“Is T for Me?”

Testosterone Replacement Therapy in Older Males

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Objectives

At the end of this presentation, the participant should be able to:

• Describe late onset hypogonadism (LOH)
• Identify diagnosis and treatment recommendations for LOH
• Discuss challenges with diagnosing and treating LOH
• Outline the most current literature assessing benefits and risks of testosterone replacement therapy
• Recommend a treatment plan for patients with LOH
Patient Case

An otherwise healthy 74-year-old man, AK, complains of sleep disturbance, lack of energy, unsteady gait, feelings of depression, lack of sexual desire, and erectile dysfunction.

His primary care physician prescribed fluoxetine 20 mg daily, but his condition has not improved after taking the medication for over 12 weeks.

He sees an advertisement for the Low T Center while watching television and makes a 3:00 PM appointment for the following afternoon.
AK’s Next Steps

Following his afternoon appointment, AK learns that his total serum testosterone concentration is 218 ng/dL.

What should the next steps be in AK’s treatment?

A. Initiate testosterone transdermal gel 50 mg daily
B. Return to the clinic in 7 – 10 days to receive testosterone cypionate 50 mg IM
C. Return to the clinic tomorrow morning to get a repeat level
D. AK is not a candidate for treatment based on his current level and/or symptoms
Testosterone

• Primary androgen in males
• Synthesized mainly from cholesterol in Leydig cells within testes (95%)
• Regulated by hypothalamic-pituitary-gonadal axis
• Bound to albumin or sex hormone binding globulin (SHBG) during transport in plasma (98%)
• Biological effect due to connection of hormone with androgen receptor

Role of Testosterone

**Skin**
- Growth of facial and body hair
- Supports collagen

**Male Sex Organs**
- Sperm production
- Prostate growth
- Erectile function

**Brain**
- Sex drive
- Positive feelings
- Cognition and memory

**Body**
- Body composition
- Fat metabolism
- Muscle formation

**Bone**
- Bone mineralization
- Red blood cell production

Testosterone Levels in Older Males

• No standardized reference range for total testosterone ($T_{\text{total}}$)
  • 264 – 916 ng/dL recommended for healthy, nonobese males aged 19 – 39 (Endocrine Society, 2017)

• No generally accepted lower limits of normal for older males (ASA, ISA, ISSAM, EAA, EAU; 2008)

• Serum $T_{\text{max}}$ occurs between 25 – 40 years

• Declines thereafter at a rate of approximately 1% per year
Symptoms of Low Testosterone

- Reduced libido and sexual activity
- Decreased spontaneous erections
- Gynecomastia
- Low trauma fracture/low bone mineral density
- Hot flashes/sweats
- Decreased energy and physical performance
- Persistent depressive disorder
- Poor concentration and memory
- Sleep disturbances
- Anemia
- Reduced muscle strength
- Increased body fat
Late-Onset Hypogonadism (LOH)

Clinical and biochemical syndrome associated with advancing age

Characterized by low serum testosterone levels and symptoms

LOH Pathophysiology

• Amount and activity of Leydig cells decreases
  • Degenerative changes
  • Progression of atherosclerosis

• Deterioration of hypothalamic-pituitary function
  • Dysregulation of hypothalamic pulse generator →
    • Disorders of pulsed GnRH secretion →
      • Reduction of frequency and amplitude of LH pulses

• SHBG levels increase
  • Proportion of bioactive free testosterone decreases

• Increase in aromatase activity
  • Metabolizes testosterone to estradiol
LOH Diagnosis
(Consensus Guidelines, 2008)

• Low serum T plus one or more symptoms
• Serum $T_{\text{total}}$ reference ranges not established
  • Diagnosis based on hypogonadism data from younger men
    • $T_{\text{total}} > 350$ ng/dL should not require treatment
    • $T_{\text{total}} < 230$ ng/dL may benefit from treatment
• Serum $T_{\text{free}}$ may be used if $T_{\text{total}}$ is not diagnostic of LOH
  • No generally accepted lower limits of normal for diagnosis of hypogonadism
    • $T_{\text{free}} < 225$ pg/mL can provide supportive evidence for treatment
• $T_{\text{total}}$ levels should be repeated at least twice
• Samples should be obtained between 7:00 and 11:00 AM to account for natural diurnal variations

