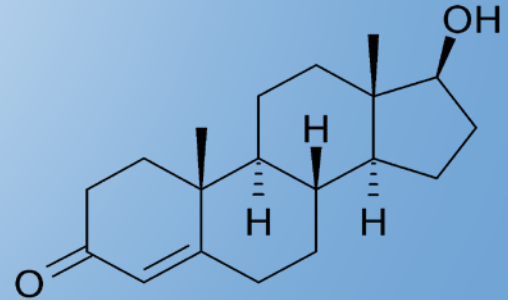


Hypogonadism

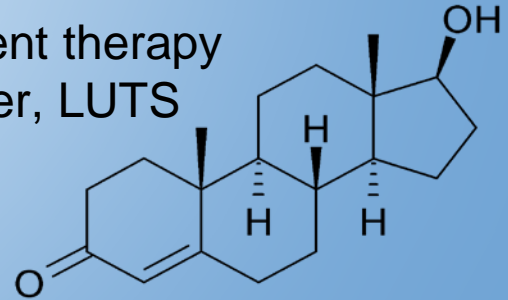
Jeremiah Murphy, MD
Mercy Urology Clinic

October 21, 2017



Objectives:

- Describe an appropriate strategy for the evaluation and diagnosis of male hypogonadism
 - Endocrine Society Clinical Practice Guideline-2010
- Review the potential benefits of testosterone replacement therapy
- Discuss the risks associated with testosterone replacement therapy
- Discuss age-related hypogonadism
- Controversial topics in testosterone replacement therapy
 - Cardiovascular risks, PSA, prostate cancer, LUTS



A Bit of History:

1849

1889

1935

1944

1990s +

Arnold
Berthold



Charles
Brown-Sequard

“Elixer of life”

Testicular Extract

Testosterone
Synthesized

Butenandt and
Ruzicka
(independant)

Nobel Prize 1939

The Male
Climacteric

Heller & Myers

Symptom
complex

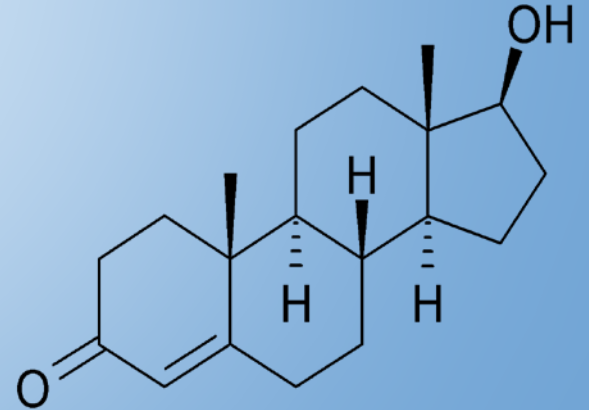
Big Business

“Low-T”

Topical preparations

“ Low-T”

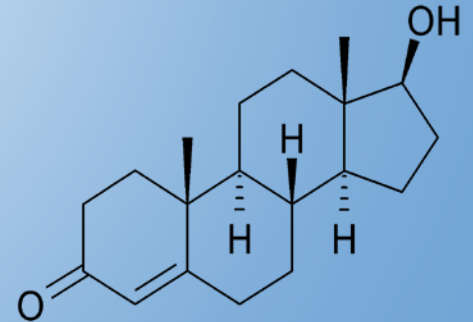
- Significant increase in the sale of Testosterone products
 - 18 million dollars in 1988
 - 1.6 billion dollars in 2011
- Direct-to-consumer advertising
- Low-T or Men’s Health Clinics
- Improved formulations



“Low-T”

- Institute of Medicine NASC 2002
 - No beneficial effect is well established

- JAMA 2013
 - 3x increase in testosterone Rx
 - 25 % never had diagnostic test for low testosterone



