Testosterone and Hypogonadism in Men

C. W. Spellman, DO, PhD
Professor and Associate Dean, Research
Dir. Medical Center Hospital Diabetes Center
Department Internal medicine, Div. Endocrinology
Texas Tech University Health Science Center
Odessa, Texas
HYPOGONADISM
Subnormal testosterone concentrations PLUS symptoms of androgen deficiency

HYPOGONADOTROPIC HYPOGONADISM
(AKA Secondary or Central hypogonadism)
Low testosterone in the presence of normal or low gonadotropins (LH, FSH)
Cause: Defects of pituitary or hypothalamus function

HYPERGONADOTROPIC HYPOGONADISM
Low testosterone in the presence of elevated gonadotropins (LH, FSH)
Causes of Hypogonadism

**Congenital**
- Klinefelter syndrome (1/400)
- Kallmann syndrome (1/10,000)
- Hemochromatosis

**Acquired**
- Pituitary disorder
- Testicular trauma
- Autoimmune syndromes
- Medications (corticosteroids, Ketoconazole, opioids)

- Cryptorchidism (8/1000)
- Defects in androgen synthesis or action
- Aging
- Obesity
- Type 2 Diabetes
- HIV/AIDS
- Chronic renal failure
- COPD/Respiratory illness

Conditions Associated With Low Testosterone

Radiation, tumors, trauma, infiltrative, granulomatous disease of the sellar region

Glucocorticoids, ketoconazole, and opioids

HIV-associated weight loss

End-stage renal disease and hemodialysis

Moderate to severe COPD

Infertility

Osteoporosis or low trauma fracture

Coronary artery disease

Falls
Conditions Associated with Low Testosterone

Hip fractures
Anemia
Rheumatoid Arthritis
Depression
Alzheimer’s (?)
Type 2 diabetes
Obesity

4. Ding EL, Song Y, JAMA 2006;295:1288–1299
6. Moffat SD, Zonderman AB, J Clin Endocrinol Metab 2002;87:5001–5007
Symptoms/Signs of Androgen Deficiency

Decreased energy or vitality, increased fatigue
Reduced libido and sexual activity
Erectile dysfunction
Reduced muscle mass and strength
Increased Fat mass
Low bone mass
Depressed mood
Anemia

Screening for Low T: Androgen Deficiency in Aging Males (ADAM) Questionnaire

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

If yes to Qu 1 or 7, or at least three other questions, low testosterone may be present

Diurnal Rhythms in Serum Testosterone in Normal Males

Testosterone (ng/dL) vs Clock Time (hours) for Young (23-28 yrs) and Old (58-82 yrs)

Universal Screening of Testosterone Levels is Not Recommended

- Endocrine Society does not recommend routine screening for low testosterone in all elderly men.
- Serum testosterone should be measured in men with signs and symptoms of androgen deficiency.
- Case detection to be considered in some conditions.
Testosterone and Aging
Relationship Between the Number of Metabolic Syndrome Components and Free Testosterone Levels in Men

Men with Coronary Artery Disease have Lower Testosterone Than Men Without CAD

English KM, Jones TH, Channer KS et al; *Eur Heart J.* 2000 Jun;21(11):890-4
Low Testosterone and Mortality in Older Men

794 men, aged 50-91 (median 73.6) yr
Testosterone <300 ng/dL
Average follow-up 11 yr

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>20 yr Follow-up</th>
<th>20 yr Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>CVD</td>
<td>1.38</td>
<td>(1.02, 1.85)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.34</td>
<td>(0.89, 2.00)</td>
</tr>
<tr>
<td>Lung dz</td>
<td>2.29</td>
<td>(1.25, 4.20)</td>
</tr>
</tbody>
</table>

Laughlin GA, Barrett-Connor E, Bergstrom J. JCEM 2008;93:68-75
Survival by Testosterone Treatment

Log Rank p = 0.029

HR by 39%

Subjects at Risk
Untreated: 1016
Treated: 15

Survival by Testosterone Treatment

<table>
<thead>
<tr>
<th></th>
<th># Patients</th>
<th># Deaths</th>
<th>Death/100 Person-Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>633</td>
<td>131</td>
<td>5.73</td>
</tr>
<tr>
<td>Treated</td>
<td>398</td>
<td>41</td>
<td>3.44</td>
</tr>
<tr>
<td>Total</td>
<td>1031</td>
<td>172</td>
<td>4.95</td>
</tr>
</tbody>
</table>

