Session 3: Testosterone Replacement Therapy: Controversies and Answers

- **Testosterone Update: Facts, Myths, Reality** – Dr Guay
- **Identification and Evaluation of the At-Risk Patient** – Dr Miner

### Learning Objectives
1. Identify the signs and symptoms of hypogonadism and their clinical presentation
2. Identify the role of hypogonadism in diabetes, obesity, metabolic syndrome, and cardiovascular disease
3. Select options available to effectively treat hypogonadism
4. Implement monitoring strategies for patients on testosterone replacement therapy

### Faculty

**Martin Miner, MD**
Chief of Primary Care and Community Medicine
The Miriam Hospital
Clinical Associate Professor of Family Medicine and Urology
Warren Alpert Medical School
Brown University
Providence, Rhode Island

Dr Martin Miner clinical associate professor of family medicine and urology at Warren Alpert Medical School in Providence, Rhode Island, has practiced preventive and primary care medicine for more than 28 years and is currently chief of family and community medicine at The Miriam Hospital. He is the author of more than 75 publications in the areas of erectile dysfunction and cardiovascular disease, benign prostatic hyperplasia and lower urinary tract symptoms in reference to male sexuality, and hormonal replacement therapy in men. Dr Miner is president elect of the American Society for Men’s Health, associate editor of the Journal of Men’s Health, and serves on multiple journal boards and reviews for several publications. He is currently active in several research studies on men’s health, and was the recipient of the dean’s teaching excellence award in 2003 and 2007.

**André T. Guay, MD, FACP, FACE**
Tufts University School of Medicine
Boston, Massachusetts
Director, Center for Sexual Function/Endocrinology
Lahey Clinic Northshore
Peabody, Massachusetts

Dr André Guay founder and director of the center for sexual function at Lahey Clinic Northshore in Peabody, Massachusetts, earned his medical degree from the New Jersey College of Medicine and Dentistry of New Jersey, Newark, then served an internship and residency in internal medicine at Saint Vincent Hospital in Worcester, Massachusetts. He continued with specialty training in endocrinology and metabolism at the Mayo Clinic in Rochester, Minnesota. Beginning as a staff physician at the Naval Medical Center in Portsmouth, Virginia, Dr Guay advanced to head of the division of endocrinology. He is affiliated
with Tufts Medical School, Boston, Massachusetts, as well as serving as senior staff physician in the department of endocrinology at the Lahey Clinic Medical Center in Burlington, Massachusetts.

Research interests span male infertility and sexual dysfunction to the relationship of breast cancer and androgens in women, with a current concentration on male and female testosterone deficiency. His numerous published works concern reproductive endocrinology and neuroendocrinology, and he has been principal investigator or collaborator on more than 25 related research projects since 1975. Recipient of the 2006 Lahey Clinic Research Prize, Dr Guay instructs endocrinology fellows at that institution.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

Dr Miner has no financial relationships to disclose.

Dr. Guay has no financial relationships to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at Miller Medical Communications, LLC, report the following:

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Suggested Reading List


SESSION 3
11am–12:15pm
Testosterone Replacement Therapy: Controversies and Answers

SPEAKERS
Martin Miner, MD
André T. Guay, MD, FACP, FACE

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Dr Miner has no financial relationships to disclose.
► Dr Guay has no financial relationships to disclose.

Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Testosterone Replacement Therapy: Controversies and Answers

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Clinical Professor of Medicine
Tufts University School of Medicine
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Lahey Clinic, North Shore
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Martin M. Miner, MD
Co-Director, Men’s Health Center
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Drug List

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<thead>
<tr>
<th>Generic Name</th>
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<tr>
<td>Testosterone buccal system</td>
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<td>Testosterone cypionate</td>
<td>Depo-Testosterone</td>
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<td>Delatestryl</td>
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<td>Testosterone pellets</td>
<td>Testopel</td>
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<td>Testosterone topical gel</td>
<td>Fortesta, AndroGel, Testim</td>
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<tr>
<td>Testosterone topical solution</td>
<td>Axiron</td>
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<tr>
<td>Testosterone transdermal system</td>
<td>Androderm, Testoderm</td>
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<td>Testosterone undecanoate</td>
<td>Andriol (not available in the United States)</td>
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Testosterone Update
Facts, Myths, Reality

André T. Guay, MD
Clinical Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts
Director, Center for Sexual Function/Endocrinology
Lahey Clinic, North Shore
Peabody, Massachusetts
How Is Hypogonadism Defined by The Endocrine Society?

- A clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa caused by the disruption of one or more levels of the hypothalamic-pituitary-testicular (HPT) axis.


Word Soup

- AD—Androgen Deficiency Syndrome
- ADAM—Androgen Deficiency Syndrome in the Aging Male
- Andropause, or Male Menopause
- LOH—Late Onset Hypogonadism
- Low T—Low Testosterone
- Male Hypogonadism
- TDS—Testosterone Deficiency Syndrome
- DEFINITION: signs and symptoms of androgen deficiency plus a biochemical level that is low or borderline (if borderline, a 3-4 month trial may be offered).


Why Do We Need Testosterone?

Does everyone need to be a baseball player?

The Reality of Testosterone

Physiological Effects of Testosterone in Male Adults

- Maintains reproductive tissues
- Stimulates spermatogenesis
- Stimulates and maintains sexual function
- Increases body weight and nitrogen retention
- Increases lean body mass
- Maintains bone mass
- Promotes sebum production, and axillary and body hair growth
- Stimulates erythropoiesis


Clinical Implications of Testosterone Deficiency

Adapted from Maggio M, Basaria S. J Sex Med. 2006;3(2):201-204.

The Dilemma Is That Low Testosterone Levels Are Associated With Increased Mortality

- VA Puget Sound 8-year study of 858 men
- Low T <250 ng/dL or a free T <0.75 ng/dL
- All-cause mortality was 34.9% in men with low T and 23.1% in men with normal T

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</th>
<th>Mortality</th>
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<tr>
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<td>Retrospective</td>
<td>856</td>
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<td>Laughlin, 2008</td>
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<td>Retrospective</td>
<td>794</td>
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<td>Khaw, 2007</td>
<td>2.39 (1.60–3.86)</td>
<td>Prospective</td>
<td>2314</td>
<td>10</td>
<td>All-cause and CVD</td>
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<td>Harting, 2010</td>
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<td>Prospective</td>
<td>1954</td>
<td>7.2</td>
<td>All-cause</td>
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<td>1954</td>
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<td>2.27 (1.45–3.40)</td>
<td>Prospective</td>
<td>920</td>
<td>6.9</td>
<td>All-cause in men with coronary disease</td>
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<td>3014</td>
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<td>Prospective</td>
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<td>Prospective</td>
<td>1568</td>
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<td>Corona, 2010</td>
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<td>Prospective</td>
<td>1687</td>
<td>4.3</td>
<td>CVD</td>
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</table>

CVD=cardiovascular disease.

The Hypothalamic-Pituitary-Testicular Axis

FSH=follicle-stimulating hormone
GnRH=gonadotropin-releasing hormone
LH=luteinizing hormone

Testosterone in the Blood

Free Testosterone
Testosterone Bound to Albumin
Testosterone Bound to SHBG

SHBG=sex hormone-binding globulin.

