Improving Quality of Life and Total Health in Men with Hypogonadism

Emerging Challenges in Primary Care: Update 2013

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Improving Quality of Life and Total Health in Men with Hypogonadism

Faculty Disclosures

- Pamela Ellsworth, MD
  Consultant – Pfizer
  Advisory Board – Pfizer, Allergan, Astellas
  Speaker – Allergan, Pfizer

- Mohit Khera, MD, MPH
  Consultant - Slate, Meda, Coloplast, Merck, Lilly and Auxilium

- Louis Kuritzky, MD
  No relationships to disclose.

Learning Objectives

After participating in this educational activity the participant should be able to:

1. To identify the prevalence, risk factors and co-morbid conditions associated with low testosterone
2. Recognize the importance of screening for low testosterone in men with erectile dysfunction prior to prescribing PDE-5 inhibitors
3. Assess the safety, efficacy and risks associated with the various testosterone formulations
4. Outline the challenges to short and long-term management and monitoring of testosterone therapy
On a scale of 1 to 5, please rate how confident you are with diagnosing and treating male hypogonadism?

1. Not all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Pre-Test Question 1

Case 1 –Arthur 67 y/o Diabetic

- Arthur is a 67 yr old obese male with type 2 DM
- Presents to PCP for routine follow-up
- States he has recently retired and his stress level is improved but he doesn’t feel any better
  - “I’ve gained 10 pounds, I just don’t have the energy or motivation to do much” and
  - “Now that I have the time, I just don’t have the interest in sex and I don’t think things are working so well”
Case 1

Based on Arthur’s age (67 yrs) alone, his risk of having androgen deficiency is:

1. < 20%
2. 20% to 40%
3. 40-50%
4. 50-60%
5. > 60%

Case 2 – Charles 67 y/o with HTN

- Charles is a 67 yr old male who complains of erectile dysfunction
  - History: HTN and gout
  - States “difficult to get a fully rigid erection” and when he does it doesn’t last long enough.
  - “Can I try one of those pills for ED doc?”

- PSH: cholecystectomy
- Meds: amlodipine, losartan, allopurinol
- ROS : denies LUTs, negative stress test, notes decreased libido and fatigue
- PE: prostate small without nodules/tenderness
Case 2

Screening for low testosterone and if indicated checking a serum testosterone prior to starting a PDE-5 inhibitor is recommended based on all of the following but:

1. Low testosterone predicts a poor response to PDE-5 inhibitors
2. Prevalence of testosterone deficiency is as high as 35% in ED patients
3. The addition of testosterone to PDE-5 inhibitors has been demonstrated to improve ED in men with testosterone level between 400 – 500 ng/dL
4. Low testosterone increases smooth muscle apoptosis, reducing erectile tissue relaxation and reducing nitric oxide production

Case 3 – Ralph 65 y/o with CAD

- Ralph is a 65 yr old morbidly obese male with type 2 DM, hypertension, dyslipidemia and hx of MI s/p angioplasty and stents. He smokes 1 pack of cigarettes per day and drinks one glass of wine in the evening.
- Chief Complaint:
  - Trouble sleeping, fatigue, and further weight gain
  - States “I am just not interested in sex anymore doc”
    “Its difficult doc, my wife sleeps in the guest bedroom because of my snoring”
- He wants testosterone therapy as he thinks it may help his energy level and libido but “my wife is worried about my heart”
Case 3 (continued)

- Meds: Simvastatin, Metformin, HCTZ, Metoprolol
- Family history: Father diagnosed at 76 yrs with prostate cancer, +CVD
- PE: BP:150/80
- Labs:
  - Serum testosterone of 300
  - FSH and LH nl
  - NL: Prolactin, PSA, CBC, TFTs and Liver profile
  - Total cholesterol 189

Case 3

Which of the following would be a concern for starting Ralph on testosterone replacement therapy?