American Society of Andrology (ASA)
European Academy of Andrology (EAA)
European Association of Urology (EAU)
International Society of Andrology (ISA)
International Society for the Study of the Aging Male (ISSAM)
European Male Aging Study (EMAS, 2010)

• Sought to determine objective criteria diagnosis

• Goals
  • Identify symptoms with statistically significant correlation with low T
  • Confirm cutoff level of T below which symptom frequency significantly increases

• Findings
  • 23.3% of men aged 40 – 79 had $T_{total} < 288$ ng/dL
  • 60.1% of men with low T were asymptomatic
  • 9 out of 32 predetermined symptoms significantly correlated with low T
    • Differences in T levels between asymptomatic and symptomatic men not significant
    • Weak overall associations between symptoms and T levels
  • T level below which symptoms emerge in older men remains unclear
    • Thresholds only identified for sexual symptoms
  • LOH prevalence in men aged 40 – 79 with at least 3 sexual symptoms is 2.1%

**LOH Diagnosis (EMAS, 2016)**

- At least three sexual symptoms
  - Lessened sexual thoughts
  - Weakened morning erections
  - Erectile dysfunction

- Repeated (at least twice) low T levels
  - $T_{\text{total}} < 231 \text{ ng/dL}$
    - OR
    - $T_{\text{total}}$ of 231 – 317 ng/dL plus $T_{\text{free}} < 143 \text{ pg/mL}$

- Other LOH symptoms may support diagnosis but are not sufficient without presence of sexual symptoms

Testosterone Replacement Therapy

• Transdermal
  • Gel 25 – 50 mg daily
  • Patch 1.2 – 2.4 mg daily
  • Topical solution 30 – 60 mg daily

• Buccal
  • Tablets 30 mg twice daily

• Intramuscular
  • Testosterone enanthate 250 mg every 2 – 3 weeks
  • Testosterone undecanoate 1000 mg every 12 weeks

• Oral
  • Testosterone undecanoate 120 – 160 mg daily

• Subcutaneous
  • Pellets 800 mg every 4 – 6 months
Treatment Recommendations (EMAS, 2016)

• Transdermal preparations are first-line
  • Pharmacokinetics closest to optimal androgen substitution
  • Mimic physiological diurnal variations
  • May be rapidly discontinued should an adverse event occur

• Injections associated with increased risk of cardiovascular events, hospitalizations, and death compared with transdermals
  • Spikes in testosterone concentrations → More variable pharmacokinetics

• Patches and gels show comparable risk profiles

• Optimal preparation should be shared decision made by patient and treating physician

JAMA Intern Med. 2015;175(7):1187-96.
AK’s Next Steps

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Comorbidities & Complexities

• Symptoms of chronic diseases associated with aging may be mistaken for low T symptoms

• Chronic diseases may lead to T suppression
  • Mild suppression of T secretion observed in men with cardiovascular disease and/or diabetes
  • High BMI
    • $T_{total}$ in a man with BMI > 30 kg/m$^2$ is 30% lower than man with BMI < 25 kg/m$^2$
    • Medications may decrease T (statins, opioids, SSRIs, K$^+$-sparing diuretics)

• Possible causes for low T should be investigated and managed
Media & Marketing

• From 2009 – 2013, televised testosterone direct-to-consumer-advertising (DCTA) increased from mean 0 to 13.6 (± 0.8) household exposures per month

• Each exposure to DCTA significantly associated with:
  • New testosterone testing ↑ 0.6%/month (36%/5 years)
  • New initiation ↑ 0.7%/month (42%/5 years)
  • Initiation without recent baseline test ↑ 0.8%/month (48%/5 years)