Decreased death was seen in younger men with T2D and CAD

Effect of Acute Testosterone Withdrawal on Fasting Glucose and Insulin Levels in Men with Hypogonadotrophic Hypogonadism

Change in hormone and cytokine levels after withdrawing Testosterone in men with Hypogonadotrophic Hypogonadism

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/dl)</td>
<td>529 ± 65</td>
<td>28 ± 8</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>31 ± 3</td>
<td>18 ± 2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>6.4 ± 1.4</td>
<td>5.5 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>12.3 ± 0.8</td>
<td>11.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.2 ± 0.2</td>
<td>2.4 ± 0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRP (µg/ml)</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>1.0 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Free fatty acids (mEq/liter)</td>
<td>0.81 ± 0.1</td>
<td>0.83 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>13.8 ± 1.6</td>
<td>12 ± 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>
HYPOGONADOTROPIC HYPOGONADISM IN TYPE 2 DIABETES
## Diabetes and Hypogonadism

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett-Connor E, 1990:</td>
<td>21% of DM men vs. 13% of non-DM men had total testosterone less than 350 ng/dL</td>
</tr>
<tr>
<td>Barrett-Connor, 1992:</td>
<td>Men with T2D had lower free &amp; total testosterone than non-diabetic men</td>
</tr>
<tr>
<td>Goodman-Gruen D, 2000</td>
<td>Men with T2D or IGT had lower total testosterone levels after adjustment for age and BMI</td>
</tr>
</tbody>
</table>

Goodman-Gruen D, Barrett-Connor E. *Diabetes Care.* 2000;23:912-918
Comparison of Hypogonadal and Eugonadal Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Hypogonadal</th>
<th>Eugonadal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>34</td>
<td>69</td>
</tr>
<tr>
<td>Age</td>
<td>57 ± 2 yrs</td>
<td>54 ± 1</td>
</tr>
<tr>
<td>BMI</td>
<td>36 ± 2 kg/m²</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>Total T</td>
<td>225 ± 18 ng/dL</td>
<td>410 ± 14</td>
</tr>
<tr>
<td>Free T</td>
<td>42 ± 3.2 pg/ml</td>
<td>88 ± 4.3</td>
</tr>
<tr>
<td>LH</td>
<td>3.15 ± 0.26 mIU/ml</td>
<td>3.91 ± 0.24</td>
</tr>
<tr>
<td>FSH</td>
<td>4.25 ± 0.45 mIU/ml</td>
<td>5.53 ± 0.4</td>
</tr>
<tr>
<td>PRL</td>
<td>6.69 ± 0.58 mIU/ml</td>
<td>6.69 ± 0.46</td>
</tr>
</tbody>
</table>

Low Testosterone in Males with T2D and Erectile Dysfunction is Usually Due to Hypogonadotropic Hypogonadism

Study: 50 men with T2D and low testosterone were evaluated for LH, FSH and Prolactin

Results: 43 low/normal LH/FSH
5 high LH/FSH
2 low LH/FSH 2nd to prolactinomas

Qu: Should all men with T2D and low testosterone be evaluated for pituitary dysfunction?

Occurrence of Hypogonadotrophic Hypogonadism in Type 2 Diabetes

Study: T2D males (n=103)
Measure Total T (TT), free T (FT)
Mean age = 54.7 ± 1.1 years (range, 28-80)
Mean BMI = 33.4 ± 0.8 (range, 17.6-63.1)
Mean duration of T2D = 7.7 ± 0.7 years

Results: 33% had low free testosterone
43.7% had low TT
Testosterone levels were not related to:
A1c,
Duration of T2D
Use of insulin or statins