1. Cardiovascular risk
2. Concomitant medications and drug-drug interactions
3. Sleep apnea
4. Smoking
Case 4 – Steve 56 y/o on T

- Steve is a 56 yr old African American male started on testosterone gel therapy for hypogonadism
- His initial labs prior to starting testosterone therapy include:
  - Serum testosterone 280 ng/dL
  - CBC normal
  - Cholesterol 180, HDL 80, LDL 100
  - PSA 1.6
  - Normal LFTs, Chem 7

Pre-Test Question 5

Case 4

Potential changes in his labs, related to the testosterone gel, that require long term monitoring include all of the following except:

1. Increase in PSA
2. Increase in Hematocrit
3. Decrease in total cholesterol
4. Increase in LFTs
How Is Androgen Deficiency Defined?

1. Laboratory evaluation only
2. Signs and symptoms of hypogonadism
3. Combination of signs/symptoms and laboratory evaluation
4. None of the above

Challenges in Defining Androgen Deficiency

• Symptoms: Nonspecific and modified by age, comorbidities, severity and duration of androgen deficiency, variation in androgen receptor sensitivity and prior testosterone therapy.

• Threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur and testosterone replacement therapy improves outcomes in general population not known

Case 1

- Arthur is a 67 yr old obese male with type 2 DM
- Presents to PCP for routine follow-up
- States he has recently retired and his stress level is improved but he doesn’t feel any better
  - “I’ve gained 10 pounds, I just don’t have the energy or motivation to do much” and
  - “Now that I have the time, I just don’t have the interest in sex and I am not sure that things are working so well”

Questions to Consider

- Does Arthur have symptoms of hypogonadism?
- What are the risk factors for hypogonadism?
- What is the prevalence of hypogonadism?
Symptoms and Signs Suggestive of Hypogonadism in Adult Male

- Reduced sexual desire and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body hair
- Very small or shrinking testes
- Low or azoospermia
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats
- Decreased energy, motivation, initiative, self-confidence
- Feeling sad or blue, depressed mood
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia
- Reduced muscle bulk and strength
- Increased body fat, BMI
- Diminished physical or work performance


How Low Is Low?

- 30% men with initial low T will have normal T on repeat
- Total testosterone usually adequate
- Free testosterone affected by SHBG
- No DEFINED “low” testosterone level and may vary with age
  - Total T < 200-250 ng/dL low
  - Total T 250 -350 ng.dL borderline

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Testosterone Distribution

- 2% SHBG Tightly Bound
- 30% ALBUMIN Weakly Bound
- FREE

68% Bioavailable = albumin bound + free


Conditions Which May Affect SHBG Levels

<table>
<thead>
<tr>
<th>Decrease SHBG concentration</th>
<th>Increase SHBG concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obesity</td>
<td>• Aging</td>
</tr>
<tr>
<td>• Nephrotic Syndrome</td>
<td>• Hepatic cirrhosis and hepatitis</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Use of glucocorticoids, progestins, androgenic steroids</td>
<td>• Anticonvulsants</td>
</tr>
<tr>
<td>• Acromegaly</td>
<td>• HIV</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>• Estrogen excess</td>
</tr>
</tbody>
</table>

Prevalence of Hypogonadism
(Androgen Deficiency)

- Hypogonadism due to all causes may affect up to 30% men\(^1\)
- Baltimore Longitudinal Study of Aging – hypogonadal defined as T < 325 ng/dl
  - > 60 yrs 20%
  - > 70 yrs 30%
  - > 80 yrs 50%
- Rate of decline in total testosterone levels – 3.2 ng/dL (0.11 nmol/L) per yr irrespective of age\(^2\)

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Biochemical Hypogonadism Prevalence: The HIM (Hypogonadism in Males) Study


