Men’s Sexual Health: Testosterone Replacement

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Business week

Testosterone’s Manly Growth
U.S. annual sales

$2b

In 2011 sales hit $1.6 billion, up 130 percent in four years

2007 2008 2009 2010 2011

$0

$1b

GRAPHIC BY BLOOMBERG BUSINESSWEEK DATA: WOLTERS KLUWER
Objectives

• 1. Learn the factors predicting and associated with low testosterone.
• 2. Understand the factors used in diagnosing low testosterone.
• 3. Review the options available for testosterone replacement and the risk of prostate cancer.

Physiology of testosterone

• Produced and secreted by the testes
  • 95% from this source
  • 5-7 mg produced per day
  • Circadian rhythm
  • Circannual rhythm
### Testosterone synthesis

- **Leydig cell**
- **Produced cholesterol**
- **Regulated by:**
  - Pulsatile GnRH
  - LH
  - Inhibited by inflammatory cytokines
- **Metabolites**
- Estradiol
- DHT

- **Cholesterol**
  - Via P450scc
  - Pregnenolone
  - Via 3 beta-HSD
  - Progesterone
  - Via P450c17
  - 17 α-Hydroxyprogesterone
  - Via P450c17
  - Androstenedione
  - Via 17 beta-HSD
  - Testosterone
  - Aromatase or 5 α reductase
  - Estradiol or DHT

### Circulation

- **Biologically inactive**
  - Bound to SHBG (50-80%)
  - Strongly binds
  - Questionable biologic role
  - SHBG
    - Decreased by obesity, insulin resistance, hypothyroid
    - Increased by estrogens, age, cirrhosis, HIV

- **Biologically active**
  - Bound to albumin (20-50%)
    - Freely dissociates
  - Free (2-3%)
    - Half life 10 minutes

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  - Strongly binds
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Associations

Diseases associated with testosterone deficiency

- Cardiovascular
- Cerebrovascular
- Respiratory
- Renal- especially ESRD
- Diabetes and metabolic syndrome
  - Longitudinal studies suggest TDS is independent predictor
- HIV
- Alzheimer’s disease
- Autoimmune disorders
Prevalence low testosterone

- Chronic opioid use – 74%
- Obesity – 52%
- Diabetes – 50%
- HIV/AIDS – 50%
- HTN – 42%
- Hyperlipidemia – 40%
- Erectile dysfunction – 36%


Mortality

- Testosterone deficiency = doubled mortality risk
  - Shores et al. Arch Intern Med. 166:1660
  - Tivesten et al. J Clin Endocrinol Metab 94:2482
  - Primarily in older men
    - Few negative studies include younger men
- NEJM 2010 Basaria et al.
  - Stopped early due to increased cardiovascular events in testosterone treated arm
  - Frail older men
Mortality

- Shores et al. J Clin Endocrinol Metab 2012
- 7 VA medical centers
- Observational study over time, comorbidity adjusted
- Outcome = mortality
- Two groups (testosterone less than 250 ng/dl)
  - Untreated (n=633)
  - Treated (n=398)

- Adjusted decreased risk of death
- HR 0.61, 95% CI 0.42-0.88
## Autoimmune disorders

- Improvements noted in RA and SLE
- Suppression of pro-inflammatory cytokines
  - Moderates antigen presenting cells
- Promotes anti-inflammatory cytokines
  - Shown in CAD and diabetes patients

## Age

- Levels fall with age
  - Decrease 1-2% per year after age 40
  - Described as late onset hypogonadism when:
    - No cause found
    - 21% of 60-80 yo
    - 35% of 80+ yo

- Decreased circadian rhythm
### Obesity

- Aromatase activity proportional to adipose tissue
  - Metabolism of testosterone
  - Negative feedback of estradiol

- Metabolic syndrome
  - Testosterone helps improve insulin resistance
  - Cause or effect?

