Male Hypogonadism

More than just a low testosterone?

KM Pantalone
Endocrinology

Conflicts of Interest

None to declare

Case 1

- A 54 year old man is referred for evaluation of low testosterone
- The patient had presented to his PCP with the complaints of diminished libido and erectile dysfunction for the past year
- He noted fatigue that has been ongoing for the past few years, worsening over time
- He has not been formally diagnosed with any medical conditions at the present time

Case 1 continued…..

- On physical exam he is obese (BMI 31)
- No evidence of gynecomastia
- Normal appearing male body habitus
- Normal testicular and prostate exam
- Laboratory evaluation noted a serum testosterone level of **180 ng/dL**
  - reference range: 249-836 ng/dL

How should this patient be evaluated?

- A) Order a testicular ultrasound
- B) Obtain MRI of the brain
- C) Testosterone is low, treat with testosterone replacement therapy
- D) Obtain a semen analysis
- E) Obtain repeat testosterone, LH/FSH

Low Testosterone

- Confronted with the finding of a low serum testosterone level, physicians should not jump to the diagnosis of hypogonadism and treat with testosterone supplementation

- Confirmation and thorough evaluation is warranted prior to making a diagnosis and/or starting therapy

Objectives

- Review signs/symptoms of low testosterone
- Review the hypothalamic-pituitary-gonadal axis
- Discuss how to evaluate the finding of low serum testosterone
- Realize the importance of determining if the etiology is 1° (testicular) or 2° (hypothalamic/pituitary)
- Review the differential diagnosis of male hypogonadism
- Review the risks and benefits of testosterone replacement therapy (TRT)
- Review the various modes of TRT

Definition

- Male hypogonadism is defined as the failure of the testes to produce adequate amounts of androgen and/or sperm

Symptoms of low testosterone

Table 1

Symptoms of Hypogonadism

Physical	Sexual	Emotional/Psychiatric
Fatigue	Decreased libido	Depression
Muscle weakness	Erectile dysfunction	Anxiety
Sparse body hair	Oligospermia	Irritability
Decreased bone mineral density		Insomnia
Fat distribution		Memory Impairment
Impaired hematopoiesis		Cognitive dysfunction
Osteoporosis		

http://www.pharmacytimes.com/publications/issue/2004/2004-10/2004-10-4595

Symptoms of Low Testosterone

Low testosterone can have a wide range of symptoms, including sexual and nonsexual ones. To see whether you may have low testosterone, answer the questions in the self -test* below.

Are you experiencing:

1. Decrease in libido (sex drive)?	Yes	No
2. Lack of energy?	Yes	No
3. Decrease in strength and/or endurance?	Yes	No
4. Loss of height?	Yes	No
5. A decreased "enjoyment of life"?	Yes	No
6. Sad and/or grumpy feelings?	Yes	No
7. Less strong erections?	Yes	No
8. A recent deterioration in your ability to play sports?	Yes	No
9. Falling asleep right after dinner?	Yes	No
10. A recent deterioration in your work performance?	Yes	No

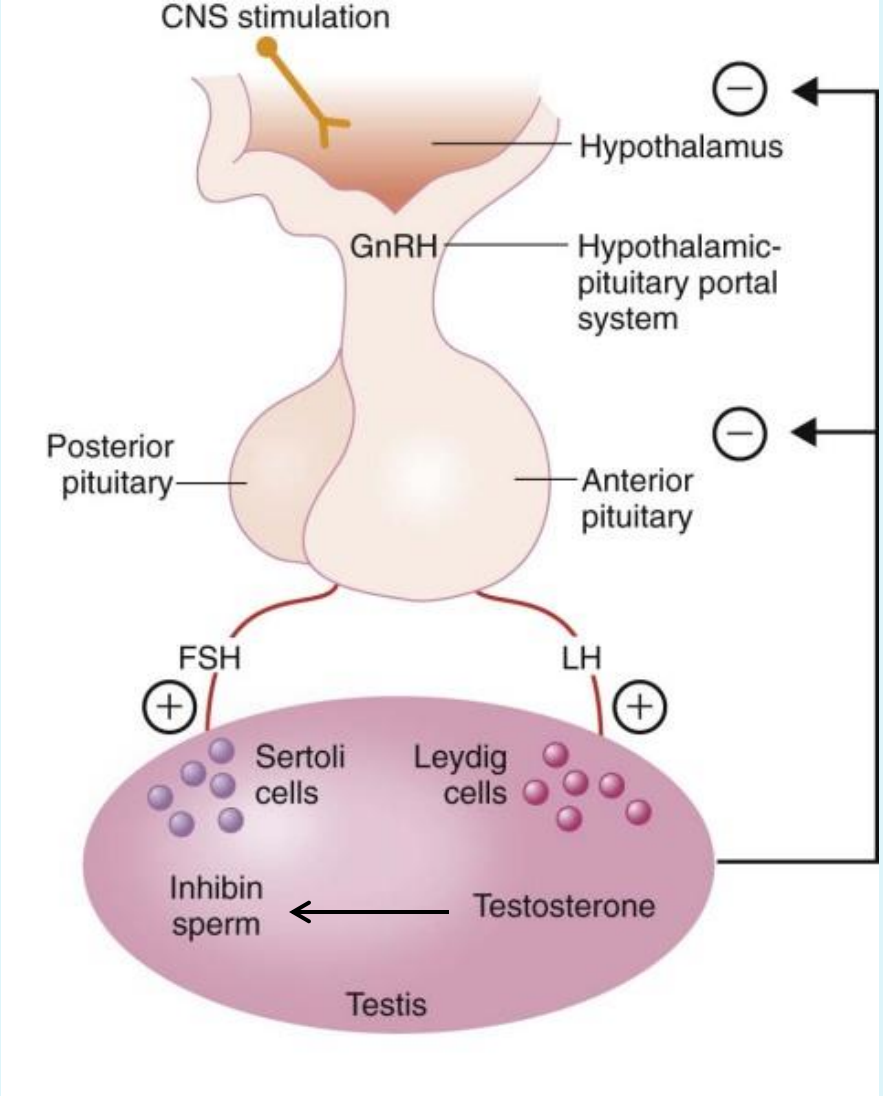
*ADAM (Androgen Deficiency in the Aging Male) questionnaire is adapted from Morley JE. *Metabolism.* 2000;49:1239-1242.

If you answered yes to question 1 or 7, or any 3 other questions, you may have low testosterone. Talk to your doctor to see if you should be tested.