Classification of Hypogonadism

<table>
<thead>
<tr>
<th>Primary Causes</th>
<th>Secondary Causes</th>
<th>Mixed Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular</td>
<td>Hypothalamic</td>
<td>Dual HPG Axis</td>
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<tr>
<td>Causes</td>
<td>Causes</td>
<td>Defects</td>
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<tr>
<td>Klinefelter</td>
<td>Kallman</td>
<td>Hemochromatosis</td>
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<tr>
<td>syndrome</td>
<td>syndrome</td>
<td>Sickler cell disease</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Constitutional</td>
<td>Glucocorticoid</td>
</tr>
<tr>
<td>Congenital or</td>
<td>delay in growth</td>
<td>treatment</td>
</tr>
<tr>
<td>acquired</td>
<td>and development</td>
<td></td>
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<tr>
<td>anorchia</td>
<td></td>
<td>Alcoholism</td>
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<tr>
<td>Testicular</td>
<td>Chronic illness</td>
<td>Aging</td>
</tr>
<tr>
<td>tumors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Prevalence of Low Testosterone in Other Conditions

HIV = 30%
ED = erectile dysfunction.


Etiology of Hypogonadism and Aging

• Age-related decreases in free testosterone more rapid than decreases in total testosterone\(^1\)

• SHBG levels increase with aging
  – Probably related to higher estradiol level from increased adipose tissue\(^1\)

• FSH and LH often mildly increased
  – Primary testicular failure in conjunction with secondary abnormality in LH burst frequency\(^2\)

• Circadian variation in serum testosterone levels often lost with aging \(^1\)

Diabetes and Hypogonadism

- Number of U.S. adults with diabetes increased from 5.5 million to 20.7 million from 1980-2010.

- Diabetic males twice as likely to be hypogonadal vs non-diabetic\(^3\)

- Prevalence of hypogonadism in diabetic men 33-50%\(^1\)

- Low testosterone predicts development of type 2 DM\(^2\)

---

DM & Biochemical Hypogonadism


The Metabolic Syndrome: Presence of Any 3 of 5 Components

1. Abnormality of blood sugar/insulin resistance
2. Enlarged waist circumference/BMI (visceral fat)
3. Elevated blood pressure
4. Elevated triglycerides
5. Decreased HDL cholesterol

Androgen deficiency/"hypogonadism"

Obesity  
Hypertension  
Dyslipidemia  
Hyperglycemia  
Insulin resistance

Androgen deficiency/"hypogonadism"

Relationship Between Total T and the Number of MetS Components

803 patients with sexual dysfunction, 236 (29.4%) diagnosed as having metabolic syndrome

*P<.0001 vs no metabolic syndrome components

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Hypogonadism Impacts Health and Quality of Life

- Social impact / emotional/cognitive
  - Decreased energy
  - Depressed mood
  - Sexual dysfunction
  - Cognitive dysfunction
- Physical impact
  - Loss of muscle mass and strength
  - Increased fat mass
  - Decreased energy
  - Reduced bone mineral density – fracture and frailty
- Other morbidities
  - Cardiovascular disease
  - Type 2 DM/Metabolic syndrome
  - Sexual dysfunction


Low Testosterone and Increased Mortality (N >500)

<table>
<thead>
<tr>
<th>Recent Studies</th>
<th>HR (95% CI)</th>
<th>Nature</th>
<th>Men, n</th>
<th>Follow-Up, y</th>
<th>Mortality</th>
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</thead>
<tbody>
<tr>
<td>Shores, 2006</td>
<td>1.88 (1.34–2.63)</td>
<td>Retrospective</td>
<td>858</td>
<td>8</td>
<td>All-cause</td>
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<tr>
<td>Laughlin, 2008</td>
<td>1.38 (1.02–1.85)</td>
<td>Prospective</td>
<td>794</td>
<td>20</td>
<td>CVD</td>
</tr>
<tr>
<td>Khaw, 2007</td>
<td>2.29 (1.60–3.26)</td>
<td>Prospective</td>
<td>2314 of 11,606</td>
<td>10</td>
<td>All-cause and CVD</td>
</tr>
<tr>
<td>Haring, 2010</td>
<td>2.32 (1.38–3.89)</td>
<td>Prospective</td>
<td>1954</td>
<td>7.2</td>
<td>All-cause</td>
</tr>
<tr>
<td></td>
<td>2.56 (1.15–6.52)</td>
<td></td>
<td></td>
<td></td>
<td>CVD</td>
</tr>
<tr>
<td>Malkin, 2010</td>
<td>2.27 (1.45–3.60)</td>
<td>Prospective</td>
<td>930</td>
<td>6.9</td>
<td>All-cause in men with coronary disease</td>
</tr>
<tr>
<td>Tivesten, 2009</td>
<td>1.65 (1.29–2.12)</td>
<td>Prospective</td>
<td>3014</td>
<td>4.5</td>
<td>All-cause</td>
</tr>
<tr>
<td>Menke, 2010</td>
<td>1.43 (1.09–1.87)</td>
<td>Prospective</td>
<td>1114</td>
<td>9</td>
<td>All-cause</td>
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<td>Vikan, 2009</td>
<td>1.24 (1.01–1.54)</td>
<td>Prospective</td>
<td>1568</td>
<td>11.2</td>
<td>All-cause</td>
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<tr>
<td>Corona, 2010</td>
<td>7.1 (1.8–28.6)</td>
<td>Prospective</td>
<td>1687</td>
<td>4.3</td>
<td>CVD</td>
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</table>

