An Update on Testosterone Replacement Therapy

Myths and Facts

May 28, 2014
11:15 AM – 12:30 PM
New York, New York

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Educational Partner

Miller Medical Communications, LLC.
Session 3: An Update on Testosterone Replacement Therapy: Myths and Facts

Current Controversies With Testosterone Therapy – Dr Morgentaler

Diagnosis and Management of Testosterone Deficiency – Dr Khera

Learning Objectives
1. Discuss possible associations between hypogonadism and diabetes, obesity, metabolic syndrome, and cardiovascular disease.
2. Identify the signs and symptoms of hypogonadism and their clinical presentation.
3. Assess current concerns surrounding testosterone therapy so as to appropriately select therapeutic options to treat select patients with hypogonadism.
4. Implement monitoring strategies for patients on TRT to ensure best outcomes.

Faculty

Abraham Morgentaler, MD, FACS
Director and Founder
Men's Health Boston
Associate Clinical Professor of Urology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Abraham Morgentaler, MD, is associate clinical professor of surgery (urology) at Harvard Medical School in Boston, Massachusetts, having joined the faculty upon completion of his residency in 1988 from the Harvard program in urology. Originally from Montreal, Canada, he received his medical degree from Harvard Medical School in 1982. In 1999 Dr Morgentaler founded Men's Health Boston, a center focusing on sexual and reproductive health for men.

An international authority on testosterone deficiency in men, Dr Morgentaler’s research has prompted reexamination of conventional concepts regarding the relationship of testosterone and prostate cancer. He has published widely on male sexual dysfunction and male reproductive disorders, with numerous works appearing in The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association, Cancer, and The American Journal of Medicine. He also is the author of the books Testosterone For Life: Recharge Your Vitality, Sex Drive, Muscle Mass, and Overall Health, and of The Viagra Myth: The Surprising Impact on Love and Relationships. Dr Morgentaler was the recipient of the New Investigator Award in 1994 granted by the American Foundation for Urologic Disease.
Mohit Khera, MD, MBA, MPH
Associate Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, Texas

Mohit Khera, MD, MBA, MPH, earned his undergraduate degree at Vanderbilt University, Nashville, Tennessee. He subsequently earned his master’s degree in business administration and his master’s degree in public health from Boston University. He received his medical degree from The University of Texas Medical School at San Antonio and completed his residency training in the Scott Department of Urology at Baylor College of Medicine, Houston. After finishing a 6-year residency in urology, he completed a 1-year fellowship in male reproductive medicine and surgery with Dr Larry I. Lipshultz.

Currently an assistant professor in the Scott Department of Urology at Baylor, he specializes in male infertility and male and female sexual dysfunction. He also serves as the director of the Laboratory for Sexual Medicine at Baylor and medical director of the Houston Hospital for Specialized Surgery. Dr Khera is an enthusiastic investigator in the laboratory. In 2006 he was awarded the American Urological Association and Pfizer Scholars Grant to study erectile dysfunction; in 2007 he was awarded an Auxilium Pharmaceutical Grant to study testosterone replacement therapy for prostate cancer patients, and in 2008 he was awarded an Allergan grant to study the effects of botulinum toxin in treating Peyronie’s disease. These studies continue, and in 2009 Dr Khera won the Sexual Medicine Society of North America Basic Science Award.

He is a widely published writer, having co-authored book chapters, including those with Dr Lipshultz for the acclaimed Campbell-Walsh Urology textbook, for Clinical Gynecology, and for the fourth edition of Infertility in the Male, edited by Lipshultz, Howards, and Niederberger. He also co-edited the third and most recent edition of the popular book Urology and the Primary Care Practitioner. He has published numerous articles in scientific journals and contributed many invited articles to other publications, such as Fertility Today Magazine. In 2010 he became associate editor of The Journal of Sexual Medicine.