Chances are, if you are overweight, physically inactive, have chronic medical problems, or married (with children) you will fail this test……..
Symptoms of low T are vague and non-specific

http://testim.com/adam-quiz.aspx

Hypothalamic-Pituitary-Gonadal Axis



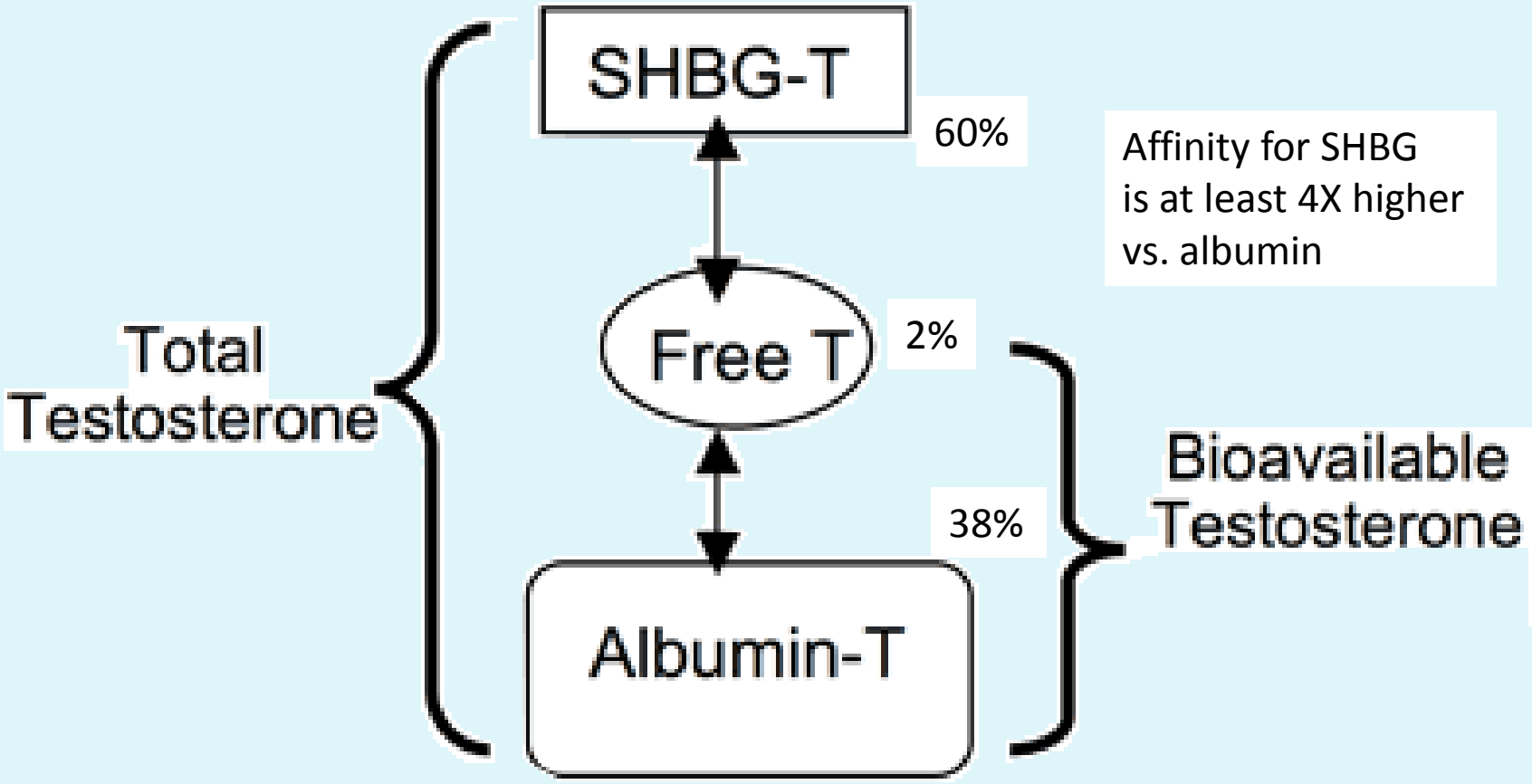
Faiman C. Cleveland Clinic Current Clinical Medicine, 2nd edition

Diurnal Rhythm

- Testosterone is highest near 8 am
  - check for deficiency when level should be highest
- Confirm the finding
  - At least one confirmatory measurement
    - early morning specimens should be obtained near 8 am
  - Acute effect of stressful illness may result in a transient lowering of testosterone levels

Beware of the night-shift worker!

Total vs. Free vs. Bioavailable Testosterone (male)



Greenspan's Basic &Clinical Endocrinology, 8th edition

What to measure?
Total-T vs. Bioavailable-T vs. Free-T

- The level of total testosterone is affected by alterations in the levels of its binding protein
  - mainly SHBG and albumin

- Free testosterone is the biologically active hormone
  - considered to be a more accurate representation of the "true" testosterone status

- Bioavailable testosterone is felt by some clinicians to be a better reflection of the true level of active hormone vs. that of the level of free testosterone alone

Reduction in SHBG level
Sex Hormone Binding Globulin

- Results in low total serum testosterone levels
- Seen in patients with obesity and/or DM-2
  - states of insulin resistance
- Also seen in other conditions such as
  - Acromegaly
  - Hypothyroidism
  - Nephrotic syndrome
  - Therapy with glucocorticoids, progestins, and androgenic steroids

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Reduction in SHBG level
Sex Hormone Binding Globulin

- In these settings checking the level of free testosterone and/or bioavailable testosterone may be more appropriate