• Initiation of testosterone often deviates from guideline recommendations

Appointments not restricted to AM

Only one test conducted

IM injection not first-line

Longer-acting IM formulations preferred
Safety Concerns

November 2013
• Vigen, et al. showed 30% increased risk of mortality, myocardial infarction, and stroke in men with low T treated with T replacement therapy (retrospective)

December 2013
• Finkle, et al. showed two-fold increase in risk of myocardial infarction in healthy men aged ≥ 65 years in first 90 days following first T prescription (retrospective)

January 2014
• FDA issues safety alert regarding risk of stroke, heart attack, and death in men using testosterone products

March 2015
• FDA requires manufacturers of T products to change labeling

FDA Labeling Requirements 2015
• Approved only for men who have low T levels caused by certain medical conditions
• Benefit and safety have not been established for treatment of low T levels due to aging
• Possible increased risk of heart attacks and strokes
Testosterone Trials (T Trials)

• Commissioned by the National Institutes of Health (NIH)
  • Funded primarily by National Institute on Aging (NIA)
  • Additional funding and study drug provided by AbbVie Pharmaceuticals

• Goal to provide stronger evidence on potential benefits and/or risks of T replacement therapy in LOH
## Trials Design

| **Objective** | To examine if testosterone treatment of elderly men with low serum testosterone concentrations will result in favorable changes in:  
| | • Abnormalities that could be due to low testosterone  
| | • Cardiovascular risk factors  
| | • Bone mineral density |
| **Design** | • Double-blinded, randomized, placebo-controlled trials  
| | • N = 790  
| | • Multicenter: 12 sites for 12 months |
| **Intervention** | • Testosterone gel (Androgel®) 1% pump bottle  
| | • Initial dose 5 g applied daily  
| | • Dose adjusted every 3 months to keep in normal range of men aged 19 - 39  
| | • Placebo gel formulated to have similar application and appearance |
### TTrials Inclusion & Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Men ≥ 65 years old</td>
<td></td>
</tr>
<tr>
<td>• $T_{total}$ &lt; 275 ng/dL</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risk &gt; 35% of overall prostate cancer or risk &gt; 7% of high-grade prostate cancer</td>
<td></td>
</tr>
<tr>
<td>• Severe lower urinary tract symptoms</td>
<td></td>
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<tr>
<td>• Alcohol or substance abuse within the past year (self-reported)</td>
<td></td>
</tr>
<tr>
<td>• High cardiovascular risk (MI or stroke within previous 3 months, unstable angina, NYHA Class III or IV heart failure, BP &gt; 160/100)</td>
<td></td>
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<tr>
<td>• SCr &gt; 2.2 mg/dL; ALT 3x ULN; HbA1c &gt; 8.5%; TSH &gt; 7.5 mIU/L</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis or treatment for cancer within previous 3 years</td>
<td></td>
</tr>
<tr>
<td>• Major psychiatric disorders that are untreated and/or unstable</td>
<td></td>
</tr>
<tr>
<td>• Use of medications that alter testosterone concentration</td>
<td></td>
</tr>
<tr>
<td>• Conditions known to cause hypogonadism</td>
<td></td>
</tr>
<tr>
<td>• Conditions that would limit ability to participate or affect interpretation of results</td>
<td></td>
</tr>
</tbody>
</table>
## Trials Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Comorbidities</th>
<th>Mean Sex Hormone Levels</th>
</tr>
</thead>
</table>
| • Age 72 years (± 5.8)  
• Ethnicity  
  • Caucasian 88.6%  
  • African-American 5.2%  
  • Other 6.2%  
• College graduates 54.2%  
• Married or living with partner 73.4%  | • Mean BMI 31.0 kg/m²  
• Mean 3 alcoholic drinks/week (± 4.3)  
• Current tobacco use: 7.6%  
• Diabetes: 37.5%  
• Hypertension: 72.4%  
• History of MI or stroke: 17.5%  
• Risk of all prostate cancer: 17.3 (± 6.0)  
• Risk of high-grade prostate cancer: 2.9 (± 1.7)  
• PDE5 inhibitor use: 7.6%  | • T<sub>total</sub> 232 ng/dL (± 63)  
• T<sub>free</sub> 62.0 pg/mL (± 21.4)  |
TTrials

