ANDROGEN DEFICIENCY

Update on Evaluation and Management

Kristen Gill Hairston, MD, MPH
Associate Professor of Internal Medicine
Section of Endocrinology and Metabolism
Wake Forest University School of Medicine

March 24, 2017
Declaration of Interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
Objectives

• Review physiologic actions of testosterone

• Describe signs and symptoms of male hypogonadism

• Review therapy for male hypogonadism
WHAT DOES TESTOSTERONE DO?
Normal H-P-G Axis

HYPOTHALAMUS

GnRH

PITUITARY

LH

FSH

TESTES

TESTOSTERONE

SPERM
The Influence of Testosterone

**Skin**
- Growth of Facial & body hair
- Supports collagen

**Brain**
- Sex Drive
- Positive Feelings
- Aids cognition and memory

**Male sex organs**
- Sperm production
- Prostate growth
- Erectile function

**Bone Marrow**
- Red Blood Cell production

**Muscle**
- Muscle mass and strength

**Bone**
- Bone density maintenance
WHAT DOES “LOW T” LOOK LIKE?
Hypogonadism

Definition

Clinical syndrome that results from failure of the testis to produce physiological levels of testosterone and a normal number of spermatozoa due to disruption of one or more axis

Bhasin S et al, JCEM 2010, 95(6):2536-2559
Symptoms and Signs

**Low Sensitivity**

- Decreased energy, motivation, initiative
- Poor concentration or memory
- Mild anemia (normocytic, normochromic)
- Sleep disturbance, increased sleepiness
- Feeling blue or sad
- Reduced muscle bulk
- Diminished physical or work performance

Bhasin S et al, JCEM 2010, 95(6):2536-2559
Signs and Symptoms

High sensitivity

- Incomplete or delayed sexual development
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort
- Loss of body hair, reduced shaving
- Infertility
- Low BMD, non-traumatic fractures
- Hot flushes, sweats

Bhasin S et al, JCEM 2010, 95(6):2536-2559
WHAT IS MY PATIENT'S FUNCTIONAL "T" LEVEL?
Circulating Total Testosterone

**SHBG DEPENDENT**
- Total T
- Free T (analog assay)

**SHBG INDEPENDENT**
- Calculated free T and bioavailable T
  - Free T (equilibrium analysis)
  - Bioavailable T (ammonium sulfate precipitation)

**BIOAVAILABLE**
- SHBG-bound (tight)
- Albumin bound (weak)
- Free T
Hypogonadism

**SHBG Affect**

**↓ SHBG → ↓ Total T**
- Moderate obesity
- Low protein
- Hypothyroidism
- Glucocorticoids
- Anabolic steroids
- Acromegaly

**↑ SHBG → ↑ Total T**
- Aging
- Hepatitis, cirrhosis
- Hyperthyroidism
- Anticonvulsants
- Estrogens
- HIV

More bioavailable than appears by total

Less free available than indicated by total testosterone
M. J. Wheeler and S. C. Barnes Measurement of testosterone in the diagnosis of hypogonadism in the ageing male Clinical Endocrinology 69
IS "LOW T" REALLY A PROBLEM?
Hypogonadism

PATHOPHYSIOLOGY ?

OR

NORMAL PHYSIOLOGY ?
Hypogonadism

PATHOPHYSIOLOGY?

OR

NORMAL PHYSIOLOGY?
Hypogonadism

Prevalence

Massachusetts Male Aging Study estimated incidence of 481,000 new cases in men 40-70.²

Hypogonadism

Prevalence

Late-onset hypogonadism

- Age-associated decrease in androgen production
  - Between the ages of 40 and 70, total and free T decrease by approx. 1.2% per year
  - ~12% of men over 50 years of age
  - ~50% of men above the age of 80 have low serum total T levels
  - 9.4% of men aged 60-80 years are diagnosed with clinical hypogonadism

- In contrast to the cessation of gonadal function in menopause, the decrease of serum T is more gradual

Harman SM et al, JCEM 86:724-731, 2001
Hypogonadism in the Aging Man

- All components of testosterone decline with normal aging
- Decline in Leydig cell count and function
- Increase SHBG, lowers bioavailable T
- Not all men with low testosterone have symptoms or need treatment

Hypogonadism in Aging Men

Caveats

- Most studies.. men not clinically or biochemically deficient
- Treatment led to supra-therapeutic levels
- Most studies have small numbers with short term evaluation
- Underpowered outcome measures
IS “LOW T” REALLY A PROBLEM....FOR MY PATIENT?
Hypogonadism

Select Conditions

**Odds Ratios**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.84</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.47</td>
</tr>
<tr>
<td>COPD</td>
<td>1.40</td>
</tr>
</tbody>
</table>

**Other Areas of Concern**

**HIV/AIDS**

30% of HIV-infected men and 50% of men with AIDS have low testosterone.\(^2\)

**Chronic Pain**

74% of men consuming sustained-action oral opioids have low testosterone.\(^3\)

Testosterone in Obese Men

Comparisons of total and free testosterone between morbidly obese men (BMI > 40) and age-matched controls.

