Testosterone Replacement Therapy

Controversies and Answers

November 13, 2013

11:00 AM – 12:15 PM

Atlanta, Georgia

Educational Partner

Miller Medical Communications, LLC.

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:

Lyerka D. Miller, PhD, has no financial relationships to disclose.

Suggested Reading List

Bhasin S, Cunningham GR, Hayes FJ, et al; for the Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95(6):2536-2559.

Dobs AS, Morgentaler A. Does testosterone therapy increase the risk of prostate cancer? *Endocr Pract*. 2008;14(7):904-911.

Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60(7):762-769.

Malkin CJ, Pugh PJ, Morris PD, et al. Low serum testosterone and increased mortality in men with coronary heart disease. *Heart*. 2010;96(22):1821-1825.

Traish AM, Guay A, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. *J Androl*. 2009;30(1):10-22.

Carruthers M. Time for international action on treating testosterone deficiency syndrome. *Aging Male*. 2009;12(1):21-28.

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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Learning Objectives

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

Generic Name	Trade Name
Testosterone buccal system	Striant
Testosterone cypionate	Depo-Testosterone
Testosterone enanthate	Delatestryl
Testosterone pellets	Testopel
Testosterone topical gel	Fortesta, AndroGel, Testim
Testosterone topical solution	Axiron
Testosterone transdermal system	Androderm, Testoderm
Testosterone undecanoate	Andriol (not available in the United States)

Testosterone Update
Facts, Myths, Reality

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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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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)

Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010. Grossmann M, et al. *Clin Endocrinol (Oxf)*. 2008. Mulligan T, et al. *Drugs Today (Barc)*. 1998;34(5):455-461. Hong BS, et al. *Int J Urol*. 2007;14(11):981-985. Seidman SN. *Psychopharmacol Bull*. 2007;40(4):205-218. Nieschlag E, et al. *Eur Urol*. 2005;48(1):1-4.

Why Do We Need Testosterone?

Does everyone need to be a baseball player?

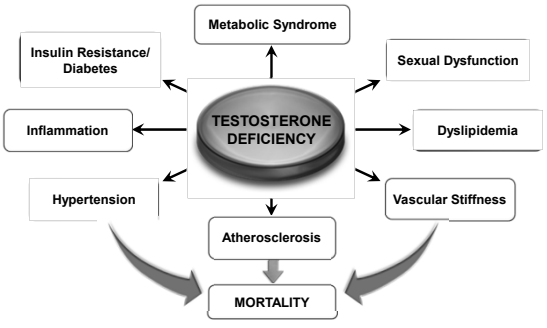
The Reality of Testosterone

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

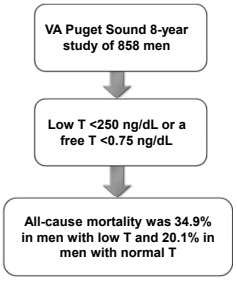
Bagatell CJ, et al. *N Engl J Med*. 1996;334(11):707-714.

Clinical Implications of Testosterone Deficiency



Adapted from Maggio M, Basaria S. *Int J Impot Res*. 2009;21(4):261-264.

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



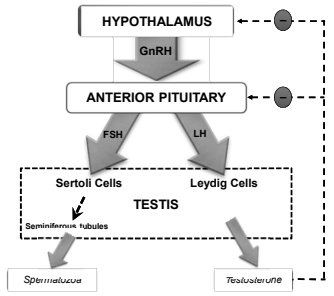
Shores MM, et al. *Arch Intern Med*. 2006;166(15):1660-1665.

Low Testosterone and Increased Mortality (N >500)

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

CVD=cardiovascular disease.

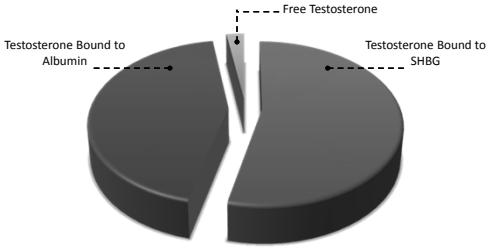
The Hypothalamic-Pituitary-Testicular Axis



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

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.
Costanzo LS. *Physiology.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2006:449.

