Male Hypogonadism

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Overview

- Evaluation of Male Hypogonadism
- Management of Male Hypogonadism
- Risks With Hormone Therapy
- Cases
- Monitoring on Hormone Therapy
- Gynecomastia

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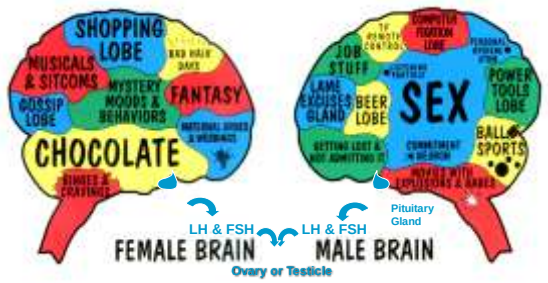
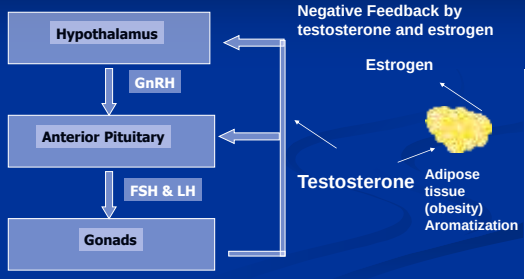
Hypothalamic Pituitary Function



HYPOTHALAMIC-PITUITARY-GONADAL AXIS



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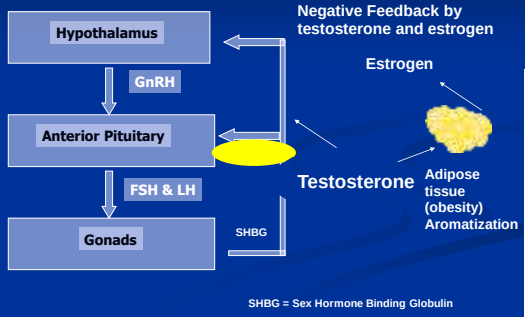

Conditions Causing Low SHBG

Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline
Shalender Bhasin et al, JCEM Volume 103, Issue 5, May 2018

Conditions Causing High SHBG

Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene

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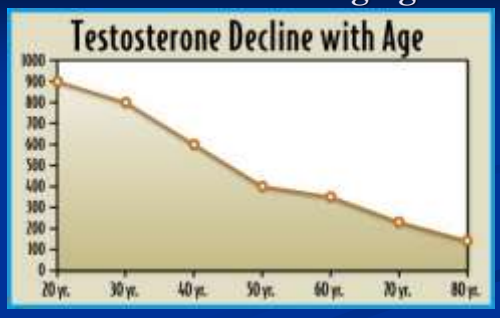
Testosterone and Aging



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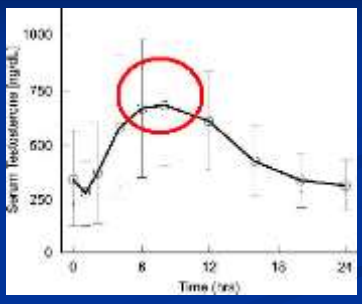
Testosterone: Diurnal Variation



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Signs and Symptoms of Hypogonadism

- Changes in mood (fatigue, depression, anger)
- Decreased body hair (feminization)
- Decreased bone mineral density
- Decreased lean body mass and muscle strength
- Decreased libido and erectile quality and frequency
- Increased visceral fat
- Hot Flashes/Sweats
- Oligospermia or azoospermia.
- Gynecomastia
- Decreased testicular volume

Non Specific Symptoms

Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

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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 you answered YES to questions 1 or 7 or any 3 other questions, you may have low testosterone.

**Adapted from Morley JE, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* 2000;49(9):1239-1242.

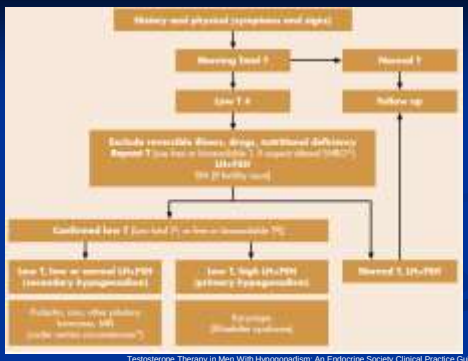
Causes of Low T

- **Common Causes**
  - Obesity (negative estrogen feedback)
  - Aging
  - Medications (narcotics, glucocorticoids)
  - Previous exogenous use of Testosterone
  - "Nutritional supplements"
  - HIV (hypothalamic, testicular, malnutrition, medications, glucocorticoids)
- Less common Causes
  - Nutritional (anorexia)
  - Previous trauma, infections, undescended testis
  - Klinefelter's syndrome
  - Kallman's syndrome
  - Autoimmune Testicular dysfunction

Evaluation of Hypogonadism

- Morning Testosterone level (before 0900)
- **Repeat morning Testosterone level**
  - Low T considered below lower limit or Free T measurement below normal
- LH, FSH, Prolactin, Estradiol, SHBG, cbc
- Karyotype (small testicular volume, high LH and FSH)
- MRI sella (low LH and FSH)?