Prevalence of Hypogonadism in Men with Type 2 Diabetes Ranges 35% to 65%

Adapted from Kapoor et al: *Diabetes Care* 2007;30(4):911–917
Hypogonadism in Type 1 and Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>T1D</th>
<th>T2D</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Hypogonadal (%)</td>
<td>3 (6%)</td>
<td>13 (26%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.09±0.75</td>
<td>34.91±1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total T (nmol/L)</td>
<td>22.97±0.99</td>
<td>11.20±0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>4.12±0.28</td>
<td>3.94±0.33</td>
<td>0.39</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>49.32±2.83</td>
<td>20.44±1.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c%</td>
<td>7.57±0.20</td>
<td>8.40±0.25</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Tomar et al, Diabetes Care. 2006 May;29(5):1120-2
Free Testosterone Levels in Young Men: Type 1 vs. Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>T1D</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26 yr</td>
<td>27 yr</td>
</tr>
<tr>
<td>BMI</td>
<td>27.4</td>
<td>38.6</td>
</tr>
</tbody>
</table>

Minimum normal 23 nmol/L

PATHOGENESIS OF HYPOGONADISM IN OBESITY AND TYPE 2 DIABETES

↑ Inflammatory cytokines

↓ GnRH release

↓ LH/FSH release

Estrogen

HYPOGONADISM

↓ Testosterone

INSULIN RESISTANCE
Increase in serum testosterone following kisspeptin infusion in men with type 2 diabetes and low testosterone

George JT et al, Clinical Endocrinology 2012
Estradiol Concentrations in Men With Type 2 Diabetes

- Hypogonadal (30 men)
- Eugonadal (72 men)

Free estradiol (pg/ml)
Free Testosterone in Lean vs Fat Mass in Men with Type 2 Diabetes

5% Weight Loss Increases Total Testosterone by 50 mg/dL
Roux-en-Y Gastric Bypass Surgery and Serum Testosterone

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>2 years after surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>46 ± 1</td>
<td>30 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Testosterone (ng/dl)</td>
<td>315 ± 201</td>
<td>626 ± 186</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calculated Free Testosterone (ng/dl)</td>
<td>5.8 ± 2.0</td>
<td>10.3 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Estradiol (ng/dl)</td>
<td>3.8 ± 1.0</td>
<td>3.0 ± 0.7</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Hammoud et al; *JCEM* 2009;94:1329-1332
Hypogonadotropic hypogonadism is frequent in T2D (33%) 
Hypogonadism is not associated with T1D 
Obesity is associated with hypogonadism (25%) 
When morbidly obese men undergo significant weight reduction, testosterone concentrations increase 
Hypogonadotropic hypogonadism of type 2 diabetes is not mediated by elevated estradiol concentrations
Testosterone Replacement Therapy Potential Benefits

- Normalization of T levels
- Improved libido
- Positive effects on fatigue (improved energy level)
- Improved mood, sense of well-being
- Increase in lean body mass and strength
- Decrease in body fat mass
- Improved bone mineral density (effects on fracture risk are currently unknown)

Bone Mineral Density After Testosterone Therapy

Change Hip BMD

Change Spine BMD

Body Composition After Testosterone Therapy

Lean Body Mass Change

Fat Body Mass Change

Serum Lipids After Testosterone Therapy

**Total cholesterol**

- Month 0: 5.0 mmol/L
- Month 6: 5.5 mmol/L
- Month 12: 6.0 mmol/L
- Month 18: 5.5 mmol/L
- Month 24: 5.0 mmol/L
- Month 30: 4.5 mmol/L

**HDL**

- Month 0: 1.0 mmol/L
- Month 6: 1.5 mmol/L
- Month 12: 2.0 mmol/L
- Month 18: 2.5 mmol/L
- Month 24: 2.0 mmol/L
- Month 30: 1.5 mmol/L

**LDL**

- Month 0: 3.0 mmol/L
- Month 6: 3.5 mmol/L
- Month 12: 4.0 mmol/L
- Month 18: 3.5 mmol/L
- Month 24: 3.0 mmol/L
- Month 30: 2.5 mmol/L

**PSA**

- Month 0: 3.0 µg/L
- Month 6: 2.5 µg/L
- Month 12: 2.0 µg/L
- Month 18: 1.5 µg/L
- Month 24: 1.0 µg/L
- Month 30: 0.5 µg/L

Change in A1c in Diabetic Men After Treatment with Testosterone

Testosterone-Replacement Therapy
Contraindications and Precautions

Contraindications
- Male breast cancer
- Prostate cancer
- Pregnant or breast-feeding women
- Uncontrolled heart failure