An active academician and a popular speaker, he has presented numerous papers at scientific meetings and has served as guest lecturer and visiting professor across the country. In 2010 he served as director of the 2-day continuing education course “Innovations in Urologic Practice.” Currently he is serving as chair of the Development Committee of the American Society of Andrology. Dr Khera freely shares his time and knowledge with the general public. He has been voted one of Houston’s Best Doctors by Health & Fitness Sports Magazine and is a frequent guest on such TV programs as Fox News’ “Ask the Doctor.” He also writes a blog on Men’s Health for the Houston Chronicle newspaper.

**Faculty Financial Disclosure Statements**
The presenting faculty reported the following:

Dr Morgentaler receives advisor honoraria from AbbVie and Auxilium Pharmaceuticals; consultant honoraria from Auxilium Pharmaceuticals; contracted research honoraria from Auxilium Pharmaceuticals, Eli Lilly, and Lipocine; and lecture honoraria from Merck & Co, Inc.

Dr Khera receives speakers bureau honoraria from Auxilium Pharmaceuticals and Eli Lilly; advisor honoraria from Auxilium Pharmaceuticals and Merck & Co, Inc; consultant honoraria from AMS, Auxilium Pharmaceuticals, Coloplast, and Merck & Co, Inc; and has ownership interest in Sprout Pharmaceuticals.

**Education Partner Financial Disclosure Statement**
The content collaborators at Miller Medical Communications, LLC., have no financial relationships to disclose.
Suggested Reading List


SESSION 3
11:15am–12:30pm

An Update on Testosterone Replacement Therapy: Myths and Facts

SPEAKERS
Abraham Morgentaler, MD, FACS
Mohit Khera, MD, MBA, MPH

PRESENTATION

An Update on Testosterone Replacement Therapy: Myths and Facts

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Upon completion of this activity, participants should be better able to:

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- Identify the signs and symptoms of hypogonadism and their clinical presentation
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Drug List

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<tbody>
<tr>
<td>Human chorionic gonadotropin</td>
<td>A.P.L., Chorex, Chorigon, Choron-10, Gonic, HCG, Novarel, Ovidrel, Profasi</td>
</tr>
<tr>
<td>Clomiphene citrate</td>
<td>Clomiplex</td>
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<tr>
<td>Anastrozole</td>
<td>Arimodex</td>
</tr>
<tr>
<td>Androgens/Testosterone Replacement Therapy</td>
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<tr>
<td>Gel</td>
<td>AndroGel, Fortesta, Testim</td>
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<tr>
<td>Solution</td>
<td>Axiron</td>
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<tr>
<td>Pellets</td>
<td>Testopel</td>
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<td>Androderm</td>
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<tr>
<td>Buccal Tablets</td>
<td>Striant</td>
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<td>IntraMuscular Injection:</td>
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<tr>
<td>Enanthate, Cypionate</td>
<td>Andro LA 200, Depo-Testosterone, Testosterone Enanthate, Testosterone Cypionate</td>
</tr>
<tr>
<td>Undecanoate</td>
<td>Axion</td>
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</tbody>
</table>

CURRENT CONTROVERSIES WITH TESTOSTERONE THERAPY

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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 Controversies

- Greatest concern for decades has been prostate cancer (PCa)
- Over past 6 months, brand new concern regarding CV risks

Goal of lecture:
- Review these 2 major issues to provide clarity regarding risks of treatment

CV=cardiovascular.

New Concerns About Testosterone Therapy

- Two new studies published over past 6 months have raised concerns regarding cardiovascular risks with T therapy
- What did those studies show?
- How do those studies fit with existing literature?
- How should this new information influence the practice of health care providers?

T=testosterone.

Physician Concerns About the Prostate in 2006

- Multinational physician survey on testosterone therapy
- Most common physician concern is prostate cancer risk

Testosterone and Prostate Cancer

Traditional View

- High T causes rapid PCa growth
- Low T is protective
- "Like feeding a hungry tumor" or "pouring gasoline on a fire"

Is Low T Protective Against PCa?

- In early 1990s I began performing prostate biopsies in "normal" men prior to T therapy to rule out PCa
- All with low T, PSA <4.0, normal DRE
- Considered a very-low-risk group

BPH=benign prostatic hyperplasia.