HR=hazard ratio; CI=confidence interval.
Who is At Risk?

The Younger

The Older

Who Should be Screened?

- Endocrine Society recommends screening in certain conditions
  - Infertility
  - Osteoporosis, low trauma fracture
  - Type 2 Diabetes Mellitus
  - Glucocorticoid, ketoconazole, opioid & other meds that affect testosterone production/metabolism
  - Sellar mass, radiation to sellar region or other diseases affecting sellar
  - End-stage renal disease, maintenance hemodialysis
  - HIV associated weight loss

Case 2

- Charles the 67 year old male with a history of HTN and gout with erectile dysfunction and decreased libido who wants an oral PDE-5 inhibitor

- Should he be screened for low testosterone?

- What is the relationship between hypogonadism and low testosterone?

Low Testosterone and Erectile Dysfunction

- Morning testosterone appropriate in men with complaints of ED – ISA, IDDM, EAU, EAA and ASA

- Prevalence of testosterone deficiency ranges from 1.7% to 35% in ED patients

- Low testosterone levels contribute to development of ED by increasing smooth muscle apoptosis, reducing erectile tissue relaxation and reducing nitric oxide production

Evaluation: History and Physical

**History**
- Libido, sexual function
- Medication use
- Anosmia, midline defects, cryptorchidism
- Trauma/surgery/infection
- Toxin – chemo, XRT
- Other endocrine abnls
- Osteoporosis/fracture
- Other ssx hypogonadism
- Voiding history


**Physical Examination**
- Blood pressure
- ? Fluid retention – edema
- Body hair
- Gynecomastia
- Genital exam – size, consistency of testes, varicocele, penile length
- DRE


