Testosterone: Current Opinion and Controversy

Ravi Kacker, MD

Metrowest Urology
(508) 655 4422
Medical Office Building at Leonard Morse Hospital
Disclosures

• MHB Labs – President and CEO of Drug Development Start-up
• Veru Healthcare – Drug Development consulting
My Experience With Testosterone

- Andrology Fellowship BIDMC – 2014
- Research and Clinical Focus: Testosterone and Metabolism
- Examination papers alleging increased cardiovascular risk
- FDA Opinion and Advisory Committee
- SMSNA Expert Colloquium and White Paper on Adult Onset Hypogonadism
- AUA Crossfires Deabate

The New York Times

Overselling Testosterone, Dangerously

Testosterone therapy linked to higher heart risk
Is Hypogonadism a Real Medical Condition?

What Causes it?

Who Should Be Treated?
Consistent syndrome despite age, type of hypogonadism, clinical setting.

Syndrome can be created by reducing T and is reversed by naturally or pharmacologically increasing T

### TABLE 1. Clinical Signs, Symptoms, and Conditions Consistent With Adult-Onset Hypogonadism and Low Testosterone Levels

<table>
<thead>
<tr>
<th>Most specific signs/symptoms</th>
<th>More general signs/symptoms</th>
<th>Conditions commonly associated with low testosterone level and adult-onset hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced sexual desire &amp; activity</td>
<td>Decreased energy, motivation, initiative</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>Delayed ejaculation</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Reduced muscle bulk &amp; strength</td>
<td>Chronic obstructive lung disease, obstructive sleep apnea syndrome</td>
</tr>
<tr>
<td>Hot flushes/sweats</td>
<td>Diminished physical or work performance</td>
<td>End-stage renal disease, hemodialysis</td>
</tr>
<tr>
<td>Decreased testicle size</td>
<td>Mild anemia (normocytic, normochromic)</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Loss of pubic hair, reduced shaving requirement</td>
<td>Depressed mood, irritability</td>
<td>Human immunodeficiency virus—associated weight loss</td>
</tr>
<tr>
<td>Increased body mass index, visceral obesity</td>
<td>Poor concentration &amp; memory</td>
<td>History of infertility, cryptorchidism, pituitary disease, delayed puberty</td>
</tr>
<tr>
<td>Height loss, low trauma fractures, reduced bone mineral density</td>
<td>Sleep disturbances, sleepiness</td>
<td>Treatment with opioids or glucocorticoids</td>
</tr>
</tbody>
</table>

Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016
• Primary Hypogonadism (testicular failure)
  • Low Testosterone despite high gonadotropins
  • Testicular hypofunction, atrophy or loss

• Secondary Hypogonadism (hypogonadotrophic hypogonadism)
  • Low or normal gonadotropins with low T levels
  • Several conditions

Kacker, Journal of Sexual Medicine, 2012
Population based study of community dwelling men:
Prevalence of (biochemical hypogonadism) is 13.8%
Most hypogonadism is secondary (11.8% vs 2.0% primary)
Age and Hypogonadism

• Both primary and compensated hypogonadism increase with age.

• Why do some men compensate for testicular hypofunction failure and why do others not?

• Secondary hypogonadism does not increase with age

Something is suppressing gonadotropins and testosterone for MOST men with hypogonadism
## Potential Drivers of Secondary Hypogonadism

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Drugs/Medications</th>
<th>Behaviors/Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Steroids</td>
<td>Sleep Disturbances</td>
</tr>
<tr>
<td>OSA</td>
<td>Opioids</td>
<td>Stress</td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td>Spironolactone</td>
<td>Long Commutes</td>
</tr>
<tr>
<td>DMII</td>
<td>Drugs that elevate SHBG (Insulin, Antipsychotics)</td>
<td>Smoking</td>
</tr>
<tr>
<td>HTN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complex Picture:
- Not every correlation with low testosterone is actually a cause
- Some effects are clearly reversible (e.g. removal of offending medication)
- **Obesity, stressful lifestyle, and sleep disturbances** are very common among men presenting with low testosterone

Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016
The “Rat Race”: Stress and Hypogonadism

- 990 men to sexual medicine clinic in Massachusetts
- Men under age 60 were most likely to have hypogonadism
- “These men did not have overt clinical depression but typically were men who worked more than 50 or 60 h a week, often at more than one job. Their jobs often involved traveling great distances and/or long commutes, along with meeting deadlines or quotas.”