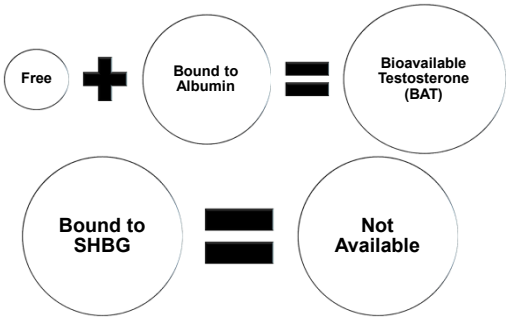
Testosterone in the Blood



SHBG=sex hormone-binding globulin.

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.

Not All Testosterone Is Available



Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.

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

Seftel A. *Int J Impot Res.* 2006;18(3):223-228.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;96(6):2536-2559.

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

Seftel A. *Int J Impot Res.* 2006;18(3):223-228.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;96(6):2536-2559.

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)

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.
Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

Hypogonadism Is Undertreated and Underdiagnosed

Boston Aging Community Health

- 24% of men aged 39-79 years had biochemical hypogonadism
- Symptomatic hypogonadism 5.6%

Hypogonadism in Males (HIM) Study

- Low testosterone in 39% of men 45+

Only 5%-35% of hypogonadal men receive treatment

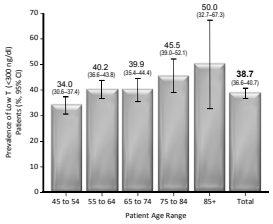
Mulligan T, et al. *Int J Clin Pract*. 2006;60(7):762-769.
Araujo AB, et al. *J Clin Endocrinol Metab*. 2007;92(11):4241-4247.
Gooren LJ, et al. *Aging Male*. 2007;10(4):173-181.

Obesity, Metabolic Syndrome, Diabetes, and Hypogonadism

FACT

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

The Incidence/Prevalence of Testosterone Deficiency



	Androgen Deficiency				
	No. of cases	No. of person-years at risk	Incidence rate (/1000 person-years)	95% CI	*P* value
Baseline					
Crude	111	9030	12.3	10.2, 14.8	
Age-specific (yr)					<.0001
40–49	20	3394	5.9	3.8, 9.1	
50–59	37	3316	11.2	8.1, 15.4	
60–70	54	2320	23.3	17.8, 30.4	

- Mulligan: prevalence in cross section of office group
- Araujo: incidence in longitudinal study of a group

Mulligan T, et al. *Int J Clin Pract*. 2006;60(7):762-769.
Araujo AB, et al. *J Clin Endocrinol Metab. 2004;89(12):5920-5926.*

Various Comorbidities Associated With Hypogonadism

Condition	Odds Ratio
Obesity	2.38
Diabetes	2.09
Hypertension	1.84
Hyperlipidemia	1.47
Osteoporosis	1.41
Asthma/COPD	1.40

COPD=chronic obstructive pulmonary disease.

Mulligan T, et al. *Int J Clin Pract*. 2006;60(7):762-769.

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

Shabsigh R, et al. *Am J Cardiol*. 2005;96(12B):67M-72M.
Nettleship JE, et al. *Front Horm Res*. 2009;37:91-107.

Hypogonadism and Cardiovascular Disease

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

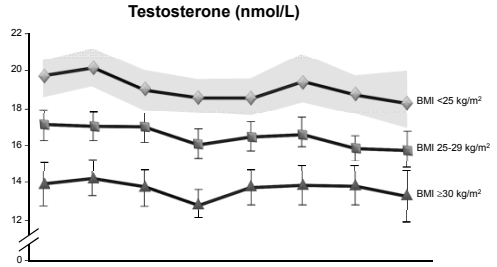
Shabsigh R, et al. Am J Cardiol. 2005;96(12B):67M-72M.
Nettleship JE, et al. Front Horm Res. 2009;37:91-107.
Page ST, et al. Asian J Androl. 2008;10(2):193-200.

Hypogonadism in Men With Diabetes *A Concerning Prevalence*

Study	Year	Prevalence (%)
Mulligan	2006	50
Rhoden	2005	34-46
Dhindsa	2004	33

Mulligan T, et al. *Int J Clin Pract*. 2006;60(7):762-769.
Rhoden EL, et al. *BJU Int*. 2005;96(6):867-870.
Dhindsa S, et al. *J Clin Endocrinol Metab*. 2004;89(11):5462-5468.