### Cardiovascular disease

- Increased CAD in patients on androgen deprivation
- Testosterone associations on lipids:
  - Negatively on LDL, TG, and total cholesterol
  - Positively with HDL
- Increased diastolic blood pressure
  - Improved on testosterone treatment
- Endothelial dysfunction
  - Testosterone regulates flow and eNOS
- Metabolic syndrome effects
Heart failure

- Small studies suggest testosterone levels lower in patients with heart failure
  - Increased levels of inflammatory cytokines in HF
  - Improvements in these levels with testosterone supplementation

Osteoporosis

- Observational studies
  - Increase risk of fracture
    - Hip HR 1.88 95% CI 1.24-2.82
    - Nonvertebral HR 1.32 95% CI 1.03-1.68
# Mood and Cognition

- Low testosterone associated with:
  - Irritability
  - Decreased short term recall
  - Poor spatial recognition tasks
  - Depression

- Mixed results with testosterone replacement

# Sexual dysfunction

- Testosterone assists to regulate eNOS
  - May limit responsiveness to PDE5-inhibitors
- Decreased morning erections
- Low volume ejaculate
- Male infertility
  - Low sperm counts
- Decreased penile sensitivity
- Delayed orgasm or anorgasmia
- Delayed ejaculation
**Low testosterone and PDE5-i**

- Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone
- Observation of low serum testosterone associated with impaired cavernous vasodilation
- Placebo-controlled, double blind
  - Randomized 75 men to placebo vs 1% gel daily
  - Visits 1, 2 screening
  - Visit 3 first day sildenafil run in
  - Visit 4 baseline, day 1 of treatment groups
  - Visit 5 – 7 at 4 week intervals
  - No differences at baseline, all morning serum T < 400 ng/dl

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**Low testosterone and PDE5-i**

- Responses to
  - difficulty maintaining erection to completion
  - feeling of orgasm
  - Overall sex life satisfaction
  - All remained significantly improved with testosterone gel
- Loss of significance for IIEF with time
  - At week 4 significant difference that was lost by week 12
## PDE5-I failures

- All require sexual stimulation
- **Sildenafil**
  - Take 30-60 minutes prior, active 4-6 hours
  - High fat causes 29% reduction in max concentration
    - Take 1-2 hours after eating
- **Vardenafil**
  - Take 30-60 minutes prior, active 4-6 hours
  - Less reduction with fat
- **Tadalafil**
  - Max serum concentration 2 hours after dose, active 36 hours
  - Little to no effect by food

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### ACHIEVING TREATMENT OPTIMIZATION WITH SILDENAFIL CITRATE (VIAGRA®) IN PATIENTS WITH ERECTILE DYSFUNCTION

ANDREW R. MCCULLOUGH, JAMES H. BARADA, AHMED FAWZY, ANDRE T. GUAY, AND DIMITRIOS HATZICHRISTOU

- Urology 2002; 60:28-38.

- 6 double-blind, placebo-controlled flexible dose studies
- Sildenafil 654 pts : placebo 622 pts

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**Figure 2.** Intercourse success rates, as determined from event log data, in men with erectile dysfunction taking sildenafil (top). Intercourse success rates in men stratified by erectile dysfunction severity (bottom).
PDE5-I failures

Failure of PDE5 inhibitor

Assessment of cause of failure

Reversible cause

Incorrect use of drug or non-compliance

Patient education and initiation of self drug with follow-up

Penile injection

Vacuum constriction device

Daily PDE5 inhibitor

Combination of:
- PDE5 inhibitor + intraurethral alprostadil
- PDE5 inhibitor + intraurethral alprostadil
- PDE5 inhibitor + vacuum constriction device

Incorrect dosage

Retrial of oral therapy with dose optimisation with follow-up

Penile prosthesis

Low Libido

Image courtesy of http://images.wellcome.ac.uk

# Diagnosis

“The trouble with testosterone”

## Signs and symptoms of low testosterone
- Decreased sexual desire (libido)
- Erectile dysfunction (ED)
- Fatigue or loss of energy
- Depressed mood
- Regression of secondary sexual characteristics
- Low bone mineral density
- Increased body fat
- Reduced muscle bulk and strength

## Conditions associated with low testosterone in the HIM Study
- Obesity
- Diabetes
- Hypertension
- Hyperlipidemia
- Asthma/COPD
Symptoms

- Fatigue
  - generally feel refreshed upon awakening
- Sexual dysfunction
- Low libido
- Moodiness/Dysphoria/poor concentration
- Reduced physical endurance
  - Poor recovery after work-outs
- Infertility
- Failure to enter puberty

Image courtesy of http://images.wellcome.ac.uk

Signs

- Lack of facial hair
- Lack secondary sexual characteristics
- Underdeveloped muscles
- Truncal obesity
- Loss of height
- Wrinkling facial skin