Traish, International Journal of Impotence Research, 2010
Sleep and Hypogonadism

- Widespread recognition of “epidemic” of sleep deprivation – books, start-ups, apps
- Blamed for fatigue, fogginess, lack of libido/sexual dysfunction, weight gain… very similar to Low T
- Association between shift work, sleep deprivation, OSA and low testosterone
• Sleep duration during shift-work associated with T and BioT
• Decreased LH and T levels in men with OSA compared to healthy controls
• Men with non-standard have higher ADAM scores vs. men with shift work (Pastuzak, Urology, 2017)

531 Singaporean Chinese men age 29-72
Goh, J Androl, 2010

Treatment can be difficult:
- Inconsistent results on T levels with treatment of OSA
- Focus on “sleep hygiene”
- Emerging field of tech, medical device, sleep science
Testosterone Deficiency Can Be Reversible

- Longitudinal Data from EMAS: 2736 men age 40-79
- Weight loss increased T and LH but this only occurred in 22/2736 = 0.8%
- Improvement also seen in response to bariatric surgery (Corona, JCEM, 2013)
• When T is withdrawn, insulin resistance is detectable in serum within 48 hours (Pitteloud, Diabetes Care, 2005)

• Level 1b evidence – T therapy improves insulin sensitivity (Huefelder, J Androl, 2009)

• Long term effects of T therapy on IR and obesity continue for years (Traish, J Cardiovascular Cardiology Therapeutics, 2017)
Behavioral changes can sometimes reverse vicious cycle and achieve recovery “naturally” – but this is relatively rare.

Testosterone therapy can be a tool to reverse metabolic dysfunction

My Opinion: Try to encourage behavioral changes, but recognize that most fail. Consider treatment in those patients with severe metabolic dysfunction.
When Should Hypogonadism Be Treated?
Biochemical Evaluation of Hypogonadism

- Remains controversial
- Total T cut-offs include 250, 300, 350 ng/dL (Morgentaler, Mayo, Clinic Proc, 2016)
- SHBG and Free T complicate picture
- Polymorphisms in AR responsiveness exist in population (Zitzman, Nat Clin Pract Urol, 2007)
- Some men with low total T levels may not actually be deficient of T
- Some men with normal total T levels may still be T deficient!

TABLE 2. Conditions in Which Serum T Level Measurement Is Suggested

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Osteoporosis, low trauma fracture</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Glucocorticoids, ketoconazole, opioid or other medications that affect T metabolism or production</td>
</tr>
<tr>
<td>Moderate to severe chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Sellar mass, radiation to the sellar region, or other diseases of the sellar region</td>
</tr>
<tr>
<td>End-stage renal disease, maintenance hemodialysis</td>
</tr>
<tr>
<td>Human immunodeficiency virus—associated weight loss</td>
</tr>
</tbody>
</table>

Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016

My Opinion/Practice: Diagnosis should be on the basis of some biochemical evidence of deficiency combined with several signs and symptoms of T deficiency. It may be reasonable to offer treatment to select men with normal total T. Not everyone with low total T needs treatment!
Benefits of Treatment

Time to see benefits may be long and require appropriate dosage. Some studies show only modest benefits (notably T–trial). Benefits from topical therapy lag behind injectable therapy.

Longer-term studies support assertion that T therapy leads to:
• Increases in muscle mass/strength
• Improvement in bone density
• Improvements in libido/sexual satisfaction
• Improvements in erectile dysfunction
• Improvement in abdominal weight, insulin sensitivity
• Observational studies: nearly 50% reduction in all cause mortality

Review of benefits of treatment:
Morgentaler, Mayo Clin Pro, 2016
Risks of Treatment

• Polycythemia/erythrocytosis
  • Hepcidin underlies effect
  • Patients on injectable T may be at greater risk (unpublished data)
  • Some patients may need periodic phlebotomy to keep HCT<54