- Bioavailable testosterone
  - T loosely bound to albumin + free T

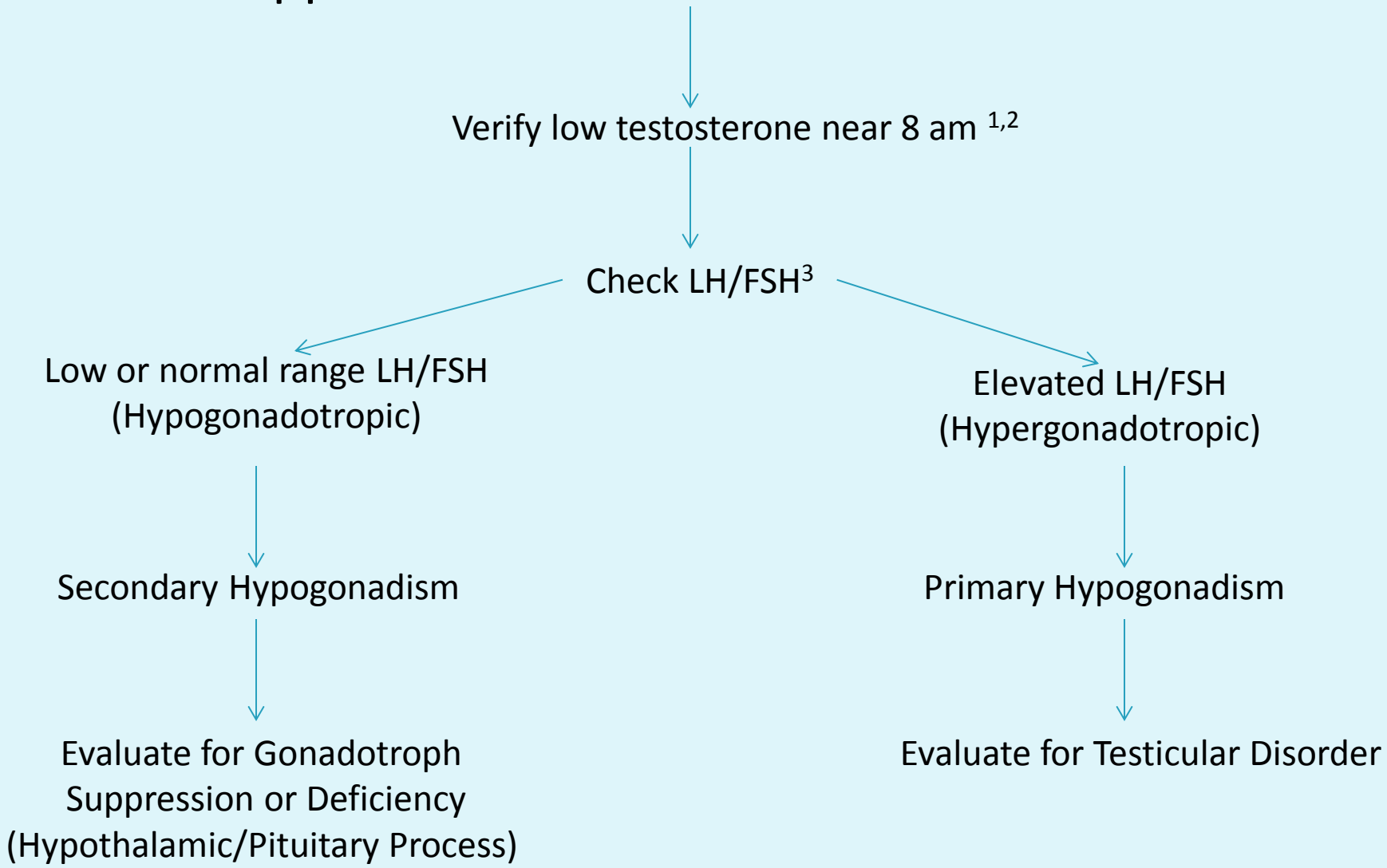
- Recall total serum testosterone is the sum of
  - SHBG-T (60%)
  - Loosely bound to albumin (38%)
  - Free testosterone (2%)

Testosterone Measurements

- Commercially available testosterone assays are not standardized well, and some are frankly unreliable
- Repeat, confirmatory measurements, especially for bioavailable/free testosterone, should always be performed by a reliable reference laboratory
- Efforts to standardize the assays are underway

Rosner W et al. J Clin Endocrinol Metab. 2007 Feb;92(2):405-13.
Rosner W et al. J Clin Endocrinol Metab. 2010 Oct;95(10):4542-8.

Approach to Low Serum Testosterone



1-Repeat confirmatory level should always be performed at a reliable reference laboratory
2-On occasion, total testosterone levels may be low but bioavailable and/or free testosterone levels may be normal
3-Initial evaluation should also include serum prolactin, TSH, free T4, and ferritin

Etiology

- Correct identification of the underlying etiology can have considerable implications in terms of the patients overall health

- It will also assist the clinician in determining when (and if) the initiation of testosterone therapy is appropriate

Primary Hypogonadism

- ↑LH/FSH in the setting of↓testosterone
  - suggests a testicular etiology

- Age of the patient at presentation, and careful questioning regarding pubertal development and fertility must be undertaken

Primary Hypogonadism

- Toxin exposure (chemotherapy)
- Congenital defects
  - Anorchia, cryptorchidism
- Karyotype abnormalities
  - Klinefelter Syndrome
- Orchitis (mumps, autoimmune)
- Testicular trauma or infarction
- Hemochromatosis
- Increase in temperature of testicular environment
  - Varicocele, large panniculus
- Medications which inhibit androgen synthesis
  - Ketoconazole

Farrer JH et al. Fertil Steril. 1985 Jul;44(1):125-32.
McDermott JH et al. J Clin Endocrinol Metab. 2005 Apr;90(4):2451-5.
Sikka SC et al. Endocrinology. 1985 May;116(5):1920-5.

Secondary Hypogonadism

- ↓ or normal LH/FSH in the setting of ↓ testosterone
  - suggests a hypothalamic/pituitary etiology

- **Congenital Disorders**
  - Inherited/Genetic defect

- **Acquired**
  - Damage to gonadotrophs
  - Suppression of gonadotrophs

Congenital Disorders

- Kallmann syndrome
  - Anosmia and GnRH deficiency
- Mutation/Deficiency of GnRH receptors
- Genetic mutations associated with pituitary hormone deficiencies
  - PROP-1 mutation

Pallais JC et al. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle, [updated 2011 Aug 18].
Romero CJ et al. J Mol Endocrinol. 2011 Jun 9;46(3):R93-R102. Print 2011.
Chevrier L et al. Mol Cell Endocrinol. 2011 Oct 22;346(1-2):21-8. Epub 2011 Apr 30.

Acquired
Damage to Gonadotrophs

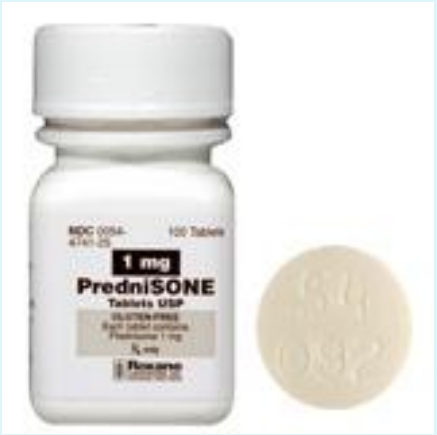
- Sellar mass/cysts
  - pituitary adenomas, craniopharyngioma, rathke cleft cyst, meningioma
- Infiltrative lesions
  - lymphocytic hypophysitis, Langerhans cell hystiocytosis, sarcoidosis, hemochromatosis, infection
- Metastatic lesions (breast, renal cell, lung)
- Trauma (head injury)
- Radiation exposure/Surgery to sellar region
- Pituitary apoplexy
- Stalk severance

Acquired
Suppression of Gonadotrophs

Numerous Causes!!!!!!!!!!

Medications

- Chronic therapy with common medications such opioids and/or corticosteroids can result in secondary hypogonadism



- GnRH analogues (leuprolide)
  - used in the treatment of prostate cancer

Colameco S et al. Postgrad Med. 2009 Jul;121(4):61-6.
Fraser LA et al. Exp Clin Endocrinol Diabetes. 2009 Jan;117(1):38-43
Morrison D et al. Respir Med. 1994 Oct;88(9):659-63.