Laboratory Evaluation

- Serum testosterone – obtain before 11am
  - Screening total T
  - Repeat – Total T, bioavailable T (includes Total T, bioavailable T and SHBG) or free T
  - LH, FSH, prolactin
  - Fasting blood lipid profile
  - Complete blood count
  - Liver function tests
  - PSA
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**Hypogonadism Algorithm**

```
Consistent Sx or Signs
PROBLEMS

Confirmed Low Testosterone

Secondary Cause

Low/WNL
LH

MRI Head
if Prolactin elevated

WNL
TST Replacement

Seek Other Dx

NO

YES

NO

YES

Rx

2o

Cause

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Case 3

- Ralph is a 65 yr old morbidly obese male with type 2 DM, hypertension, dyslipidemia and is compliant on therapy

- He complains of troubles sleeping, fatigue, further weight gain and states “I am just not interested in sex anymore doc”

- “Its frustrating doc, my wife sleeps in the guest bedroom because of my snoring”

- He wants testosterone therapy as he thinks it may help his energy level and libido

- Labs: serum testosterone of 250, FSH and LH in the high nl range, prolactin nl, PSA nl, CBC nl, TFTs nl, Liver profile nl, Total cholesterol 189
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**ARS Question**

Is there any further evaluation you would consider prior to treating Ralph?

1. Stress test
2. Evaluation for sleep apnea
3. MRI of head for evaluation of pituitary adenoma
4. No

---

**Conditions in Which TRT is Not Recommended**

- Moderate to high risk of adverse outcomes
  - Unevaluated prostate nodule or induration
  - PSA > 4 ng/ml (> 3 ng/ml in higher risk pts)
  - Hematocrit > 50%
  - Severe lower urinary tract symptoms assoc with BPE (ie AUA/IPSS > 19)
  - Uncontrolled/poorly controlled CHF
  - Untreated sleep apnea

- Very high risk of adverse outcomes
  - Metastatic prostate cancer
  - Breast cancer

(Bhasin S et al. J Clin Endocrinol Metab 2010; 95(6): 2536-2559)
Case

- Joe is an oligospermic 45 yr old male undergoing infertility therapy with hypogonadism secondary to a history of bilateral intra-adominal testes.

What formulation of testosterone therapy would you consider for Joe?

Would you caution Joe regarding any formulations of testosterone therapy?
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### Testosterone Formulations Available and Approved for Use in U.S.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Regimen</th>
<th>Pharmacokinetic profile</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>T enanthate or cypionate</td>
<td>150-200mg IM q 2wk or 75-100mg/wk</td>
<td>Supraphysiological T that declines to low T over interval</td>
<td>inexpensive; self-admin; dose flexibility</td>
<td>Requires injection, peaks and troughs in T levels</td>
</tr>
<tr>
<td>1% T gel or solution</td>
<td>sachets, tubes and pumps 5-10 T gel - 50-100mg T QD</td>
<td>Physiological level T and E2</td>
<td>Restores T, dose, flexibility, easy to use, min skin issues</td>
<td>Potential of skin-skin transfer, skin irritation, mod high DHT levels</td>
</tr>
<tr>
<td>Transdermal T patch</td>
<td>1 or 2 patches QD-5-10mg T/day – nonpressure area</td>
<td>Restores T, DHT, E2</td>
<td>Ease of use, restores T</td>
<td>Some have low-nT and need 2 patches QD – skin irritation</td>
</tr>
<tr>
<td>Buccal, bioadhesive T tablets</td>
<td>Absorbed from bucal mucosa – 30mg BID</td>
<td>Restores T and DHT</td>
<td>Restores T</td>
<td>Gum-related adverse events in 16% men</td>
</tr>
<tr>
<td>T pellets</td>
<td>10-12 pellets SubQ, dose and regimen vary with formulation</td>
<td>T peaks at 1 mos – sustained for 3-6 mos, varying with formulation</td>
<td>Restores T</td>
<td>Surgical incision for insertion, pellets may extrude</td>
</tr>
</tbody>
</table>

### Testosterone Risks

- One of my patients presented to my office for a routine follow up.
- I walked in to see her and she was covering her mouth with a tissue.
- I asked if she was feeling alright.
- She said that her husband's testosterone gel replacement that I had been prescribing to him was apparently working very well for him and her.
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With that she pulled away her tissue to show me the results!

Different Testosterone Levels After Replacement Therapy

Adapted from Bhasin and Bremner. J Clin Endocrinol Metab. 1997;82:3-8
Monitoring Treatment

- Morning T level
  - 2-3 wks of starting gel, patch or buccal T
