MALE HYPOGONADISM: WHO TO TEST, HOW TO EVALUATE, AND WHO TO TREAT

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No financial relationships or other conflicts of interest to disclose
Learning Objectives

- Define Male Hypogonadism
- Analyze patient cases to determine presence of hypogonadism
- Create a differential diagnosis in male patients suspected of hypogonadism
- Specify the circumstances under which you should (and should not) test for hypogonadism.
- Recognize the potential side effects from treatment with testosterone and how to monitor during treatment.
How To Vote via Texting

What is your favorite color?

- Text a **CODE** to **# # # # # #**
- Tweet @poll and a **CODE**
- Submit responses at PollEv.com/username

<table>
<thead>
<tr>
<th>Color</th>
<th>Code</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue</td>
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<td></td>
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<tr>
<td>Green</td>
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<tr>
<td>Yellow</td>
<td>176646</td>
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</tbody>
</table>

**TIPS**
1. Standard texting rates only (worst case US $0.20)
2. We have no access to your phone number
3. Capitalization doesn’t matter, but spaces and spelling do
Your poll will show here

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Early Animal Experiments

Arnold Berthold, 1849
“A radical change took place in me. I fully regained my old powers. My limbs showed a decided gain of strength. With regard to the facility of intellectual labor, a return to my previous ordinary condition became quite manifest.”

Dr. Brown-Sequard, 1878
Synthesis of Testosterone
Nobel Prize, Chemistry, 1939

Adolf Butenandt (Germany)

Leopold Ruzicka (Switzerland)

“Until recently, very little was known about the sex hormones.”
The Benefits of Optimal Testosterone

- Sharper Mind
- Confident
- Happy
- Increased Muscle Mass
- Healthy Heart
- Strong Erections & Healthy Libido
- Strong Bones
- Plenty of Energy
- Increased Fat Tissue
- Increased Risk of ED & Low Libido
- Increased Risk of Alzheimer's Disease
- Increased Risk of Osteoporosis

Man with Optimal Testosterone

Man with Deficient Testosterone
Increased Demand for Testosterone

Gel Segment Growth ($)
Dec 2011 L12M: 25.3%
Case #1

- Chief Complaint: Erectile dysfunction
- HPI: 24 year old tall male law student with no past medical history, presents to you for concerns about development of erectile dysfunction.
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Case #1: History

- Normal energy
- Normal libido
- No recent HAs or vision changes, history of testicular masses, symptoms of hyperthyroidism
- Normal puberty development
- No history of anemia, GU infections or STDs, corrective testicular surgeries
- No history of excessive alcohol consumption or illicit drug use
- Taller than the rest of his family
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Case #1: Physical Exam

- 6’2” with a 6’5” wingspan
- BMI 23.2
- Thin with minimal muscle growth
- Slightly high-pitched voice
- Normal visual fields and acuity
- Scant beard growth
- No gynecomastia
- Cranial nerves intact, but unable to smell strong odors
- Dense pubic hair in a diamond-shaped pattern, bilaterally descended testis of slightly small size (10-15 mL in volume) without masses
Case #1: Differential Diagnosis

- Hypogonadism!!
"… a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis."

- Endocrine Society Clinical Practice Guidelines.

Massachusetts Male Aging Study

Measured testosterone levels in three consecutive decades

Adjusted for chronic illness, general health, medications, smoking, BMI, employment, and marital status

# Baltimore Longitudinal Study of Aging

<table>
<thead>
<tr>
<th>Age</th>
<th>Low T</th>
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</thead>
<tbody>
<tr>
<td>21-45</td>
<td>2.5%</td>
</tr>
<tr>
<td>50’s</td>
<td>12%</td>
</tr>
<tr>
<td>60’s</td>
<td>19%</td>
</tr>
<tr>
<td>70’s</td>
<td>28%</td>
</tr>
<tr>
<td>80’s</td>
<td>48%</td>
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**Cutoffs:** total testosterone <325 ng/dL

![Graph showing percentage of Low T by age](chart.png)
Who should be tested?

