Andropause: Androgen Deficiency in the Aging Male
Diagnosis, Treatment, Safety

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United States Age Demographics

United States Census Bureau

Year

Men > 65 years (millions)
Prevalence of Low T:
13 million men in the US

The relative risk of Low T is greater with each 10-year increase in age.

Is the Increase in T Rx patient or industry Driven?

• Sharp increase in T rx in last 10-15 years
  • Leading to concerns about market driven over prescription

• 2007 FDA indicated that as few as 5% of the hypogonadal population was treated

• 2010 reviewed of industry data showed no T product in the top 25 most marked drugs in the U.S.

1. USFDA http://www.fda.gov/fdac/departs/196_update.html
Defining Hypogonadism and Andropause

• In older men often referred to as “Andropause” or ADAM (Androgen Deficiency in the Aging Male)
  • Unlike menopause not all men will suffer Andropause and the onset is slow over years
  • Leading to some controversy if the name Andropause is misleading

Defining Hypogonadism and Andropause

• ↓ testosterone (hypogonadism) can be associated with a symptom complex affecting:
  • Libido
  • Energy
  • Body fat
  • Mentation
  • Bone density
  • Muscle mass
Testosterone’s Impact on the Male Body

- **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

- **Pancreas**
  - Increases insulin sensitivity

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AACE Hypogonadism Task Force *Endocrinol Pract* 2002;8:439-456

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Classification and select causes of Low T

- **Primary (testicular)**
  - Congenital - Klinefelter’s and variants
  - Mumps and other viruses
  - Trauma
  - Aging
  - HIV/AIDS

- **Secondary (pituitary and/or hypothalamus)**
  - Aging
  - Chronic Illness
  - HIV/AIDS

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Hypothalamus
Anterior pituitary
Testosterone
LH
FSH
Sperm
Sexes
Hair and skin
Inovada
Muscle
Behavior
Lipids

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Hypogonadism with Aging

- Approximately 700 million Leydig cells at birth
- Men lose 6 million cells/yr after age 20
- Loss of Leydig cells correlates with progressive loss of T production with age (primary failure)
- Decreased GnRH pulse amplitude results in decreased T production (secondary failure)


Male Hormonal Status: Changes with Age as SHBG Increases

Adapted from Heaton and Morales. Sex Dysfunction in Medicine. 2000;1:105-111.
## Making the Diagnosis of Low T

- Symptoms & signs
- Questionnaires
- Confirmatory blood tests
- High risk populations

## Key Signs and Symptoms to Consider

**2010 Endocrine Society Guidelines**

Suggested signs and symptoms that would require a serum testosterone level

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased energy or motivation</td>
<td>Increased body fat, body mass index</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>Diminished Libido / erectile dysfunction</td>
<td>Low bone mineral density</td>
</tr>
<tr>
<td>Poor concentration and memory</td>
<td>Loss of body hair (axillary and pubic) hair, reduced shaving</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Endocrine Society Guidelines, 2010
ADAM Questionnaire: 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 emotions 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?

If you answered "Yes" to question 1 or 7, or if you answered "Yes" to any 3 questions in total, you may wish to talk to your doctor about having a blood test to determine your testosterone level. Fill this questionnaire to your doctor to help start the discussion.


Confirmatory Blood Tests: 2nd Andropause Consensus Panel

- Total T < 300 ng/dl
  - Definitely low
- Total T 300-400 ng/dl
  - Repeat testing
  - Clinical considerations
  - Check Free T
- Total T > 400 ng/dl
  - Probably OK

Available at:
18% of men in a cohort study of 3,700 men with ED had low T
30% of HIV-infected men and 50% of men with AIDS may have Low T
33-50% of men with Type 2 Diabetes may have Low T
74% of men on sustained-action opioids (chronic pain) may have Low T

Testosterone Replacement Therapy

• Modes of Delivery
• Benefits of Therapy
## Current Therapies

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>3-4 times daily</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Every 1-2 weeks</td>
</tr>
<tr>
<td>Nonscrotal patch</td>
<td>Once daily</td>
</tr>
<tr>
<td>Absorbable gel</td>
<td>Once daily</td>
</tr>
<tr>
<td>Mucoadhesive (Buccal)</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Long acting Intramuscular</td>
<td>Every 10 weeks</td>
</tr>
<tr>
<td>Subdermal Pellets</td>
<td>Every 3-4 months</td>
</tr>
</tbody>
</table>

### IM Testosterone

![IM Testosterone](image-url)
IM Testosterone Enanthate 250 mg
Once Every 2 Weeks