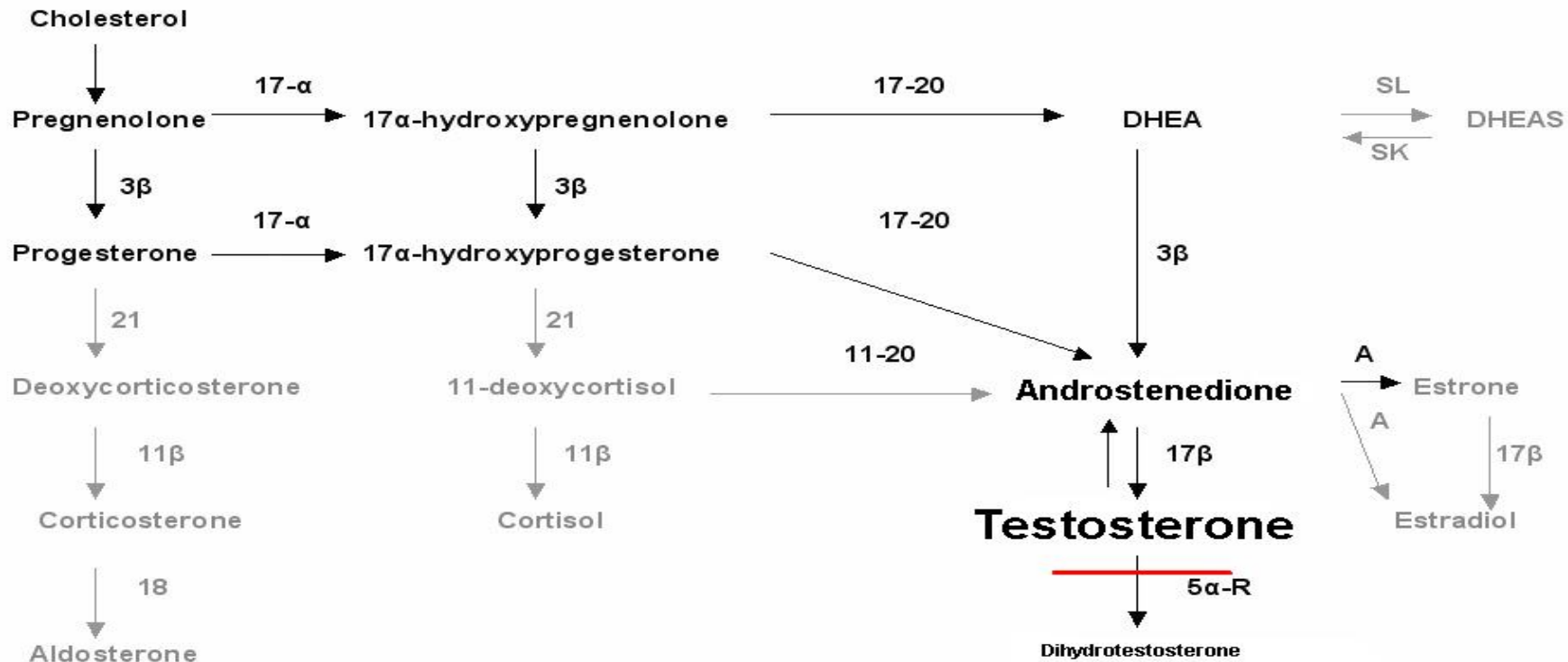
- FDA 2015

Men's Health Issues 2017:

- Erectile Dysfunction
- Vitality
- Physical
- PSA and Prostate Disease
- Bone and Joint Health
- Cardiovascular Disease
- Dietary Health/Health Maintenance

Testosterone:

- Testosterone is important
- Direct and indirect effects on every organ system in the body
- Low testosterone may be a crucial factor in chronic disease states
- Shifting demographics-aging population
- Estimated over 5 million men are affected
- Benefits of treatment can be significant