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**Origin of the Prohibition Against T Therapy in Men with PCa**

Huggins et al:
- Stated that 3 men received T injections
- Results given for 2 men
- One previously castrated


**T and Prostate Cancer**

The general conclusion that "Cancer of the prostate is activated by testosterone injections" (Huggins and Hodges, 1941) was based on...

A single patient!


**Global Pooled Longitudinal Study of Hormones and PCa Risk**

- 3886 men with PCa
- 6448 age-matched controls
- No significant relationship between androgens and PCa
- Highest 20% T vs lowest 20% – No Difference


**T and Prostate Cancer in Placebo Arm of REDUCE Trial**

- 3255 men
- Prostate biopsies at 2 years and 4 years
- PCa risk NOT associated with serum T or DHT
- Men with high T, no greater PCa risk


**T and Prostate Cancer**

- Meta-analysis of 19 placebo-controlled T therapy studies in men with low or low-normal T
- Comparison of men treated with T vs placebo revealed no difference in:
  - PCa
  - PSA >4.0 ng/mL
  - Urinary symptom scores


**Serum testosterone and PSA**

Serum Testosterone
Prostate cancer growth/PSA

Molecular Basis for Saturation

AR becomes maximally bound to androgen (saturated) at ~4 nmol/L (120 ng/dl)


AR=androgen receptor.

T Therapy in Men With Untreated PCa

- T therapy in 13 men with untreated PCA (surveillance)
- Median duration T therapy 2.5 years (1-8 years)
- All with follow-up biopsies (avg 2/person)


T Therapy in Men With Untreated PCA

- All men experienced symptomatic benefit
- No increase in PSA
- No increase in prostate volume
- No definite cancer progression
- 54% of biopsies—no cancer seen


Low T and Prostate Cancer Risk

- Multiple studies revealed association between low testosterone levels and the following PCA features:
  - Higher grade (Gleason score)
  - Advanced stage at surgery
  - Increased risk for recurrence after surgery
  - Decreased survival

Nearly Everything We Were Taught About T and Pca Is Wrong

- No evidence high T causes PCa
- Low T is not protective
- Evidence consistent with saturation curve for PSA response to T, and possibly PCA growth
- Low T associated with high-grade PCA
- T therapy offers symptomatic benefits to some men with PCA
- Be careful: Minimal safety data
Low T Levels Associated With Increased Mortality

Serum Testosterone and Mortality in Male Veterans

Low T as a Predictive Marker for Cardiovascular Mortality

- N=11,606 men (no cancer or CVD)
- 825 men died matched with 1489 living men in control group
- Mean follow-up 7 years
- "In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes"

Log-rank test; $\chi^2=14.4$, P=.001.

Serum Testosterone and Mortality in Male Veterans

Cumulative Survival Based on Bioavailable T

N=930 Men With Coronary Heart Disease Followed for 6.9 ± 2.1 Years
Mortality: Low T 21%, Normal T 12%

Low Testosterone and Increased Mortality (N>500)

Risk of Heart Attack Increases With Age

Limitations

- Uncontrolled
- Unknown whether observed rate is higher, lower, or unchanged for similar men without T Rx
- Events unverified (87% accuracy)
- Comparison with PDE5i – classic apples and oranges
- Dissimilar groups (low T vs ED) treated with dissimilar medications (T vs PDE5i)


Pre-Rx rate: 3.48 events/1000 person-years
Post-Rx rate: 4.75 events/1000 person-years
Difference: 1.27 events/1000 person-years
Data available, but not reported for >90 days after T Rx – Why??

Conclusion: Study is non-informative


Excluded Men

- Once MI or stroke occurred, men were no longer in the risk-set
- Irrelevant whether or not they received T
- If included, this increases number of events in no-T group by 71% (1132 + 1587)

Second Correction Published March 5, 2014

- 1132 to 128: shift >1000 men
- 397 to 1301: shift >900 men
- 100 women/1132 = 9%
- Major errors and nearly 10% contamination of dataset by ineligible (wrong sex) population
- Only identified upon post-publication review of data
World’s Experts Petition JAMA to Retract T Study