- Sexual Function Trial
- Physical Function Trial
- Cardiovascular Trial
- Bone Trial
- Cognitive Function Trial
- Anemia Trial
- Vitality Trial
## Sexual Function Trial: Snyder (2016)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Group (n = 230) Testosterone 1% gel</td>
<td>Inclusion&lt;br&gt;- Self-reported decreased libido&lt;br&gt;- Score of ≤ 20 on sexual-desire domain of Derogatis Interview for Sexual Functioning in Men-II (DISF-M-II, range 0 – 33)&lt;br&gt;- Partner willing to have intercourse twice a month</td>
<td>Primary&lt;br&gt;- Change in score for sexual activity (question 4) on Psychosexual Daily Questionnaire (PDQ-Q4, range 0 – 12)&lt;br&gt;Secondary&lt;br&gt;- Change in score on erectile function domain of International Index of Erectile Function (IIEF, range 0 – 30)&lt;br&gt;- Change in score of sexual-desire domain of DISF-M-II Tests administered at baseline, 3, 6, 9, and 12 months.</td>
</tr>
<tr>
<td>Control Group (n = 229) Placebo</td>
<td>Exclusion&lt;br&gt;- See exclusion criteria for TTrials</td>
<td></td>
</tr>
</tbody>
</table>

### Sexual Function Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Testosterone N = 230</th>
<th>Placebo N = 229</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 6</td>
<td>Month 12</td>
<td>Month 6</td>
</tr>
<tr>
<td>PDQ-Q4</td>
<td>0.6 (1.5)(^a)</td>
<td>0.2 (1.6)</td>
<td>-0.1 (1.2)</td>
</tr>
<tr>
<td>IIEF</td>
<td>3.3 (6.5)</td>
<td>3.1 (6.9)</td>
<td>0.5 (6.1)</td>
</tr>
<tr>
<td>DISF-M-II</td>
<td>3.5 (6.0)</td>
<td>2.6 (6.5)</td>
<td>0.8 (5.6)</td>
</tr>
</tbody>
</table>

\(^a\)Mean (SD) changes in score
Sexual Function Trial

Conclusions

• Men who received testosterone reported better sexual function, including activity, desire, and erectile function

• Effect sizes were low to moderate but may be of clinical significance
# Physical Function Trial: Snyder (2016)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 387</td>
<td>Inclusion</td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td>- Self-reported difficulty walking or climbing stairs</td>
<td>- Percentage of men who increased distance walked in 6-minute walk test by ≥ 50 m</td>
</tr>
<tr>
<td></td>
<td>- Gait speed of &lt; 1.2 m/second on 6-minute walk test</td>
<td>Secondary</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>- Percentage of men who whose score on physical-function domain of Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, range 0 – 100) increased by ≥ 8 points</td>
</tr>
<tr>
<td></td>
<td>- Not ambulatory</td>
<td>- Changes from baseline in 6-minute walking distance and SF-36 score</td>
</tr>
<tr>
<td></td>
<td>- Disabling neuromuscular or arthritic conditions</td>
<td>Tests administered at baseline, 3, 6, 9, and 12 months.</td>
</tr>
</tbody>
</table>

## Physical Function Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Testosterone N = 191</th>
<th>Placebo N = 196</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 6</td>
<td>Month 12</td>
<td>Month 6</td>
</tr>
<tr>
<td>Increase ≥ 50 m in 6-minute walk</td>
<td>24/174 (13.8)(^a)</td>
<td>35/172 (20.3)</td>
<td>23/171 (13.5)</td>
</tr>
<tr>
<td>6-minute walking distance (m)</td>
<td>8.2 (41.5)(^b)</td>
<td>14.3 (45.9)</td>
<td>7.8 (41.4)</td>
</tr>
<tr>
<td>Increase ≥ 8 in SF-36 physical function score</td>
<td>72/171 (42.1)</td>
<td>66/173 (38.2)</td>
<td>73/159 (45.9)</td>
</tr>
<tr>
<td>SF-36 physical function score</td>
<td>6.5 (16.7)</td>
<td>5.8 (17.5)</td>
<td>4.8 (17.0)</td>
</tr>
</tbody>
</table>

