Testosterone Treatment: Myths Vs Reality

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Endogenous Testosterone is an important hormone in the Male Body

- Plays a key role in the development of male reproductive tissues, particularly the penis and the prostate
- Responsible for the development of secondary male sexual characteristics:
  - Male hair distribution
  - Muscle mass
- Also plays a key role in carbohydrate, fat, and protein metabolism

Testosterone is essential to the musculoskeletal and metabolic systems throughout a man’s body, including:

- Basal metabolic rate
- Secondary sexual characteristics
- Body hair distribution
- Muscle growth
- Electrolyte and water balance
- Protein formation
- Bone growth and strength

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Regulation of Testes Function in the Adult Male

The hypothalamic pituitary gonadal (HPG) axis regulates the production of testosterone.

The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which in turn stimulates the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

LH stimulates the interstitial testicular Leydig cells to produce testosterone.

Negative feedback loop: Increasing amounts of testosterone inhibit GnRH secretion from the hypothalamus in a negative feedback loop. Decreased GnRH in turn results in decreased FSH and LH production, leading to decreased testosterone and sperm production.

FSH stimulates Sertoli cell function and spermatogenesis.

Testosterone: In the healthy male, approximately 6 bursts of testosterone secretion occur daily following a circadian rhythm that delivers an early morning high and an early evening low.

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Primary hypogonadism is defined as low testosterone in which there is testicular dysfunction/defect and can be caused by certain medical conditions (e.g., cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchietomy, Klinefelter’s syndrome, chemotherapy, or toxic damage from alcohol or heavy metals).
Secondary hypogonadism is defined as low testosterone in which there is pituitary or hypothalamic dysfunction/defect and can be caused by certain medical conditions (e.g., gonadotropin or luteinizing hormone-releasing (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation, or Kallmann syndrome).
The Endocrine Society guidelines to diagnose hypogonadism

1. **History and physical**

2. **Morning total testosterone**

3. **Normal total testosterone**

   - **Follow-up**

   - **Normal testosterone, LH+FSH**

   - **Confirmed Low Testosterone** (Low Testosterone, or free or bioavailable testosterone)

   - **Low Testosterone, low or normal LH+FSH** (secondary hypogonadism)

   - **Low Testosterone, high LH+FSH** (primary hypogonadism)

   - **Prolactin, iron, other pituitary hormones, MRI (under certain circumstances)**

   - **Karyotype (Klinefelter syndrome)**

   - **Exclude reversible illness, drugs, nutritional deficiency**

   - **Repeat testosterone (use free or bioavailable testosterone if suspect altered SHBG)**

   - **For lab results equaling Low Testosterone**

Identifying Possible Signs and Symptoms of Male Hypogonadism

More specific signs and symptoms

• Incomplete or delayed sexual development
• Reduced sexual desire (libido) and activity
• Decreased spontaneous erections
• Breast discomfort, gynecomastia
• Loss of body (axillary and pubic) hair, reduced shaving
• Very small or shrinking testes
• Height loss, low trauma fracture, low bone mineral density
• Hot flushes, sweats
Identifying Possible Signs and Symptoms of Male Hypogonadism

Less specific signs and symptoms

• Decreased energy, motivation, initiative, and self-confidence
• Feeling sad or blue, depressed mood
• Poor concentration and memory
• Sleep disturbance, increased sleepiness
• Mild anemia (normochromic, normocytic, in the female range)
• Reduced muscle bulk and strength
• Increased body fat, body mass index
The Diagnosis of Adult Male Hypogonadism Requires an **Etiology and Two Tests of Morning Total Testosterone**

- **Check**
  - Review the medical history in men with consistent signs and symptoms, and identify a specific etiology of primary or secondary hypogonadism

- **Test**
  - Perform a *morning* total testosterone test using a reliable assay

- **Exclude**
  - If testosterone levels are low, exclude reversible illness, drugs, and nutritional deficiency. Evaluation for testosterone deficiency should not be made during acute or subacute illness

- **Re-test**
  - Confirm hypogonadism with a second morning serum total testosterone test and an LH+FSH test and perform Semen fluid analysis if there is a fertility issue

- **Diagnose**
  - **Primary hypogonadism**: low testosterone level, high LH+FSH
  - **Secondary hypogonadism**: low testosterone level, low or normal LH+FSH
Tests Used in the Diagnosis of Hypogonadism

