Testosterone replacement improves sexual function

p<0.001 at all time points versus baseline

Chief Complaint: Erectile dysfunction
HPI: 63 year old male lawyer presents to you for concerns about development of erectile dysfunction and decreased libido.
He also has diabetes, hypertension, obstructive sleep apnea, and normocytic anemia for many years.
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Case #2: History

- Further clinical 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
  - Same height as rest of family
  - Has noticed increasing hot flushes over the last year
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Case #2: Physical Exam

- 5’11” with a 6’ wingspan
- BMI 27.3
- Normal appearing male with normal muscle growth
- Normal-pitched voice
- Normal visual fields and acuity
- No gynecomastia
- Cranial nerves intact, able to smell strong odors
- Dense pubic hair in a diamond-shaped pattern, bilaterally descended testis of slightly small size (15 mL in volume) without masses but **firm**
Case #2: Differential Diagnosis

- Normal male aging?
- Hypogonadism!!
Endocrine Society Practice Guidelines

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
Diagnosis of Androgen Deficiency

1. Signs and/or Symptoms
2. Morning total testosterone
3. Confirm testing
Case #2: Evaluation

- Labs
  - 8am total testosterone: 177 ng/dL (reference 280-800)
  - Repeat 8am total testosterone: 184 ng/dL
Further Evaluation of Low Testosterone

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

Elevated LH, FSH
- Evaluation of etiology
Case #2: Evaluation

- 8am total testosterone: 177 ng/dL (reference 280-800)
- Repeat 8am total testosterone: 184 ng/dL

Next Step…

- Primary versus secondary:
  - FSH 23.9 (reference 2-12 mIU/mL)
  - LH 32.7 (reference 2-10 mIU/mL)
- What is this called?
  - Hypergonadotrophic Hypogonadism
Hypergonadotrophic Hypogonadism

- Klinefelter's Syndrome
- Cryptorchidism, surgical castration, anorchidism
- Infections (???)
- Radiation exposure
- Drugs (chemotherapy, ketoconazole, steroids)
- Autoimmunity
- Chronic illness (CRI, cirrhosis, HIV)
Case #2: Evaluation

- 8am total testosterone: 77 ng/dL (reference 280-800)
- Repeat 8am total testosterone: 84 ng/dL
- Primary versus secondary:
  - FSH 23.9 (reference 2-12 mIU/mL)
  - LH 32.7 (reference 2-10 mIU/mL)
- What is this called?
  - Hypergonadotrophic Hypogonadism
- Evaluation of etiology:
  - Mumps infection as a child
  - BMD showed osteoporosis
Is low testosterone associated with cardiovascular risk factors and cardiovascular disease and mortality?
Low Testosterone and the Metabolic Syndrome

Androgen Deficiency

Hyperglycemia

Hypertension

Insulin Resistance

Dyslipidemia
# Low Testosterone is Associated with the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypogonadal patients (n = 836)</th>
<th>Eugonadal patients (n = 1326)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>547 (65.4)</td>
<td>678 (51.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>506 (60.5)</td>
<td>670 (50.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>258 (30.9)</td>
<td>237 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>270 (32.3)</td>
<td>225 (17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prostatic disease/disorder</td>
<td>165 (19.7)</td>
<td>226 (17.0)</td>
<td>0.121</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>155 (18.5)</td>
<td>211 (16.0)</td>
<td>0.113</td>
</tr>
<tr>
<td>Insomnia/sleep disturbance</td>
<td>129 (15.4)</td>
<td>185 (14.0)</td>
<td>0.342</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>102 (12.2)</td>
<td>118 (8.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Headaches (within the last 2 weeks)</td>
<td>70 (8.4)</td>
<td>125 (9.4)</td>
<td>0.405</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>28 (3.3)</td>
<td>29 (2.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>15 (1.8)</td>
<td>15 (1.1)</td>
<td>0.199</td>
</tr>
<tr>
<td>Not reported</td>
<td>0 (0.0)</td>
<td>4 (0.3)</td>
<td>nr</td>
</tr>
</tbody>
</table>

Low Testosterone Contributes to Metabolic Syndrome

- Metabolic Syndrome
- Abdominal Obesity
- Fasting Hyperglycemia
- Hypertriglyceridemia

Low testosterone is associated with low mortality.
Is low testosterone associated with low bone mineral density, high fat mass, and low muscle mass?

Would treatment with testosterone replacement improve these issues?
Testosterone Therapy Improves Bone Density

![Graph showing the effect of testosterone treatment on bone density](image)

Testosterone improves lean body mass and total fat mass

* p<0.01 change from baseline

- **Lean Body Mass**
  - 6 months
  - 12 months

- **Fat Mass**
  - 6 months
  - 12 months

Mean change from baseline (kg)
Case #3

- Chief Complaint: Erectile dysfunction
- HPI: 63 year old male lawyer presents to you for concerns about development of erectile dysfunction and decreased libido.
- He also has diabetes, hypertension, obstructive sleep apnea, BPH, and obesity.
Is Low T making you feel like a shadow of your former self?