Glass AR et al. JCEM (1977) 45:1211
Hypogonadism

**Obesity Impact**

1. Increased aromatase activity → LH/FSH suppression by estrogen

2. Leptin resistance → decreased stimulation of GnRH and inhibition of steroidogenesis

3. Heat stress apoptosis of testicular cells

4. Storage of “obesogens”

Hypogonadism and T2DM

- Twice as likely to be hypogonadal compared with a non-diabetic man.
  - Hypogonadotropic (secondary) hypogonadism
  - No relation between the degree of hyperglycaemia and testosterone concentration

- Low testosterone predict the development of T2DM
  - Lowest free testosterone tertile 4x times as likely to have diabetes than highest free testosterone tertile.
  - Type 1 diabetes does not seem to be associated with hypogonadism

The prevalence of subnormal free testosterone (FT) concentrations in diabetic and nondiabetic men by age
**Hypogonadism**

*Endocrine Society Recommendations*

- 25% of men with T2DM have subnormal levels

- Associated with
  - High CRP
  - Obesity
  - Mild anemia
  - 2-3x increased risk of CV events/death

- Treatment results
  - Increased insulin sensitivity
  - Decrease in waist circumference
  - Increased libido
  - No improvement in ED

Dandona et al, JCEM 96:2643-3651, 2011
Decreased LH pulsatility during waking and sleeping hours

SLEEP APNEA

Decreased levels of testosterone at baseline and peaking hours

Hypogonadism

Diagnostic Formula

• S/S of androgen deficiency

• Frankly low total T levels, in AM, x 2

• Low free or bioavailable, if concern about SHBG

• Illness, drugs or nutritional deficiency ruled out
BUT WHY?
PUTTING IT TOGETHER...
Normal H-P-G Axis

HYPOTHALAMUS → GnRH → PITUITARY

PITUITARY → LH → TESTES

PITUITARY → FSH → TESTES

TESTES → TESTOSTERONE

TESTES → SPERM
PRIMARY HYPOGONADISM

CAUSES

- Surgery
- Radiation
- Genetic and developmental disorders
- Liver and kidney disease
- Infection
- Autoimmune disorders
- Idiopathic / late-onset
H-P-G Axis

CAUSES

• Medications
  • Opiates
  • High dose steroids
  • Recreational drugs

• Surgery

• Hyperprolactinemia

• OSA

• Trauma

• Eating disorders (transiently)

• Excessive exercise (transiently)
H-P-G Axis

HYPOTHALAMUS → GnRH → PITUITARY → LH/FSH → TESTES → TESTOSTERONE → SPERM

- **PRIMARY HYPOGONADISM**
  - Older men
  - Age related defects in testicles and HPA function

- **SECONDARY HYPOGONADISM**
  - Combined:
    - Hematochromatosis
    - Sickle cell disease
    - Thalassemia
    - Glucocorticoid therapy
    - Alcoholism
    - DAX-1 mutations

- **COMBINED HYPOGONADISM**
  - Glucocorticoid therapy
  - Alcoholism
  - DAX-1 mutations
  - Older men
  - Age related defects in testicles and HPA function
Hypogonadism
Evaluation

• Diagnostic yield can be improved by obtaining MRI in those with inappropriate LH/FSH AND:
  - Total levels < 150 ng/dL
  - Panhypopituitarism
  - Persistent hyperprolactinemia
  - Tumor mass effect (HA, vision changes, visual field defect

Bhasin S et al, JCEM 2010, 95(6):2536-2559
FIXING THE PROBLEM......
## Hypogonadism

### Treatment considerations

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients with breast and prostate cancer</td>
<td>- Palpable nodule or induration</td>
</tr>
<tr>
<td>- Patients with HCT &gt; 50%</td>
<td>- PSA &gt; 4 ng/mL or PSA &gt; 3 ng/mL in high risk men</td>
</tr>
<tr>
<td>- Untreated severe OSA</td>
<td>- (AA or 1st degree relative)</td>
</tr>
<tr>
<td>- Poorly controlled CHF</td>
<td>- Severe lower UTI</td>
</tr>
<tr>
<td>- Desiring fertility</td>
<td>- Prevalent CAD</td>
</tr>
</tbody>
</table>

