Testosterone and Aging: revisiting physiology to understand the risks and benefits of treating “Low T”

Stephanie T. Page, MD, PhD
Associate Professor
University of Washington
Seattle, WA

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Disclosures

Besins and Abvie have provided testosterone and placebo gel for investigator-initiated clinical studies
Clinical Uses for Androgen Manipulation in Men

ACCEPTED
- (-) Androgen deprivation for prostate cancer
- (+) Treating Hypogonadism (primary, central IHH, postsurgical)

CONTROVERSIAL
- Sarcopenia
- Aging with “low T”
- Male hormonal contraception
- ? Diabetes ? MetSyn?

Testosterone is a Billion Dollar Industry

Skyrocketing
Prescriptions for testosterone have risen sevenfold since 1998.

Dispensed testosterone prescriptions

Source: NCHS, Data from retail and mail order pharmacies.

Newsweek, Sept 29, 2003, page 50
CLINICAL CONTROVERSY: Testosterone and Aging

"Low T": Longitudinal Changes in serum Testosterone with Age

Multi-organ effects of sex steroids

Androgens
Estrogens

LIPIDS
GONADS
SPERMATOGENESIS

Cardiovascular Disease
Metabolic Syndrome
Diabetes

ERYTHROPOESIS
BONE

FAT

Prostate Cancer
BPH

Male Hormonal Contraceptio.

Metabolites of T are important mediators of end organ effects

T $\rightarrow$ DHT (1% in blood)
5α-reductase

T $\rightarrow$ E (1%)
aromatase

• Androgens: Lean body mass, prostate

• Estradiol: Fat mass, sexual function

Finkelstein J et al NEJM 2013
Clinical Controversies: Do Androgens contribute to Prostate Cancer or Cardiovascular Disease in Men?

- No “Men’s Health Initiative”: no long term, large studies examining health outcomes (Pca, MI, DM, death)
  - DATA > 10 YEARS AWAY (7 YEARS, 7,000 MEN)
- Recently completed “T Trial” in men NOT powered for morbidity/mortality endpoints; 800 men, one year

Approach: re-examining physiology

- Recognize gaps in knowledge (NO LARGE RCT)
- Use epidemiologic evidence to drive hypotheses
- Intervention studies to understand how androgen manipulation changes tissue hormone levels, gene expression, and clinically important endpoints: Prostate, CVD risk factors
Paradigm: GnRH clamp (Acyline) + T add back → Tissue

GnRH Antagonist

+/- Exogenous Testosterone +/- Arom Inhibitor

Body composition
Lipids
Prostate
Fat
Insulin sensitivity

LH
FSH

Testes

Sertoli Cells

Leydig Cells

Testosterone
Estradiol

GnRH

Hypothalamus

Pituitary

Acyline: a rapid and effective GnRH antagonist
Androgens and the Prostate

- Prostate is androgen sensitive

- $5\alpha$-reductase inhibitors, which block conversion of $T \rightarrow \text{DHT}$ within the prostate, are associated with a 25% ↓ risk of developing prostate cancer (PCPT, REDUCE)
  - But increased risk of higher grade disease

- Epidemiologic data and limited data with androgen replacement not compelling that higher serum androgens increase risk for prostate disease

Intraprostatic Androgen Micro-Environments

- Serum T: DHT = 10:1
- Prostate T: DHT = 1:10
- DHT 10x Potency of T

Geller J et al Prog Clin Biol Res 1979 33:103
Mohler J et al Canc Res 10:440
Intraprostatic Androgens in Healthy Men during Androgen “ablation”

- Normal men, age 35-55, PSA < 2
- Treatment (n=4/group) x 4 weeks:
  - Intact (Placebo)
  - Medical castration (GnRH antagonist, Acyline)
  - Medical castration plus T (Acyline + T)
- Blood sample and prostate biopsy at 4 weeks

Intraprostatic androgens are plentiful in healthy men during androgen “ablation”

- Serum Androgens (ng/ml)
- Intraprostatic Androgens (ng/g)
- Testosterone
- DHT

Page ST et al JCEM 2006 91:3850
Intraprostatic androgens during medical castration support AR-regulated processes

- **Gene array analysis:** Changes in known androgen regulated genes observed, but robust expression still present (few genes differentially regulated >2.5 fold)
  - PSA still 3rd most highly expressed message

- **Immunohistochemistry:** proliferation, apoptosis, AR expression = PLACEBO

**Top 20 Down-Regulated Genes in Epithelial Samples:**

Castrate vs. Placebo


Increasing serum DHT 7x ↑ in serum DHT does not alter intraprostatic androgens nor AR-regulated gene expression

- **No differences** between treatment groups:
  - AR-regulated gene expression (arrays)
  - PSA
  - Prostate volume
  - International Prostate Symptom Score (IPSS)

Page ST et al JCEM 2011
TRT in hypogonadal men does not increase intraprostatic androgens

- TE 150 mg/2 weeks vs. placebo
- T < 300 ng/ml + sx
- Prostate bx. before and after 6 months T
- N = 40

- No change in prostate cell turnover or AR-regulated gene expression

Marks LS et al. JAMA. 2006; 296:2351.