- NO CONSISTENT SIGNS POST-PUBERTY
  - Even with Klinefelter’s syndrome (XXY)
Do you have a decrease in libido (sex drive)?
Do you have a lack of energy?
Do you have a decrease in strength and/or endurance?
Have you lost height?
Have you noticed a decreased “enjoyment of life”?
Are you sad and/or grumpy?
Are your erections less strong?
Have you noticed a recent deterioration in your ability to play sports?
Are you falling asleep after dinner?
Has there been a recent deterioration in your work recently?
### The Massachusetts Male Aging Study/ Smith Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your age?</td>
<td></td>
</tr>
<tr>
<td>60 years and older = 2 points</td>
<td></td>
</tr>
<tr>
<td>Have you ever been told by a health professional you have diabetes? If yes, are you receiving treatment?</td>
<td></td>
</tr>
<tr>
<td>Receiving treatment for diabetes = 3 points</td>
<td></td>
</tr>
<tr>
<td>Have you ever been told by a health professional you have asthma? If yes, are you receiving treatment?</td>
<td></td>
</tr>
<tr>
<td>Receiving treatment for asthma = 1 point</td>
<td></td>
</tr>
<tr>
<td>How much do you usually sleep?</td>
<td></td>
</tr>
<tr>
<td>Less than 5 hours per night = 1 point</td>
<td></td>
</tr>
<tr>
<td>Do you smoke cigarettes?</td>
<td></td>
</tr>
<tr>
<td>Formerly = 2 points</td>
<td></td>
</tr>
<tr>
<td>Never smoked = 2 points</td>
<td></td>
</tr>
<tr>
<td>Have you recently been bothered by headaches?</td>
<td></td>
</tr>
<tr>
<td>Yes = 2 points</td>
<td></td>
</tr>
<tr>
<td>Do you like directing other people's work?</td>
<td></td>
</tr>
<tr>
<td>No = 1 point</td>
<td></td>
</tr>
<tr>
<td>Height and weight- find your height and score for weight.</td>
<td></td>
</tr>
<tr>
<td>Not depicted</td>
<td></td>
</tr>
<tr>
<td>2 points for overweight and 3 points for obese</td>
<td></td>
</tr>
</tbody>
</table>

### Utility of questionnaires

<table>
<thead>
<tr>
<th>ADAM</th>
<th>MMAS</th>
<th>AMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Low</td>
<td>Testo</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>&lt; 300</td>
<td></td>
</tr>
</tbody>
</table>

< 300 ?
### Diagnosis

- Symptoms = non-specific
- Signs = non-consistent
- Questionnaires = non-specific
- Blood tests?

### Testosterone assays

- Total testosterone
  - Measure between 7-10 AM
  - Preferably 2 separate days
  - No well defined range
    - Under 200 ng/dl likely hypogonadal and above 600 ng/dl likely eugonadal
  - Affected by illness, sexual activity, exercise
  - Assays usually fairly accurate

- LH, prolactin, TSH, FSH
Bioavailable and free

- **Free testosterone**
  - Only accurate with equilibrium dialysis
  - Difficult to do
  - Can calculate
  - Need SHBG and albumin levels

- **Bioavailable testosterone**
  - Calculated or ammonium sulfate precipitation
  - Labor intensive

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**Diagram:**

History and physical (symptoms and signs)

- Morning Total T
  - < 300 ng/dL
  - Low T

Exclude reversible illness, drugs, nutritional deficiency

Repeat T [free or bio T if suspected altered SHBG]

LH + FSH

SFA (fertility issue)

Follow-up

- Confirmed low T [e.g., T < 300 ng/dL or free or bio T < normal (e.g., < 5 ng/dL)]
- Normal T, LH + FSH
- Low T, low or normal LH + FSH
  - Karyotype [Klinefelter's syndrome]
- Low T, high LH + FSH
- Normal T, LH + FSH

Legend:

T = Testosterone, bio = bioavailable testosterone, SFA = synch test for analysis, 1 = primary testicular failure, 2 = secondary hypogonadism, SHBG = sex hormone-binding globulin, ng = nanograms, ml = milliliters

* In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 300 ng/dL (10.4 nmol/L); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory.

* In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 25 ng/dL (0.17 nmol/L). (Approximate lower limit of normal in those major commercial laboratories using equilibrium dialysis, or calculated from total testosterone and SHBG, however, this range may vary in different laboratories.)