Bhasin S et al, JCEM 2010, 95(6):2536-2559
Hypogonadism

Treatment Options

• Intramuscular injections
  – Cypionate
  – Enanthate

• Transdermal preparations
  – Patch (Androderm)
  – Gel (Androgel, Testim, Fortesta, Axiron)

• Buccal

• Pellets
Testosterone Enanthate 250 mg Administered IM Every 3 Weeks

400-700 ng/dL one week after injection

AndroGel vs. Androderm
Mean Steady-state Concentrations

24-Hour Concentrations on Day 90 of Therapy

Treatment Monitoring

@ 3 months

- **Serum testosterone**
  - IM testosterone: midpoint between injections, level near middle of reference range
  - Patch: 3-12 hrs after applying new patch
  - Gel: timing not critical

- **Prostate**
  - DRE @ 3 months, then annually
  - PSA @ 3 months, then annually
  - Prostate biopsy if PSA > 4 ng/mL, PSA increases by > 1.4 ng/mL in 12 months, or PSA velocity > 0.4 ng/mL/yr

- **Red cell mass**
  - CBC at 3 months, then annually
  - If Hct > 54%, stop therapy, monitor for return to reference range, then resume therapy at a lower dose
Androgens and BPH

• Hypogonadal men have small prostates

• In hypogonadal men receiving testosterone treatment, prostatic volume increases, but to no greater volume than that of normal age-matched controls

• PSA levels rise with androgen therapy but should remain within the reference range

• Maximal increase in volume and PSA occurs by three months and should not continue with long-term therapy

Gruenewald et al 2003 Testosterone Supplementation Therapy for Older Men: Potential Benefits and Risks
Androgens and CVD

- Association between low T and all cause mortality (but may be marker of illness)
- Replacement changes risk factors (fat mass, insulin resistance, MetS)
- *MAY* increase MI and CVA in pts with prevalent CAD
- Care should be taken in replacing simply for androgen deficiency of aging

Endocrine Practice. 2015; 21:1066-1073
SO
“Not Myself Syndrome”

- Low T
- Type 2 DM
- Obesity
- Stress
- Aging population
Final Thoughts

• Testing should still be driven by symptoms
  • Not usually top cause of ED
  • Men with T2DM → high priority
  • Must evaluate and treat sleep apnea, first

• Diagnosis should only be made with **unequivocally low levels AND symptoms**

• Levels should be tested in the morning AND on multiple occasions

• Resolution of symptoms should be seen in a finite period of time (expectation management)

• Monitoring is very important
  • PSA
  • CBC
  • Testosterone levels
QUESTIONS?
THANK YOU
KGHAIRST@WAKEHEALTH.EDU
A 57 yo man presents to clinic for evaluation of fatigue and decreased libido. He reports that his has been an issue for the last 6 months. His PMH is significant for T2DM, morbid obesity. He reports that he does sleep for 6-7 hours nightly, but snores a lot. His diabetes is managed with oral agents and his a1c is 7.2%. 
What is the next best test to order?

A. Prolactin levels
B. Testosterones levels
C. Hemoglobin a1c
D. Sleep study
E. Growth Hormone levels
What is the next best test to order?

A. Prolactin levels
B. Testosterones levels
C. Hemoglobin a1c
D. Sleep study
E. Growth Hormone levels
Case 1

Testosterone-replacement therapy has been associated with exacerbation of sleep apnea or with the development of sleep apnea, generally in men treated with higher doses of parenteral testosterone who have other identifiable risk factors for sleep apnea. Upper-airway dimensions are unaffected by testosterone-replacement therapy, suggesting that androgen replacement contributes to sleep-disordered breathing by central mechanisms rather than by means of anatomical changes in the airway.
Case 2

A 45 yo man presents to your clinic with concerns of fatigue, weight gain (about 10 pounds in last year) and mild erectile dysfunction. He reports that he will be getting re-married in the next month. He and his new wife would like to try and get pregnant relatively soon. His PMH is significant for HTN (treated with metoprolol) and tobacco abuse. You check a testosterone level and both free and total levels are low.
The next best step is to...

A. Start testosterone therapy
B. Send patient to andrologist/reproductive endocrinologist
C. Start patient on PDE5-inhibitor
D. Refer to marital counseling
E. Stop his beta blocker
The next best step is to...

