Perspectives in Men’s Health

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Update on Hypogonadism and Testosterone Replacement Therapy
The Primary Care Perspective

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Disclosures

Dr Miner: consultant: Auxilium Pharmaceuticals, Inc., Bayer Schering Pharma, Boehringer Ingelheim, Endo Pharmaceuticals

Research support: GSK
Learning Objectives

Explain the role of testosterone in overall health and the burden of testosterone deficiency

Recognize the role of hypogonadism in obesity, metabolic syndrome, diabetes, cardiovascular disease, and erectile dysfunction (ED)

Identify the signs and symptoms of hypogonadism and their complex clinical presentation

List the options available to treat hypogonadism

Monitor potential adverse effects of treatment
How Is Hypogonadism Defined?

- "Hypogonadism is a clinical condition characterized by low serum testosterone levels occurring in association with specific signs and symptoms."

- Other terminologies for hypogonadism:
  - Decline of testosterone and male androgens in men of any age
  - Andropause: hypogonadism in older men or androgen deficiency in aging men (ADAM)
  - Late-onset hypogonadism (LOH)
  - Partial androgen deficiency in aging men (PADAM)

How Is Hypogonadism Defined?

A symptom complex in the presence of low levels of testosterone\textsuperscript{1,2}

Age-related changes in physiologic function affected by testosterone levels\textsuperscript{2}

Increased BMI
Low bone mineral density
Reduced cognition and memory
Depressed mood
Decreased sexual desire and function
Reduced strength and energy

BMI = body mass index.

Clinical Manifestations of Hypogonadism

<table>
<thead>
<tr>
<th>Physical/Metabolic</th>
<th>Psychological(^1,2)</th>
<th>Sexual(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased bone mineral density(^1,2)</td>
<td>• Depressed mood</td>
<td>• Diminished libido</td>
</tr>
<tr>
<td>• Decreased muscle mass and strength(^1,2)</td>
<td>• Diminished energy, sense of vitality, or well-being</td>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td>• Gynecomastia(^1,2)</td>
<td>• Impaired cognition and memory</td>
<td>• Difficulty achieving orgasm</td>
</tr>
<tr>
<td>• Anemia(^1,2)</td>
<td></td>
<td>• Decreased spontaneous erections</td>
</tr>
<tr>
<td>• Frailty(^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased body fat or BMI(^1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fatigue(^1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Production and Regulation of Testosterone

Hypothalamus

GnRH

Pituitary

LH

and

FSH

Testes

(Leydig cells)

Testosterone

Testes

(Sertoli cells)

Spermatogenesis

S. Urquhart 2007
Classification of Hypogonadism

Primary\textsuperscript{1,2}
- Testicular Disorders
  - Klinefelter syndrome
  - Orchitis
  - Congenital or acquired anorchia
  - Testicular tumors
  - Testicular Torsion

Secondary\textsuperscript{1,2}
- Hypothalamic Causes
  - Kallmann syndrome
  - Constitutional delay in growth and development
  - Chronic illnesses

- Pituitary Causes
  - Hypopituitarism
  - Pituitary tumors:
    - Ischemia
    - Space Occupying Lesions
    - Granulomatous disease

Mixed\textsuperscript{2}
- Dual HPG Axis Defects
  - Hemochromatosis
  - Sickle cell disease
  - Thalassemia
  - Glucocorticoid treatment
  - Alcoholism

HPG = hypothalamic-pituitary-gonadal.

Epidemiology and Prevalence of Hypogonadism: The Baltimore Aging Study

Percentage of men, by decade, with a testosterone value in the hypogonadal range—total T <11.3 nmol/L (325 ng/dL)

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 - 59</td>
<td>12%</td>
</tr>
<tr>
<td>60 - 69</td>
<td>19%</td>
</tr>
<tr>
<td>70 - 79</td>
<td>28%</td>
</tr>
<tr>
<td>80+</td>
<td>49%</td>
</tr>
</tbody>
</table>

Prevalence of Symptomatic Androgen Deficiency in Men

Boston Area Community Health

N=1,475 men, aged 39-79 (better ethnic mix)

24% of the men had TT <300 ng/dL

11% of the men had free T <5 ng/mL

Crude prevalence of symptomatic hypogonadism was 5.6%

Increases substantially with age

Better overall estimate is that 4-5 million men in the US have hypogonadism

Araujo et al (NERI) J Clin Endo Metab 2007; 92: 4241-4247
Prevalence and Under-treatment in the United States

BACH Survey estimated crude prevalence of symptomatic androgen deficiency is 5.6%¹

819,000 men receive testosterone therapy³
(breakdown by age)

BACH, Boston Area Community Health Survey.