Not All Testosterone Is Available

Free + Bound to Albumin = Bioavailable Testosterone (BAT)
Bound to SHBG = Not Available

Primary Hypogonadism

- Known as Hypergonadotropic Hypogonadism
- What occurs?
  - Testicular dysfunction
  - Normal hypothalamic/pituitary function
- What results are seen?
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Elevated gonadotropin levels, LH and FSH


Secondary Hypogonadism

- Known as Hypogonadotropic Hypogonadism
- What occurs?
  - Normal testicular function
  - Hypothalamic/pituitary dysfunction
- What results are seen?
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Low or low-normal gonadotropin levels, LH and FSH

Combined Primary and Secondary Hypogonadism

- Known as **Mixed Hypogonadism**
  - Aging
  - Hemochromatosis
- What occurs?
  - Testicular dysfunction
  - Hypothalamic/pituitary dysfunction
- What results are seen?
  - Low testosterone levels
  - Impairment of spermatogenesis
  - Low or low-normal gonadotropin levels (variable)

Obesity, Metabolic Syndrome, Diabetes, and Hypogonadism

**FACT**
- It is not known whether hypogonadism is the cause or the consequence of these conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
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<tr>
<td>Obesity</td>
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<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Hyperlipidemia</td>
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Hypogonadism and Cardiovascular Disease

**MYTH**
- Men have a higher risk of cardiovascular disease, so it must be testosterone
Hypogonadism and Cardiovascular Disease

**FACT**
- Vascular tissue contains androgen receptors


**FACTS**
- Low testosterone is associated with increased cardiovascular events and the following risk factors:
  - Dyslipidemia (including low high-density lipoprotein [HDL])
  - Hypertension
  - Obesity
  - Diabetes
- Testosterone has an inverse relationship with the following:
  - Body mass index
  - Waist circumference
  - Low-density lipoprotein (LDL)
  - Triglycerides
  - Insulin resistance


Hypogonadism in Men With Diabetes
A Concerning Prevalence

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
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<tr>
<td>Mulligan</td>
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<tr>
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<td>Dhindsa</td>
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</tbody>
</table>


Obesity, Metabolic Syndrome, and Hypogonadism

**Risks associated with obesity**
- Type 2 diabetes
- Low total testosterone levels
- Reduced SHBG levels

**Elements of metabolic syndrome are correlated with low testosterone**
- Central obesity
- Hypertension
- Reduced HDL
- Raised triglycerides
- Raised fasting plasma glucose


European Male Aging Study (EMAS)
Relationship between age, BMI, and hormones

European Male Aging Study (EMAS)
Connecting Hypogonadism-Obesity-Insulin Resistance

"Silent Killers" – The Metabolic Syndrome

Abdominal obesity
Insulin resistance
Dyslipidemia
Hypertension
Low Testosterone

Visceral fat tissue

3-fold risk for CVD


BMI and waist circumference are not the same...
Count on waist circumference

189 cm, 93 kg = BMI 26
190 cm, 94 kg = BMI 26

Waist circumference > Waist circumference
Testosterone < Testosterone

Connecting Hypogonadism With Osteoporosis

Primary causes
- Corticosteroid use
- Cushing syndrome
- Hypogonadism
- Excessive alcohol or tobacco consumption

Secondary causes
- Secondary smoke exposure
- Low calcium intake
- Vitamin D deficiency or insufficiency


Osteoporosis and Hypogonadism

FACTS
- Testosterone and estradiol levels positively associated with BMD (stronger for estradiol)
- Testosterone replacement increased spine BMD and trabecular connectivity
- However, studies are limited and none used fracture as an end point

BMD= bone mineral density.


Identification and Evaluation of the At-Risk Patient

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Symptoms and Signs Suggestive of Hypogonadism

More Specific Symptoms and Signs
- Incomplete or delayed sexual development
- Reduced libido
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body hair (axillary or pubic), reduced shaving
- Very small (<5ml) or shrinking testis
- Inability to father children (azospermia, oligospermia)
- Height loss, osteoporosis, low trauma fracture, low BMD
- Hot flushes, sweats