17α : 17α-hydroxylase

17,20 : 17,20-lyase

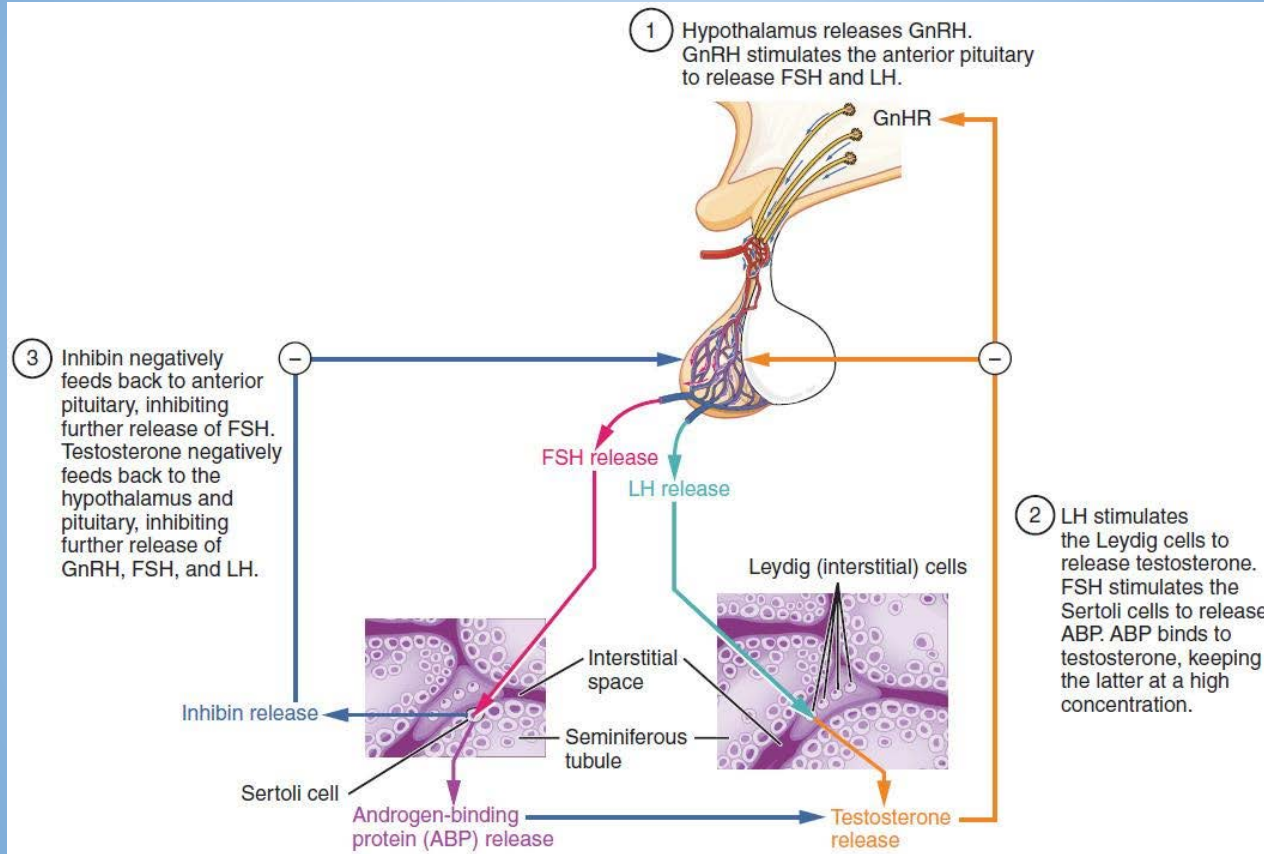
21 : 21-hydroxylase

3β : 3-HSD (hydroxysteroid dehydrogenase)

17β : 17β-HSD (hydroxysteroid dehydrogenase)

5α-R : 5α-reductase

Testosterone:



Testosterone:

- Primary Circulating Androgen
 - Libido, Anabolic effects, Hematologic effects, Bone Metabolism, Mood, Insulin, CV effects
- Adrenal Cortex 5%
- Androgen Receptor (AR) present in most tissues
- AR + Ligand conformational change- DNA-binding transcription factor that regulates gene expression

Testosterone Effects:

- Muscle Mass
- Bone Formation
- Sexual Function
- Via DHT
 - Facial and Body Hair
 - Scalp Hair Loss
 - Prostate Growth
 - Acne
- Via Estradiol
 - Bone Health
 - Cognitive and Verbal Function

CLINICAL PRACTICE GUIDELINE

Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

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Objective: The objective was to provide guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a professional writer. The Task Force received no corporate funding or remuneration.

Evidence: The Task Force used systematic reviews of available evidence to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence, using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation group.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during three group meetings, several conference calls, and e-mail communications. The drafts prepared by the panelists with the help of a professional writer were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Committee, and Council. The version approved by the Council was placed on The Endocrine Society's web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

THE TASK FORCE used systematic reviews of available evidence to inform its key recommendations. The number 1 indicates a strong recommendation and is associated

with the phrase "we recommend"; 2 denotes a weak recommendation and is associated with the phrase "we suggest."

