium Pharmaceuticals, Malvern, PA, USA; **Miriam Hospital Men’s Health Center, Warren Alpert School of Medicine, Brown University, Providence, RI, USA

- Multicenter registry of hypogonadal men (n=849) treated with TRT and followed for 12 months
- Sexual function measured by the Brief Male Sexual Function Inventory (BMSFI)
- BMSFI scores significantly increased from baseline at 12 months (27.4 to 33.8, *P < 0.001*) and at each visit in all domains (sex drive/libido, erectile function, ejaculatory function)
- Patients already on PDE5i therapy also had a significant increase in BMSFI scores after starting TRT

Khera et al  JSM 2011 Nov;8(11):3204-13
Conclusion

• Androgen deficiency affects approximately 20-40% of men while late onset hypogonadism is seen in 4-8% of men

• Low testosterone can be diagnosed by a simple blood test and a questionnaire

• There are now safe and effective ways to increase a man’s testosterone

• There is no data to support that testosterone causes prostate cancer

• Raising a man’s testosterone can improve his cognitive ability, REM sleep, erections, libido, muscle mass, fat deposition, bone mineral density, and possibly his life span
Too Much Testosterone Can Be Harmful To Your Health
Adverse events associated with testosterone administration

• Purpose: Assess the safety and efficacy of testosterone treatment in older men who have limited mobility

• Methods
  • Older men (74)
  • Two treatment groups:
    • TRT
      • 15 grams of gel
      • Much higher incidence of CAD, HTN, hyperlipidemia
      • Limited mobility
    • Placebo
      • Healthier population
  • Assessed risk for cardiovascular events
    • MI, stroke, HTN, edema

Basaria et al. NEJM 2010 Jul 8;363(2):109-22
Results

• 209 men

• TRT group
  • 23 cardiovascular event- (retrospective)
    • 2 MIs
  • Significant improvement in muscle strength and muscle mass compared to placebo

• Placebo
  • 5 cardiovascular events
    • No MIs

Conclusion

• “Small sample size of the trial and the unique population prevent broader inference from being made about the safety of testosterone therapy”

• “It is essential to recognize the role that chance may have played in the outcomes we observed”
Low Testosterone Levels and Diabetes/Metabolic Syndrome

Androgen deficiency “hypogonadism”

Obesity  Hypertension  Dyslipidemia  Hyperglycemia  Insulin resistance

Metabolic syndrome
Visceral Fat: the Vicious Circle

Androgens and Erectile Function

Nitric Oxide Synthase

Phosphodiesterase Type 5 Activity

Veno-occlusive Erectile Function

Penile Nerve Function

Androgens
Androgens Regulate NOS Activity

- Androgens regulate the expression of nNOS and eNOS in corpora cavernosa
- Castrated animals have a significant decrease in nNOS expression in the penis
- Testosterone replacement results in normal nNOS expression in penile nerve fibers
- NO-mediated relaxation of cavernosal smooth muscle is thought to be androgen dependent

1 Baba et al. BJU Int 2000; 85;953
3 Syme et al J Urol. 2007 Jan;177(1):390-4
Androgens Regulate Phosphodiesterase type 5 (PDE5) Expression

• Androgen treatment up-regulates the gene and protein expression of PDE5 activity \(^1\) \(^2\)

• In organ bath assays with isolated cavernosal strips:\(^2\)
  • Androgen deprivation reduced the muscle relaxation effects of PDE5 inhibitor (sildenafil) after nerve stimulation
  • Testosterone replacement restored this muscle relaxation effect

• PDE5i were administered to castrate and control animals before pelvic nerve stimulation \(^3\)
  • **Control**: PDE5i significantly enhanced intercavernosal pressures (ICP)
  • **Castrate**: PDE5i did not enhance ICP

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\(^1\) Traish et al. Endocrinology 1999; 140:1861
\(^2\) Morelli et al. Endocrinology 2004; 145:2253
\(^3\) Traish et al. J Androl 2003; 24:381
Androgens and Penile Nerve Function

- 45 rats underwent bilateral cavernosal neurotomy
- All had unilateral nerve graft using the genitofemoral nerve
- Rats randomized to castrate, intact (non-castrate), and testosterone treated (supraphysiological levels) arms
- At 3 months, grafts were explored and electrostimulation was performed with intracavernous pressure responses recorded

Androgens and Penile Nerve Function

- Animals were treated for 7 days with vehicle alone, testosterone, or estradiol one week after bilateral orchietomy
- Intact control animals received vehicle only
- Systemic arterial blood and intracavernosal pressures (ICP) were measured in each animal before and after electrical stimulation of the cavernosal nerve

Traish et al. Endocrinology 1999; 140:1861
Results

PNS = Peripheral Nerve Stimulation

Traish et al. Endocrinology 1999; 140:1861
Androgens and Erectile Function

- Nitric Oxide Synthase
- Phosphodiesterase Type 5 Activity
- Veno-occlusive Erectile Function
- Penile Nerve Function
- Androgens
Decreased Androgens Contribute to Veno-occlusive Erectile Dysfunction

- Loss of Fibroelastic Properties
- Increased Deposition of Connective Tissue
- Increased Subtunical Fat Deposition
- Loss of Trabecular Smooth Muscle
- Veno-occlusive Erectile Dysfunction
Androgens and Corpora Cavernosa Fibroelastic Properties

- Tunica albuginea of corpora cavernosa of animals 4 weeks after castration were compared to controls
- Thickness of the tunica albuginea
  - Controls = 0.16 ± 0.03 mm
  - Castrated = 0.04 ±0.01 mm \( p<0.05 \)
- Elastic fibers in the tunica were replaced by collagen fibers resulting in a loss of its elasticity

Androgens and Cavernosal Connective Tissue

- Decreased androgens result in increased connective tissue and corporal fibrosis by causing a:
  - **Decrease in**:
    - Vascular Endothelial Growth Factor (VEGF),
    - Fibroblast Growth Factor (FGF)
    - Insulin-like Growth Factor (IGF-1)
  - **Up-regulation of**:
    - Connective tissue growth factor (CTGF)
    - Transforming Growth Factor Beta 1 (TGFβ-1)

- ▼Androgens = ▲corporal fibrosis

Androgens and Cavernosal Smooth Muscle

- Animals were treated for 7 days with vehicle alone, testosterone, or estradiol one week after bilateral orchiectomy.
- Intact control animals received vehicle only.
- Smooth muscle content was assessed by Masson’s trichrome staining and computer-assisted histomorphometry.

Traish et al. Endocrinology 1999; 140:1861
Results

C= control, V= castrate, T= testosterone treated, E= estradiol treated

Traish et al Endocrinology 1999; 140:1861
Results

C = control, V = castrate, E = estradiol treated, T = testosterone treated
Androgens and Subtunical Adipose Deposition

• Penile tissue from orchiectomized animals demonstrated subtunical adipose deposition.¹

• Neonatal animals exposed to DES or estradiol have increased fat deposition in their corpora cavernosa. ²

• Differentiation of pluripotent stem cells are androgen dependent and testosterone promotes muscle lineage and inhibits adipogenic lineage.³

² Goyal et al. J Androl 2005; 26:32
³ Singh et al. Endocrinology 2003; 144:5081.
Can testosterone replacement therapy in a hypogonadal post-prostatectomy patient improve erectile function rates?
The Focus of Erectile Preservation Following Radical Prostatectomy