Testosterone Topical:
Daily Application

- Clear
- Colorless
- Hydroalcoholic
- Continuous transdermal delivery

Testosterone Levels after Replacement Therapy with Patch, Gel or Injection

Established Benefits of Normalizing T levels

- Positive impact on ED and libido
- Improve energy level, mood and strength
- Increased bone mineral density
- Increased lean mass and decreased waist circumference

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

• In Diabetic men
  ➢ Improved insulin sensitivity
  ➢ Reduced blood glucose
  ➢ Reduced HbA1c


Decreased Libido and Fatigue

![Graph showing decreased libido and fatigue in studies](image)
**Sexual Function:**
Objective Assessment Rigiscan® Erectile Index (n=20)

<table>
<thead>
<tr>
<th>Erectile Index (%)</th>
<th>Base</th>
<th>Tip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypogonadal baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone Replacement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Testosterone Gel: Significantly Improves Key Symptoms of Hypogonadism**

  - **Lean Body Mass** +4.9 lbs (P<0.05)
  - **Fat Mass** -3.97 lbs (P<0.01)
  - **Sexual Desire** Significant improvement from baseline
  - **Sexual Performance** Significant improvement from baseline

Adapted Dean J, Reviews in Urology, Volume 6, Supplement 6, 2004.
Testosterone Treatment of Elderly Men: Bone Mineral Density (BMD)


Monitoring of TRT

<table>
<thead>
<tr>
<th>Test</th>
<th>1-2 mo.</th>
<th>3-6 mo.</th>
<th>Yr.</th>
<th>Goal / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Evaluate whether symptoms have responded to treatment or if there are adverse effects</td>
</tr>
<tr>
<td>T Level</td>
<td>X</td>
<td></td>
<td></td>
<td>Therapy should aim to raise serum testosterone levels into the mid-normal range</td>
</tr>
<tr>
<td>PSA / DRE</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Obtain urological consultation if:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- PSA &gt; 4.0 ng/mL (Note: age-specific) or increased &gt; 0.75 ng/mL within any 12 month period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Detection of a prostatic abnormality on DRE</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>X</td>
<td>X</td>
<td></td>
<td>If hematocrit is &gt;54%, stop therapy until hematocrit decreases to a safe level</td>
</tr>
</tbody>
</table>

Adapted from Endocrine Society Guidelines. July 2006
Potential Risks of Treatment with Testosterone Replacement Therapy

Areas of Concern with TRT
- BPH
- Prostate Cancer
- Heart Disease
### Potential Risks in Testosterone Replacement Therapy

**Patients to Avoid**
- Known or suspected cancer of the prostate or breast
- Prostate nodule or induration found on DRE
- Unexplained PSA elevation
- Erythrocytosis (hematocrit >50%)
- Severe LUTS with BPH (IPSS >17)
- Unstable severe CHF (Class III or IV)

**Other Potential AE’s**
- Erythrocytosis
- Acne and oily skin
- Reduced sperm production and fertility
- Detection of subclinical prostate cancer
- Growth of metastatic prostate cancer

Adapted from the Endocrine Society Guidelines. 2010.

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### TRT and CV RISK in the News

**Manopause?!**

**Increased Risk of NC Following Testosterone**

**Original Investigation**

**Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels**

- Rebecca Varg, MD, MSc, Carni Orenstein, MD, Anna E. Barbour, PhD, Gail S. Gransell, MD, Thomas H. Meinders, MD, PhD, Douglas M. Brain, MD, John C. Hinson, MD, E. Michelle K. Johnson, MD, Karen Lin, MD, James B. McEwen, MD, Margaret A. Warren, MD, Anne L. Brumbaugh, MD, PhD, Paul V. Ramlall, MD, PhD, Alan K. Roehl, MD, PhD

**Abstract**

**Background**

A serum total testosterone level less than 12 ng/dL is associated with an increased risk of cardiovascular disease. However, data are lacking on the effects of testosterone therapy on cardiovascular outcomes and mortality. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular disease was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

**Objectives**

To assess the association between testosterone therapy and all-cause mortality.
JAMA Article

Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels

- was a retrospective analysis of a dataset of 8709 men in the VA health system who had undergone coronary angiography.
- Among men with testosterone concentrations less than 300ng/dl, the authors reported an increased rate of heart attacks, strokes, and deaths in men who received a testosterone prescription compared with men who did not.
- Although no significant differences in event rates were noted at any year of follow-up, a significant increase of 29% for testosterone-treated men was reported over the course of the study.


JAMA Article

Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels

- Curiously, the percentage of men who suffered an event was actually lower by one half for the testosterone group compared with the no-testosterone group (10.1% vs 21.2%).

