Diagnosis and Management of Testosterone Deficiency

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Objectives

1. Identify appropriate testing for testosterone deficiency
   1. Symptoms
   2. 2 early AM testosterone, FSH/LH, prolactin, hemoglobin

2. Develop treatment options including testosterone and non-testosterone therapies
   1. Testosterone formulations: gel, patch, injection, long lasting
   2. Non-testosterone options: clomiphene, anastrazole

3. Comprehensively discuss potential risks
   1. fertility,
   2. CV disease, prostate, sleep apnea
   3. body changes

I have no financial or other disclosures. I will discuss off-label use of some medications and this is marked

What is Testosterone?
What is Testosterone?

- The key sex hormone for men
- Develops male sexual traits
  - Muscle mass, strength
  - Facial and body hair
  - Bone density and linear growth
  - Maturation of sex organs
  - Sperm production

Physiological Effects

Prenatal: Development of male reproductive tract, prostate, seminal vesicles; (via DHT) development of male external genitalia

Infancy: “brain masculinization”?

Puberty: pushes from boys to men
Symptoms of Low Testosterone (Hypogonadism)

- Non-sexual Symptoms
  - Lower energy
  - Depressed mood

- Non-sexual Signs
  - Increased body fat
  - Reduced muscle mass
  - Anemia
  - Bone density loss

- Sexual Symptoms
  - Lower sex drive

- Sexual Signs
  - Poorer erections
What are normal values?

![Graph showing testosterone levels](image)

**Figure 2 - Testosterone level groups (ng/dL)**

**Figure 1 - Age groups.**

AN Junior, IntBrazUrol 2011

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Epidemiology

  - 12.3/1000 person-years
  - 481,000 new cases per year in American men
- Longitudinal, population-based studies of aging men have demonstrated that both TT and FT decline with age along with an increase in SHBG levels
- Prevalence of *symptomatic* androgen deficiency 5.6% (TT<300 and symptoms)

Potential scope of androgen deficiency

By 2025, approximately 6.5 American men 30-80 years old affected


Prevalence of *symptomatic* androgen deficiency in men.

TRT Usage by Age Over Time

Guidelines

No Groups Recommend Screening
2018 American Urological Association Guideline
2018 Endocrine Society Guideline
Causes/Associations

- High blood pressure 40%
- High cholesterol 40%
- Diabetes up to 50%
- Overweight up to 50%
- HIV 30%
- Alcoholism
- Chronic opioid use
- Sleep apnea

Hypogonadism Diagnosis

Initial Screening: A blood test
Total testosterone
- MORNING draw, before 10am
- Nadir values ~15% lower than peak morning values
- May be up to 50% lower in younger patients
- Even at same collection time, individual variability of 10%

No clear consensus
US Food and Drug Administration <300 ng/dL
International consensus statement
- T >350 does NOT require treatment
- T<230 with symptoms does require treatment

Other screening tests may include
- PSA for prostate cancer: age 55-69, family history
- Red cells (hematocrit)
Hypogonadism Diagnosis

Symptomatic hypogonadism AND
2 morning testosterone level <300ng/dL AND
no other medical or modifiable factors that might contribute to symptoms
Contraindications/Considerations

History of prostate cancer, breast cancer
Elevated PSA or palpable prostate nodule that have not been evaluated with biopsy
Hct >50%
Severe obstructive sleep apnea
Severe LUTS/BPH
Severe CHF
Desired future fertility

When is treatment not necessary?

- Do Not Use for
  - Body building
  - “Normal” T levels
  - Fertility
  - To treat prostate cancer
What if I don’t treat?

- Symptoms will continue
- If you have significant heart disease, therapy may actually decrease risk of more heart disease though this remains very controversial

Treatment Options

- Testosterone replacement therapy (TRT)
- Non-Testosterone therapy

Non-T therapies have the advantage of increasing serum T levels without suppressing sperm production

- First choice in men wishing to preserve fertility, or in subfertile men with abnormal semen parameters and low testosterone
Non-Testosterone Therapy: SERMs

- Off-Label Selective estrogen receptor modulators
- Block central Estrogen Receptor, inhibiting central feedback inhibition and stimulating increased endogenous production of LH, promotes testosterone production
- Clomiphene citrate 25mg 3 times weekly up to 50mg daily
  - Expect T increase by 150+ points
  - Side effects: blurred vision, hot flashes, headache

Non-Testosterone Therapy: SERMs

- Clomiphene citrate 25mg 3 times weekly up to 50mg daily
  - Expect T increase by 150+ points
  - Side effects: blurred vision, hot flashes, headache
  - Follow up: labs in 3-4 weeks. (Total T, FSH or LH, estradiol). symptoms should be improved here too. if not, titrate dose up and repeat labs/symptom check in 3-4 weeks.
Non-Testosterone Therapy: hCG

Natural LH analog that stimulates testicular production of Testosterone
Prevents testicular atrophy
hCG 500-2000 units IM or SC 2-3x/week

Follow up: labs in 4 weeks. (Total T, LH, estradiol). symptoms should be improved here too. if not, titrate dose up and repeat labs/symptom check in 4 weeks.
Non-Testosterone Therapy
Aromatase inhibitors