\(^a\) No. (%)

\(^b\) Means (SDs)
Physical Function Trial

Conclusions

• Testosterone showed no benefit with respect to walking distance
• Men who received testosterone more likely to report improved walking ability

# Vitality Trial: Snyder (2016)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| N = 474 | **Inclusion**  
- Self-reported low vitality  
- Score of < 40 on Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT, range 0 – 52) | **Primary**  
- Percentage of men whose score on FACIT-Fatigue scale increased by ≥ 4 points |
| Treatment Group (n = 236)  
Testosterone 1% gel | **Exclusion**  
- See exclusion criteria for Testosterone Trials | **Secondary**  
- Change from baseline in FACIT-Fatigue  
- Score on vitality scale of SF-36 (range 0 – 100)  
- Scores on Positive and Negative Affect Schedules (PANAS, range 5 – 50)  
- Score on Patient Health Questionnaire for depression (PHQ-9, range 1 – 27) |
| Control Group (n = 238)  
Placebo | Tests administered at baseline, 3, 6, 9, and 12 months. |

## Vitality Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Testosterone N = 236</th>
<th></th>
<th>Placebo N = 238</th>
<th></th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 6</td>
<td>Month 12</td>
<td>Month 6</td>
<td>Month 12</td>
<td></td>
</tr>
<tr>
<td>Increase ≥ 4 in FACIT-Fatigue score</td>
<td>144/217 (66.4)(^a)</td>
<td>147/203 (72.4)</td>
<td>126/196 (64.3)</td>
<td>120/191 (62.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>FACIT-Fatigue score</td>
<td>7.4 (9.1)(^b)</td>
<td>8.0 (8.4)</td>
<td>5.9 (9.2)</td>
<td>6.7 (9.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>SF-36 vitality score</td>
<td>7.2 (14.6)</td>
<td>8.2 (15.3)</td>
<td>4.5 (11.2)</td>
<td>6.1 (13.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>PANAS positive affect score</td>
<td>0.9 (3.8)</td>
<td>0.7 (3.9)</td>
<td>0.0 (3.3)</td>
<td>0.2 (3.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>PANAS negative affect score</td>
<td>-0.4 (2.4)</td>
<td>-0.6 (2.1)</td>
<td>0.4 (2.6)</td>
<td>-0.1 (2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHQ-9 depression score</td>
<td>-1.7 (3.8)</td>
<td>-1.8 (3.7)</td>
<td>-0.5 (3.7)</td>
<td>-1.1 (3.8)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

\(^a\)No. (%)