Hypogonadism in Males
HIM Study

An Epidemiological Study to Estimate the Population Prevalence of Hypogonadism in the US

Hypogonadism in Males
HIM Study
An Epidemiological Study to Estimate the Population Prevalence of Hypogonadism in the US

2650 sites contacted

95 sites enrolled patients in 25 states

47 Family Practice, 44 Internal Medicine, 3 Endocrinology, 1 Urology

2,165 patients enrolled

Prevalence of hypogonadism: 38.7%

Hypogonadism: TT < 10.4 nmol/L

The Prevalence of Low Testosterone Increases with Age (<300 ng/dL)

Over 1/3 of men over 45 years of age have a low testosterone level

Odds Ratio of Selected Co-Existing Diseases


<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Odds Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.33 (1.90, 2.85)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.04 (1.67, 2.50)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.80 (1.50, 2.14)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.59 (0.77, 3.30)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.55 (0.91, 2.62)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.49 (1.25, 1.78)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.42 (1.07, 1.88)</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>1.20 (0.95, 1.50)</td>
</tr>
<tr>
<td>Prostate Disease</td>
<td>1.19 (0.95, 1.49)</td>
</tr>
</tbody>
</table>
Case Study: Adam

A 48-year-old man presents with ED, fatigue, depressed mood, and distress in the marital relationship. Low libido. Medical history otherwise unremarkable.

Weight 220 lb  BMI 35.5

Height 5’ 6”

Waist circumference 44”

BP 140/90

Genital exam normal

DRE normal

DRE = digital rectal exam.
What would be your next step?

1. Refer to marital counseling
2. Refer to psychiatrist
3. Order labs including testosterone
4. Prescribe PDE5 inhibitor and check testosterone
5. Prescribe testosterone

PDE5 = phosphodiesterase type 5.
Low Testosterone Also Predicts All-Cause Mortality in Older Men

Population-based Study—12-Year Follow-up

<table>
<thead>
<tr>
<th>Testosterone (ng/dL)</th>
<th>Median Hormone Level (ng/dL)</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;370</td>
<td>436</td>
<td>1.00</td>
</tr>
<tr>
<td>300-370</td>
<td>331</td>
<td>0.93 (0.73, 1.19)</td>
</tr>
<tr>
<td>241-299</td>
<td>273</td>
<td>1.15 (0.90, 1.47)</td>
</tr>
<tr>
<td>&lt;241</td>
<td>204</td>
<td>1.44 (1.12, 1.84)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, waist-hip ratio, alcohol use, current smoking, exercise

*Adjusted for trend = 0.002

Men with low and equivocal serum T levels had increased all-cause mortality and shorter survival times.

- VA Puget Sound study of 858 men
- 8 year follow-up
- Low T <250 ng/dL or a free T <0.75 ng/dL
- All-cause mortality was 34.9% in men with low T and 20.1% in men with normal T.

Shores MM. Arch Intern Med. 2006;166(15):1660-1665
Increasing endogenous Testosterone levels are inversely related to mortality due to all causes, CV causes, and cancer.

N-2314 men aged 42-78 y.
In spite of differences among various labs, total testosterone level is commonly considered hypogonadal when it is below:

1. 400 ng/dL
2. 300 ng/dL
3. 200 ng/dL
4. 100 ng/dL
5. 50 ng/dL
International Society for the Study of the Aging Male (ISSAM) and European Academy of Andrology (EAU) Guidelines 2008

- Total T: drawn between 7:00 am - 11 am
- No lower limit for normal
- Total T > 12 nmoL/l (350 ng/dL) do not generally require repletion
- Patients with Total T < 8 nmoL/l (230 ng/dL) will usually benefit from T Rx
Androgen Deficiency in Hypogonadal Men

Laboratory Diagnosis

If repeat serum total T between 250 and 350 ng/dL

Measure serum free T level by equilibrium dialysis

or

Measure serum SHBG and calculate free T or bioavailable T (bT)

Equilibrium dialysis or calc free T

Direct measurement of non-SHBG-bound T or calculate bioavailable T
What Level of Serum Testosterone Is Diagnostic for Hypogonadism?

- **AACE Guidelines**
  - TT* <200 ng/dL
  - Free T <50 pg/mL
  - Bioavailable T <70 ng/dL

- **Endocrine Society Guidelines**
  - TT <200 ng/dL = diagnostic
  - TT 200-320 ng/dL = equivocal range of hypogonadism
  - Free T <6.5 ng/dL or bioavailable T <15 ng/dL differentiates eugonadism from hypogonadism

- **ISA, ISSAM, EAU:** TT <346 ng/dL If TT < 150, order Proactin level

*Most frequently used laboratory test for the diagnosis of hypogonadism.
ISA = International Society of Andrology; ISSAM = International Society for the Study of the Aging Male; EAU = European Association of Andrology

What Testosterone Level Warrants Treatment?