  - 8 wks if injectable form of T used – check T level midway between injections – goal 400-700ng/dl 1 wk after injection

- Check T levels 3 to 6 months after start therapy

- Baseline PSA, at 3-6 months, per prostate cancer screening

- Hematocrit at baseline, 3-6 months and yearly
  - d/c if Hct > 54% until decreases to safe level, reinitiate at lower dose

- Lipid profile after 6-12 months then yearly


Monitoring Cont.

- DRE and prostate-related symptom assessment q 6-12 mos

- Assess for gynecomastia, alopecia

- Assess for fluid retention

- Sleep apnea – TRT may worsen sleep apnea

- Impaired spermatogenesis – TRT can cause oligospermia or azoospermia which may not be reversible

- Weight gain

- Acne

Case 4

• Steve the 56 yr old African American male was started on 7.5mg of testosterone gel QD with an increase in his PSA from 1.6 to 3.1 during the first year of treatment

• Is this a concern?

• What are the potential affects of testosterone replacement therapy on the prostate and PSA?

• What change in PSA is acceptable?

Urologic Consultation Recommended if:

• If an increase in serum or plasma PSA > 1.4 ng/ml within any 12 month period of T treatment

• PSA velocity of > 0.4ng/ml/yr using PSA level after 6 mos of T admin as reference

• Detection of prostate abnormality on DRE

• AUA/IPSS symptom score > 19

(Bhasin S et al. J Clin Endocrinol Metab 2010; 95(6): 2536-2559)
Case 2

- Charles the 67 yr old male with a history of HTN and gout with ED and decreased libido who failed an oral PDE-5 inhibitor

- Can testosterone replacement therapy improve his response to ED therapy?

1. Yes
2. No
3. Not sure

Testosterone Replacement Therapy in Hypogonadal Men with ED
Impact on Response to PDE-5 Inhibitors

- 30%-35% of ED patients fail PDE-5 inhibitors – in some due to testosterone deficiency

- Animal studies - pharmacologic activity of PDE-5 inhibitors appears to be androgen dependent

- Testosterone deficiency seems to predict a poor response to PDE-5 inhibitors and addition of testosterone helpful in 5 uncontrolled trials

Testosterone Replacement Therapy in Hypogonadal Men who Fail PDE-5 Inhibitors

- Double blind Placebo controlled study
- 173 men, 45-80 yrs, failed PDE-5 inhibitors
- Baseline total T ≤ 3 ng/ml or bioavailable T ≤ 1ng/ml.
- Tadalafil 10mg QD x 4 wks, if not successful, randomized to PBO vs 1% testosterone gel (50mg/5g) increased to 10mg if needed – 12 weeks

CONCLUSION

- T + PDE-5 inhibitors beneficial in men with low baseline T levels (≤ 3ng/ml)
- The lower the baseline T, the better the effect

(Buvat J et al. J Sex Med 2011; 8: 284-93)

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Case 1

Arthur the 67 yr old obese male with type 2 DM
- Weight gain
- Lack of energy and motivation
- Lack of interest in sex and a question of erectile dysfunction

Aside from the impact on sexual awareness will testosterone replacement therapy have any other benefit to Arthur?
Improving Quality of Life and Total Health in Men with Hypogonadism

**The effect of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRIUS)**

Mohit Khera, Rajib K. Bhattacharya, Gary Blick, Harvey Kushner, Dat Nguyen & Martin M. Miner

1 Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA; 2 University of Kansas Medical Center, Kansas City, KS, USA; 3 Circle Medical LLC, Norwalk, CT, USA; 4 Auxilium Pharmaceuticals, Malvern, PA, USA, and 5 Miriam Hospital Men’s Health Center, Warren Alpert School of Medicine, Brown University, Providence, RI, USA

- Multicenter, 12-month observational registry ($N = 849$) of hypogonadal men prescribed testosterone gel
- Depression symptoms measured using PHQ-9
- Baseline - 92.4% some level of depressive symptoms, 17.3% severe depressive symptoms
- After 12 months of TRT - patients with severe depressive symptoms decreased from 17.3% to 2.1%
- Those on anti-depressants experienced significant improvement in PHQ-9 at 12 months

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**Metabolic Syndrome Reversed After 52 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>Adult Treatment Panel III</th>
<th>International Diabetes Federation</th>
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<td>31.3</td>
<td>81.3</td>
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<tr>
<td>D+E+T group</td>
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P = .004

P = .003