Disclaimer: Clinical Practice Guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of healthcare providers and each patient's individual circumstances.

Conclusions: We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unprovocably low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using accurate assays. We recommend testosterone therapy for asymptomatic men with androgen deficiency, who have low testosterone levels, to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or enlargement or prostate-specific antigen greater than 3 ng/ml without further urological evaluation, erythrocytosis (hematocrit > 50%), preexisting obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score (IPSS) greater than 19, or class III or IV heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan. (*J Clin Endocrinol Metab* 91: 1995-2010, 2006)

Evidence grading: ⊕⊕⊕⊕ denotes very low quality evidence; ⊕⊕⊕⊕, low quality; ⊕⊕⊕⊕, moderate quality; and ⊕⊕⊕⊕, high quality. Numbers to the left of individual recommendations correspond to numbers in the text. Hence, there may

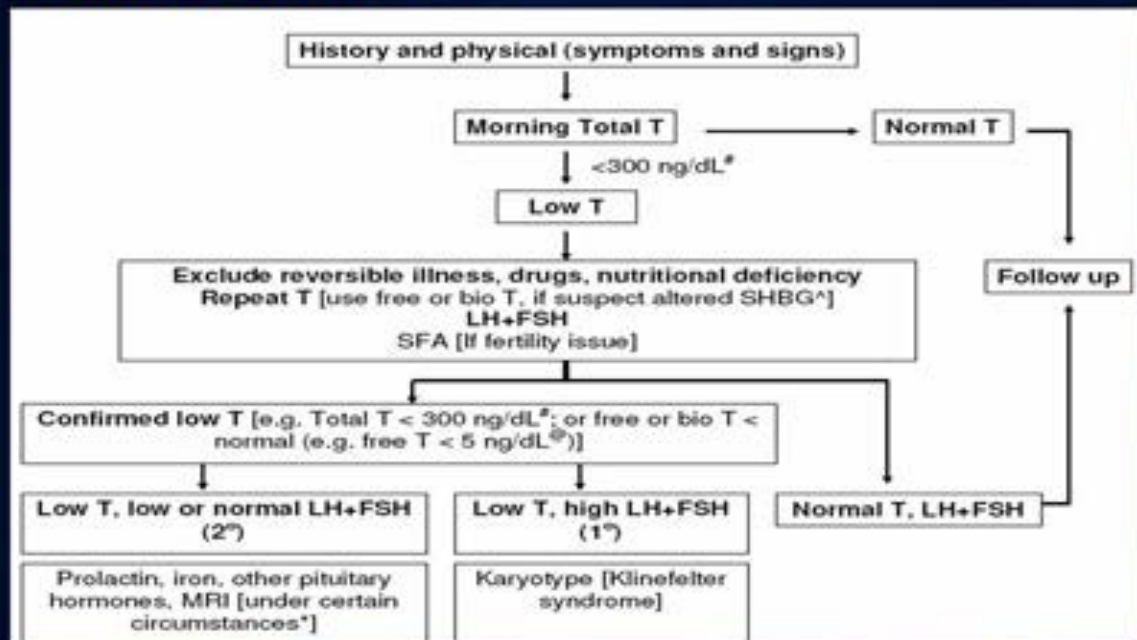
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Abbreviations: CI, Confidence interval; ED, erectile dysfunction; HPG, hypothalamic-pituitary-gonadal; LBM, lean body mass; MRI, magnetic resonance imaging.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

indispensable:

Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline



History and Physical Exam

Signs and Symptoms*



Morning Total Testosterone

*Only screen men if signs or symptoms are present.
Universal screening is not recommended.

*Don't test during an acute illness or hospitalization
(suppressed rhythm/IL-1)

*Symptoms are nonspecific

Fill Out the ADAM Questionnaire

If you're wondering what your symptoms may mean, you can fill out the ADAM questionnaire. It was developed by a physician and is used extensively by healthcare providers to help identify men who may have low testosterone. However, in order to confirm that you have Low T, your doctor will perform a blood test to determine if your testosterone levels are within an acceptable range.

Remember, only your healthcare provider can determine if your symptoms really add up to Low T.