Obesity

- Obesity and the related conditions are independently associated with decreased plasma testosterone
  - Obstructive sleep apnea
  - Insulin resistance and/or type 2 diabetes mellitus

Mah PM et al. Mol Cell Endocrinol. 2010 Mar 25;316(2):180-6

Obstructive Sleep Apnea

- Disturbances in the sleep cycle, regardless of the underlying cause, can result in decreases in the serum testosterone levels
  - likely by disruption of the normal diurnal rhythm
- Often, correction of the underlying sleep disturbance can result in normalization of the serum testosterone levels
- Caution must be used, and a thorough evaluation for sleep apnea should take place in high risk individuals (obese)
- Testosterone replacement therapy can adversely affect ventilatory drive and induce or worsen obstructive sleep apnea!

Santamaria JD et al. Clin Endocrinol (Oxf). 1988 May;28(5):461-70.
Grunstein RR et al. J Clin Endocrinol Metab. 1989 Feb;68(2):352-8.
Matsumoto AM et al. Clin Endocrinol (Oxf). 1985 Jun;22(6):713-21.

Insulin Resistance/DM-2

- Insulin resistance
  - Low total testosterone but normal free testosterone
    - Reduction in SHBG
  - Low levels of free testosterone can also be observed, particularly in morbid obesity, but the cause remains unclear
  - Decrement is proportional to the degree of obesity

- Testosterone levels have been reported to be lower in obese men with diabetes than in those with obesity alone
  - Decrement comparable in magnitude to the effects of other chronic diseases
  - Suggests that low testosterone **may simply be a marker of poor health**

Dhindsa S et al. Diabetes Care. 2010 Jun;33(6):1186-92.
Gascon F et al. Eur J Endocrinol. 2000 Jul;143(1):85-9.
Grossman M. J Clin Endocrinol Metab. 2011 Aug;96(8):2341-53.
Zumoff B et al. J Clin Endocrinol Metab. 1990 Oct;71(4):929-31.

Obesity and Children

Table 1	Lean	Obese	p
Number of subjects	25	25	
Age	16.5±1.4	16.0±1.5	0.17
BMI	20.9±2.2	36.0±5.3	<0.001
BMI Z Score	-0.1±0.9	2.4± 0.4	<0.001
BMI percentile	49±25	99±1	<0.001
Race: Caucasians	17 (68%)	15(60%)	0.21
African Americans	7(28%)	5(20%)	
Others	1(4%)	5(20%)	
Sys BP	120±11	130±10	0.001
Dia BP	68±9	74±11	0.06
Heart Rate	67±13	75±15	0.05
Tanner stage	4.7±0.5	4.7±0.5	0.9
TT (nmol/l)	616.7 ng/dL	302.6 ng/dL	<0.001
cFT (nmol/l)	0.44±0.18	0.26±0.11	<0.001

Testosterone concentrations (fasting, 8-10am) of young obese pubertal and post pubertal males are 40-50% lower than those with normal BMI

Mogri M et al. Clin Endocrinol (Oxf). 2012 Sep 13. [Epub ahead of print]

Hemochromatosis

- Hereditary Hemochromatosis
  - A common autosomal recessive disease characterized by an increase in iron absorption
  - Both 1° and 2° hypogonadism can occur with long-standing iron overload
    - 2° is much more common
- Iron overload, regardless of the cause, can result in hypogonadism

McDermott JH et al. J Clin Endocrinol Metab. 2005 Apr;90(4):2451-5.

Elevated Prolactin (Hyperprolactinemia)

- Medications
  - Dopamine antagonists (antipsychotics, metoclopramide)
- Pituitary adenomas
  - microadenomas < 10 mm
  - macroadenomas ≥ 10 mm
  - lactotroph hyperfunction
    - stalk compression interrupting/reducing the tonic suppression of prolactin secretion by dopamine
- Hypothyroidism
- Stress (seizure), Chronic renal failure, Cirrhosis
- Chest wall injury (trauma, active herpes zoster)

Excess Estrogen

- Exogenous
  - Exposure to estrogen containing contraceptives/creams
- Endogenous
  - Testicular or adrenal estrogen-secreting tumors
  - Rare syndrome of aromatase excess

Valensi P et al. Acta Endocrinol (Copenh). 1987 Jul;115(3):365-72.
Young S et al. Am J Surg Pathol. 1995 Jan;19(1):50-8.
Zayed A et al. J Endocrinol Invest. 1994 Apr;17(4):275-8.
Stratakis CA et al. J Clin Endocrinol Metab. 1998 Apr;83(4):1348-57.

Anabolic Steroids

- Exposure to anabolic steroids can result in secondary hypogonadism and testicular atrophy
  - Deliberate or inadvertent exposure
  - May persist for years after cessation of the anabolic agents
- If clinical suspicion exists, a urine anabolic steroid screen can be obtained

Anorexia

- Anorexia nervosa is certainly far less common in males than in females
  - Excessive exercise, Low BMI

- Chronic malnutrition and cachexia, regardless of the cause, can result in secondary hypogonadism
  - Malabsorptive conditions: Crohn's and celiac disease
  - Advanced cancer
  - Renal Failure (ESRD)

Russ MJ et al. Psychosomatics. 1986 Oct;27(10):737-9.
Rigotti NA et al. JAMA. 1986 Jul 18;256(3):385-8.

Acute Illness

- Gonadotroph Sick Syndrome
  - Hypogonadism is a relatively common finding in any critical illness
  - Analogous to euthyroid sick syndrome with respect to the hypothalamic-pituitary-thyroid axis
  - It is transient, and resolves with resolution of the underlying medical condition
    - sepsis, myocardial infarction, etc.
- Testosterone levels are invariably low
  - Checking is not recommended in this setting

Woolf PD et al. J Clin Endocrinol Metab. 1985 Mar;60(3):444-50.

HIV

- HIV can cause primary or secondary hypogonadism
- Can occur with active HIV infection, in patients whom control of viral replication has been obtained with HAART, and even in patients who have normalized CD4+ cell counts

- Development of hypogonadism in HIV patients is mutlifactorial
  - Weight loss
  - Opportunistic infections (pituitary/hypothalamus or testes)
  - Illicit drugs (heroin)
  - Medications
    - opioids, ganciclovir, ketoconazole, megestrol [appetite stimulant], cytoxan [malignancy]

Cohan GR. AIDS Read. 2006 Jul;16(7):341-5, 348, 352-4.