FIGURE: Actual percentage of individuals who experienced an adverse cardiovascular event in the testosterone (T)-treated and untreated groups in the study by Vigen et al. The authors reported a higher rate of adverse events in the T-treated group using inverse stabilized propensity weighting in which an event was counted as more than 1 event in the T-treated group and less than 1 event in the untreated group. MI = myocardial infarction.

JAMA Article
Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels

- The authors came to an opposite conclusion resulting from complex statistical modeling based on more than 50 variables, including time. However, this modeling failed to include substantially lower baseline testosterone levels.
- These statistical adjustments resulted in an estimated cumulative event rate for the testosterone group of >30% compared to the actual rate of only 10.1%. This multiplier effect for events also multiplies the magnitude of errors, raising considerable concern regarding the reliability of results.

<table>
<thead>
<tr>
<th>TABLE 1. Professional Societies Calling for Retraction of Kope et al.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society for Men’s Health (ASMH)</td>
</tr>
<tr>
<td>Brasilian Society of Andrology and Pathology</td>
</tr>
<tr>
<td>Canadian Men’s Sexual Health Council</td>
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<tr>
<td>Canadian Society for the Study of the Aging Male (CSAAM)</td>
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<tr>
<td>European Society for Sexual Medicine (ESSM)</td>
</tr>
<tr>
<td>German Society for Men’s Health</td>
</tr>
<tr>
<td>Hokkaido Andrologic Association</td>
</tr>
<tr>
<td>International Society for Men’s Health (ISMH)</td>
</tr>
<tr>
<td>International Society for Sexual Medicine (ISSM)</td>
</tr>
<tr>
<td>Italian Association of Andrology</td>
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<tr>
<td>Italian Society of Andrology and Social Medicine</td>
</tr>
<tr>
<td>Japan Andrology Council for Men’s Health</td>
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<td>Japanese Society for Men’s Health</td>
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<tr>
<td>Korean Society for Sexual Medicine and Andrology</td>
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<tr>
<td>Malaysian Men’s Health Initiative</td>
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<td>Malaysian Society of Andrology and the Study of the Aging Man</td>
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<tr>
<td>Men’s Health Initiative of British Columbia (Canada)</td>
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<td>Mexican Association of Bone and Mineral Metabolism</td>
</tr>
<tr>
<td>Mexican Sociedad de Medicina Sexual y de Andrologia</td>
</tr>
<tr>
<td>Society for Men’s Health, Singapore</td>
</tr>
<tr>
<td>Society for the Study of Androgen-Deficiency</td>
</tr>
<tr>
<td>Society for the Study of Anthropology and Stereotypes, Singapore</td>
</tr>
</tbody>
</table>


PloS One Article
Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men

- Retrospective review of insurance company database
- Reported rates on non-fatal MI in the 90 day period after T Rx
- Compared to the prior 12 mo MI rates
- The authors reported rate ratio of MI post Rx as 1.36 and the rate in men older than 65 yrs was 2.19
- Comparison used was MI rate post Rx for PDE5 inhibitor
Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men

- Database was limited to diagnosis codes, procedure codes and Rx info
- No info regarding CV related risk factors
  - DM, HTN, hyperlipidemia, smoking, obesity
- No Follow up to verify an event occurred
- Not limited to primary admitting diagnosis or any other limiting factor

The post Rx MI rate likely represents an approximation (limited by collection technique) of the naturally occurring MI rate in this group.

However, the pre RX MI rate really reflects the willingness of Docs to prescribe TRT to men with recent MI.

- Any reluctance to rx TRT in men with recent MI would drastically alter the pre RX MI rate by selection bias

The overall MI rate would be low reported as 4.75 events per 1000 person-years

- Compared to 13 expected events per 1000 person-years referencing the NIH heart attack risk calculator and inputting the age 54, average age of the cohort and favorable modifiers
- MI rate was 1/3 the predicted
PloS One Article
Increased risk of non-fatal myocardial infraction following testosterone therapy prescription in men

• Lastly on this study the comparison to PDE5 inhibitors is like comparing apples and oranges
  • Different likely patient demographics
  • PDE5’s are vasodilators and may have cardio protective effects

TRT and CV Risk

• SMSNA Position Statement
• As a professional society dedicated to the effective and safe treatment of individuals with sexual dysfunction and men’s health overall, the Sexual Medicine Society of North America is aware of recent concerns regarding cardiovascular risks associated with the use of testosterone therapy. This concern stems from two journal articles, one published in November 2013 in the Journal of the American Medical Association, and the other published in January 2014 in the journal, Plos One. Neither of these reports was a planned experimental study with control groups and defined goals. Instead these were retrospective analyses of data collected for other reasons. These types of analyses are prone to bias and error, and results are often irreproducible (3). For this reason, this type of study is generally not used for medical decision-making, although in some cases these may prompt further investigation with an experimental study.