1. Have you had a decrease in libido (sex drive)? Yes No
2. Have you had a lack of energy? Yes No
3. Do you have a decrease in strength and/or endurance? Yes No
4. Have you lost height? Yes No
5. Have you noticed a decreased "enjoyment of life?" Yes No
6. Are you sad and/or grumpy? Yes No
7. Are your erections less strong? Yes No
8. Have you noticed a recent deterioration in your ability to play sports? Yes No
9. Are you falling asleep after dinner? Yes No
10. Has there been a recent deterioration in your work performance? Yes No

If you answered yes to questions 1 or 7 or any 3 other questions, you may have low testosterone. A simple blood test can determine your testosterone level. Talk with your doctor.

Symptoms:

- Specific
 - Decreased sexual desire/Libido
 - Decreased spontaneous erections
 - Gynecomastia
 - Loss of body hair, reduced shaving
 - Loss of Height
 - Low BMD
 - Low trauma fracture
- Less specific
 - Decreased energy
 - Decreased motivation
 - Feeling sad
 - Decreased concentration or memory
 - Sleep disturbance
 - Mild anemia
 - Decreased muscle mass
 - Increased body fat
 - Diminished work/physical performance

Summary



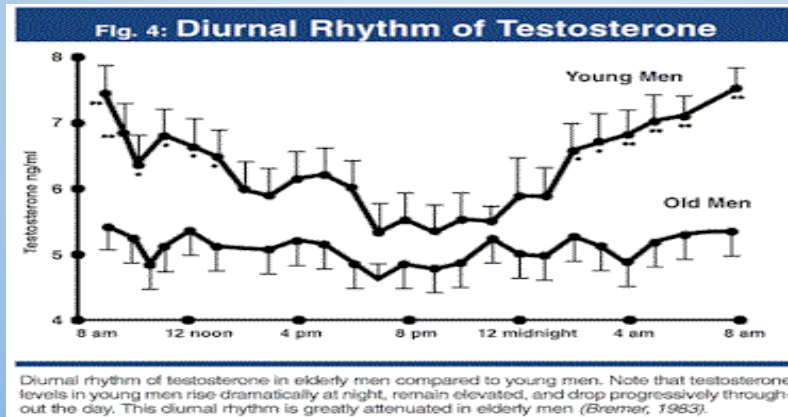
- Muscle vs Fat
- Sexual Function
- Physical function
- Mood/Concentration
- Sleep
- Energy/Vitality
- Bone density

History and Physical Exam



Morning Total Testosterone

- Check Total testosterone in the am 7-9 am
- Testosterone levels peak at around 8 am