Aging (? Andropause)

- Most reports have suggested an age-related decrease in testosterone levels
  - Particularly in those > 65 years of age
- There also appears to be a loss of circadian rhythm in some, but not all, reports
- It appears that factors such as functional status and overall health may play a more important role in the pathophysiology of hypogonadism in males of advanced age rather than age alone

Feldman HA et al. J Clin Endocrinol Metab. 2002 Feb;87(2):589-98.
Bremner WJ et al. J Clin Endocrinol Metab. 1983 Jun;56(6):1278-81.
Diver MJ et al. Clin Endocrinol (Oxf). 2003 Jun;58(6):710-7.

Chronic Medical Conditions

- Liver cirrhosis, renal failure (ESRD), and rheumatoid arthritis, etc., can play a role in the development of secondary hypogonadism
  - The pathogenesis may involve dysfunction in all components of the hypothalamic-pituitary-gonadal axis
- Multifactorial
  - Metabolic disturbances
  - High frequency of acute illness and hospitalization
  - Medications (corticosteroids, etc.)

Handelsman DJ et al. Endocrinol Metab Clin North Am. 1993 Mar;22(1):145-61.
Handelsman DJ et al. Clin Endocrinol (Oxf). 1995 Sep;43(3):331-7.
Lim VS et al. Am J Med. 1975 May;58(5):655-62.
Tengstrand B et al. J Rheumatol. 2009 May;36(5):887-92. Epub 2009 Feb 27.
Tengstrand B et al. Rheumatology (Oxford). 2002 Mar;41(3):285-9.

Alcohol Abuse

- Alcohol can have adverse effects at all levels of the hypothalamic-pituitary-gonadal axis

- Resulting in low serum testosterone and reduced spermatogenesis

Emanuele MA et al. Alcohol Health Res World. 1998;22(3):195-201.

Severe Primary Hypothyroidism

- Can result in hypopituitarism
- Pituitary function usually recovers with restoration of euthyroidism

Meikle AW. Thyroid. 2004;14 Suppl 1:S17-25. Review.
Vagenakis AG et al. Ann Intern Med. 1976 Aug;85(2):195-8.

Pubertal Delay

- Depending on the age of presentation, differentiating pubertal delay vs. permanent hypogonadotropic hypogonadism can be challenging

Fertility

- In the male presenting with low serum testosterone, semen analysis is not routine

- Usually reserved for patients presenting with the primary complaint of infertility

Case Concluded

- The patient's low serum testosterone was confirmed on subsequent measurements near 8 am
  - 128 and 182 ng/dL (reference range 249-836)

- LH 1.4 mIU/mL (reference range 1.2-8.6)
- FSH 2.7 mIU/mL (reference range 1.3-9.9)
  - Both inappropriately normal in the setting of the low serum testosterone

- Further evaluation noted a TSH of 248 µIU/mL (reference range 0.4-5.5) and a slight elevation of prolactin 24.6 ng/mL (reference range 1.6-18.8)

Case Concluded

- The patient was started on levothyroxine therapy and after 3 months was noted to be euthyroid (TSH 1.8 µIU/mL) and with normalization of the serum prolactin
- Testosterone levels at that time were found to be 350 and 420 ng/dL (near 8 am)
- The cause of this patient's secondary hypogonadism was severe hypothyroidism and secondary mild hyperprolactinemia
- This case serves to illustrate that thorough evaluation is warranted ***prior to*** initiating testosterone therapy

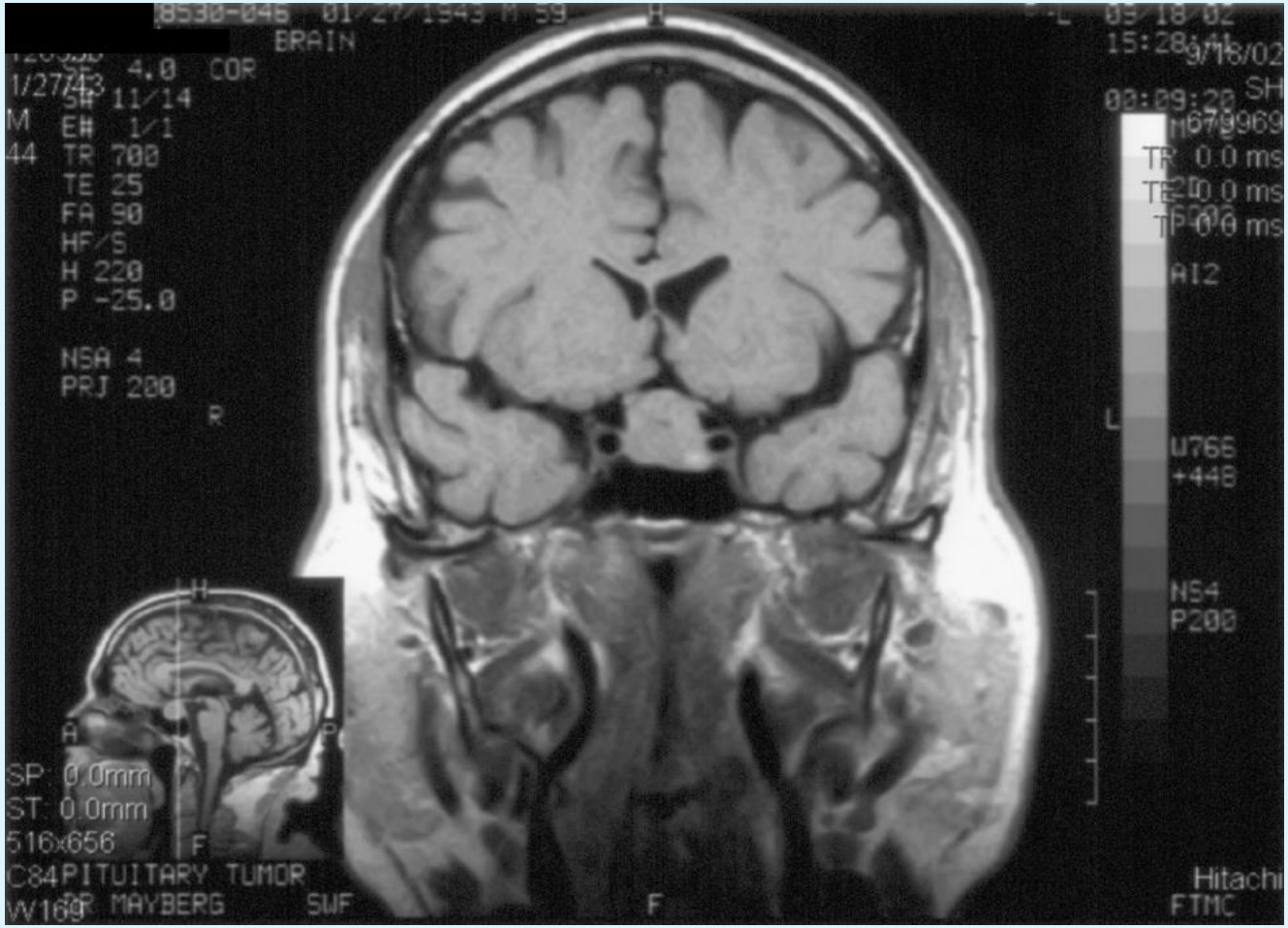
Case 2

- 41 year old male reports low testosterone noted on blood tests. His PCP ordered the test after the patient reported the inability to obtain an erection
- He has been on Zoloft for ten years, he thought it was just the Zoloft
- Reports zero sex drive
- His wife initially accepted this thinking it was related to his depression and medications
- Physical exam BMI 39, no gynecomastia, no testicular mass, no abnormal striae