The *Endocrine Society* Guidelines recommend morning total testosterone as the initial diagnostic test for low testosterone

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Testosterone (TT)</td>
<td>Measures the total circulating level of both free testosterone and bound forms of testosterone, specifically albumin-bound testosterone and sex hormone-binding globulin (SHBG)-bound testosterone</td>
</tr>
</tbody>
</table>

Unbound testosterone (also known as free testosterone) ~2%

Testosterone that is bound to albumin ~38%

Testosterone that is bound to sex hormone-binding globulin (SHBG) ~60%
### Tests Used to Confirm Differential Diagnosis

#### Additional Diagnostic Tests

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free Testosterone (FT)</strong>*</td>
<td>Amount of biologically active testosterone circulating unbound. Testosterone is present in the circulation, both in protein-bound and in nonprotein-bound (&quot;free&quot; or unbound) forms.</td>
</tr>
<tr>
<td><strong>Calculated Free Testosterone (cFT)</strong></td>
<td>Widely used method for accurately assessing free testosterone concentrations using one of a number of clinically validated formulas and measurements of SHBG, albumin, and total testosterone concentrations. Useful in clinical situations where SHBG concentrations may be low or high, including obesity, diabetes, and age older than 65 years</td>
</tr>
<tr>
<td><strong>Bioavailable Testosterone (BAT)</strong></td>
<td>Albumin-bound testosterone (weaker bond than SHBG) and free testosterone. BAT represents the fraction of circulating testosterone that readily enters cells and is believed to better reflect the bioactivity of testosterone than does the simple measurement of serum total testosterone</td>
</tr>
</tbody>
</table>
# Tests Used to Confirm Differential Diagnosis

## Additional Tests: May Be Part of Confirmatory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Luteinizing Hormone (LH)</strong></td>
<td>LH is produced by the pituitary gland and controls Leydig cell secretion of testosterone</td>
</tr>
<tr>
<td><strong>Follicle-Stimulating Hormone (FSH)</strong></td>
<td>FSH stimulates seminiferous tubule and testicular growth and is involved in the early stages of spermatogenesis</td>
</tr>
<tr>
<td><strong>Sex Hormone-Binding Globulin (SHBG)</strong></td>
<td>Circulates in the serum and binds both male and female hormones with high affinity. In men, SHBG binds to circulating testosterone and dihydrotestosterone</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Albumin weakly binds testosterone and has little effect on the free testosterone concentration when albumin concentrations are in the normal range. Used in the calculation of cFT</td>
</tr>
<tr>
<td><strong>Prolactin</strong></td>
<td>Hyperprolactinemia inhibits gonadotropin secretion and can produce hypogonadism in men with low or inappropriately “low normal” LH and FSH levels</td>
</tr>
</tbody>
</table>
The Endocrine Society guidelines to diagnose hypogonadism

1. **History and physical**
2. **Morning total testosterone**
   - For lab results equaling Low Testosterone
     - Exclude reversible illness, drugs, nutritional deficiency
     - Repeat testosterone (use free or bioavailable testosterone if suspect altered SHBG)
3. **Confirmed Low Testosterone**
   - Low Testosterone, low or normal LH+FSH (secondary hypogonadism)
     - Prolactin, iron, other pituitary hormones, MRI (under certain circumstances)
   - Low Testosterone, high LH+FSH (primary hypogonadism)
     - Karyotype (Klinefelter syndrome)
4. **Normal total testosterone**
5. **Follow-up**
6. **Normal testosterone, LH+FSH**

**References**

Causes of primary hypogonadism in males

Congenital abnormalities

- Klinefelter syndrome
- Cryptorchidism
- Varicocele
- Other chromosomal abnormalities

Acquired diseases

- Infections, esp mumps
- Radiation
- Medicines: glucocorticoids, ketoconazole, chemical toxins
- Trauma
- Testicular torsion
- Chronic diseases: Hepatic cirrhosis, AIDS, Chronic renal failure
## Delivery Options and Regimens