Symptoms and Signs Suggestive of Hypogonadism

**Less Specific Symptoms and Signs**
- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

**Case: Henry…. History**
- Henry, a 48-year-old man, university professor, and his wife meet with his PCP for a second opinion after being diagnosed with hypogonadism and offered TRT
- Low sexual desire in spite of happy marriage, mild ED, and not as focused during lectures in past 2 years
- Both parents diagnosed with type 2 diabetes in their early 50s
- Multiple allergies and gastric esophageal reflux disease
- PMH positive for HTN, dyslipidemia

**Henry: Current Medications**
- Omeprazole
- Loratadine
- Multivitamins
- Herbs (Maca Root)
- Atorvastatin 20 mg
- Lisinopril 20mg/HCTZ 12.5 mg

**Henry: Physical Examination**
- Height: 68 inches
- Weight: 205 lb
- Waist circumference: 40 inches
- BMI: 31.2 kg/m²
- Stage 1 obesity
- BP 140/82 on treatment
- Genital examination: normal
- DRE: normal

**Screening for Hypogonadism**

**FACTS**
- No symptoms are unique to hypogonadism
- Screening with testosterone level is appropriate when presented with symptoms
- Diagnosis of hypogonadism is made when 1 or more symptoms are combined with 2 low testosterone levels <300 ng/dL

**MYTH**
- Only symptomatic patients should be screened
High Prevalence of Hypogonadism in Various Conditions May Warrant Screening

EXPERT OPINION

- Infertility
- Osteoporosis, low trauma fracture
- Type 2 diabetes mellitus
- Glucocorticoid, ketoconazole, opioids, or other medications that affect testosterone metabolism or production
- Moderate to severe COPD
- Sellar mass, radiation to the sellar region, or other diseases of the sellar region
- End-stage renal disease, maintenance hemodialysis
- HIV-associated weight loss
- Dyslipidemia
- Hypertension

COPD=chronic obstructive pulmonary disease.


The ADAM Questionnaire

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 the answer is "yes" to question 1 or 7, or at least 3 of the other questions, low testosterone may be present.


The Diagnosis of Hypogonadism

- Total Testosterone <300 ng/dL
- Free Testosterone <50 pg/mL
- Bioavailable Testosterone <70 ng/dL

*Btotal testosterone is the most frequently used laboratory test for the diagnosis of hypogonadism in the medical literature.


What Is Considered to Be a Low Serum Testosterone Level?

- Total Testosterone <300 ng/dL
- Free Testosterone <50 pg/mL
- Bioavailable Testosterone <70 ng/dL


Treatment Goals

- Manage expectations by partnering with the patient
- Match appropriate treatment to the individual patient
- Increase blood testosterone levels to the normal (eugonadal) range and avoid supraphysiological peaks
- Ameliorate or cure symptoms


Common Sense in Initiating Testosterone

- Joint decision of informed patient and provider
- Short-acting preparations are better in the beginning to assess tolerability
- Start low and go slow

Henry: Laboratory Results

- Total testosterone – 230 and 210 ng/dL (300 ng/dL-1000 ng/dL)
- Free testosterone – 30 pg/mL (<50 pg/mL)
- Follicle-stimulating hormone – 6 IU/L [1 - 18]
- Luteinizing hormone – 9 IU/L [2 - 18]
- Prolactin – normal; Iron – normal
- TG 200 mg/dL; HDL 34 mg/dL
- Thyroid-stimulating hormone – 3.20 [0.52 - 4.89]
- Fasting blood sugar – 109 mg/dL
- PSA – 0.7 ng/mL

Henry: Conclusion

- HTN is one of the most common comorbidities with TD
- Treatment with TRT plus lifestyle changes are much more effective than TRT alone
- TRT may reverse early type 2 diabetes
- TRT may or may not improve ED; this remains controversial


Non-pharmacological Treatments Include:

- Reversal of OSA
- Exercise and weight loss
- Stress reduction (yoga, meditation)
- Reduction of opioid therapy
- Return to normal sleep architecture and quantity
- Cognitive behavioral treatment of anxiety
- All improvements in cardiometabolic health