\(^b\)Means (SDs)
Vitality Trial

Conclusions

• Testosterone showed no benefit to vitality as assessed by the FACIT-Fatigue scale
• Testosterone associated with small but significant benefits with respect to mood and depressive symptoms
• Men in testosterone group more likely to report improved energy
## Anemia Trial: Roy (2017)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 62</td>
<td><strong>Inclusion</strong></td>
<td><strong>Primary</strong></td>
</tr>
</tbody>
</table>
| Treatment Group (n = 27) Testosterone 1% gel | - Unexplained anemia  
- Baseline Hgb ≤ 12.7 g/dL | - Dichotomous Hgb response (≥ 1 g/dL from baseline) |
| Control Group (n = 35) Placebo | **Exclusion** | **Secondary** |
| | - Baseline Hgb < 10.0 g/dL | - Continuous change in Hgb |
| | - Men with anemia of known cause (N=64) included in exploratory analysis only  
- Renal insufficiency  
- Myelodysplasia  
- Iron deficiency  
- Folate deficiency  
- B₁₂ deficiency  
- Anemia of inflammation  
- Hemolytic anemia  
- Plasma cell dyscrasia and/or monoclonal gammopathy | **Exploratory** |
| | Tests administered at baseline, 3, 6, 9, and 12 months | - Dichotomous Hgb response and continuous change in Hgb in men with anemia of known cause (N=64) and nonanemic men (N=657) |
## Anemia Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Hgb (dichotomous)$^a$</th>
<th>Hgb (continuous)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 6</td>
<td>Month 12</td>
</tr>
<tr>
<td><strong>Unexplained anemia (N=62)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (n=27)</td>
<td>8/22 (36)</td>
<td>13/24 (54)</td>
</tr>
<tr>
<td>Placebo (n=35)</td>
<td>3/27 (11)</td>
<td>2/27 (15)</td>
</tr>
<tr>
<td><strong>Anemia of known cause (N=64)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (n=29)</td>
<td>10/26 (38)</td>
<td>13/25 (52)</td>
</tr>
<tr>
<td>Placebo (n=35)</td>
<td>2/25 (8)</td>
<td>5/27 (19)</td>
</tr>
<tr>
<td><strong>No anemia (N=657)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (n=336)</td>
<td>125/314 (40)</td>
<td>115/305 (38)</td>
</tr>
<tr>
<td>Placebo (n=321)</td>
<td>11/298 (4)</td>
<td>11/285 (4)</td>
</tr>
</tbody>
</table>

$^a$No. (%) for dichotomous outcomes

$^b$Means (SDs) for continuous outcomes
Anemia Trial

Conclusions

• Testosterone significantly increased hemoglobin levels in men with unexplained anemia, anemia of known cause, and nonanemic men
• Anemia corrected in majority of treated men by month 12 with 58.3% correction in unexplained anemia group and 60% correction in group with anemia of known cause
Cognitive Function Trial: Resnick (2017)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 493</td>
<td>Inclusion</td>
<td>Primary</td>
</tr>
<tr>
<td>Treatment Group (n = 247)</td>
<td>- Subjective memory complaints</td>
<td>- Delayed paragraph recall (Logical Memory II, score range 0 to 50)</td>
</tr>
<tr>
<td>Testosterone 1% gel</td>
<td>- Score of 4 or 5 on at least 1 item of the Memory Assessment Clinics Questionnaire (MAC-Q)</td>
<td>Secondary</td>
</tr>
<tr>
<td>Control Group (n = 246)</td>
<td>- Objective memory performance</td>
<td>- Visual memory (Benton Visual Retention Test, score range 0 to -26)</td>
</tr>
<tr>
<td>Placebo</td>
<td>- Score more than 1 SD below the performance for young men (aged 20-24 years) but not greater than 2 SD below the scores of age-matched men on tests of delayed paragraph recall or visual memory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>- Executive function (Trail-Making Test B – A, score range -290 to 290)</td>
</tr>
<tr>
<td></td>
<td>- Do not meet criteria for AAMI</td>
<td>- Spatial ability (Card Rotation Test, score range -80 to 80)</td>
</tr>
<tr>
<td></td>
<td>- Scores of ≥ 80 on Modified Mini- Mental State Examination (3MSE)</td>
<td>Tests administered at baseline, 6 months, and 12 months</td>
</tr>
</tbody>
</table>

## Cognitive Function Trial Results

<table>
<thead>
<tr>
<th>Testosterone N = 247</th>
<th>Placebo N = 246</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 6</td>
<td>Month 12</td>
</tr>
<tr>
<td>Delayed paragraph recall (Logical Memory II)</td>
<td>1.1&lt;sup&gt;a&lt;/sup&gt; (-0.1 – 2.3)</td>
<td>1.3 (-0.1 – 2.5)</td>
</tr>
<tr>
<td>Visual memory (Benton Visual Retention Test)</td>
<td>0.2 (-0.4 – 0.9)</td>
<td>0.3 (-0.4 – 0.9)</td>
</tr>
<tr>
<td>Executive function (Card Rotation Test)</td>
<td>0.6 (-1.9 – 3.0)</td>
<td>0.6 (-1.8 – 3.1)</td>
</tr>
<tr>
<td>Spatial ability (Trail-Making Test B – A)</td>
<td>-2.1 (-12.4 – 8.2)</td>
<td>-0.0 (-10.3 – 10.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean (SD) changes in score