- 25 (now 29) societies—Endocrinology, Andrology, Men's Health, Sexual Medicine—submitted April 10, 2014
- >160 distinguished researchers/clinicians
- 8 professors emeriti
- >60 full professors
- 9 journal editors
- 32 countries (all continents except Antarctica)
- "Gross data mismanagement and contamination" Study "no longer credible"

Societies Petitioning JAMA to Retract T Study

- American Society for Men's Health (ASMH)
- Brazilian Society of Endocrinology and Metabolism
- Canadian Male Sexual Health Council, an affiliate of the Canadian Urological Association
- Canadian Society for the Study of the Aging Male (CSSAM)
- European Society for the Study of the Aging Male (ESSAM)
- European Society for Sexual Medicine (ESSM)
- Indonesian Andrologist Association
- International Society of Men's Health (ISMH)
- International Society for Sexual Medicine (ISSM)
- Italian Society of Andrology
- Italian Society of Andrology and Sexual Medicine (SIAMS)
- Japan-ASEAN Council on Men’s Health & Aging
- Japanese Society of Men’s Health
- American Society for Men's Health (ASMH)
- Japanese Society of Men's Health
- Korean Society for Sexual Medicine and Andrology
- Malaysian Men's Health Initiative
- Malaysian Society of Andrology and Study of the Aging Male
- Men's Health Initiative of BC (British Columbia, Canada)
- Mexican Association of Bone and Mineral Metabolism (AMMOM)
- Middle East Society for Sexual Medicine (MESSM)
- Russian Society for Men's Health
- South Asian Society for Sexual Medicine (SASSM)
- Sexual Medicine Society of North America (SMSNA)
- Latin American Society for Sexual Medicine (SILAM)
- Society for Men's Health Singapore
- Society for the Study of Androgen Deficiency
- Society for the Study of Andrology and Sexology, Singapore (SSASS)

Survival of Treated vs Untreated T-deficient Men

- N=1031
- Men >40 years
- T<250 ng/dL
- Mortality:
  - 20.7% untreated
  - 10.3% T treated
  - P<.0001


T Deficiency in DM Associated With Increased Mortality, Reversed With T Therapy

- 581 men T2DM
- Follow-up 5.8 years
- Low T defined <300 ng/dL (10.4 nmol/L)
- Men with low T untreated
  - HR 2.3 (CI 95% 1.3-3.9; P=.004)
- T therapy – Reduced from 19.2% to 8.4%

DM=diabetes mellitus.

T Gel vs Placebo in Men With Angina

- 46 men with known angina
- Randomized to T gel 5 mg vs placebo
- 12 weeks
- Primary end point: Time to 1-mm ST-segment depression on treadmill exercise
- Statistically significant increase in time to ischemia with T vs placebo

T vs Placebo in Chronic Heart Failure

Randomized double-blind study of T vs placebo, added to optimal medical therapy
- N=70
- Median age 70 years
T provided:
- Increased functional capacity
- Improved large-muscle strength
- Improved glucose metabolism


Summary: T and Cardiovascular Risk

- No large prospective trials
- Numerous observational studies indicate association between low T and increased mortality
- Modest number of smaller RCTs indicating benefit of T vs placebo in men with CVD
- T therapy improves CVD risk factors
- Still no direct RCT evidence that T therapy associated with increased CV risks

RCTs=randomized clinical trials.

Diagnosis and Management of Testosterone Deficiency

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Discussion

- Diagnosis of testosterone deficiency
- Prevalence of testosterone deficiency
- Testosterone replacement treatment options
- Monitoring strategies

Is Testosterone Replacement Therapy Truly Evidence-Based Medicine?