- T is normally converted to estradiol in peripheral adipose tissues by aromatase at 0.3% daily
- First choice for men with T:Estradiol ratio <10
- Anastrozole 1mg PO every other or daily
  - expect Estradiol down and T up 100-200 points
  - Side effects: blurred vision, headache

Follow up: labs in 4 weeks. (Total T, LH, estradiol). symptoms should be improved here too. if not, titrate dose up and repeat labs/symptom check in 4 weeks.
TRT – Testosterone Replacement Therapy

Mechanism of Non-injectable:
- Transdermal patch q24h (2mg or 4mg)
- Transdermal gel q24h applied to upper arm, axilla
- Buccal tablets q12h 30mg PO BID
Testosterone Replacement Therapy

IM injection
- T-proprionate q24h
- T-cypionate or T-enanthate start at 200mg every other week
  - Generic, less expensive than non-injectables
  - Can achieve higher blood levels than non-injectables
  - Patients can be taught self-injection
  - Peak measured 24h after 1st injection, trough measured immediately prior to 2nd injection
    - Target peak 700-1200 ng/dL
    - Target trough 400-600 ng/dL
    - Adjustments in dose affect peak level, and adjustments in dosing interval affect trough level

Subcutaneous pellet
- Inserted into buttock or flank via 5min office procedure
- Lasts 3-5 months
- Attractive option for men who are unable or unwilling to learn self-injection
- Dose: 6-10 pellets, 450-750mg
- Check T level after 1 month and At 3 months. If <400, replace or consider increasing dose
Testosterone Replacement Therapy

T Undecanoate 750mg  
Office administered gluteal injection  
Weeks 0, 4, then every 10  
No dose adjustment possible as only 1 dose made

Dose Adjustment

Goal Range 450-600 with symptom improvement, not "Cure"

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Adjustment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>change to higher dose</td>
</tr>
<tr>
<td>Gel</td>
<td>increase # of applications</td>
</tr>
<tr>
<td>IM</td>
<td>increase by 50mg</td>
</tr>
<tr>
<td>Pellets</td>
<td>reduce frequency (q3month) or increase #</td>
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</tbody>
</table>
Dose Adjustment

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bioavailability</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Gel</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>IM Cypionate or Enanthate</td>
<td>95%</td>
<td>8 days</td>
</tr>
<tr>
<td>IM Undecanoate</td>
<td>95%</td>
<td>33 days</td>
</tr>
<tr>
<td>Pellet</td>
<td>99%</td>
<td></td>
</tr>
</tbody>
</table>

for most, minimal oral bioavailability

Formulation Adjustment

What if there is no symptom improvement?
Whether or not goal T is in range

Goal Range 450-600 with symptom improvement, not "Cure"

Switch to any other form. Try and get guys to IM injections because the bioavailability is so good (and it is cheap)
Side Effects of TRT

- Acne
- Breast soreness or swelling (gynecomastia)
- High red cell count (erythrocytosis, polycythemia)
- Swelling of feet/ankles (fluid retention)
- Smaller testicles
- Infertility
- Lightheadedness
- Gels can cause skin irritation/rash
- Gels cannot contact children and pregnant women

Major Safety Concerns

- Men with known breast or prostate cancer
- Elevated PSA or abnormal prostate exam require biopsy first
- Kidney, liver disease may have increased water retention
- High red blood cell count >50%
- May worsen sleep apnea
- Blocks sperm production so avoid if trying to have children
Additional Safety Concerns: Prostate Cancer

- Prostate cancer is very testosterone sensitive
- Treatment for men who develop metastatic prostate cancer is total blockage of testosterone
- Testosterone therapy does not cause new Prostate Cancer
- After prostate cancer treatment, surgery or radiation, testosterone therapy is likely safe but no RCT to show this. Follow the PSA closely

Carson CC JUrol 2015

Additional Safety Concerns: Heart Disease

Major concerns that TRT can raise heart risk
Blood clots, stroke, heart attack

Conflicting studies that TRT may actually reduce heart disease risk

FDA continues to study this. Label changed March 2015 to reflect possible increased risk of heart attack and stroke
Expectations of Treatment

- Improved energy
- Improved sex drive
- Increased muscle mass
- Decrease body fat
- Improved bone density
- Help sleep
- *May improve erections in only 50%*

Follow up on Treatment

Therapy is often life-long

Repeat blood testing 1-3 months after initiation, and after any adjustments
  - Testosterone level
  - Red cell count (H/H)
  - PSA for prostate cancer if >40 years
Then annually with physical exam
Summary

General Population Screening: No
Diagnosis: Symptoms AND T<300-350
Treatment Risks: possible CV, worsening OSA and BPH. Infertility
Does not cause prostate cancer.
Treatment options: gels, injections, pellets
Follow Up: 3-6 months. If no benefit, switch doses/modalities but stop after 6 months. Interval labs (PSA, CBC, Testosterone)

Conclusion

Advocating for comprehensive male care
- controlling diabetes and high blood pressure
- Stop smoking and adjust sleep

Consider Testosterone testing only if symptomatic

Not a panacea for all ailments
References