* In some reference laboratories, the lower limit of the range established in your reference laboratory.

* Perform cranial imaging (MRI) to exclude polycoria and/or hypothalamic tumour or infiltrative disease. If severe secondary hypogonadism (e.g., T < 100 ng/dL), perform luteinising, testosterone, and luteinising, and/or symptoms of altered endocrine function, or visual field defect, or present.
Treatment options
Supplementation

- Topical
  - Gel- Axiron, Androgel, Testim, Fortesta,
  - Patch- Androderm, Testoderm
- Oral
  - Clomid off-label
- Injection (IM)
  - Testosterone enanthate, testosterone cypionate
- Buccal
  - Striant
- Pellet
  - Testopel

Striant

- Buccal absorption
  - No risk transfer
  - First pass if swallowed
- Tmax 0.4-12 hrs
- Half life 5.7 hrs

- Side effects
  - 9% gum irritation
  - 4% taste bitter
**Pellet (Testopel)**

- Every 4-6 mo
- 75 mg pellets
- Tmax
  - 63 days
- Half life
  - 71 days
- Side effects
  - Pellet extrusion
  - infection

**Gel**

Axiron – under arm  
Fortesta – internal thighs  
Testim and Androgel – shoulders, chest, upper arm, upper back

Half life of 10 – 100 minutes  
Tmax around 4 hours

Alcohol base  
Risk of transfer to partner, children
Intramuscular injection

- Altered form of testosterone to increase half life
  - Ester form
  - Tmax 24 hours
  - Half life 8 days
  - Recommended starting dose:
    - 100 mg IM once per week or 200 mg every 2 weeks

- Inexpensive

Clomid

- Clomiphene citrate
  - Off-label but inexpensive
  - FDA approved for women
  - Selective estrogen receptor modulator
    - Increase FSH and LH
    - Maintain spermatogenesis

- Side effects
  - Headache, bloating, hot flashes, breast tenderness
  - ? DVT
Side effects of testosterone supplementation

- Polycythemia
  - Erythropoiesis stimulated
  - HCT increases more likely with supraphysiologic doses
- Suppress spermatogenesis
- Sleep apnea
  - Potential for worsening of untreated sleep apnea
- Gynecomastia
- Hepatotoxicity
  - Oral formulations except clomid

Prostate safety

- Currently no conclusive evidence testosterone therapy increases risk of prostate cancer or BPH
- PSA levels
  - Mixed clinical results
  - Tend to see initial rise that stabilizes
- BPH
  - Prostate events increased in meta-analysis
  - Mostly prostate biopsy
Prostate cancer

- No increased risk of prostate cancer in men with higher serum testosterone levels
- Meta-analysis of testosterone replacement trials do not show increased prevalence of prostate cancer
- Few small studies suggest increased risk of high grade cancer in hypogonadal men
- Risk of cancer with Prostatic Intraepithelial Neoplasia
  - Precancerous
  - After one year replacement, no increase prostate cancer

Saturation model

![Saturation model graph](image)
Replacement after prostate cancer treatment

- Few publications
  - Three retrospective studies after radical prostatectomy
    - No reported increase in PSA
    - Less than 100 patients
- Abstracts
  - No PSA recurrence in 133 pt, 21 high risk after prostatectomy
  - Two PSA recurrences after radiation therapy
  - Patients on surveillance
    - 12 of 14 men- no signs of progression on repeat biopsy


Following for prostate safety

- PSA prior to initiation of therapy
  - Biopsy for:
    - PSA velocity >0.4 ng/mL per year
    - PSA increase 1.4 ng/mL over 12 mo
    - PSA greater than 4 ng/mL
- PSA at 3 months
  - Consider addition of HCT, testosterone and estradiol
### Contraindications to testosterone supplementation

- Metastatic prostate cancer
- Breast cancer
- Unevaluated prostate nodule or PSA >4 ng/ml
- HCT > 50%
- Severe BPH
- Poorly controlled CHF

### Summary

- Testosterone is commonly associated with many chronic illnesses
  - CAD, DM, metabolic syndrome, ESRD, obesity, age, COPD
  - Low libido a key marker
- Diagnose base on symptoms PLUS low serum testosterone
  - Below 300 ng/dl
- Treatment options based on patient desire and cost
  - Repeat lab evaluation at 3 months