Labs

- Testosterone, Serum **20 ng/dL** (249-836)
- Testosterone, Free **0.59 ng/dL** (5.00-21.00)
- LH and FSH undetectable
- TSH 1.05 µIU/mL (0.34-5.60)
- Free T4 0.76 ng/dL (0.58-1.64)
- IGF-1 75 ng/mL (70-307)
- ACTH stim test normal
- Prolactin **276.4 ng/mL** (1.60-18.80)

MRI


BRAIN
4.0 COR
S# 11/14
E# 1/1
TR 700
TE 25
FA 90
HF/S
H 220
P -25.0
NSA 4
PRJ 200
TR 0.0 ms
TE 0.0 ms
TP 0.0 ms
A12
U766
+448
N54
P200
SP 0.0mm
ST 0.0mm
516x656
C84 PITUITARY TUMOR
DR MAYBERG
SWF
Hitachi
FTMC

Damage vs. Suppression

Levels of LH/FSH are often much lower, or even undetectable with gonadotroph damage

vs.

Levels of LH/FSH seen in the setting of gonadotroph suppression

The degree of testosterone lowering is often more profound with gonadotroph damage vs. gonadotroph suppression

Time of onset/duration has profound influence as well

Key Points

- Testosterone measurements should occur near 8 am
- A low serum testosterone value should always be confirmed by a reliable reference laboratory
- The definition of a low testosterone level varies from lab-to-lab
  - In general, values <200-250 ng/dL are clearly low in most laboratories, and values between 250-350 ng/dL may be considered borderline low
- Determine if the etiology is primary (testicular) or secondary (hypothalamic/pituitary)
- Acute illness and treatment with opioids, anabolic steroids, or corticosteroids can cause hypogonadism

My Suggested Approach

- Verify low Testosterone near 8 am
  - at least 1 confirmatory measurement
- Check LH/FSH, Prolactin, TSH/FT4, Ferritin
  - High yield
- Review medications and take detailed history and physical
- Further evaluation may include MRI brain, testicular US, and complete anterior pituitary hormone assessment
  - age, history, and testosterone level usually determine degree of further evaluation
  - refer to endocrinology at this stage if unsure

MRI
Secondary Hypogonadism

- The yield of pituitary-hypothalamic imaging in older men is fairly low in the absence of other pituitary hormone abnormalities/deficiencies
- There are limited data regarding appropriate criteria for performing pituitary imaging studies
- Many experts recommend imaging in patients with secondary hypogonadism when:
  - the total testosterone level is very low (e.g. <100-150 ng/dL)
  - there are abnormalities of multiple hypothalamic-pituitary axes
  - no clear identifiable etiology
  - if clinical symptoms warrant further testing with imaging
    - visual field deficits, cranial nerve palsy, etc.

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Who should undergo assessment of testosterone status?

- Screening for androgen deficiency in the asymptomatic general population is not recommended

- The non-specific nature of many of the signs and symptoms of androgen deficiency makes it difficult to give concrete recommendations as to who should have testosterone levels measured

- Those with the complaint of ED should have their testosterone level assessed

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Who should **NOT** undergo assessment of testosterone status?

- Those who are acutely ill and hospitalized
- Those who are severely obese and are complaining of fatigue
- Testosterone levels should be assessed only after the acute illness has resolved and, in a severely obese patient with fatigue, only after a thorough evaluation for sleep apnea has been undertaken

Treatment

- Discuss the R/B/A of treatment
  - This conversation between the physician and patient should include dialogue regarding the uncertainty of the risks and benefits of testosterone supplementation in the older male population
  - Treatment is only recommended in patients with clinically significant symptoms of androgen deficiency
  - Simply treating low T values is not recommended
  - Treat the underlying cause, if one can be found
    - May require referral to specialist

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Treatment

- Make decision on individual basis

- You prescribe the testosterone, you do the f/u testing and monitoring!
  - PSA
  - HCT
  - DRE
  - Baseline, at 3 and 6 months, and then annually

