Actual Candidates for Testosterone Therapy

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Testosterone

It's the damndedest thing...
Definition

Testosterone deficiency is a clinical syndrome with a characteristic set of symptoms and/or signs, associated with serum androgen concentrations below the range seen in healthy young men.

- ISA, ISSAM, EAU, EAA and ASA recommendations
## Symptoms of Low Testosterone

<table>
<thead>
<tr>
<th>Sexual</th>
<th>Constitutional</th>
<th>Cognitive</th>
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</thead>
<tbody>
<tr>
<td>- Low libido</td>
<td>- Anemia</td>
<td>- Insomnia</td>
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<tr>
<td>- Orgasm</td>
<td>- Decreased Muscle</td>
<td>- Mood</td>
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<tr>
<td>- Delayed orgasm</td>
<td>- Strength</td>
<td>- Irritability</td>
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<tr>
<td>- Decreased quality</td>
<td>- Endurance</td>
<td>- Depression</td>
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<td>- Low ejaculate vol.</td>
<td>- Body composition (fat vs. lean muscle)</td>
<td>- Lethargy</td>
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<tr>
<td>- Erection Dysfunction</td>
<td>- Decreased bone density / fractures</td>
<td>- Decreased short-term memory</td>
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<td>- Decreased nocturnal erection</td>
<td>- Hot flashes / sweating</td>
<td>- Decreased motivation</td>
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<tr>
<td>- Decreased genital sensation</td>
<td></td>
<td>- Decreased sense of overall well-being</td>
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</tbody>
</table>
LOW TESTOSTERONE
Endocrine Society Clinical Guidelines

- “There is no total T level that accurately distinguishes between those who do have low T and those who do not”

- 2006 version
  - Two AM Total Testosterone levels < 300ng/dL (10.4 nmol/L) set as the diagnostic threshold
  - Recommended against in men with:
    - PSA >3ng/ml without further urologic evaluation
    - Hematocrit >50% or Known Hyperviscosity syndrome
    - Untreated obstructive sleep apnea
    - Highly symptomatic BPH (IPSS >19)
    - Also CHF, PCa, BCa or prostate nodule

- 2010 version
  - Clinicians were referred to their own laboratory’s reference ranges
  - Still AM x2
  - Initially no change in contraindications but later update softened on restrictions in those with sleep apnea or BPH
Reference Range Issues

  - 25 Labs: 12 academic, 12 community medical laboratories, and one national laboratory.
  - 8 different Total Testosterone assays but 17 different reference ranges
  - The low reference value for total testosterone ranged from 130 to 450 ng/dL (350% difference) the upper value ranged from 486 to 1,593 ng/ dL (325% difference).
- 4 different Free Testosterone assays but 13 different reference ranges
- All reference values were based on a standard statistical model without regard for clinical aspects of hypogonadism.

- Total testosterone levels demonstrate decreased consistency and reliability below 11pmol/L (~300ng/dL) if using radioimmunoassay
ISA /ISSAM / EAU / EAA /ASA Joint Recommendation

• There are no generally accepted lower limits of normal total testosterone. There is, however, general agreement that:

  • TT 12 nmol/L (350 ng/dL) does not usually require substitution.
  • TT 8 nmol/L (230 ng/dL) usually benefit from testosterone treatment.
  • Between these levels: Measuring FT by equilibrium dialysis or calculating it from TT and SHBG levels may be helpful. A lower limit of 225 pmol/L (65 pg/mL) is accepted by many.

• International Consensus Panel agreed with this and added that a 3-6 month trial of TTh may be considered in equivocal cases.
Risk factors for elevated SHBG levels: liver disease, hyperthyroidism, HIV, and aging. Also may be idiopathic.
MUSTACHE?

YOU MEAN VISIBLE TESTOSTERONE?
specifically, Late-Onset Hypogonadism

- Three Sexual Symptoms

- Plus either
  - Total testosterone level of less than 11 nmol/L (~320ng/dl)
  - Free testosterone level of less than 220 pmol/L (~64pg/ml)

- No good numerical correlation seen with non-sexual symptoms

- No absolute cut-off

Wu et al, NEJM 2010
Prevalence of Symptoms – Testosterone Levels

Zitzmann M et al, JCEM 2006

Total testosterone nmol/L

Patients (n)

~425 ng/dl

74

20

84

Loss of libido p < 0.001
Loss of vigour p < 0.001

69

15

65

Obesity p < 0.001

~350

~300

67

Feeling depressed p = 0.001
Disturbed sleep p = 0.004
Lacking concentration p = 0.002
Diabetes mellitus type 2 p < 0.001

~300

75

Hot flushes p < 0.001
Erectile dysfunction p = 0.003

Increasing prevalence of symptoms with decreasing testosterone concentrations

Zitzmann M et al, JCEM 2006
Symptomatic Response by Baseline Level

- **Group 1**  TT 0-200ng/dl
- **Group 2**  TT 201-300ng/dl
- **Group 3**  TT 301ng/dl or GREATER