Evaluation of Low T



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Treatment Guidelines: Who To Treat?

- Only men with symptoms and signs consistent with testosterone (T) deficiency
- And unequivocally and consistently low serum T concentrations or low free testosterone on repeated testing
- Men who have had proper initial evaluation for cause of low T

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Treatment Guidelines: Who Not to Treat

- Patients planning fertility in the near term
- History of breast or prostate cancer
- A palpable prostate nodule or induration
- PSA level > 4 ng/mL, PSA > 3 ng/mL in men at increased risk of prostate cancer (*e.g.*, African Americans and men with a first-degree relative with diagnosed prostate cancer) without further urological evaluation
- Elevated hematocrit
- Untreated severe obstructive sleep apnea
- Severe lower urinary tract symptoms
- Uncontrolled heart failure
- MI or stroke within the last 6 months
- Thrombophilia

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Treatment Guidelines: Prostate

- In men 50-69 and have a life expectancy > 10 yrs
  - Discuss risks and benefits of prostate cancer monitoring
  - Engage the patient in "shared decision making"
  - For patients who choose prostate monitoring
    - Baseline evaluation (DRE, PSA)
    - Evaluation 3-12 months after starting T
- In men 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer)
  - discuss prostate cancer risk with the patient and offer monitoring options

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Treatment Guidelines: Older men with age-related decline in testosterone concentration

- Andropause
  - Age related testicular and pituitary dysfunction
- Endocrine Society does not recommend therapy for age related decline in T
- In men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentration:
  - Offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits

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Testosterone Therapies

Depo Tesosterone Enanthate or Cypionate	50-100mg IM Weekly 100-200mg IM q 2 wks
Tesosterone Gel 1% or 1.6%	5-10gm daily to skin (non -genital)
Testosterone Patch	2-4mg patch, 1-2 nightly, back, thigh or upper arm
Buccal Mucosa Tesosterone	30 mg of a bioadhesive buccal T tablet to buccal mucosa Q 12 hrs
Testosterone Pellets	Pellets implanted SQ q 3-6 months
Testosterone Solution	60 mg of testosterone (1 pump or 1 twist actuation of 30 mg of testosterone to each axilla) Daily
Intranasal Testosterone	11 mg two or three times daily

Testosterone Injection Pharmacokinetics

Day 1 Day 3/4 Day 7 Day 14

Me, J. Canales, MD, May, 2019

Testosterone Gel Pharmacokinetics

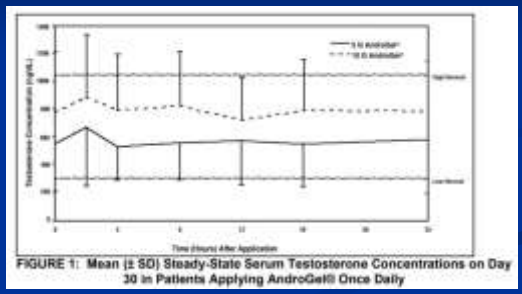


FIGURE 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying AndroGel® Once Daily

Testosterone Gel: Precautions

- Patients should wash their hands immediately with soap and water application of AndroGel
- Patients should cover the application site(s) with clothing after the gel has dried (e.g. a shirt)
- If another person comes in contact with AndroGel, wash with soap and water immediately
- Changes in body hair distribution, significant increase in acne or other signs of virilization of the female partner should be brought to the attention of the provider.

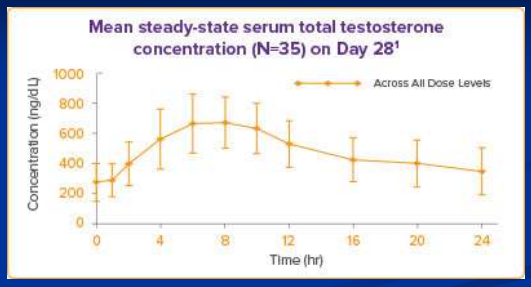
https://www.accessdata.fda.gov/

Testosterone Gel: Contact Exposure

- Clinical Study: men and their female partners
  - 2-12 hours after application of gel
  - Male and female partners engaged in 15 minutes of "vigorous skin to skin contact"
- Results
  - Female partners had a >2 fold increase in serum testosterone levels above baseline
  - When a shirt was used by the male partner, no increase in testosterone was seen in the female partner