• Suppression of endogenous production => infertility

• Acne/Oily Skin

• Breast Symptoms/Gynecomastia

Concerns about: abuse/dependence

Rhoden, NEJM, 2004
### Cardiovascular Disease

- Vast majority of papers on T and CV risk support safety and benefit of T
- A few recent high-profile papers have raised concern around risk:
  - Statistical errors
  - Use of questionable statistical endpoints
- Concern persists around signals of unclear clinical significance: non-calcified plaque, palpitations, diastolic BP (none consistent)
- Absence of widespread problems despite concerns and medicolegal focus

### My Opinion/Practice:
- Cardiometabolic benefits appears to significantly outweigh risk
- Important to monitor hematocrit

### Prostate Cancer

- Historical concern – lowering T still main treatment of metastatic prostate cancer!
- Rise of T levels above “saturation point” do not appear to encourage prostate cancer.
- Higher testosterone levels not associated with increased prostate cancer risk.
- Lack of harm in patients after prostatectomy, radiation therapy
- T given to men on active surveillance for prostate cancer – no pathologic progression on serial biopsies.

### My Opinion/Practice:
- Will offer T to symptomatic men who have had definitive treatment for PCa or low risk disease
- Experimental for PCa in metastatic disease (under consent or IRB)
- Appropriate to consider in palliative cases

Warnings on potential cardiovascular and prostate risk persist on FDA label for all T products
Key References for CV and PCa Risk of T therapy


• Miner, et al. The state of testosterone therapy since the FDA’s 2105 labeling changes: indications and cardiovascular risk. Clin Endocrinology, 2018
Treatment with Testosterone

- **Topical Treatments:**
  - Patches
  - Gels

- **Injectable Testosterone**
  - Testosterone cypionate
  - Testosterone undecanoate

- **Implants:** Testosterone pellets

- Increasing complexity of insurance approvals.

- Self-injection with generic testosterone cypionate is least expensive and highly effective.
Treatment of Secondary Hypogonadism

- Goal – increase testicular production by stimulating or administering gonadotropins
- Useful for patients who wish to maintain fertility, testicular function, or where there are concerns about abuse or dependence

Human Chorionic Gonadotropin
- FDA approved
- Injection 3x per week

Clomiphene Citrate (Selective Estrogen Receptor Modulators)
- Off label Oral medication
- Limited symptomatic benefit – estrogens important to male sexual function, bone density.
Physiology of hCG

- Best known as serum marker for pregnancy – several roles in physiology
- Produced by syncytiotrophoblast cells found in placenta and in gonads
- hCG mimics actions of LH to stimulate endogenous testosterone production
- Binds to same receptor as LH on fetal and adult testicular Leydig cells
hCG and Testosterone

Liu et al, JCEM, 2002:
• Double-blind Randomized Controlled Trial: 40 men with androgen deficiency treated with hCG injections twice weekly or placebo
• Stable increase in serum testosterone levels within the normal range after 3 months of treatment

Roth et al, JCEM, 2010:
• 37 healthy men received a GnRH antagonist and were treated with low doses of hCG daily or Testosterone gel for 10 days
• Dose-response relationship between hCG and serum testosterone levels

Linear dose response relationship between low-dose hCG and serum T
Adapted from Roth et al, JCEM, 2010

hCG Preserves Fertility and Intra-Testicular Testosterone Production in Men on Testosterone Therapy

- 29 normal healthy fertile men
- Randomized to receive testosterone enanthate 200mg per week plus hCG at a doses of 0, 125, 250, or 500IU twice weekly
- Despite supraphysiologic doses of T, high levels of intra-testicular testosterone were maintained with administration of low-dose hCG


Table 3. Semen analysis in 7 patients with transdermal and 19 with injectable TRT

<table>
<thead>
<tr>
<th>TRT</th>
<th>Mean ± SD Sperm Count/Million</th>
<th>Mean ± SD % Motility</th>
<th>Mean ± SD FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before:</td>
<td>Total</td>
<td>Motile</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>35.5 ± 28.3</td>
<td>43.6 ± 70</td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>33.7 ± 38</td>
<td>49.8 ± 44</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.08</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>After:</td>
<td>Total</td>
<td>Motile</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>30.8 ± 15</td>
<td>37 ± 36</td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>30.6 ± 26.8</td>
<td>46.7 ± 39</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>0.99</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>
Questions/Discussion