Effects of TRT on Surrogate Markers for Cardiovascular Risk

1. Decreases in serum cholesterol as early as 4 wks (most by 3 months), max effect at 12 months
2. Decrease in triglycerides at 4 wks, max effect at 12 wks
3. LDL decreases but slower response, max effect at 24 months
4. Variable effect on HDL
5. Testosterone cypionate injections may be associated with adverse effects on HDL (21% decrease with 300mg IM dose)

Impact of TRT on CVD

1. Men with chronic stable angina, ischemic threshold increased after 4wks with TRT
2. Exercise capacity in men with CHF increased after 12wks (improvement in skeletal muscle performance)
3. Testosterone gel vs PBO in elderly frail men trial terminated due to a greater number of cardiac events in the TRT group
   - More severe CAD in TRT group
   - Allowed for rapid escalation to 150mg (> recommended dosing)
   - Inadequate validation of many of the events

References:

Clinical Manifestations Of Late-Onset Hypogonadism and Their Anticipated Response To Treatment

<table>
<thead>
<tr>
<th>System/Function</th>
<th>Aging</th>
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<tr>
<td>Erectile Function</td>
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<td>↑</td>
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<tr>
<td>Sexual desire</td>
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<td>↑</td>
</tr>
<tr>
<td>Mood/cognition</td>
<td>→/↓</td>
<td>↑ (suspected not/not proved)</td>
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<td>↓</td>
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<tr>
<td>Sleep disturbances</td>
<td>→/↓</td>
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<td>Vasomotor (hot flashes)</td>
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<td>Quality of life</td>
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<td>Hematocrit</td>
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<td>Bone mass</td>
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<tr>
<td>Hair and skin changes</td>
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</table>

Modified from Campbell’s Urology. Chapter 29, page 811. 10th edition

Conclusions

• Risk of male hypogonadism increases with age
• Male hypogonadism has a significant impact on QoL and health
• Obesity and type 2 DM associated with male hypogonadism
• Men with ED should be assessed for other signs and symptoms of hypogonadism and if present should be screened for hypogonadism
• Diagnosis of hypogonadism relies on presence of symptoms and low T
• Evaluation includes H & P plus T level, other labs as indicated
• TRT improves symptoms and variety of QoL and health parameters
• TRT is not contraindicated in men with CVD, rather it may be beneficial, except those with severe CHF
• An understanding of the risks of testosterone therapy and careful monitoring is indicated
Case 1

Based on Arthur’s age (67 yrs) alone his risk of having androgen deficiency is:

1. < 20%
2. 20% to 40%
3. 40-50%
4. 50-60%
5. > 60%

Post-Test Question 1

Case 2 – Charles 67 y/o with HTN

- Charles is a 67 yr old male who complains of erectile dysfunction
  - History: HTN and gout
  - States “difficult to get a fully rigid erection” and when he does it doesn’t last long enough.
  - “Can I try one of those pills for ED doc?”

- PSH: cholecystectomy
- Meds: amlodipine, losartan, allopurinol
- ROS: denies LUTs, negative stress test, notes decreased libido and fatigue
- PE: prostate small without nodules/tenderness
Case 2
Screening for and if indicated checking a serum testosterone prior to starting a PDE-5 inhibitor is recommended based on all of the following but:

1. Low testosterone predicts a poor response to PDE-5 inhibitors
2. Prevalence of testosterone deficiency is as high as 35% in ED patients
3. The addition of testosterone to PDE-5 inhibitors has been demonstrated to improve ED in men with testosterone level between 400 – 500 ng/dL
4. Low testosterone increases smooth muscle apoptosis, reducing erectile tissue relaxation and reducing nitric oxide production

Case 3 – Ralph 65 y/o with CAD
- Ralph is a 65 yr old morbidly obese male with type 2 DM, hypertension, dyslipidemia and hx of MI s/p angioplasty and stents. He smokes 1 pack of cigarettes per day and drinks one glass of wine in the evening.
- Chief Complaint:
  - Trouble sleeping, fatigue, and further weight gain
  - States “I am just not interested in sex anymore doc”