https://www.accessdata.fda.gov/

Testosterone Patch



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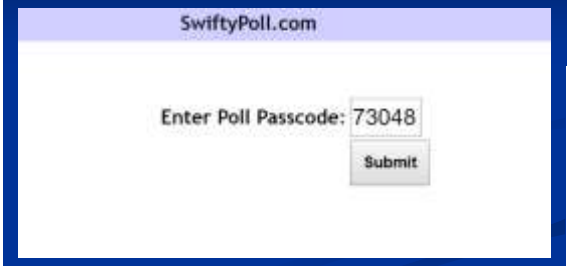

Testosterone Benefits

- Improvement in bone mineral density
  - No data for fracture reduction
- Sexual Function
  - Improved libido, erectile function, and sexual activity
  - Does not improve ejaculatory function
- Mood
  - Improvement in general mood
  - No improvement in depressive symptoms
- Increases fat free mass and muscle strength
  - Reduces whole body, intraabdominal, and intermuscular fat

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Testosterone Side Effects

- Prostate hypertrophy (elevation in PSA)
- Erythrocytosis
- Increased sleep apnea risk/severity
- Acne/Oily Skin
- **Impaired fertilty**
- Water retention
- Gynecomastia
- Potential for partner contact (gel)
- Stimulation of prostate cancer already present
- Increased cardiovascular risk?
  - Older men > 60 or 65, with pre-existing CAD or high risk

Testosterone: CVD Risk

- There have been no RCTs that were large enough or long enough to determine the effects of T-replacement therapy on major adverse cardiovascular events (MACE)
- No conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men
- FDA Announcement 3/3/15
  - Required manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone

Testosterone Monitoring

- Therapy should aim to raise serum T concentrations into the mid-normal range
- Evaluate patient 3-6 months after starting
- Monitor T levels in 3-6 months
  - Injections: If mid-interval T is >600 ng/dL (24.5 nmol/L) or <350 ng/dL (14.1 nmol/L), adjust dose or frequency
  - Transdermal gels: assess T concentrations 2–8 h following the gel application, after the patient has been on treatment for at least 1 wk
  - Transdermal patches: assess T concentrations 3–12 h after application; adjust dose to achieve T concentration in the mid-normal range.
- CBC baseline then q 3-6 months for first year then yearly

Testosterone Therapy: Urology Referral

- Urology Evaluation
  - If in the first 12 months of treatment the PSA increases > 1.4ng/mL above baseline or
  - If the PSA rises above 4.0 ng/mL or
  - If there is abnormality detected on digital rectal exam

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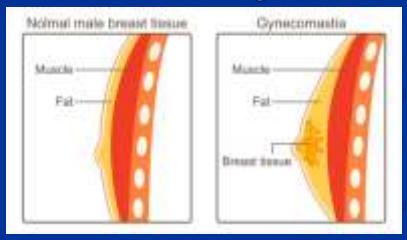
Gynecomastia

- Breast tissue formation with enlargement of the breast and tenderness, often retro-areolar
- Due to Testosterone/Estrogen imbalance



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Gynecomastia: Causes

- Low testosterone
  - Aging, Obesity
- Medications
  - Digoxin, Cimetidine, Spironolactone, Luprolide, Narcotics
- Iatrogenic (too much testosterone)
  - Supplement "Boosters"
- Alcohol, Marijuana
- Tumor
  - HCG
  - Estrogen

Gynecomastia: Work Up

- Medication List
- Good history
  - Alcohol, marijuana use, weight lifting supplements
- Physical Exam
  - Breast
  - Testis
- Laboratory
  - HCG, morning T, SHBG (T panel), LH, FSH, Estradiol, TSH, prolactin

Gynecomastia: Treatment

- Weight loss
- Stop alcohol
- Stop offending medication if possible
- Surgery
- Off label Medications (not FDA approved for this purpose)
  - Tamoxifen 10mg BID
  - Anastrozole 1mg daily

Common Pitfalls

- Not checking morning Testosterone
- Not checking free fraction of Testosterone
- Not repeating Testosterone level
- Not obtaining history of supplement use
- Starting Testosterone without appropriate work up… then referring to endocrine.
- Not measuring Testosterone at the correct time when on therapy
- Recommend weight loss for the obese patient first
- Not performing sleep apnea testing for fatigue

Conclusions

- Testosterone Physiology
- Evaluation of Hypogonadism
- Management of Hypogonadism
- Risks and Benefits with Testosterone Therapy
- Gynecomastia causes and management