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



BMI=body mass index.

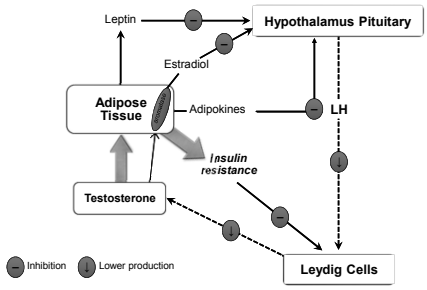
Camacho EM, et al. *Eur J Endocrinol*. 2013;168(3):445-455.
Wu FC, et al; European Male Aging Study Group. J Clin Endocrin Metab. 2008;93(7):2737-2745.

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

Seftel AD. *Int J Impot Res*. 2006;18(2):115-120.
Kapoor D, et al. *Clin Endocrinol (Oxf)*. 2005;63(3):239-250.
Dandona P, et al. *Aging Male*. 2008;11(3):107-117.
International Diabetes Federation. *IDF Communications*. 2006:24.

Connecting Hypogonadism-Obesity-Insulin Resistance

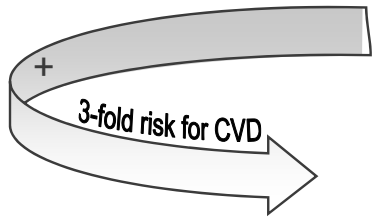


Dandona P, et al. *Curr Mol Med*. 2008;8(8):816-828.
Kapoor D, et al. *Clin Endocrinol (Oxf)*. 2005;63(3):239-250.

"Silent Killers" – The Metabolic Syndrome

Visceral fat tissue

Abdominal obesity
Insulin resistance
Dyslipidemia
Hypertension
?Low Testosterone



Sattar N, et al. *Circulation*. 2003;108(4):414-419.

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

Abbasi AA, et al. *Am J Med Sci*. 1995;310(6):229-234.
Ebeling PR. *N Engl J Med*. 2008;358(14):1474-1482.

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.

Mellström D, et al. *J Bone Miner Res*. 2006;21(4):529-355.
Travison TG, et al. *J Clin Endocrinol Metab*. 2009;94(3):853-860.
Ebeling PR. *N Engl J Med*. 2008;29:1474-1482.
Wang C, et al. *Clin Endocrinol (Oxf)*. 2001;54(6):739-570.
Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Identification and Evaluation of the At-Risk Patient

Martin M. Miner, MD
Co-Director, Men's Health Center
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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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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

Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;96(6):2536-2559.

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

PCP = primary care provider.

Henry: Current Medications

- Omeprazole
- Loratadine
- Multivitamins
- Herbs (Maca Root)
- Atorvastatin 20 mg
- Linsinopril 20mg/HCTZ 12.5 mg

Henry: Physical Examination

- Height: 68 inches
- Weight: 205 lb
- Waist circumference: 40 inches
- BMI: 31.2 kg/m^2
- Stage 1 obesity
- BP 140/82 on treatment
- Genital examination: normal
- DRE: normal

HTN = hypertension.

Symptoms and Signs Suggestive of 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

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.

Screening for Hypogonadism

MYTH

- Only symptomatic patients should be screened

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.

High Prevalence of Hypogonadism in Various Conditions May Warrant Screening

EXPERT OPINION

- Infertility
- Osteoporosis, low trauma fracture
- Type 2 diabetes mellitus
- Glucocorticoid, ketoconazole, opioid, 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.

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2010;96(6):2536-2559.

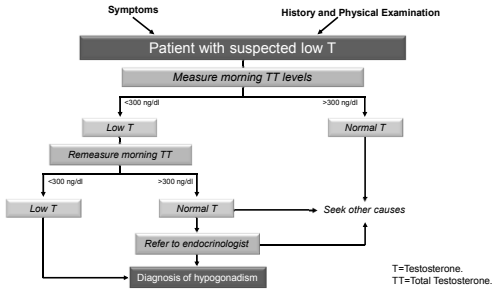
The ADAM Questionnaire

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

Morley A, et al. *Metabolism.* 2000;49(9):1239-1242.