Low testosterone or Low T, can cause a medical condition called hypogonadism (hih-poh-goh-nahd-izm). It's estimated to affect millions of men in the U.S. Your doctor can tell if you have hypogonadism by giving you a medical exam to assess your signs and symptoms, then by performing certain blood tests.
He also complains of:
- Decreased energy, motivation, initiative, and self-confidence
- Recent depressed mood
- Poor concentration and memory
- Increased sleepiness
- Lack of ability to build muscle bulk and strength at the gym
- Poor work performance
What are you looking for on physical exam?

- 5’11” with a 6’ wingspan
- BMI 34.1
- Normal-pitched voice
- Normal visual fields and acuity
- Mild gynecomastia
- Cranial nerves intact, able to smell strong odors
- Dense pubic hair in a diamond-shaped pattern, bilaterally descended testis of normal size (20-25 mL in volume) without masses
Case #3: Differential Diagnosis

- Hypogonadism?
- Obesity, insulin resistance?
- Normal male aging?
Case #2: Evaluation

- 8am total testosterone: 277 ng/dL (reference 280-800)

- Repeat testing
  - 8am total testosterone: 264 ng/dL
  - SHBG: 24 (13-71 nmol/L)
  - Calculated free testosterone: 206 pmol/L (230-610 pmol/L)
There is a normal age-related decline in testosterone.
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Potential adverse effects of therapy

- Erythrocytosis
- Acne, oily skin
- Breast tenderness, gynecomastia
- Leg edema and worsening heart failure
- Induction or worsening of sleep apnea
- Male-pattern balding
- Reduced sperm production and infertility
- Detection of subclinical prostate cancer
- Growth of metastatic prostate cancer
- Growth of breast cancer
- Modest decrease in HDL in older men
- Cardiovascular endpoints and mortality??
Testosterone and Prostate Cancer

- Testosterone therapy may cause growth of and is contraindicated with metastatic prostate cancer.
- It is associated with higher PSA levels and rates of prostate biopsy.
- There is no evidence of de novo prostate cancer.
Adverse Events Associated with Testosterone Administration

## Cardiovascular Events

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome and chest pain</td>
<td>Syncope resulting in hospitalization</td>
</tr>
<tr>
<td>Angioplasty and coronary-artery bypass grafting</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Atrial fibrillation with RVR, SOB, CHF which necessitated hospitalization</td>
<td>Elevated blood pressure</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Arrhythmia–ectopy noted on ECG before exercise testing</td>
</tr>
<tr>
<td>Congestive heart failure exacerbated</td>
<td>Elevated blood pressure</td>
</tr>
<tr>
<td>Death, suspected myocardial infarction</td>
<td>Carotid bruit and carotid-artery plaque identified on ultrasound</td>
</tr>
<tr>
<td>Ectopy on ECG (premature ventricular contractions, couplets)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
</tbody>
</table>
Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O’Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

IMPORTANCE Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

OBJECTIVES To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.

DESIGN, SETTING, AND PATIENTS A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.
Survival Outcomes

VA CATH STUDY

- No testosterone therapy
- Testosterone therapy

Survival, %

HR, 1.29 (95% CI, 1.04-1.58)
Log-rank P = .02

Days
Study Analyses Limitations

- Small observational studies
- Details of blood work unknown (time of day, quality of assay)
- High cardiovascular risk factors
- High doses of testosterone
- No monitoring while on treatment
- Testosterone levels often drawn during acute illness
- Intervention group included anyone who had ever filled just one prescription
- Study was powered for mobility and strength and NOT for CV outcomes (TOM Trial)
- Brief follow-up (only 1 year)
So who should be treated?

- “…symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density.”
Contraindications for Testosterone Therapy

- Prostate cancer or concerning prostate issues
  - Severe lower urinary tract symptoms
  - Unevaluated prostate nodule
  - Elevated PSA
- Breast cancer
- Erythrocytosis
- Unstable CHF or CAD
- Untreated obstructive sleep apnea
- Those desiring fertility
- Those not clearly hypogonadal!!
Testosterone Treatment Options

- **Recommended:**
  - Intramuscular testosterone injections every 1-4 weeks
  - Testosterone patches applied nightly
  - Testosterone gel applied daily

- **Not recommended**
  - Buccal testosterone tablet every 12 hours
  - Testosterone pellets implanted subcutaneously every 3 to 6 months
Serum Concentration with Injection versus Topical

![Graph showing serum concentration over time for patch or gel versus injection.](Figure 1. Testosterone levels after replacement with gel, patch, or injection.)