- Total testosterone <300 ng/dL
  - US Food and Drug Administration
  - American Society of Andrology
  - Endocrine Society 2006
Morning total testosterone: 160 ng/dL
LH: low
Prolactin: normal
Thyroid functions: normal
Liver and kidney functions: normal
LDL: 160
Fasting glucose: 105
CBC: normal

CBC = complete blood count; LDL = low-density lipoprotein.
What would be your next step?

1. Prescribe testosterone
2. Prescribe PDE5 inhibitor
3. Prescribe testosterone + PDE5 inhibitor
4. Initiate weight loss program
5. Prescribe statin and oral hypoglycemic
"Silent Killers" – Components of the metabolic syndrome

- Dyslipidemia
- Arterial Hypertension
- Insulin Resistance / DM Type 2

Visceral fat tissue

3-fold risk for CVD

BMI and BMI are not the same...
Count on waist circumference

189 cm, 93 kg = BMI 26

190 cm, 94 kg = BMI 26

Waist circumference > Testosterone

< Testosterone
There is an increased risk of hypogonadism in men with MS and its individual components, including insulin resistance.

Traish AM J. Androl. 2009b;302-23-32
Low Testosterone Levels are Associated with the Development of Metabolic Syndrome

In the MMAS, lower total T levels were predictive of metabolic syndrome, especially among those men with a body mass index below 25 kg/m².

Kupelian V et al. J Clin Endocrinol Metab. 2006;91(3):843-850
Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring

Ernani Luis Rhoden, M.D., and Abraham Morgentaler, M.D.

Review of English-language literature re T and PCa

Number of articles in PSA era (1985-2004) regarding effect of TRT in men with PCa...

Number of Articles in PSA Era (1985-2004) Demonstrating TRT Causes PCa Progression… None!
Prostate cancer risk doubled for men with the lowest testosterone values.

N=345
\(aP=.04\)

Morgentaler A, Rhoden EL. *Urology* 2006;68(6):1263-1267
Is High T a Problem for PCa?

Collaborative pooled worldwide analysis of 18 longitudinal studies

3886 men with PCa, 6438 controls

No association of PCa with serum androgens

Men with PCa have similar T concentrations as men without PCa

Men with highest T at no greater risk of PCa than men with lowest T

Prostate Health Assessment

DRE
PSA
Consult with urologist

PSA >4.0 ng/mL

PSA velocity >0.4 ng/mL/y (using PSA level after 6 mo of therapy)

Detection of prostate abnormality on DRE

AUA prostate symptom score >19 with bother if PCP uncomfortable

AUA = American Urological Association.
Prostate Health Assessment Results

IPSS: 11
DRE: normal
PSA: 0.7

IPSS = international prostate symptom score.
How would you counsel the patient?

1. Testosterone therapy can be initiated safely
2. Referral to a urologist is necessary prior to testosterone therapy
3. Prostate biopsy will be necessary to rule out cancer
4. Consider alternatives to testosterone therapy
5. Not sure
Effects of Testosterone Replacement in the Hypogonadal Man

- ↑ Muscle strength/mass
- ↑ Exercise tolerance
- ↑ Mood/well-being
- ↑ Cognition
- ↑ Libido
- ↓ CV risk factors
- ↓ Abdominal fat
- ↑ Erectile function
- ↑ Sexual function
- ↑ Quality of life
- ↑ Erythropoiesis
- ↑ Insulin sensitivity
- ↑ Bone mineral density
- Hair and beard effects
- Skin effects

Effects on semen parameters

Improved CV profile

Quality of life
TRT improves insulin resistance, glycaemic control, visceral adiposity and hyperlipidemia in hypogonadal men with diabetes II

Double-blind placebo-controlled crossover study in 24 hypogonadal men over the age of 30 y with diabetes II.

Methods: IM testosterone 200 mg or placebo every 2 weeks for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase.

3 mo Testosterone Treatment in 24 Hypogonadal Men (mean age: 64 yrs.) with Type 2 Diabetes Reduces HbA$_{1c}$ – 5 out of 10 Insulin-Dependent Patients Reduced their Insulin Dosages by a mean of 7 Units

3 mo Testosterone Treatment in 24 Hypogonadal Men (mean age: 64 yrs.) with Type 2 Diabetes Reduces Waist Circumference and WHR

A double-blind, placebo-controlled, crossover study

Goals

- Treat signs and symptoms of hypogonadism
- Achieve and maintain eugonadal serum testosterone levels
- Individualize therapy to specific patient needs

Potential Benefits

- Restore libido and erectile function
- Increase energy and improve mood
- Improve body composition
  - ↓ Fat mass
  - ↑ Lean body mass
  - Possibly ↑ muscle strength
- Stabilize or increase BMD; perhaps reduce fractures

Options in Testosterone Replacement Therapy

- IM: testosterone propionate, enanthate, or cypionate; testosterone undecanoate in development
- Buccal testosterone
- Transdermal patches
- Transdermal gel
- Oral: not approved in US
- Subcutaneous pellets