Rhythm is blunted by illness or sleep disturbance

Check only in baseline state

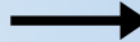
History and Physical Exam



Morning Total Testosterone



<300 ng/dL



Normal



Follow up

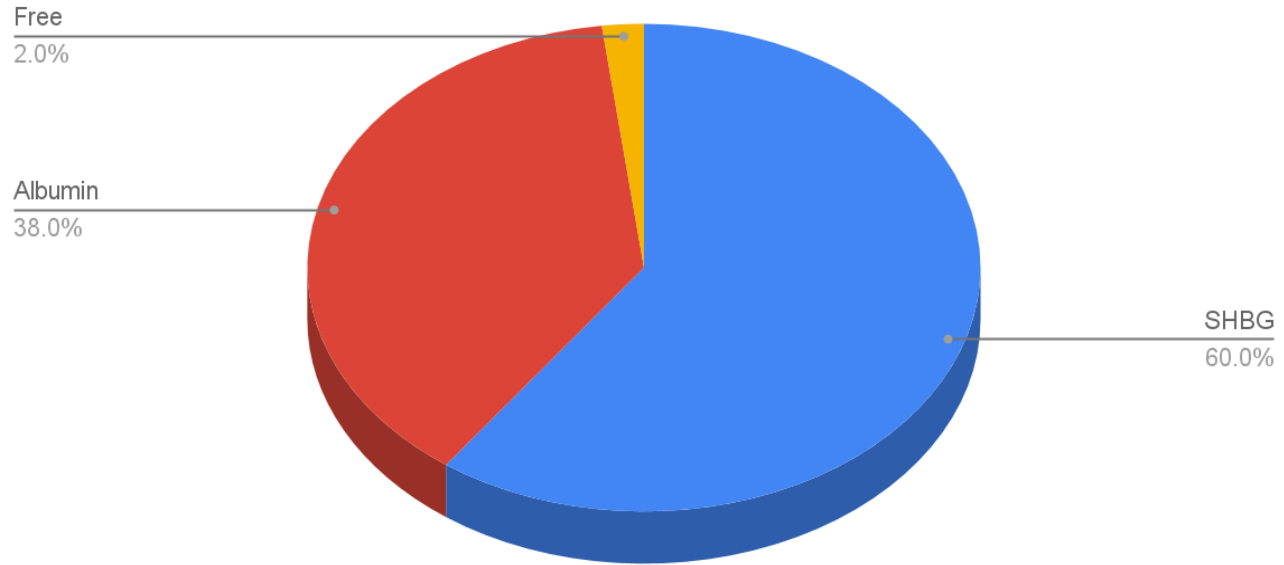
Low Testosterone

Low Testosterone (<300 ng/dL)

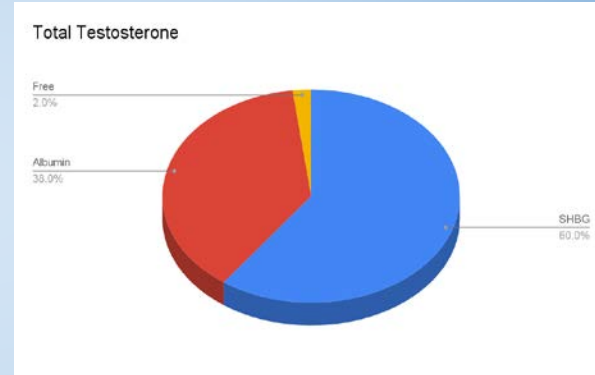


- Exclude reversible illness, drugs, nutritional deficiency
- Repeat AM free and total testosterone
- LH and FSH
- 30 % of men with initially low testosterone will have a normal level on repeat testing

Total Testosterone



- Total Testosterone significantly by SHBG
- Glycoprotein that binds androgen and estrogen
 - Decreased SHBG
 - Hypothyroidism
 - Obesity
 - Diabetes
 - Androgens
 - Increased
 - Age related increase
 - Hyperthyroidism
 - Malnutrition
 - Liver disease



Low Testosterone (<300 ng/dL)



- Low total testosterone but normal free-T
 - Symptoms unlikely related to low testosterone
- Normal Testosterone, LH + FSH



Follow up

Low Testosterone (<300 ng/dL)



Low T, low or normal LH + FSH

(Secondary Hypogonadism)

- Prolactin
- Iron
- Pituitary hormones
- MRI selected cases

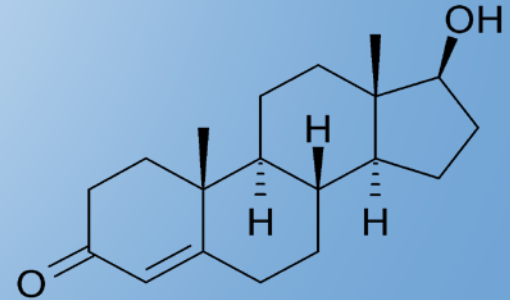
Low T, High LH + FSH

(Primary Hypogonadism)

- Klinefelter syndrome
- Receptor gene mutations
- Cryptorchidism
- Disorders of androgen synthesis

Testosterone and Replacement Considerations:

- Anabolic Effects
 - Testosterone increases lean body mass
 - Decreases fat
 - Effects stem cell differentiation
 - Increases protein synthesis
 - Inhibits protein degradation
- Hematologic Effects
 - Increases red cell mass
 - Increases HgB concentration
 - Erythrocytosis more pronounced with IM injections
 - Less with transdermal formulations
 - Must follow HgB levels



Testosterone and Replacement Considerations:

- Bone Metabolism Effects
 - Multiple pathways
 - Testosterone \Rightarrow Estradiol inhibits bone resorption
 - Testosterone replacement increases BMD
 - Does T-replacement decrease fracture risk ?