Increasing serum T does not increase intraprostatic DHT
Summary: Do Androgens Drive Prostate Disease?

- Little evidence that serum androgen concentrations predict prostate disease
- 5alpha-reductase inhibitors that lower DHT reduce incidence of low grade but not necessarily high grade prostate cancer
- Changes in serum androgen levels are not reflected in the intraprostatic environment
- Long-term intervention studies are needed, current evidence does not support the notion that serum androgens in the physiologic range drive prostate disease

Summary: Intraprostatic Androgens

- Is the assumption that alterations in serum androgens have parallel effects within the prostate correct? **NO**
- Does raising serum androgens as part of a male hormonal contraceptive regimen alter intraprostatic androgens or androgen-regulated processes? **Probably not**....raising serum DHT does not increase intraprostatic DHT or androgen-regulated gene expression
Clinical Controversy: Do Androgens contribute to Cardiovascular Disease in Men?

- No “Men’s Health Initiative”: no long term, large studies examining health outcomes (MI, DM, death)
  - DATA > 10 YEARS AWAY (7 YEARS, 7,000 MEN)

- Observational data in older men inconsistent

Observational Data: Androgens & CVD in Older Men

- LOW Androgen Concentrations: associated with earlier mortality; suggests protective
  - Rancho Bernando, VA, MMAS, Mr. Os

- LOW Androgen Concentrations: Androgen deprivation therapy ↑ incidence of CVD, DM2: suggests protective

- ↑ Androgen Concentrations: Recent observational data examining testosterone prescriptions mixed results
Mechanism:
Examining effects of androgens on CVD Risk factors

Physiologic effects of Androgens:
Testosterone ↑ fat-free mass and ↓ fat mass

Bhasin S et al JCEM 2005
Benefits of Testosterone:

↑ Strength, Muscle Mass ↔ ↑ Physical Function

![Graph showing improvements in physical performance over time with testosterone treatment.](attachment:image.png)

Page et al. JCEM 2004

Androgen withdrawal acutely increases Insulin Resistance in young men

![Graph showing changes in serum testosterone and HOMA-IR over study days with and without androgen withdrawal.](attachment:image.png)

- similar results in older men (M Smith et al.), and men IHH

Increased serum adiponectin is observed with T withdrawal but not E2 withdrawal

- and ↑ inflammatory markers (MCP-1, Leptin)  
Rubinow et al Clin Endocrinol 2011

What about effects of exogenous T Insulin Resistance? MIXED
TIMES2 Trial: Androgens improve IR in hypogonadal men with DM2
HOMO-IR

But multiple, small RCT in older men with Low T not convincing
Clinical Controversy: Do Androgens contribute to CVD risk factors in Men?

- Summary of observational data: MIXED
- Body composition changes: favorable

- Insulin Resistance:
  - Summary of RCT: MIXED
    - Next step: looking at tissue hormone levels (fat and muscle), ongoing

- No effects on blood pressure
- What about Lipids?

Androgens and Lipids

- Exogenous androgens in men
  - ↓ TC, lower ↓ LDL
  - ↓ HDL-C
  - Route of administration likely important
  - Androgen deprivation ≠ exogenous androgens given within the physiologic range (lesser effects)

? what effect risk mild ↓ HDL-C has on CVD risk
Central role of HDL in CVD under fire

- CETP inhibitor studies: ↑ HDL ⇒ ↑ CVD events
- AIM-HIGH: niacin + statin no better than statin alone despite higher HDL

ARE THERE BETTER METRICS FOR ASSESSING HDL FUNCTION (as opposed to HDL-C= HDL-cholesterol concentration)?

The Dysfunctional HDL Hypothesis

HDL

- Cholesterol Efflux
- Particle size
- Proteins
- Anti-inflammatory

Dysfunctional-HDL

↓ Cholesterol Efflux

- Altered particle size
- Altered Proteins
- Pro-inflammatory

J. Heinecke
We can assay HDL efflux capacity

J774 cells (macrophages)

SERUM

PEG precipitation

Apo-B containing particles

Highest v. lowest efflux by quartiles:
OR 0.38 (0.25-0.58)
P<0.001


Metrics of HDL function: lower HDL-mediated cholesterol efflux is associated with CVD

- **Efflux better predictor of CVD status than HDL-C**
- **No intervention data**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.92 (1.26-2.93)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.89 (1.11-2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.80 (0.95-1.75)</td>
<td>0.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.01 (0.86-1.16)</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.85 (0.70-1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Efflux capacity</td>
<td>0.75 (0.63-0.90)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