  - “Its hard doc, my wife sleeps in the guest bedroom because of my snoring”
- He wants testosterone therapy as he thinks it may help his energy level and libido but “my wife is worried about my heart”
Case 3 (continued)

- Meds: Simvastatin, Metformin, HCTZ, Metoprolol
- Family history: Father diagnosed at 76 yrs with prostate cancer, +CVD
- PE: BP: 150/80

- Labs:
  - Serum testosterone of 300
  - FSH and LH nl
  - NL: Prolactin, PSA, CBC, TFTs and Liver profile
  - Total cholesterol 189

Case 3

Which of the following would be a concern for starting Ralph on testosterone replacement therapy?

1. Cardiovascular risk
2. Concomitant medications and drug-drug interactions
3. Sleep apnea
4. Smoking
Case 4 – Steve 56 y/o on T

- Steve is a 56 yr old African American male started on testosterone gel therapy for hypogonadism
- His initial labs prior to starting testosterone therapy include:
  - Serum testosterone 280 ng/dL
  - CBC normal
  - Cholesterol 180, HDL 80, LDL 100
  - PSA 1.6
  - Normal LFTs, Chem 7
  - Normal Chem 7

Potential changes in his labs, related to the testosterone gel, that require long term monitoring include all of the following except:

1. Increase in PSA
2. Increase in Hematocrit
3. Decrease in total cholesterol
4. Increase in LFT’s
Post-Test Question 5

On a scale of 1 to 5, please rate how confident you are with diagnosing and treating male hypogonadism?

1. Not all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Post-Test Question 6

How likely are you to implement strategies learned from this presentation in your practice?

1. Very Likely
2. Somewhat Likely
3. Unlikely
4. Not Applicable
Which of the statements below describes your approach to diagnosing and treating male hypogonadism?

1. I do not manage male hypogonadism, nor do I plan to this year.

2. I did not manage male hypogonadism before this course, but as a result of attending this course I’m thinking of managing it now.

3. I do manage male hypogonadism and this course helped me change my treatment methods.

4. I do manage male hypogonadism and this course confirmed that I don’t need to change my treatment methods.

Questions?
Improving Quality of Life and Total Health in Men with Hypogonadism

Testosterone treatment and mortality in men with low testosterone levels

Shores M J Clin Endocrin Metab 2012 Jan;97(6):2050-8, Epub 2012 Apr 11

NACE - Emerging Challenges in Primary Care: Update 2013
Male Hypogonadism - 39
Benefits of TRT – What is the evidence?

• Bone mineral density
  – 8 studies demonstrate improvement in BMD\(^1\)
  – Nursing home patients – of those who sustained hip fracture 66% hypogonadal (T<300ng/DL)\(^2\)

• Mood/cognitive function
  – 6 of 13 studies showed TRT improved at least some aspects of cognitive function and/or mood\(^1,3\)

• Body Composition and Muscle Strength –
  – 15/17 studies found TRT increased lean body mass and/or decreased fat mass – effect on strength less consistent \(^1\)

Assessing the Benefits of TRT – What is the evidence?

• Improving Metabolic Syndrome, Type 2 DM, CVD
  – 14 reviewed studies of effects of TRT on glycemic control, serum lipids and CVD 2 mos to 3 years duration \(^1\)
    • TRT decreases fat mass
    • Evidence that TRT improves glycemic control and lipid profile somewhat weaker and less consistent – level C
    • Statistically significant improvements in waist circumference, fasting blood glucose and BP in MetS+ patients after 12 months of TRT\(^2\)


\(^2\)Miner M et al. Postgraduate Medicine 2008; 120(3): 130-153; \(^2\)Bhattacharya et al. BMC Endocrine Disorders 2011, 11:18,
Testosterone Deficiency and Cardiovascular Disease

- Low testosterone associated with increased mortality

  - MMAS – men with low T nearly twice as likely to die from all causes and CVD compared to those with normal T\textsuperscript{1}

  - EPIC study – baseline T levels inversely related to deaths from all causes, CVD and malignancy after controlling for confounders\textsuperscript{2}

  - Ranchero Bernardo Study – low T predicted increased risk of CV mortality (HR 1.38) as did low bioavailable T levels\textsuperscript{3}

\textsuperscript{1}Khaw KT et al. Circulation 2007; 116: 2694-701; \textsuperscript{2}Stellato RK et al. Diabet Care 2000; 23: 490-4; \textsuperscript{3}Oh J et al. Diabet Care 2002; 25: 55-60

TRT Decreased Cardiac Events/Procedures-
Meta-analysis of 1000 patient-years

Y axis – events