The Diagnosis of Hypogonadism



T=Testosterone.
TT=Total Testosterone.

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.
Bhasin S, et al. *J Clin Endocrinol Metab.* 2006;91(6):1995-2010.
Arver S, et al. *Front Horm Res.* 2009;37:5-20.
ASA Position Statement. *J Androl.* 2006;27(2):133-134.
Rosner W, et al. *J Clin Endocrinol Metab.* 2007;92(2):405-413.

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

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

Brawer MK. *Rev Urol.* 2004;6 suppl 6:S9-S15.
AACE Hypogonadism Task Force. *Endocr Pract.* 2002;8:439-456.

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

Dandona P, et al. *Int J Clin Pract.* 2010;64(6):682-696.

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

Bhasin S, et al. *J Clin Endocrinol Metab.* 2006;91(6):1995-2010.

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

Mulligan T, et al. *Int J Clin Pract*. 2006;60(7):762-769. Heufelder AE, et al. *J Androl*. 2009;30:726-733. Jones TH, et al. *Diabetes Care*. 2011;34(4):828-837.

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)

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Intramuscular Injections

Pros	Cons
◆ History (available for 50 years)	◆ Pain
◆ Self administration	◆ Frequency of injections (every 2-4 weeks)
◆ Inexpensive	◆ Symptomatic peaks and troughs resulting in variations in breast tenderness, libido, emotional stability, energy
◆ Flexibility of dosing	

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Transdermal Patches

Pros	Cons
◆ Nonscrotal patches	◆ Scrotal patches
◆ Nighttime application results in good approximation of normal circadian plasma testosterone levels	◆ Skin irritation
◆ Flexibility of dosing	

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Transdermal Gels and Solutions

Pros	Cons
◆ Application sites (upper arm, shoulder, axilla)	◆ Transfer to others (risk is minimized with high-dose, low-volume preparations)
◆ Low skin irritation	◆ Low skin irritation
◆ Invisibility of application	
◆ Flexibility of dosing	
◆ Various concentrations	

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Buccal Tablets

Pros	Cons
◆ Application site	◆ Application site
◆ Relative invisibility	◆ Inadvertent loss of tablet
◆ Bypass first-pass hepatic metabolism	◆ Gum and buccal irritation, alteration in taste
◆ Slow release	◆ Twice-daily dosing
	◆ No dose titration

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Subcutaneous Pellets

Pros	Cons
◆ History (started in 1940s)	◆ Painful application
◆ Relative invisibility	◆ Surgical procedure unlikely to be used by the PCP
◆ Long-acting	◆ Long-acting
◆ Slow release	◆ Inconvenient removal
	◆ No dose titration
	◆ Procedure can result in infection, fibrosis, or pellet extrusion

PCP=primary care physician.

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.
Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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

Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.

Results of Therapy

EXPERT OPINION, NOT EXPERT EVIDENCE

- Improvement in insulin resistance
- Decrease abdominal fat
- Decrease cardiovascular risk factors

Mårin P, et al. *Eur J Med*. 1992;1(6):329-336.
Kapoor D, et al. *Eur J Endocrinol*. 2006;154(6):899-906.
Dandona P, et al. *Int J Clin Pract*. 2010;64(6):682-696.
Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

Effects on Diabetes From Testosterone Therapy

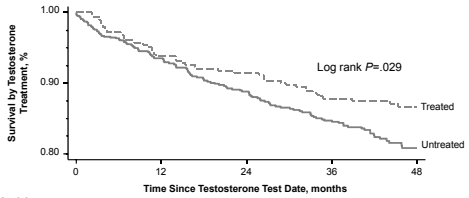
Study Design	◆ A 12-month, multicenter, prospective, randomized, double-blind, placebo-controlled study
Population	◆ 220 hypogonadal men with type 2 diabetes and metabolic syndrome
Results	◆ **Significantly improved** insulin resistance in all patients (by 15.2% at 6 mos and by 16.4% at 12 mos) ◆ **Significantly 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.

Jones TH, et al. *Diabetes Care*. 2011;34(4):828-837.

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)



At risk, n					
Untreated	1016	639	557	496	193
Treated	15	301	321	323	146

TRT=testosterone replacement therapy.