Meet George

- George is a 44-year-old male with DM, HTN, obesity, and history of back pain
- He complains of decreased energy and new onset ED for the past 9 months
- He is married and has a 6-month-old daughter

HTN=hypertension.
George — Physical Examination

- Height: 5’ 4”
- Weight: 220 lb
- Waist circumference: 42”
- BP: 157/90
- Testis 14 cc, normal circ phallus
- DRE 30 gm, benign

Clinical Diagnosis

- Non-specific symptoms:
  - erectile dysfunction
  - decreased muscle mass and strength
  - increased body fat
  - decreased bone mineral density and osteoporosis
  - depressed mood
  - decreased libido
- None of these symptoms, individually, are specific to a low androgen state
- Endocrine guideline recommendation: Diagnosis of androgen deficiency should be made only in men with consistent symptoms and signs and unequivocally low serum testosterone levels

Laboratory Diagnosis

- Prolactin
  - “…serum prolactin is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) or when secondary hypogonadism is suspected”
  - 3 non-randomized retrospective series (Level 3)
- Problems with testosterone and free testosterone testing
  - Variations between total testosterone assay methods
  - Variation in reference ranges for total testosterone
    - Study of 25 different testosterone reference laboratories
    - Lower reference value: 130 to 450 ng/dL (350% difference)
    - Upper reference value: 486 to 1593 ng/dL (325% difference)

At What Levels Should We Treat? re Total Testosterone

- For most symptoms, the average testosterone threshold corresponds to the lower limit of the normal (approximately 300 ng/dL), with a greater likelihood of having symptoms below this threshold than above it
- Threshold of testosterone levels vary for various symptoms of androgen deficiency and target organs, and among individuals
- Age adjusted?

Prevalence of Androgen Deficiency

The Effect of Testosterone

<table>
<thead>
<tr>
<th>Skin</th>
<th>Hair growth, balding, sebum production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Synthesis of serum proteins</td>
</tr>
<tr>
<td>Bone</td>
<td>Accelerated linear growth, closure of epiphyses</td>
</tr>
<tr>
<td>Male Sexual Organs</td>
<td>Prostate growth, and function</td>
</tr>
<tr>
<td>Brain</td>
<td>Libido, mood</td>
</tr>
<tr>
<td>Muscle</td>
<td>Increased in strength and volume</td>
</tr>
<tr>
<td>Kidney</td>
<td>Stimulation of erythropoietin production</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>Stimulation of stem cells</td>
</tr>
</tbody>
</table>

Physical Signs of Low Testosterone

**Physical Signs**
- Increased body fat, BMI
- Reduced muscle bulk and strength
- Low bone mineral density
- Loss of body hair (axillary and pubic)

Symptoms of Low Testosterone

**Symptoms**
- Decreased energy or motivation
- Diminished libido, erectile and ejaculatory dysfunction
- Diminished work performance
- Poor concentration and memory
- Sleep disturbance
- Depression

Physical Signs

- Multicenter, 12-month observational registry (N=849) of hypogonadal men prescribed testosterone gel
- Depression symptoms were measured using PHQ-9
- Before treatment with TRT, 92.4% demonstrated some level of depressive symptoms, with 17.3% having severe depressive symptoms
- After 12 months of TRT, patients with severe depressive symptoms decreased from 17.3% to 2.1%
- Patients already on antidepressants also experienced a significant improvement in PHQ-9 at 12 months

Link Between Low Testosterone and Osteoporosis

**MicroMRI of Tibia**

<table>
<thead>
<tr>
<th>Control</th>
<th>Well connected, predominantly plate-like trabecular network of the control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadal Man</td>
<td>More disconnected, predominantly rod-like architecture of the hypogonadal man</td>
</tr>
</tbody>
</table>

Prevalence of Low Testosterone in Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
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<td>Obesity</td>
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<tr>
<td>Diabetes</td>
<td>42</td>
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<tr>
<td>AIDS</td>
<td>19</td>
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<tr>
<td>Hypertension</td>
<td>42</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>50</td>
</tr>
<tr>
<td>Other Conditions</td>
<td>50</td>
</tr>
</tbody>
</table>

MRI=magnetic resonance imaging.

Chronic Opioid Use

- 100 million (33%) of US adults have chronic pain
- In 2009, there were 257 million opioid prescriptions dispensed from US retail pharmacies
- Prevalence of hypogonadism among men on long-term opioid therapy can be as high as 75%

Relieving Pain in America. Institute of Medicine, 2010; www.cdc.gov.

Diagnosis of Low Testosterone

Diagnosing Low Testosterone

- **Signs and Symptoms**
  - ADAM questionnaire
- **Clinical Laboratory Blood Tests**
  - Testosterone (<300ng/dL)
  - Other hormones related to low testosterone

ADAM=Androgen deficiency in the aging male.