Testosterone Therapies

- Buccal system
- Transdermal gel
- Transdermal gel
- Transdermal patch system
- Injection

STRIANT is a trademark of Columbia Laboratories, Inc.
Testim is a trademark of Auxilium Pharmaceuticals, Inc.
AndroGel is a registered trademark of Unimed Pharmaceuticals, Inc., a Solvay Pharmaceuticals, Inc. Company.
Androderm is a registered trademark of Watson Laboratories, Inc.
Delatestryl is a registered trademark of Savient Pharmaceuticals.
## Risks Associated With Testosterone Replacement Therapy

<table>
<thead>
<tr>
<th>RISK</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oily skin, acne, skin reactions</td>
<td>Skin irritation more common with nonscrotal patches</td>
</tr>
<tr>
<td>Breast enlargement or tenderness</td>
<td>Often transient and abates with continued treatment</td>
</tr>
<tr>
<td>Sleep apnea??</td>
<td>Not reported as a consequence of treatment, but consider COPD in heavy smokers or overweight persons a relative contraindication</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Uncommon, but associated with age, sleep apnea, smoking history, and COPD</td>
</tr>
<tr>
<td>Liver function abnormalities or tumors</td>
<td>Rare with injectable esters and transdermal formulations</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>May occur in first few months of treatment</td>
</tr>
<tr>
<td>Symptomatic BPH and prostate cancer</td>
<td>Modest and inconsistent increases in prostate volume</td>
</tr>
</tbody>
</table>

**COPD** = chronic obstructive pulmonary disease  
Monitoring of Men Receiving TRT

Baseline

Determine voiding symptoms via history or IPSS
Determine history of sleep apnea
Digital rectal exam (DRE)
T levels, PSA, Hct, Hgb

Assess treatment efficacy at 1-2 mo; adjust dosage for suboptimal response

Evaluate patient at 3 mo and annually thereafter to assess symptom response and any adverse events

IPSS = International Prostate Symptom Score
Monitoring of Men Receiving TRT

(cont’d)

Check Hct and Hgb at 3 mo, then annually; if Hct >54%, stop therapy

Perform DRE and check PSA at 3-6 mo, then follow guidelines for screening (Q6month level, PSA, Hct, and DRE)

Measure BMD after 1-2 yr of therapy in men with osteoporosis

Evaluate formulation-specific adverse events at each visit

IPSS = International Prostate Symptom Score

## Testosterone Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone cypionate/enanthate¹,²</td>
<td>50-400 mg every 2 wk</td>
</tr>
<tr>
<td>Testosterone undecanoate (TU)</td>
<td>750 mg at baseline, 4 wk, and every 10 wk</td>
</tr>
<tr>
<td>(in development in the United States)</td>
<td>thereafter</td>
</tr>
<tr>
<td><strong>Implants</strong></td>
<td></td>
</tr>
<tr>
<td>Testosterone pellets⁴</td>
<td>150-450 mg (2-6 pellets) every 3-6 mo</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
</tr>
<tr>
<td>Topical gel⁵,⁶</td>
<td>5-10 g daily</td>
</tr>
<tr>
<td>Transdermal patch system⁷</td>
<td>5 mg daily</td>
</tr>
<tr>
<td><strong>Buccal</strong></td>
<td></td>
</tr>
<tr>
<td>Buccal system⁸</td>
<td>30 mg every 12 h</td>
</tr>
</tbody>
</table>

### Formulation-Specific Adverse Effects

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
<td></td>
</tr>
<tr>
<td>Testosterone cypionate/enanthate</td>
<td>Mood fluctuations or changes in libido</td>
</tr>
<tr>
<td></td>
<td>Pain at injection site</td>
</tr>
<tr>
<td></td>
<td>Erythrocytosis</td>
</tr>
<tr>
<td>TU (in development in the United States)</td>
<td>Pain at injection site</td>
</tr>
<tr>
<td>Implants</td>
<td></td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>Potential infections or expulsion</td>
</tr>
<tr>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td>Topical gel</td>
<td>Skin-to-skin transference</td>
</tr>
<tr>
<td>Patch system</td>
<td>Skin irritation</td>
</tr>
<tr>
<td>Buccal</td>
<td></td>
</tr>
<tr>
<td>Buccal system</td>
<td>Alterations in taste and irritation of gums and oral mucosa</td>
</tr>
</tbody>
</table>
Conclusions

Hypogonadism and TRT

A symptom complex in the presence of low levels of testosterone

Age-related changes in physiologic function affected by testosterone levels

Hypogonadism is associated with significant reduction of quality of life, important comorbidities and maybe increased mortality

TRT in carefully selected patients provides satisfactory results

Expanding options for TRT

TRT = testosterone replacement therapy.