Shores MM et al. *J Clin Endocrinol Metab*. 2012;97(6):2050-2058.

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

English KM, et al. *Circulation*. 2000;102(16):1906-1911. Webb CM, et al. *Circulation*. 1999;100(16):1690-1696. English KM, et al. *Eur Heart J*. 2000;21(11):890-894. Hak AE, et al. *J Clin Endocrinol Metab*. 2002;87(8):3632-3639. Haddad RM, et al. *Mayo Clin Proc*. 2007;82(1):29-39. Basaria S, et al. *N Engl J Med*. 2010;363(2):109-122.

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

LUTS=lower urinary tract symptoms.

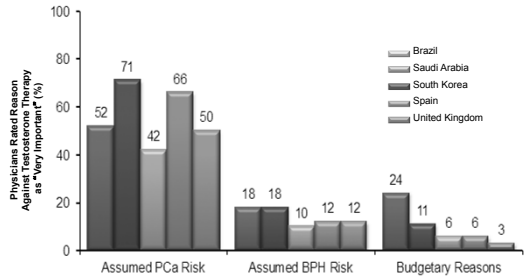
Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.

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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.

Provider Concerns Regarding Testosterone



PCa=prostate cancer.

Cooren LJ, et al. *Aging Male*. 2007;10(4):173-181.

MYTH

Testosterone replacement therapy will cause prostate cancer

Prostate Cancer in Trials of Testosterone Replacement Therapy

Study	Duration (months)	Prostate Cancer	
		Placebo	Testosterone
Haijar et al. (1997)	24	0/27	0/45
Sih et al. (1997)	12	0/15	0/17
Dobs et al. (1999)	24	-	2/33
		-	1/33
Snyder et al. (1999)	36	0/54	1/54
Snyder et al. (2000)	36	-	0/18
Wang et al. (2000)	6	-	0/76
		-	0/73
		-	1/78
Kenny et al. (2001)	12	0/33	0/34

Table adapted from:
Rhoden EL, et al. *N Engl J Med*. 2004;350(5):482-492.

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

PSA=prostate-specific antigen.

Gooren LJ, et al. *Aging Male*. 2007;10(4):173-181. Rhoden EL, et al. *N Engl J Med*. 2004;350(5):482-492. Raynaud JP. *J Steroid Biochem Mol Biol*. 2006;102(1-5):261-266. Wang C, et al. *J Androl*. 2009;30(1): 1-9. Carroll P, et al. *Urology*. 2001;57(2):217-224.

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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.
Wang C, et al. *J Androl*. 2009;30(1):1-9.
Hijazi RA, et al. *Annu Rev Med*. 2005;56:117-137.
Miner MM, et al. *Cleve Clin J Med*. 2007;74 suppl 3:S38-S46.
Rhoden EL, et al. *N Engl J Med*. 2004;350(5):482-492.

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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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 of >0.4 ng/mL-yr after 6 months of therapy ◆ Detection of abnormality on DRE ◆ AUA/IPSS score of >19
Adverse Effects	◆ At each visit ◆ Can be formulation specific

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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

Measuring Testosterone: *When to Check*

Injectable Testosterone – enanthate or cypionate	◆ 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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

Summary of 2010 Endocrine Guidelines

Do Not Treat

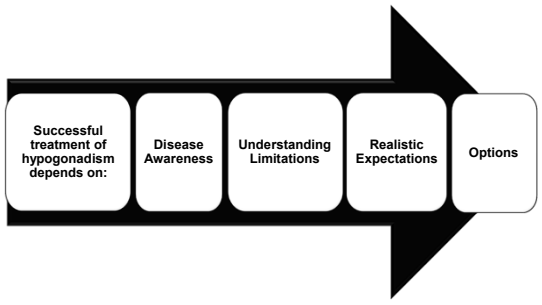
- Patients with breast or prostate cancer
- A palpable prostate nodule or induration
- Abnormal PSA
- Consider consultation in high-risk patients
- Patients with erythrocytosis
- Untreated severe sleep apnea
- Severe lower urinary tract symptoms with International Prostate Symptom Score >19
- Uncontrolled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

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;96(6):2536-2559.

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



Question & Answer