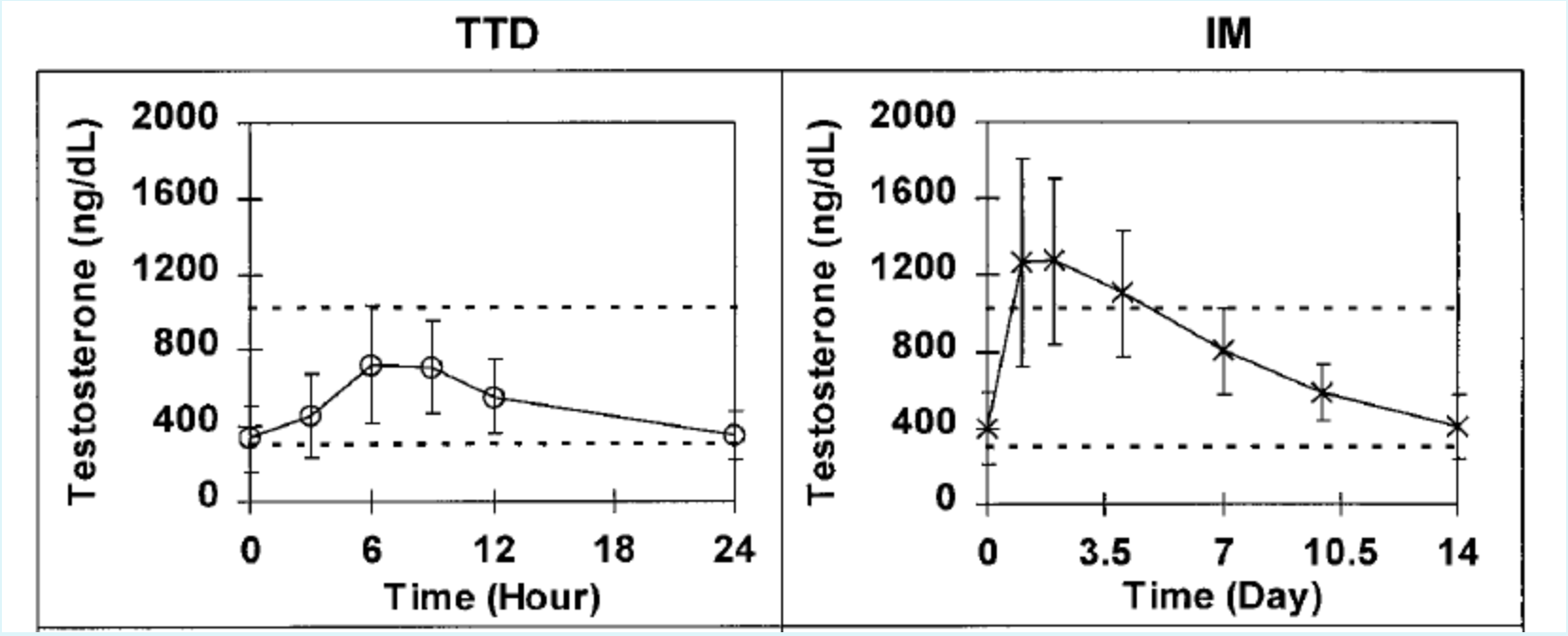
Treatment Options

- Available modalities of testosterone replacement therapy (TRT) in the United States include:
  - Depot-testosterone –IM cypionate or enanthate
  - Topical solutions-Axiron
  - Gels-Testim, Androgel, or Fortesta
  - Patches-Androderm
  - Subcutaneous testosterone pellets-Testopel
  - Buccal-Striant SR

Oral Testosterone

- NOT approved for use in the United States
- Testosterone undecanoate has been used
  - available only in Canada and Europe
- Methyltestosterone, still available in the United States, should not be used since hepatotoxicity can be fatal
  - Prolonged use of the oral methyltestosterone formulation is associated with hepatocellular carcinoma, peliosis hepatitis, and other types of hepatotoxicities
  - Not seen with the other replacement preparations

Transdermal vs. IM



Started 5 mg via Androderm patch Q evening

Started 200 mg IM T enanthate Q 2 weeks

Dosage adjustments were allowed for both groups if adverse events occurred or morning T levels were outside the normal range of 306-1031 ng/dL.

Dobs AS et al. J Clin Endocrinol Metab. 1999 Oct;84(10):3469-78.

Treatment Goals
Serum Testosterone Levels

- Transdermal preparations
  - mid-normal range
  - approximately 400-600 ng/dL
- IM testosterone cypionate or enanthate
  - approximately 400-700 ng/dL midway between injections
  - some advocate trough of 300-350 ng/dL
- Subcutaneous pellets
  - within the normal range at the end of the dosing interval

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Role of anti-estrogen therapy in the treatment of low serum testosterone

- Although the use of anti-estrogen therapy (Clomiphene) or aromatase inhibitors for the sole purpose of raising serum testosterone is endorsed by some, this is not a common practice in the United States and it is generally discouraged by most specialists

- However, these medications may be warranted in the setting of infertility where their utility is beyond that of merely increasing the levels of serum testosterone

Contraindications

- According to the most recent Endocrine Society Guidelines, testosterone therapy is not recommended in patients with:
  - Breast or prostate cancer
  - Palpable prostate nodule or induration or PSA > 4 ng/ml without further urological evaluation
    - PSA > 3 ng/ml in individuals at high risk for prostate cancer
      - African Americans
      - Men with 1st degree relatives who have prostate cancer
  - Erythrocytosis (hematocrit > 50%)
  - Hyperviscosity
  - Untreated obstructive sleep apnea
  - Severe lower urinary tract symptoms with American Urology Association (AUA)/International Prostate Symptom Score (IPSS) greater than 19
  - Class III or IV heart failure (uncontrolled or poorly controlled)
  - Those desiring fertility

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Stop therapy

- If HCT should rise to greater than 54%
  - Cessation of testosterone therapy should occur until HCT decreases to a safe level
  - Evaluate the patient for hypoxia and sleep apnea
  - If indicated, therapy should be reinitiated at a reduced dose

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Stop Therapy and Consult Urology

- Verified serum or plasma PSA concentration greater than 4.0 ng/ml
- An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment
- A PSA velocity of more than 0.4 ng/ml·yr using the PSA level after 6 months of testosterone administration as the reference
  - PSA velocity should be used only if there are longitudinal PSA data for more than 2 yr
- Detection of a prostatic abnormality on digital rectal examination
- An AUA/IPSS of more than 19

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

PSA Measurement

- The whole issue regarding PSA measurements has recently come under scrutiny and updated guidelines in the future may deemphasize this practice in men receiving testosterone supplementation

Chou R et al. Ann Intern Med. 2011 Dec 6;155(11):762-71.

Testosterone Replacement Therapy and Prostate Cancer

- Since androgen deprivation leads to the regression of prostate cancer, there has been concern that TRT may lead to growth or *de novo* development of prostate cancer
- Historically, TRT has been strongly prohibited in patients with prostate cancer
- However, recent data has challenged this paradigm

Coward RM et al. BJU Int. 2009 May;103(9):1179-83.
Sarosdy MF. Cancer. 2007 Feb 1;109(3):536-41.
Khera M. Sex Med. 2009 Mar;6 Suppl 3:234-8.
Szmulewitz R et al. Eur Urol. 2009 Jul;56(1):97-103.
Morgentaler A et al. J Urol. 2011 Apr;185(4):1256-60.

Low Testosterone and Cardiovascular Risk

- Low testosterone levels are associated with an increase in the incidence of cardiovascular events and mortality
  - Independent of multiple risk factors and several pre-existing medical conditions
  - Mean/Median age >70 years

Laughlin GA et al. J Clin Endocrinol Metab. 2008 Jan;93(1):68-75.
Tivesten A et al. J Clin Endocrinol Metab. 2009 Jul;94(7):2482-8.

Low Testosterone and Cardiovascular Risk

- This does not mean treating the low testosterone ameliorates this risk
  - Analogous to problems seen with HRT in women

- Health status and age at initiation of supplementation may be important
  - The low T may simply be a marker of overall poor health

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 8, 2010 VOL. 363 NO. 2

Adverse Events Associated with Testosterone Administration

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ABSTRACT

BACKGROUND

Testosterone supplementation has been shown to increase muscle mass and strength in healthy older men. The safety and efficacy of testosterone treatment in older men who have limitations in mobility have not been studied.

METHODS

Community-dwelling men, 65 years of age or older, with limitations in mobility and a total serum testosterone level of 100 to 350 ng per deciliter (3.5 to 12.1 nmol per liter) or a free serum testosterone level of less than 50 pg per milliliter (173 pmol per liter) were randomly assigned to receive placebo gel or testosterone gel, to be applied daily for 6 months. Adverse events were categorized with the use of the Medical Dictionary for Regulatory Activities classification. The data and safety monitoring board recommended that the trial be discontinued early because there was a significantly higher rate of adverse cardiovascular events in the testosterone group than in the placebo group.