<table>
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<th>Delivery Method</th>
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<tr>
<td>Buccal tablet</td>
<td>Controlled-release, bioadhesive tablets 2 times daily</td>
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<tr>
<td>Topical gel</td>
<td>Available in sachets, tubes, and pumps applied topically 1 time daily, as directed</td>
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<tr>
<td>Topical solution</td>
<td>Applied topically 1 time daily via pump with applicator</td>
</tr>
</tbody>
</table>
| Intramuscular injections (product dependent) | IM every 1 to 2 weeks (or even every 3 or 4 weeks.)  
IM every 10 weeks                   |
| Testosterone patch                  | 1 or 2 patches, applied 1 time daily on nonpressure areas               |
| Subcutaneous pellets                | Implanted SC; dose and regimen vary with formulation                   |
| Nasal gel                           | Applied intranasally to both nostrils 3 times daily                     |
Testosterone Replacement Therapy Monitoring

Regularly monitor patients on TRT

At every visit, monitor:
- Symptom response
- Adverse events
- Formulation-specific adverse events

Endocrine Society Guidelines for TRT monitoring

<table>
<thead>
<tr>
<th>TRT monitoring</th>
<th>Baseline</th>
<th>Each visit</th>
<th>3–6 months</th>
<th>Annually</th>
<th>1–2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom response</td>
<td></td>
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<tr>
<td>Adverse events</td>
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<td>Formulation specific adverse events</td>
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<tr>
<td>Testosterone levels</td>
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<tr>
<td>Hematocrit</td>
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<tr>
<td>BMD of lumber spine/femoral neck</td>
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<tr>
<td>DRE</td>
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<td>PSA</td>
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Testosterone Replacement Therapy (TRT) May Not Be Appropriate For All Patients

**Not Appropriate**

TRT is NOT recommended for patients with:

- Metastatic prostate cancer
- Breast cancer
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS >19
- Venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) risk
- Risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death
- Those desiring fertility
- Uncontrolled or poorly controlled congestive heart failure
- Untreated severe obstructive sleep apnea
- PSA >4 ng/mL (>3 ng/mL in men at high risk for prostate cancer, such as African Americans or men who have first-degree relatives with prostate cancer)
- Unevaluated prostate nodule or induration
- Hematocrit >50%
Testosterone Replacement Therapy (TRT) May Not Be Appropriate For All Patients

Appropriate

TRT is recommended for patients with low testosterone due to an associated condition:

• Evaluate patients for specific and nonspecific symptoms and signs of androgen deficiency to identify the possible etiology
• Before initiating therapy, confirm hypogonadism with 2 morning serum total testosterone tests due to an associated condition and an LF+FSH test; add Semen fluid analysis test if fertility issue
• Conduct a free or bioavailable testosterone test if altered SHBG is suspected (as in untreated thyroid disease.)
• Confirm the etiology. Then initiate TRT only in patients with unequivocally low serum testosterone levels (<300 ng/dL)

Two cases: Myths vs Reality

- Joe is a 79 year old man. Healthy. He is on HCTZ for HTN. He walks 2 miles every day. He is socially active. He complains to you of low libido. His TT in AM was 375. His second TT in AM is 364.

- Exam is normal.

- Is the need to treat him with T a myth or a reality?

- What if his TT level when he was 39 y/o was 495?
Two cases: Myths vs Reality

- Joe is a 45 y/o man with a history of type 2 diabetes for 7 years. His diabetes is controlled with metformin. His weight is 289 pounds. He is also on Lipitor, Lisinopril, and ASA. He takes Vicodin twice a day for back pain.

- He C/O of low libido, fatigue, and depression

- Genital Exam is normal (WNL or NAD whatever your pick is!)

- His TT in AM was 259. His TT again came 243.

- Is treating him with T a myth or a reality?

- What if he has also a h/o CABG?

- What if he was 83 y/o with above history (but without CAD)?

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**Summary: Diagnosis and Management of Hypogonadal Patients**

**Diagnosis of hypogonadism: test and re-test**
- Identify possible signs and symptoms of male hypogonadism
- Remember that the diagnosis of hypogonadism in men requires two tests of morning total testosterone
- Be sure to follow the Endocrine Society Guidelines to diagnose hypogonadism

**Treatment of hypogonadism:**
- Understand testosterone replacement therapy options and guidelines for monitoring
- Identify which patients are appropriate and which patients are not appropriate for treatment

**Patient follow-up:**
- Schedule follow-up visits
- Monitor patient response to treatment
- Consider all therapeutic options
And Finally.....

The **Myth** is to treat any man with symptoms suggestive of hypogonadism with testosterone without confirming he is hypogonad,

and the **Reality** is to treat such a man only after you confirm he is hypogonad by a blood test and by identifying an etiology for his hypogonadism.