Reyes-Vallejo J Sex Med 2007;4:1757-1762
FDA

- Recommends using TT <300
- No recommendation re: Free T

Primary hypogonadism
  - cryptorchidism
  - bilateral torsion
  - orchitis
  - orchiectomy
  - Klinefelter’s syndrome
  - Chemotherapy, or toxic damage

Hypogonadotropic hypogonadism
  - Idiopathic LH/GnRH deficiency
  - Pituitary-hypothalamic tumor
  - Trauma
  - Radiation

- Recommends Against treatment of age-related hypogonadism

WARNINGS AND PRECAUTIONS
- Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer
- Potential for Secondary Exposure to Testosterone
- Polycythemia
- Venous Thromboembolism
- Cardiovascular Risk
- Hepatic Adverse Effects
- Sleep Apnea
- Lipids
Healthcare Insurance

• Blue Cross Blue Shield Federal Employee Program
  • Policy 5.08.33

• 2 levels between 8-10am less than 300ng/dL on different days
• Total testosterone 800ng/dL or less
• PSA <4 in patients over 40
• Absence of prostate cancer/palpable nodules. Documented DRE
• If diagnosed with BPH - he must be monitored, if documentation of worsening BPH coverage may be withheld
• Documented absence of un-treated sleep apnea
• Documented baseline evaluation and periodic reassessments of CV risk for MI, angina, stroke
• Annual HCT, PSA, and Testosterone levels
• No consideration for low Free T
"Low T? How's the rest of my alphabet?"
Contraindications

- **Sleep Apnea**
  - Multiple RCTs show no worsening in sleep related parameters after testosterone therapy vs. placebo in men with OSA
  - In healthy men without obstructive sleep apnea, TTh was not associated with development of sleep apnea
    - Seftel AD, Mayo Clin Proc. 2015
  - Significant covariation with low testosterone based on shared risk factors
    - Hanafy HM, JSM 2007

- **Liver Disease / Dyslipidemia**
  - Only associated with use of methyltestosterone

- **Infertility**
  - Multiple alternatives
    - Clomiphene (SERMs)
    - hCG
    - Aromatase inhibitors
  - In difficult cases, recent trials of hybrid TTh/hCG
Contraindications

- BPH
  - Multiple RCTs in patients with and without BPH
  - No worsening of LUTS by IPSS vs. placebo
    - Even when sub-stratified by severity
  - Statistical increase in prostate volume

- Unchanged Prohibition
  - Male Breast Cancer
  - Polycythemia

- Prostate Cancer
  - Multiple RTCs, no increased risk of development
  - Growing acceptance for men
    - Successfully treated
    - On Active Surveillance
      - Morgentaler, J Urol 2016

- Controversial
  - Cardiovascular Disease
  - Stroke
  - Spontaneous Venous Thromboembolism
THE TESTOSTERONE IS STRONG IN THEM!
Screening Questionnaires

- “Questionnaires such as Aging Male Symptom Score (AMS) and Androgen Deficiency in Aging Men (ADAM) are not recommended for the diagnosis of hypogonadism because of low specificity”

Check if you have any of the following:

- 1. Do you have a decrease in libido (sex drive)?
- 2. Do you have a lack of energy?
- 3. Do you have a decrease in strength and/or endurance?
- 4. Have you lost height?
- 5. Have you noticed a decreased "enjoyment of life"?
- 6. Are you sad and/or grumpy?
- 7. Are your erections less strong?
- 8. Have you noticed a recent deterioration in your ability to play sports?
- 9. Are you falling asleep after dinner?
- 10. Has there been a recent deterioration in your work performance?

If you checked question 1 or 7 or any 3 other questions, you may have low testosterone. A simple blood test can determine your testosterone level. Talk with your doctor to see if you should be tested.
The CAG repeat polymorphism ([CAG]n) in exon 1 of the AR

Greater the number of repeats - the less responsive the AR

CAG repeat length >24 can be symptomatic with low normal TT

- Present in 10-15% of men
- Varies by ethnicity
- At least in part moderates individual variation in response to T levels
  - Zitzmann et al., JSM 2010

Recognition of this has been incorporated into the European guidelines
What I do

- Treat with exogenous testosterone for symptomatic men
  - TT <350
  - Low Free Testosterone
  - In men with no desire to maintain fertility

- Symptomatic men with borderline levels
  - Offer Trial of therapy
    - Critical to obtain f/u blood levels
    - Continue trial duration based on primary symptoms
  - Not a lifelong decision - upon withdrawal of testosterone, gonadotropins return within 2-4 weeks

- Do not withhold treatment for
  - BPH /Sleep Apnea
  - Do follow HCT, T levels, PSA but not LFTs or Lipids