• Testosterone not associated with improved memory or other cognitive functions
### Bone Trial: Snyder (2017)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 211</td>
<td><strong>Inclusion</strong></td>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>Treatment Group (n = 110)</td>
<td>- See inclusion criteria for TTrials</td>
<td>- Percent change from baseline in volumetric bone mineral density (vBMD, mg/cm³) of spine trabecular bone</td>
</tr>
<tr>
<td>Testosterone 1% gel</td>
<td><strong>Exclusion</strong></td>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Control Group (n = 101)</td>
<td>- Taking a medication known to affect bone, except for over-the-counter calcium and vitamin D preparations</td>
<td>- vBMD (mg/cm³)</td>
</tr>
<tr>
<td>Placebo</td>
<td>- Did not have at least 1 evaluable lumbar vertebra</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dual-energy x-ray absorptiometry (DXA) T-score at any site of &lt; -3.0</td>
<td>- Spine peripheral and whole bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hip trabecular, peripheral, and whole bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Estimated strength of sites Tests administered at baseline and 12 months</td>
</tr>
</tbody>
</table>

## Bone Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Testosterone N = 110</th>
<th>Placebo N = 101</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spine trabecular bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>7.5 (4.8 – 10.3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8 (-1.9 – 3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>10.8 (7.4 – 14.3)</td>
<td>2.4 (-1.0 – 5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Spine peripheral bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>4.0 (2.9 – 5.2)</td>
<td>1.1 (0.0 – 2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>7.2 (5.2 – 9.2)</td>
<td>1.5 (-0.5 – 3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Spine whole bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>5.5 (4.0 – 6.9)</td>
<td>1.2 (-0.2 – 2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>9.0 (6.4 – 11.6)</td>
<td>1.9 (-0.6 – 4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hip trabecular bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>1.6 (0.8 – 2.4)</td>
<td>0.1 (-0.6 – 0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>1.5 (0.5 – 2.5)</td>
<td>0.5 (-0.5 – 1.5)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Hip peripheral bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>1.6 (0.9 – 2.3)</td>
<td>0.7 (-0.0 – 1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>1.4 (0.7 – 2.0)</td>
<td>0.4 (-0.3 – 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hip whole bone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vBMD (mg/cm³)</td>
<td>1.7 (1.0 – 2.4)</td>
<td>0.4 (-0.2 – 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Strength</td>
<td>2.5 (1.4 – 3.5)</td>
<td>0.6 (-0.4 – 1.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean change (95% CI)

Bone Trial

Conclusions

• Testosterone significantly increased vBMD and estimated bone strength in all bone types in both hip and spine

• Results support a larger, longer trial to determine whether testosterone reduces fracture risk in order to determine clinical significance
# Cardiovascular Trial: Budoff (2017)

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 138</td>
<td>Inclusion</td>
<td>Primary</td>
</tr>
<tr>
<td>Treatment Group (n = 73)</td>
<td>- See inclusion criteria for TTrials</td>
<td>- Noncalcified plaque volume</td>
</tr>
<tr>
<td>Testosterone 1% gel</td>
<td>Exclusion</td>
<td>Secondary</td>
</tr>
<tr>
<td>Control Group (n = 65)</td>
<td>- eGFR &lt; 60 mL/min/1.73 m²</td>
<td>- Total plaque volume</td>
</tr>
<tr>
<td>Placebo</td>
<td>- Known allergy to iodinated contrast medium</td>
<td>- Coronary artery calcium score</td>
</tr>
<tr>
<td></td>
<td>- Weight &gt; 136 kg</td>
<td>Tests administered at baseline</td>
</tr>
</tbody>
</table>
# Cardiovascular Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Testosterone N = 73</th>
<th>Placebo N = 65</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncalcified plaque volume (mm$^3$)</td>
<td>54 (12 – 97)$^a$</td>
<td>14 (-29 – 56)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total plaque volume (mm$^3$)</td>
<td>75 (22 – 128)</td>
<td>28 (-24 – 81)</td>
<td>0.006</td>
</tr>
<tr>
<td>Coronary artery calcium score</td>
<td>64 (-19 – 146)</td>
<td>91 (7 – 174)</td>
<td>0.310</td>
</tr>
</tbody>
</table>