- Mood and Cognition
 - T-replacement improves the positive/reduces the negative
 - Effects on depression unclear. Ongoing research
 - Improves visual cognition
 - Improves verbal memory
 - Improves verbal fluency

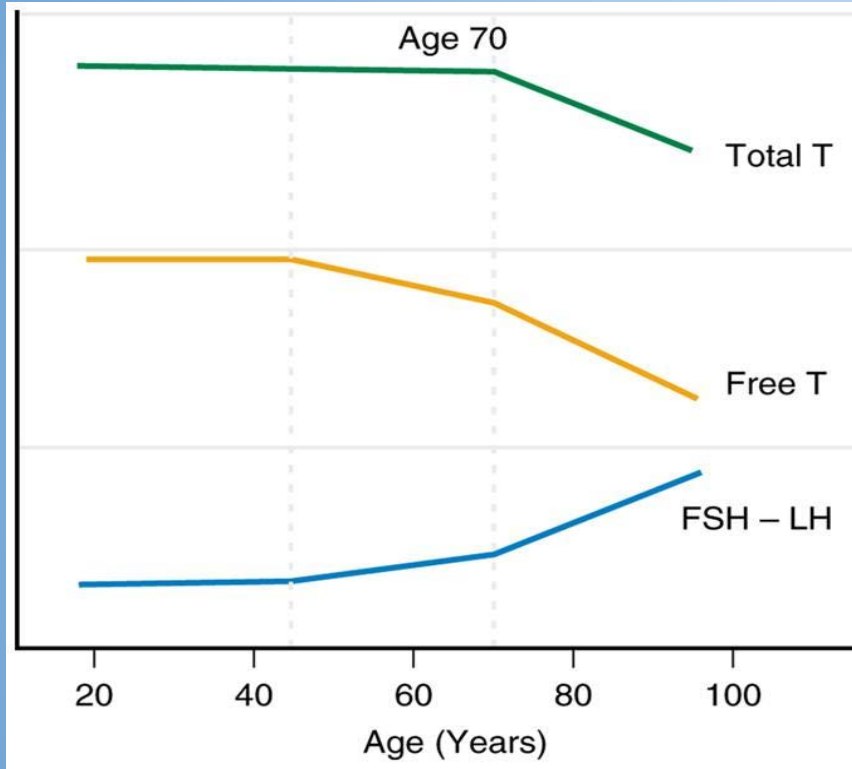
Testosterone and Replacement Considerations:

- Chronic disease states
 - Centrally mediated effect
 - Stress
 - Malnutrition
 - Opiate use
 - Infection
- Aging Male
 - Growing population >65 years old
 - Desire to maintain physical and sexual function
 - Greater percentage of older men have lower testosterone

Testosterone in the Aging Male:

- European Male Aging Study
J. Clin Endocrinol Metab 2008 93:2737
- Massachusetts Aging Study
J. Clin Endocrinology Metab 2007;
92:549
- New Mexico Aging Process Study
Metabolism 1997; 46:410

The Aging Male



- Decrease in both total and free T
- 100 ng/dL from 20 to 80
- 0.4%/year
- Loss of diurnal variation
- Increased SHBG
- Mild elevation in FSH + LH
- Mixed primary and secondary hypogonadism

The Testosterone Trials (NEJM 2016; 374:611):

- Multicenter seven placebo-controlled trials
- Looked at one year efficacy of testosterone in older men with established low-T
- Looked at effects on:
 - Sexual Function
 - Physical Function
 - Vitality
 - Cognitive Function
 - Anemia
 - Bone Density
 - Cardiovascular Risk Factors

The Testosterone Trial Results:

- Sexual Function
 - Moderate improvement in activity and sexual desire
- Physical Function
 - No significant difference between treatment group and placebo
- Vitality
 - No significant difference but men on testosterone did report a better mood
- Cognitive Function
 - No change over baseline (with exception in some improvement in executive function when subject groups combined)

The Testosterone Trial Results:

- Anemia
 - Significant improvement in hemoglobin of 1 g/dL or more in treatment group
- Bone density
 - Testosterone significantly increased BMD (lumbar, hip and peripheral)
- Cardiovascular risks
 - Increase in noncalcified coronary artery plaque volume
 - No CV events reported
 - Unclear clinical significance
 - Plaque formation? concern about testosterone use in older men

More on Cardiovascular Risks:

- Mixed opinions on testosterone effects
- Beneficial?
 - Rottenham Study-Lower testosterone associated with increased atherosclerosis
 - Carotid Artery Study
 - TRT-improved exercise tolerance
 - Improved HDL levels
 - ? Cardioprotective
- Detrimental?
 - VA study-retrospective. TRT increased risk for MI, Stroke
 - Flawed study. Controversial

Cardiovascular Risks:

Large, Long-term studies are needed to further evaluate the risks of testosterone replacement therapy and CV risks.