Pharmacologic Treatment Options

- Intramuscular injections
- Transdermal patches
- Transdermal gels and solutions
- Buccal tablets
- Subcutaneous pellets
- Oral tablets or capsules (not available in the United States)


Intramuscular Injections

Pros
- History (available for 50 years)
- Self administration
- Inexpensive
- Flexibility of dosing

Cons
- Pain
- Frequency of injections (every 2-4 weeks)
- Symptomatic peaks and troughs resulting in variations in breast tenderness, libido, emotional stability, energy


Transdermal Patches

Pros
- Nonscrotal patches
- Nighttime application results in good approximation of normal circadian plasma testosterone levels
- Flexibility of dosing

Cons
- Scrotal patches
- Skin irritation

Transdermal Gels and Solutions

Pros
- Application sites (upper arm, shoulder, axilla)
- Low skin irritation
- Invisibility of application
- Flexibility of dosing
- Various concentrations

Cons
- Transfer to others (risk is minimized with high-dose, low-volume preparations)
- Low skin irritation


Buccal Tablets

Pros
- Application site
- Relative invisibility
- Bypass first-pass hepatic metabolism
- Slow release

Cons
- Application site
- Inadvertent loss of tablet
- Gum and buccal irritation, alteration in taste
- Twice-daily dosing
- No dose titration


Subcutaneous Pellets

Pros
- History (started in 1940s)
- Relative invisibility
- Long-acting
- Slow release

Cons
- Painful application
- Surgical procedure unlikely to be used by the PCP
- Long-acting
- Inconvenient removal
- No dose titration
- Procedure can result in infection, fibrosis, or pellet extrusion

PCP=primary care physician:

Results of Therapy

FACTS
- Restore sexual functioning and libido
- Restore sense of well-being
- Prevent loss or improve bone density
- Restore muscle mass and strength
- Improves mood


Effects on Diabetes From Testosterone Therapy

Study Design
- A 12-month, multicenter, prospective, randomized, double-blind, placebo-controlled study

Population
- 220 hypogonadal men with type 2 diabetes and metabolic syndrome

Results
- Significantly improved insulin resistance in all patients (by 15.2% at 6 mos and by 16.4% at 12 mos)
- Significantly improved HDL (0.049 mmol/L) and LDL cholesterol (0.210 mmol/L), lipoprotein-a (0.31 mmol/L) in selected groups
- Significantly improved sexual health (increase of 4.8 on IIEF)


IIEF=International Index of Erectile Function.
Survival of Treated Versus Untreated Testosterone-Deficient Men in VA Population: Does TRT Improve Mortality?

- 1031 men aged >40 years, testosterone <250 ng/dL
- Mortality: 10.3% treated, 20.7% untreated (P<.0001)

Mortality: 10.3% treated, 20.7% untreated (P<.0001)

Cardiovascular Effects From Testosterone Therapy

**FACTS**

- Several studies suggest that high testosterone levels may have favorable effect on risk of cardiovascular disease
- A 2007 meta analysis of randomized trials showed only weak support for exogenous testosterone replacement on cardiovascular events
- In 2010, a study on older men with limitations in mobility and high prevalence of chronic disease was stopped after showing increased risk of cardiovascular adverse events: TOM Study
- Large randomized trials are needed to better assess consequences of testosterone on cardiovascular risk

Precautions in Using Testosterone

- BPH or LUTS
- Edema in patients with preexisting cardiac, renal, or hepatic disease
- Gynecomastia
- Precipitation or worsening of sleep apnea
- Azoospermia; testicular atrophy
- Erythrocytosis

Contraindications in Using Testosterone

- Male breast cancer
- Prostate cancer: but not absolute
- Known allergic reactions or sensitivities to substrates used in all types of TRT