$^a$Mean change (95% CI)
Testosterone associated with significant increase in noncalcified coronary artery plaque volume of 41 mm$^3$ and total plaque volume of more than 47 mm$^3$ than placebo.

Testosterone may increase risk of atherosclerosis. More information is needed to assess risk of major cardiovascular events and determine clinical significance.
TTrials—Strengths & Limitations

**Strengths**

- Placebo-controlled, double-blind design
- Excellent participant retention in all subgroups and overall trials

**Limitations**

- Results apply only to men 65 years and older with low testosterone due to aging
- Homogeneous population (i.e., healthy Caucasian males with good support system)
- Inclusion criteria for $T_{\text{total}}$ not unequivocally low
- Endpoints for Bone and Cardiovascular trials are surrogate endpoints only
- Small sample size for each subgroup
## TTrials Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Function</td>
<td>• Increased sexual activity, sexual desire, and erectile function</td>
</tr>
<tr>
<td>Physical Function</td>
<td>• Did NOT increase walking distance</td>
</tr>
<tr>
<td></td>
<td>• Improved reported walking ability</td>
</tr>
<tr>
<td>Vitality</td>
<td>• Did NOT improve FACIT-Fatigue score</td>
</tr>
<tr>
<td></td>
<td>• Improved mood and depressive symptoms and reported energy levels</td>
</tr>
<tr>
<td>Anemia</td>
<td>• Increased Hgb in men with unexplained anemia, anemia of known cause, and nonanemic men</td>
</tr>
<tr>
<td></td>
<td>• Corrected Hgb in majority of anemic men</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>• Did NOT improve memory or other cognitive functions</td>
</tr>
<tr>
<td>Bone</td>
<td>• Increased vBMD and estimated bone strength at all test sites</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>• Increased both noncalcified coronary artery plaque volume and total plaque volume</td>
</tr>
</tbody>
</table>
An otherwise healthy 74-year-old man, AK, complains of sleep disturbance, lack of energy, unsteady gait, feelings of depression, lack of sexual desire, and erectile dysfunction. He has had two subsequent morning $T_{\text{total}}$ levels of 218 ng/dL and 211 ng/dL, respectively.

What should the next steps be in AK’s treatment?

A. Initiate testosterone transdermal gel 50 mg daily
B. Return to the clinic in 7 – 10 days to receive testosterone cypionate 50 mg IM
C. AK is not a candidate for treatment based on his current levels
D. AK is not a candidate for treatment based on his current symptoms
Consider T replacement therapy
Transdermal preferred

Low (≤ 230 ng/dL)
Repeat T\textsubscript{total}
Measure LH and FSH

Borderline (231 – 350 ng/dL)
Repeat T\textsubscript{total}
Calculate T\textsubscript{free}

T\textsubscript{free} low (< 225 pg/mL)

T\textsubscript{free} normal (≥ 225 pg/mL)

Normal (> 350 ng/dL)
Investigate other causes

Abnormal gonadotropins → Investigate pituitary causes

Symptoms of hypogonadism (including at least one sexual symptom)

Assess comorbidities: Do not start T replacement therapy if CV risk.
Monitor: Clinical response, T\textsubscript{total}, Hgb, bone scans every 6 – 12 months
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Nathan Pope, PharmD, BCACP, FACA
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H-E-B Pharmacy

Evaluator
Samantha Vogel, PharmD
PGY2 Psychiatric Pharmacy Resident
Seton Healthcare Family
References