George — Laboratory Results

- Total testosterone – 230 and 210 ng/dL
- Free testosterone – 30 pg/mL
- Follicle-stimulating hormone – 6 IU/L
- Luteinizing hormone – 9 IU/L
- Prolactin – normal
- Iron – normal
- TSH – normal
- Fasting glucose – 109 mg/dL
- PSA – 0.7 ng/mL

TSH=thyroid stimulating hormone.

ADAM Questionnaire
(Androgen Deficiency in the Aging Male)

Validated screening tool for males aged ≥40 years


Production of Testosterone


FSH=follicle-stimulating hormone; GnRH=gonadotropin-releasing hormone; LH=luteinizing hormone.
Classification of Hypogonadism

<table>
<thead>
<tr>
<th>Primary Causes</th>
<th>Secondary Causes</th>
<th>Mixed Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular Causes</td>
<td>Hypothalamic Causes</td>
<td>Pituitary Causes</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>Kallmann syndrome</td>
<td>*Hypomammatism</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Constitutional delay in growth and development</td>
<td>*Sickle cell disease</td>
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<tr>
<td>Congenital or acquired anorchia</td>
<td>Pituitary tumors</td>
<td>Glucocorticoid treatment</td>
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<tr>
<td>Testicular tumors</td>
<td>Chronic illness</td>
<td>Alcoholism</td>
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<tr>
<td>Aging</td>
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</table>

HPG=hypothalamic-pituitary-gonadal.


Diurnal Variation in Serum Total Testosterone Levels

Testosterone Distribution

Male Hormonal Status Changes With Age as SHBG Increases

Important Considerations Before Starting TRT

- Does George want to have any more children?
- Is he on chronic opioids for his back pain?
- What other causes could be contributing to his ED and fatigue?

Treatment of Low Testosterone
Pharmacologic Treatment Options

- Intramuscular injections
- Transdermal patches
- Transdermal gels and solutions
- Buccal tablets
- Subcutaneous pellets


Monitoring Therapy (Part 1)

- Symptoms
  - Evaluate response 3 to 6 months after treatment initiation; then annually

- Measuring Testosterone
  - 3 to 6 months after initiation
  - Aim to raise level into mid-normal range
  - Monitoring guidelines depend on chosen therapy

- Hematocrit
  - Check at 3 to 6 months; then annually

- Osteoporosis
  - Measure bone mineral density after 1 to 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 to 6 months and then in accordance with guidelines

- Urologic Consultation
  - PSA increase >1.4 ng/mL in any 12-month period
  - PSA velocity of >0.4 ng/mL-yr after 6 months of therapy
  - Detection of abnormality on DRE
  - AUA/PPS score of >19

- Adverse Effects
  - At each visit
  - Can be formulation-specific

AUA=American Urological Association; IPSS=International Prostatic Symptom Score.

Results of Therapy

- Improvement of sexual functioning and libido
- Improvement of bone density
- Increase in lean body mass and decrease of fat mass
- Improvement in mood


Pharmacologic Treatment Options

<table>
<thead>
<tr>
<th>Delivery System</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular injection (enanthate; cypionate)</td>
<td>History (available for 50 years)</td>
<td>Pain</td>
</tr>
<tr>
<td>Intramuscular injection (undecanoate)</td>
<td>Infrequent dosing (every 10 weeks)</td>
<td>Less fluctuation in testosterone levels</td>
</tr>
<tr>
<td>Subcutaneous pellets</td>
<td>History (started in 1940s)</td>
<td>Relative invisibility</td>
</tr>
</tbody>
</table>

REMS=Risk Evaluation and Mitigation Strategy.