Provider Concerns Regarding Testosterone

**MYTH**

Testosterone replacement therapy will cause prostate cancer
Prostate Cancer in Trials of Testosterone Replacement Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (months)</th>
<th>Prostate Cancer</th>
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<tr>
<td>Haijar et al. (1997)</td>
<td>24</td>
<td>0/27 0/45</td>
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<td>Sin et al. (1997)</td>
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<td>0/13 0/17</td>
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<td>24</td>
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<td>0/54 1/54</td>
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<td>Kenny et al. (2001)</td>
<td>12</td>
<td>0/33 0/34</td>
</tr>
</tbody>
</table>


Prostate Cancer and Testosterone Therapy

**FACTS**
- Fear of causing prostate cancer leaves many appropriate patients untreated
- No evidence of causality of testosterone use and development of prostate cancer
- Testosterone will stimulate growth of existing prostate cancers
- Obtain consult for any concern
  - PSA abnormal per guidelines
  - Abnormal PSA


BPH and Testosterone Therapy

**FACTS**
- Patients with BPH treated with testosterone are at increased risk of worsening signs or symptoms
- Correlation of voiding volume to prostate size is poor
- Prostate size may increase in first 6 months, but generally to normal volume seen in eugonadal men
- Monitoring is strongly advised


Monitoring Therapy (Part 1)

- **Symptoms**: Evaluate response 3-6 months after treatment initiation and then annually
- **Measuring Testosterone**: 3-6 months after initiation
  - Aim to raise level into mid-normal range
  - Monitoring guidelines depend on chosen therapy
- **Hematocrit**: Check at 3-6 months, then annually
- **Osteoporosis**: Measure bone mineral density after 1-2 years

Monitoring Therapy (Part 2)

- **Prostate**
  - DRE at 3 months, then yearly
  - In men aged older than 40 years, check baseline PSA, at 3-6 months and then in accordance with guidelines
- **Urologic Consultation**
  - PSA increase >1.4 ng/mL in any 12-month period
  - PSA velocity >0.4 ng/mL per year after 6 months of therapy
  - Detection of abnormality on DRE
  - AUA/IPSS score of >19
- **Adverse Effects**
  - At each visit
  - Can be formulation specific

Monitoring Therapy (Part 3)

- **Injectable Testosterone**: Measure level midway between injections
- **Transdermal Patches**: Assess level 3-12 hours after application
- **Buccal Tablets**: Assess immediately before or after application of fresh system
- **Transdermal Gels and Solutions**: Any time after patient has been on for a week
- **Testosterone Pellets**: Measure at end of dosing interval, Adjust pellets or interval

AUA=American Urological Association; IPSS=International Prostatic Symptom Score.
Summary of 2010 Endocrine Guidelines

- **Diagnose**
  - Only in men with consistent signs and unequivocally low serum testosterone levels
  - Do not screen in general population; however, consider measurement in disease conditions with high prevalence

- **Measure**
  - Morning total testosterone level
  - Confirm abnormal level and, if in question, assess free or bioavailable testosterone

- **Treatment Goals**
  - Induce and maintain secondary sex characteristics as well as sexual function
  - Improve sense of well-being
  - Improve muscle mass and strength, and bone mineral density


Do Not Treat

- Patients with breast or prostate cancer
- A palpable prostate nodule or induration
- Abnormal PSA
- Consider consultation in high-risk patients
- Patients with erythrocytosis
- Untreated severe sleep apnea
- Severe lower urinary tract symptoms with International Prostate Symptom Score >19
- Uncontrolled or poorly controlled heart failure


The Primary Care Physician Is Essential to Disease Awareness in This Underserved Population

- Knowledge of the patient
- Long-term follow-up
- Concerns of drug safety
- Partner involvement in some cases
- Psychosocial connections
- Monitoring comorbid conditions

Conclusion

Successful treatment of hypogonadism depends on:

- Disease Awareness
- Understanding Limitations
- Realistic Expectations
- Options

Question & Answer