Precautions
- Benign prostatic hyperplasia, severe
- Hematocrit >55%
- Edema in patients with cardiac, renal, or hepatic disease

PSA and Testosterone

Qu: Does Testosterone replacement increase PSA?
~30%; increases PSA to normal levels

Qu: Does Testosterone increase prostate volume?
~15%
PSA concentrations After Testosterone or Placebo Treatment

Testosterone and Prostate Cancer

Qu: Does testosterone replacement increase prostate cancer incidence?  
No

Qu: Does hypogonadism protect against prostate cancer?  
No
Prostate cancer prevalence increases as T levels decline.

No significant differences in testosterone levels between those who develop prostate cancer and those who do not.

Prevalence of prostate cancer in testosterone-treated patients similar to that in general population.

No compelling evidence that testosterone has a causative role in prostate cancer.

Huggins C, Hodges CV. *Cancer Res.* 1941;1:293-297


<table>
<thead>
<tr>
<th></th>
<th>Without PIN</th>
<th>PIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>58.3 ± 8.9</td>
<td>62.3 ± 8.7</td>
</tr>
<tr>
<td>Mean PSA ± SD (ng/dl):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before TRT</td>
<td>1.53 ± 1.6</td>
<td>1.49 ± 1.1</td>
</tr>
<tr>
<td>At 12 mos</td>
<td>1.78 ± 1.6</td>
<td>1.82 ± 1.1</td>
</tr>
<tr>
<td>Change</td>
<td>0.25 ± 0.6</td>
<td>0.33 ± 0.6</td>
</tr>
</tbody>
</table>
Evaluate patient 3 months after testosterone initiation, then annually for response to treatment and symptom resolution.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T Concentrations</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>PSA and DRE Age &gt;40 years</strong></td>
<td>✓</td>
<td>✓</td>
<td>In accordance with prostate cancer screening guidelines, depending on the age and race of the patient</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td>✓</td>
<td></td>
<td>After 1-2 years of T therapy in hypogonadal men with osteoporosis or low trauma fracture consistent with regional standard of care</td>
</tr>
</tbody>
</table>

Guidelines for Testosterone Replacement Therapy in Hypogonadal Adult Men

When TRT is initiated, the therapeutic target should be to raise serum T level into a range that is mid-normal for healthy young men

Total Testosterone ~550-750ng/dL

If hematocrit is >55%, stop therapy, reduce dose, and/or evaluate for hypoxia and sleep apnea

Guidelines for Testosterone Replacement Therapy in Hypogonadal Adult Men

Refer to Urologist if

An increase in serum PSA >1.4 ng/mL within any 12-month period of T replacement

A PSA velocity of >0.4 ng/mL/yr using the PSA level at 6 months after initiation of T replacement as the reference

Case

54 yr old man presents with CC of fatigue, loss libido, erectile dysfunction with an unsatisfactory response to sildenafil 100 mg

PMHx: T2D, HTN
Meds: Lisinopril 10 mg bid
Metformin 1500 mg HS
Simvastatin 40 mg QOD

PE
VS: BP 145/90 BMI 34
No gynecomastia
Testicular vol 20 ml, normal DRE

Lab
Normal CMP, CBC, non-HDL 98
A1C 6.9%
T 220 ng/dL (280-1000) FT 33 pg/ml (35-155)
LH 4.5 IU/L (2-12) FSH 6.3 IU/L (1-12)

What is the next step in this patient’s evaluation?
1. Is this patient hypogonadal?
2. Would you treatment with testosterone?
3. Should Prolactin be measured?
4. Should other anterior pituitary hormones be measured?
5. Should MRI of pituitary be done?
6. Should bone mineral density be measured?
Clinical Evaluation of Men with Hypogonadotrophic Hypogonadism

Obtain DEXA if total testosterone <150ng/dL or history of low trauma fracture

Measure Prolactin to rule out prolactinoma

MRI of pituitary and assessment of anterior pituitary function if:
- Total testosterone is <150ng/dL
- Prolactin level is persistently elevated
- Headache or visual field defects

Evaluate for hemochromatosis if clinically indicated