- Start testosterone therapy
- **Send patient to andrologist/reproductive endocrinologist**
- Start patient on PDE5-inhibitor
- Refer for pre-marital counseling
- Stop his beta blocker
Exogenous testosterone decreases the body’s endogenous production of testosterone. The testes will not respond to exogenous testosterone for sperm production. Instead, there will be a decrease in FSH production and a decrease in spermatogenesis.

Patients who have low normal testosterone and/or erectile function and desire fertility should be evaluated by andrologist/reproductive endocrinologist first to determine sperm quality and quantity prior to starting any therapy.
A 52 yo man presents to your afternoon work-in clinic complaining of continued fatigue (for the last 4 months), depressed mood, decreased libido, headaches and weight gain. His PMH is significant for hypothyroidism and chronic back pain. He reports that he and his wife have decided to file for divorce and they are putting the house on the market.

His blood sugar and blood pressure are WNL. You check a total testosterone level that day and it is 175 ng/dL (250-1100 ng/dL).
Your next step is to…

A. Order a head MRI
B. Start testosterone therapy
C. Repeat an am testosterone, then order an LH and FSH, if low.
D. Start patient on PDE5-inhibitor
E. Refer to counseling
Your next step is to...

A. Order a head MRI
B. Start testosterone therapy
C. Repeat an am testosterone, then order an LH and FSH, if low.
D. Start patient on PDE5-inhibitor
E. Refer to counseling
While this patient does have a low testosterone, the levels were drawn in the afternoon. It is important to confirm low testosterone concentrations. In men with an initial testosterone level in the mildly hypogonadal range, up to 30% of such men had a normal testosterone level on repeat. Also, 15% of healthy young men may have a testosterone level below the normal range in a 24-hour period.

Also, once identified to be truly low, the cause of hypogonadism must be determined. If LH and FSH are low in the presence of low testosterone, then an MRI should be done, particularly in the presence of new headaches.
Hypogonadism

Fertility

H-P-G Axis

HYPOTHALAMUS

GnRH

PITUITARY

LH

FSH

TESTES

ENDOGENOUS TESTOSTERONE

SPERMATOGENESIS
• Fortesta (2 %) delivering 0.5 g of gel (10 mg) per pump

• Starting dose is 40 mg, (front and inner thighs), maximum of 70 mg

• Each depression yields 30 mg

• Starting dose of 30 mg (axilla)

• Low as 30 mg and as high as 120 mg

• Most need 30 to 90 mg to achieve normal levels

• 5 g → 50 mg
• 10 g → 100 mg
• Shoulders/upper arms
Hypogonadism

Patch

- 2 mg (9.7 mg)
- 4 mg (19.5 mg)

- Recently changed from 2.5mg/5mg

- Titrate based on a patient's morning serum concentration ~ 2 weeks after starting

- Any skin surface other than genitals

- ~20% complain of skin irritation

Androderm® full Prescribing Information, Watson Pharma, Inc. October 2011
### Hypogonadism Treatment - Androderm®

#### Transitioning from Old Dosing

<table>
<thead>
<tr>
<th>Current 2.5mg/5 mg dosage</th>
<th>2 mg/4 mg equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Start 2 mg patch</td>
</tr>
<tr>
<td>5.0 mg</td>
<td>Start 4 mg patch</td>
</tr>
<tr>
<td>7.5 mg</td>
<td>Start 6 mg combination</td>
</tr>
</tbody>
</table>

#### Titration Method

<table>
<thead>
<tr>
<th>Morning [T]</th>
<th>Dosage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 400 ng/dL</td>
<td>increase by 2 mg patch</td>
</tr>
<tr>
<td>400-930 ng/dL</td>
<td>no change in therapy</td>
</tr>
<tr>
<td>&gt;930 ng/dL</td>
<td>Decrease by 2 mg patch</td>
</tr>
</tbody>
</table>
Hormone Replacement Injection

Advantages

• Works in almost all hypogonadal men
• Frees patient from daily administration
• Titratable
• Cheapest of the three options

Disadvantages

• IM injection
• Peaks and troughs
Hormone Replacement

Gels

• 1% formulation
  – packets → 2.5 g (25mg) and 5.0g (50mg)
  – pump → 1.25g (12.5mg) per pump
  – Starting dose 50 mg(4) → 100 mg (8)

• 1.65 % formulation
  – pump → 1.25g (20.25 mg) per pump
  – Allows 20.25 mg(1) → 81 mg (4)
  – Shoulders and upper arms only