Prostate Cancer/BPH:

- Most epidemiologic studies have shown no association between testosterone levels and the incidence of prostate cancer
- Treatment may stimulate growth in previously undiagnosed prostate cancer
- No studies suggest testosterone replacement therapy as a cause of prostate cancer
- Prostate cancer is partially testosterone dependant. Low testosterone + prostate cancer is a more virulent disease.
- Prostate enlargement was minimal. Small decrease in max flow rate

Summary:

- Testosterone replacement therapy is increasing
- The diagnosis requires a careful evaluation
- Treatment requires an established diagnosis and symptoms
- The benefits of testosterone therapy may be significant in patients with symptoms
- The benefits for age-related hypogonadism appear limited (sexual function, anemia, bone health)
- The relationship between testosterone replacement therapy and CV disease remains unclear.

Testosterone Replacement Therapy: Goals

- Improve libido, mood and general well-being
- Increase muscle mass
- Prevent bone loss

Testosterone Replacement Therapy: Contraindications

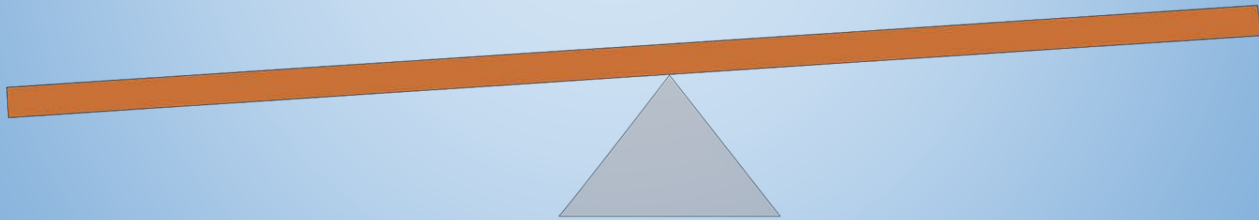
- Prostate/ Breast Cancer
- Hct >55%
- BPH
- Sleep Apnea
- CHF

Benefits:

- Increased muscle mass
- Sex drive
- Improved mood
- Vitality
- Cognition
- Bone density
- CV benefit?

Risks:

- Erythrocytosis
- Gynecomastia
- Worsening OSA
- Infertility
- CV risks?



Testosterone Replacement Therapy: IM Injections

- Testosterone Cypionate (Depo-Testosterone)
 - $\frac{1}{2}$ life 8 days
 - 200 mg every other week
- Testosterone Enanthate
 - $\frac{1}{2}$ life 4.5 days
 - 100 mg every week
- Testosterone Undecanoate (Aveed)
 - 750 mg IM q 10 weeks (1000mg/12 weeks)
- Inexpensive
- Symptom fluctuation due to peaks and nadir
- Increased polycythemia
- MD visits for injection
- Can be taught to do this at home with closer monitoring

Testosterone Replacement Therapy: Gels

- Androgel, Testim, Axiron
- Convenient
- Simple to use
- Very effective
- Most physiologic replacement
- Gels can transfer (partner/kids)
- Less skin irritation

Testosterone Replacement Therapy: Patches

- Limited by \$\$\$
- Skin irritation

Testosterone Replacement Therapy: Buccal Disc

- Striant
 - 30 mg buccal disc q 12 hours
- \$\$\$

Testosterone Replacement Therapy: Oral

- Not used in US
- Europe 2-3x daily with food

Testosterone Replacement Therapy: Subcutaneous pellets

- Testopel
- 6-10 Pellets
- Last 3-9 months
- Expensive
- Clinical response slower
- Abused “Low-T” clinics



Testosterone Replacement Therapy: Goal

- Target should be a testosterone in the mid-normal range 400-700 ng/dL
 - Do not adjust based on symptoms
 - Adjust dose or frequency

- Hemoglobin
 - Check at baseline at at 3-6 months then every 6-12 months
 - Halt therapy if HCT >54%
 - Adjust dose or frequency after HCT returns to normal level

- PSA
 - Baseline
 - Repeat at 3-6 months then every 6-12 months based on risks

Thank you

B.Z. Toons

by Brian Zalkowski