Androgens and HDL-C

- **HYPOTHESES:**
  - Androgen withdrawal increases HDL-C but has a negative effect on HDL function
  - Correction of hypogonadism lowers HDL-C but improves HDL function

- **Confounders:**
  - **Dose:** High doses of exogenous androgens decrease HDL-C
  - **Route:** Oral androgens > transdermal or injectables
  - **Patients:** correction of hypogonadism to normal, physiologic levels minor effect

Androgen Deprivation increases HDL-C and HDL-Efflux (2)

- **EFFLUX / HDL-C DOWN 8 % (not significant. P=0.17))**
- Numbers too small to correct for changes in HDL-C
- Retrospective: Correction of age-associated hypogonadism with transdermal gel for 3 months (n=17): no change in HDL-C, no change in efflux

Rubinow 2012 J. Lipid Res
Rubinow Steroids 2011
**Alternate metrics of HDL function:**

*HDL proteome analyses, HDL particle analyses*

HDL of patients with CVD is enriched in specific proteins

**Vaiser,...Heinecke**

_JCI 2007_

**HDL particle number or subspecies may be enriched in patients with CVD**

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**Sex Steroid Deprivation Alters the HDL Proteome**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Day 0</th>
<th>Day 28</th>
<th>p value</th>
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<tbody>
<tr>
<td>Lp(a)</td>
<td>5.4 (2.2)</td>
<td>1.2 (2.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>31.9 (8.3)</td>
<td>38.4 (6.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>3.6 (3.1)</td>
<td>5.6 (3.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>ApoE</td>
<td>2.5 (0.5)</td>
<td>2.0 (0.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>SERPINA1</td>
<td>10.7 (2.9)</td>
<td>12.7 (1.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>ApoA-2</td>
<td>1332 (31)</td>
<td>1399 (204)</td>
<td>0.56</td>
</tr>
<tr>
<td>ApoA-III</td>
<td>259 (71)</td>
<td>321 (31)</td>
<td>0.53</td>
</tr>
<tr>
<td>ApoE</td>
<td>51 (15)</td>
<td>51 (17)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* p < 0.015

•**Retrospective:**

Correction of age-associated hypogonadism with transdermal gel for 3 months (n=17) altered HDL proteome observed (PON1, ApoA-IV, PON3)

Rubinow 2012 J. Lipid Res
Rubinow et al Steroids 2012
Summary and Ongoing studies

- **Androgens and Prostate Disease**
  - Observational data does not show clear association between endogenous androgen levels and PCa risk
  - RCT data does not point to increased risk (although increased risk for biopsy)
  - Physiology suggests that increasing serum androgen levels within the normal range (for young men) **DOES NOT** increase Intraprostatic Androgen levels nor AR-regulated gene expression
  - Ongoing studies to examine dose-response effects in different tissues

**NEED LONG TERM RANDOMIZED CLINICAL TRIAL**

What do we tell our patients?

**Androgens and CVD RISK**

- Epidemiology and observational studies mixed; unclear whether increased risk of CVD events for older men taking testosterone
- Pre-existing CVD or frailty may be a relative contraindication to treating “Low T”
  - **CONSIDER:** indication, age, likelihood of benefit, how low T is, route and dose all likely important
  - What are you treating? Cost?

**NEED LONG TERM RANDOMIZED CLINICAL TRIAL**
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Summary and Ongoing studies

◆ Androgens and CVD risk factors
  ◆ Observational data does not show clear association between endogenous androgen levels and CVD risk
  ◆ Recent observational data suggesting T-prescriptions increase CVD events counter to other studies suggesting T might be protective. Older, frail men may be more risk.
  ◆ Physiology associated with increased androgen levels MIXED: body comp favorable, IR equivocal, Lipids mixed
  ◆ Ongoing studies to examine HDL-C function, effects of T and E in fat
  ◆ NEED LONG TERM RANDOMIZED CLINICAL TRIAL
Androgen withdrawal acutely increases Insulin Resistance in young men

- similar results in older men (M Smith et al), and men IHH

Caution: Exogenous Testosterone and ↑ CVD in older, frail men

- Previous RCT data no AE
- TOM TRIAL: very frail, older men (avg age 75) with low T given higher dose T (up to 15g)
  - stopped by DSMB due to increase CVD events (200/250 enrolled)
  - 50% had pre-existing CVD
  - “events” included edema (how many???)
  - “atherosclerosis” events 7 total, 6 in T: 1 in placebo
- Similar study in Europe did not observe same (n=260)
  - (Wu et al JCEM 2010)
Increased serum adiponectin is observed with T withdrawal but not E2 withdrawal.

Rubinow et al Clin Endocrinol 2011

- and ↑ inflammatory markers (MCP-1, Leptin)