RESULTS

A total of 209 men (mean age, 74 years) were enrolled at the time the trial was terminated. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the participants. During the course of the study, the testosterone group had higher rates of cardiac, respiratory, and dermatologic events than did the placebo group. A total of 23 subjects in the testosterone group, as compared with 5 in the placebo group, had cardiovascular-related adverse events. The relative risk of a cardiovascular-related adverse event remained constant throughout the 6-month treatment period. As compared with the placebo group, the testosterone group had significantly greater improvements in leg-press and chest-press strength and in stair climbing while carrying a load.

CONCLUSIONS

In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy. (ClinicalTrials.gov number, NCT00240981.)

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This article (10.1056/NEJMoa1000485) was published on June 30, 2010, at NEJM.org.

N Engl J Med 2010;363:109-22.

Testosterone supplementation in older men with a poor functional status and high prevalence of chronic disease may result in an increase in adverse cardiovascular outcomes

Benefits of Testosterone Supplementation

- Feeling better/Improved quality of life
- Increase in lumbar spine bone mineral density
- Increase in lean body weight, reduction in fat mass
- Improvement in muscle strength
- Improved sexual function
- ? Effect on depression
- ? Improved cognition

Bhasin S et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.

Effects of TRT

- Systematic review and Meta-analysis of 30 trials included 1642 men, 808 of whom were treated with testosterone
- Negligible change in major lipid fractions:
  - LDL
  - HDL
  - Tg
- Inconsequential changes in blood pressure and glycemia

Haddad RM et al. May Clin Proc 2007 Jan;82(1):29-39.

Effects of TRT

- In the aging, overweight male with type 2 diabetes and subnormal testosterone levels, treatment should be the implementation of lifestyle measures such as weight loss and exercise
  - May raise testosterone **and** provide multiple health benefits
- Simply providing testosterone supplementation may alter body composition in a metabolically favorable manner, but changes are modest and have not consistently translated into reductions in insulin resistance or improvements in glucose metabolism
  - May actually cause more harm than good
  - Jury is still out

Grossman M. J Clin Endocrinol Metab. 2011 Aug;96(8):2341-53.

Treatment

- At the present time, the clinical benefits and long-term risks of testosterone replacement therapy for patients with low testosterone secondary to type 2 diabetes, obesity, chronic medical conditions, or an age-related decline are unclear
  - The etiologies in older men

- Need clinical trials of long enough duration to clearly establish the benefits and risks of testosterone replacement in these populations

Bhasin S et al. Best Pract Res Clin Endocrinol Metab. 2011 Apr;25(2):251-70.
Dandona P et al. J Clin Endocrinol Metab. 2011 Sep;96(9):2643-51.

What to do?

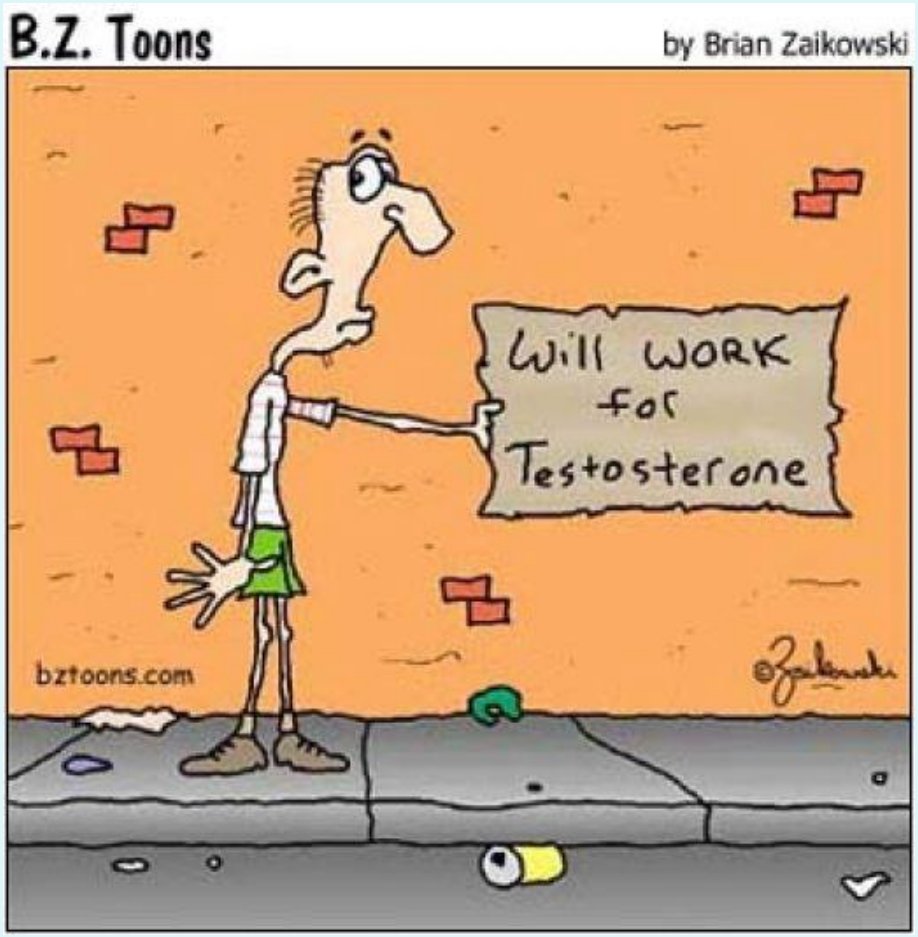
- Despite the uncertainties, a 3 month trial in patients in whom the risks and benefits are unclear is not unreasonable
- May be worthwhile in terms of improving quality of life
- In the majority of patients, a positive response is usually delayed
  - physicians should be suspect when dramatic improvements are reported very soon after the initiation of supplementation

What to do?

- Remember, TRT should **NOT** replace healthy lifestyle changes
  - Regular exercise, weight loss, diet modifications
  - May also provide the patient with symptom resolution
- There has been a dramatic increase in TRT initiation for non-specific symptoms of low testosterone in older androgen-deficient men
  - Significant risk of “overtreating”
  - Much remains unknown about the overall long-term risks and benefits of TRT

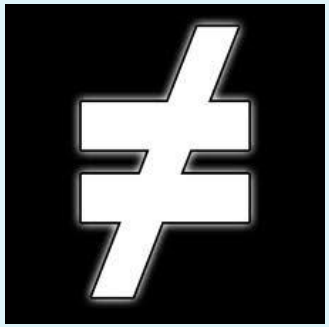
McGill JJ et al. Cleve Clin J Med. 2012 Nov;79(11):797-806.

Everybody wants to feel better……



Testosterone therapy is not for everyone, nor is testosterone deficiency the explanation for everyone's fatigue, erectile dysfunction, and lack of libido

Etiology of fatigue in older men is likely multifactorial……



Testosterone Therapy