Pharmacologic Treatment Options

<table>
<thead>
<tr>
<th>Delivery System</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Transdermal gels and solutions</td>
<td>Application sites (upper arm, shoulder, axilla)</td>
<td>Transfer to others (risk is minimized with high-dose, low-volume preparations)</td>
</tr>
<tr>
<td>Buccal tablets</td>
<td>Application site</td>
<td>Inadvertent loss of tablet</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>Nonerrostal patches</td>
<td>Night-time application results in approximation of normal circadian levels</td>
</tr>
</tbody>
</table>

Precautions in Using Testosterone

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

Pathophysiology of ED and LUTS:

**NO/NOS Theory**

- Nitric oxide (NO) discovered by Rajfer et al.
- Chemical mediator of penile erection
- Diabetics and Hypertension
- Age
- Diabetes
- Smoking
- Dyslipidemia
- Hyperinsulinemia

**SMC contraction**

- Structural changes
- Functional changes
- Noncompliance
- Outlet resistance

**SMC apoptosis**

**LUTS**

- Testosterone stimulates NO/NOS

Changes From Baseline to 12-Month Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Testosterone Therapy Group, Mean Change (SD)</th>
<th>Control Group, Mean Change (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA value, ng/mL</td>
<td>0.322 (0.916)</td>
<td>0.305 (0.907)</td>
<td>.399</td>
</tr>
<tr>
<td>AMS score</td>
<td>0.2 (8.8)</td>
<td>−0.5 (7.7)</td>
<td>.289</td>
</tr>
<tr>
<td>IPSS</td>
<td>−4.1 (6.6)</td>
<td>−0.5 (6.7)</td>
<td>.042</td>
</tr>
<tr>
<td>UFM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFR, mL/s</td>
<td>4.2 (9.1)</td>
<td>−0.19 (4.27)</td>
<td>.031</td>
</tr>
<tr>
<td>VV, mL</td>
<td>44 (112)</td>
<td>−24 (80)</td>
<td>.008</td>
</tr>
<tr>
<td>PVR, mL</td>
<td>4.9 (44.2)</td>
<td>−0.8 (31.1)</td>
<td>.723</td>
</tr>
<tr>
<td>Systemic body muscle volume score</td>
<td>0.61 (1.33)</td>
<td>−0.30 (0.66)</td>
<td>.035</td>
</tr>
</tbody>
</table>

Testosterone Stimulates NO/NOS in Bladder and Prostate

- Testosterone receptor
- NO/NOS: Testosterone stimulates NO/NOS
- Bladder
- Detrusor
- Prostate
- Urethra

 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

Changes From Baseline to 12-Month Follow-up

- Fifty-two hypogonadism men with BPH randomized to receive testosterone (ART group) as 250 mg of testosterone enanthate every 4 weeks or to the untreated control group
- International Prostatic Symptom Score (IPSS), uroflowmetry data, post-voiding residual volume (PVR), and systemic body muscle volume at baseline and 12 months were evaluated

Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomized controlled study – Shigehara K et al.

Androgens make the prostate "smarter": a randomized controlled study – Shigehara K et al.

BPH=benign prostatic hyperplasia; LUTS=lower urinary tract symptoms.


Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomized controlled study – Shigehara K et al.

Androgens make the prostate "smarter": a randomized controlled study – Shigehara K et al.

ART=androgen replacement therapy.

Testosterone and Male Infertility

Intratesticular Testosterone (ITT) and Spermatogenesis

- ITT concentration is 50x-100x higher than in serum
- Exogenous T suppresses ITT production
- Spermatogenesis is dramatically compromised at ITT concentrations <20 ng/mL


Management Strategies Raising Testosterone and Preserving Fertility

- Human Chorionic Gonadotropin (hCG)
- Clomiphene citrate
- Aromatase inhibitors

Conclusion

- Our current diagnosis and management of hypogonadism needs further evidence-based support
- Androgen deficiency affects approximately 20% to 40% of men, while symptomatic androgen deficiency, or LOH, is seen in 4% to 8% of men
- Hypogonadism can be diagnosed by a simple blood test and a questionnaire
- There are many safe and effective ways to increase a man's testosterone

Conclusion

- Testosterone may improve urinary function through modulating NO/NOS activity
- Testosterone is a natural contraceptive and should not be given to men who are trying to achieve a pregnancy
- Raising endogenous testosterone through hCG, Arimidex, and clomiphene citrate will preserve fertility

Questions