http://www.smsna.org/V1/index.php/about/position-statements
Hypogonadism and CV RISK

- Multiple studies prior showing that CV risk is linked to low testosterone and that replacement therapy may lower risks


Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis

- 75 studies reviewed
- 3016 men treated with T and 2446 treated with placebo
- Mean treatment 34 weeks
- Found no significant association between T therapy and CV events
- Studies in men with metabolic derangements revealed a protective effect

Decreased Life Span and Hypogonadism

- Several longitudinal population-based studies have demonstrated reduced longevity in men with low T levels


Affects of TRT on Prostate
Prostate Volume in Testosterone Treated and Untreated Hypogonadal Men

- 3 groups of age matched men
  - 47 new hypogonadal men
  - 78 hypogonadal men on T for 6 months
  - 75 normal men
- Prostate volume, PSA, and hormones measured


Prostate Volume in Testosterone Treated and Untreated Hypogonadal Men (cont.)

- Prostate Volume & PSA lower in untreated men
- No clinically significant difference in prostate volume between T treated men and normal men
- PSA rose to normal levels but not significantly higher in T treated men

Summary

• Androgen deficiency in adult men is often underdiagnosed

• As men age, T levels gradually diminish, often to hypogonadal levels

• Andropause is characterized by changes in:
  • Body fat/lean muscle ratio
  • Bone mineral density
  • Cognition, memory, and mood
  • ↓ sexual desire and function

• TRT can increase hormone levels to normal ranges, significantly improve symptoms and is safe with proper monitoring
Normal Patients

- Prostate cancer rate in 7 published TRT trials was similar to screening trials of general population\(^1\)
- PSA values do not significantly increase after TRT\(^2\)\(^-\)\(^4\)
- Most studies have NOT demonstrated an association between elevated testosterone and prostate cancer\(^5\)

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

- 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


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

![Prostate Tissue Affects of TRT Bar Chart]

- Serum Levels
- 0 - 700 ng/g
- Testosterone, DHT
- Baseline 6 Months Baseline 6 Months
- TRT (n=21) Placebo (n=19)
- * p < .001
- ** p < .002
Affects 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.

High Risk (HGPIN)

- 75 hypogonadal men treated with TRT for 12 months
- All men underwent prostate biopsy prior to TRT
  - 55 men had benign biopsies (-PIN)
  - 20 men with PIN (+PIN)
- Results
  - No significant change in PSA in either group
  - One patient in +PIN group found to have prostate cancer on biopsy after abnormal DRE

Morgentaler, J Urol 170:2348-51, 2003
Testosterone Replacement 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


TRT after Radical Prostatectomy

- Population studied:
  - Hypogonadal symptomatic men after radical prostatectomy
  - Treated with daily 1% testosterone gel (Testim or Androgel)
- Inclusion criteria:
  - Negative surgical margins
  - Undetectable PSA
- Safety monitoring:
  - Every 3 months for first year and then semi-annually
  - DRE, PSA, H/H, T and FT
- Efficacy measurements:
  - Androgen Deficiency in Aging Males (ADAM) questionnaire
  - Quantitative ADAM (qADAM) questionnaire
- Primary endpoints:
  - Changes in PSA value (safety)
  - Changes in ADAM and qADAM questionnaires (efficacy)
Results

- N = 21 men
- 51-80 years old (mean 63.1)
- Testosterone replacement therapy (TRT) was initiated an average of 54 months (1-181 months) after radical prostatectomy
- Patients followed an average of 18 months (7-66 months) after TRT
Testosterone After Radical Prostatectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of</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</td>
<td>10</td>
<td>19</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>197</td>
<td>591</td>
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<tr>
<td>Kaufman</td>
<td>7</td>
<td>24</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>97</td>
<td>434</td>
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<tr>
<td>Brawer *</td>
<td>1</td>
<td>14</td>
<td>undetectable</td>
<td>undetectable</td>
<td>150</td>
<td>517</td>
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<tr>
<td>Lipshultz</td>
<td>21</td>
<td>17</td>
<td>0.005</td>
<td>0.005</td>
<td>275</td>
<td>440</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>18.5</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>180</td>
<td>496</td>
</tr>
</tbody>
</table>


*TRT following RRP and XRT

Conclusion

- TRT is safe and effective in treating patients following a radical prostatectomy
- Clinicians should be aware of these findings and consider earlier initiation of TRT in these symptomatic patients