- No routine screening in the general population.
- In patients with “specific” clinical manifestations.
- When patients report the “less specific” symptoms and signs.
- Consider “case detection” with certain clinical disorders.
### More Specific Symptoms
- Incomplete or delayed sexual development, eunuchoidism
- ↓ sexual desire (libido) & activity
- ↓ spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially <5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

### Less Specific Symptoms
- ↓ energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- ↓ muscle bulk and strength
- ↑ body fat, body mass index
- ↓ physical or work performance
Consider “case detection” with certain clinical disorders

- Pituitary disease
- Glucocorticoids and opioids use
- HIV-associated weight loss
- End-stage renal disease
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low trauma fracture
- Type 2 diabetes mellitus
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Potential Benefits of Testosterone Replacement

- Cardiovascular profile
- Bone density
- Body composition
- Sexual function
- Muscle strength and mass
- Fat distribution
- Facial and body hair
- Red blood cell production
- Fertility
- Quality of life
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Diagnosis of Androgen Deficiency

Signs and/or Symptoms
Diagnosis of Androgen Deficiency

Signs and/or Symptoms

Morning total testosterone

Use of “reliable assay”
Avoid testing during concurrent illness
Consider free testosterone measurement in certain circumstances
Testosterone evaluation must be done in the morning.
Serum Testosterone is Affected by Protein Binding

- Albumin-bound T: 38%
- SHBG-bound T: 60%
- Free T: 2%

T = testosterone
Only 2% is free testosterone and 98% is bound

Appleton and Lange; 1997: 403-433.
Case #1: Evaluation

- Labs
  - 8am total testosterone: 77 ng/dL (reference 280-800)
Diagnosis of Androgen Deficiency

- Signs and/or Symptoms
- Morning total testosterone
- Confirm testing

Use of “reliable assay”
Avoid testing during concurrent illness
Consider free testosterone measurement in certain circumstances
Case #1: Evaluation

- Labs
  - 8am total testosterone: 77 ng/dL (reference 280-800)
  - Repeat 8am total testosterone: 84 ng/dL
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Further Evaluation of Low Testosterone

Low/Normal LH, FSH
- Pituitary function
- Evaluation of etiology
- Pituitary MRI

Elevated LH, FSH
- Evaluation of etiology
- Testicular imaging
Case #1: Evaluation

- 8am total testosterone: 77 ng/dL (reference 280-800)
- Repeat 8am total testosterone: 84 ng/dL

Next Step…

- Primary versus secondary:
  - FSH 3.9 (reference 2-12 mIU/mL)
  - LH 2.7 (reference 2-10 mIU/mL)
- What is this called?
  - Hypogonadotropin Hypogonadism
Differential Diagnosis:

- Failure of GnRH stimulation
- Pituitary lesion (adenoma, craniopharyngioma, empty sella, metastases, lymphocytic hypophysitis, infiltration)
- Drugs (exogenous testosterone use, steroids, opiates)
- Hyperprolactinemia
- Chronic or acute illness
- Obesity, DM2
- Prior trauma, radiation exposure
- Alcohol or marijuana use
8am total testosterone: 77 ng/dL (reference 280-800)

Repeat 8am total testosterone: 84 ng/dL

Primary versus secondary:
- FSH 3.9 (reference 2-12 mIU/mL)
- LH 2.7 (reference 2-10 mIU/mL)

What is this called?
- Hypogonadotropic Hypogonadism

Evaluation of etiology:
Case #1: Evaluation

- Corpus callosum
- Ventricle
- Optic nerve
- Brainstem:
  - Midbrain
  - Pons
  - Medulla oblongata
- Spinal cord
- Frontal lobe
- Parietal lobe
- Occipital lobe
- Pituitary stalk
- Pituitary gland
- Nasal cavity
- Air in sphenoid sinus
- Cerebellum
Case #1: Evaluation

- 8am total testosterone: 77 ng/dL (reference 280-800)
- Repeat 8am total testosterone: 84 ng/dL
- Primary versus secondary:
  - FSH 3.9 (reference 2-12 mIU/mL)
  - LH 2.7 (reference 2-10 mIU/mL)
- Evaluation of etiology:
  - MRI normal
  - TSH, FT4, ACTH, am cortisol, prolactin, IGF-1 all normal
  - CBC, iron, TIBC, ferritin all normal
Hypogonadotrophic hypogonadism secondary to Kallmann syndrome

- Congenital gonadotropin-releasing hormone (GnRH) deficiency
- Can be inherited as an autosomal dominant, autosomal recessive, or X-linked condition
- Management depends on fertility