

# Testosterone Deficiency: Diagnosis, Management, and the Role of Primary Care

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# Conflict of interest

- Active speaker's bureau for Abbott regarding continuous glucose monitoring
- Former speaker's bureau for Sanofi, AZ, BI

# Outline

- Diagnosis of Testosterone Deficiency
- Differential Diagnosis
- Treatment considerations
- Side effects/monitoring
- When to Refer

# Diagnosis of Testosterone Deficiency

- 34 year old male present with a history of testosterone deficiency
- Works in the Army at Ft Leonard Wood
- Has been following locally with a “low T” clinic
- Initiated on testosterone injections
- Reports doses were increased due to “not getting his T up”
- Presented due to not wanting to pay cash further for the monthly fee
  - Wanted to get covered under insurance

# 34 year old male Army guy

- Initial work up: 2 years found to have afternoon testosterone of 320.
- No additional work up at that time
- Started on testosterone injections 100 mg weekly
- Titrated in time to 100 mg Mondays and Thursdays
  
- He had further labs and testosterone now 1500
  - Was told to continue current doses
  
- He felt like something was off and wanted a second opinion and wanted this covered by insurance

# 34 year old Army guy on testosterone

- First question I always ask is what is the cause of the low testosterone?
  - Primary testicular defects
  - Pituitary illness
  - Hypothalamic illness
- His only work up was 1 testosterone level drawn in the afternoon and started on treatment.

# Endocrine Practice Guidelines



[Endocrine.org/clinical-practice-guidelines](https://www.endocrine.org/clinical-practice-guidelines)

Adrenal, hypoglycemia, bone health, male reproduction, CV endo, neuroendocrine, diabetes, obesity, endocrine cancer, peds endo, female reproduction, transgender medicine

Free guidelines even for non-endocrine society members

# Symptoms of hypogonadism

- Specific

- **Incomplete/delayed sexual development**
- **Loss of body hair(axillary and pubic)**
- **Very small testes <6 ml**

- Suggestive symptoms

- Decreased libido
- Decreased spontaneous erections or new ED
- Gynecomastia
- Eunuchoid shape
- Infertility
- Hot flashes
- Osteoporosis

- Nonspecific symptoms

- Lack of energy, motivation, initiative, self confidence (what they read on the internet)
- Poor concentration/memory
- Sleep disturbances
- Mild unexplained anemia
- Reduced muscle bulk/strength
- Increased body fat

(I feel like a low T commercial as I type this column)

# Symptoms of Testosterone Deficiency



## Early symptoms

- Decreased libido
- Decreased vigor
- Mood changes

## Later symptoms

- Decreased muscle mass
- Loss of body hair

Hot Flashes rarely occur but can be found with severe and/or rapid decline of testosterone levels.

# Screening for hypogonadism



## 8 am fasting serum total testosterone

- Most labs 300-1000 is the reference range
- Bound to SHBG
  - Obesity reduce SHBG which may give false low testosterone levels
  - Aging increases SHBG which may mask underlying hypogonadism
  - May be reasonable to screen with a free testosterone in these instances

Testosterone decreased throughout the day

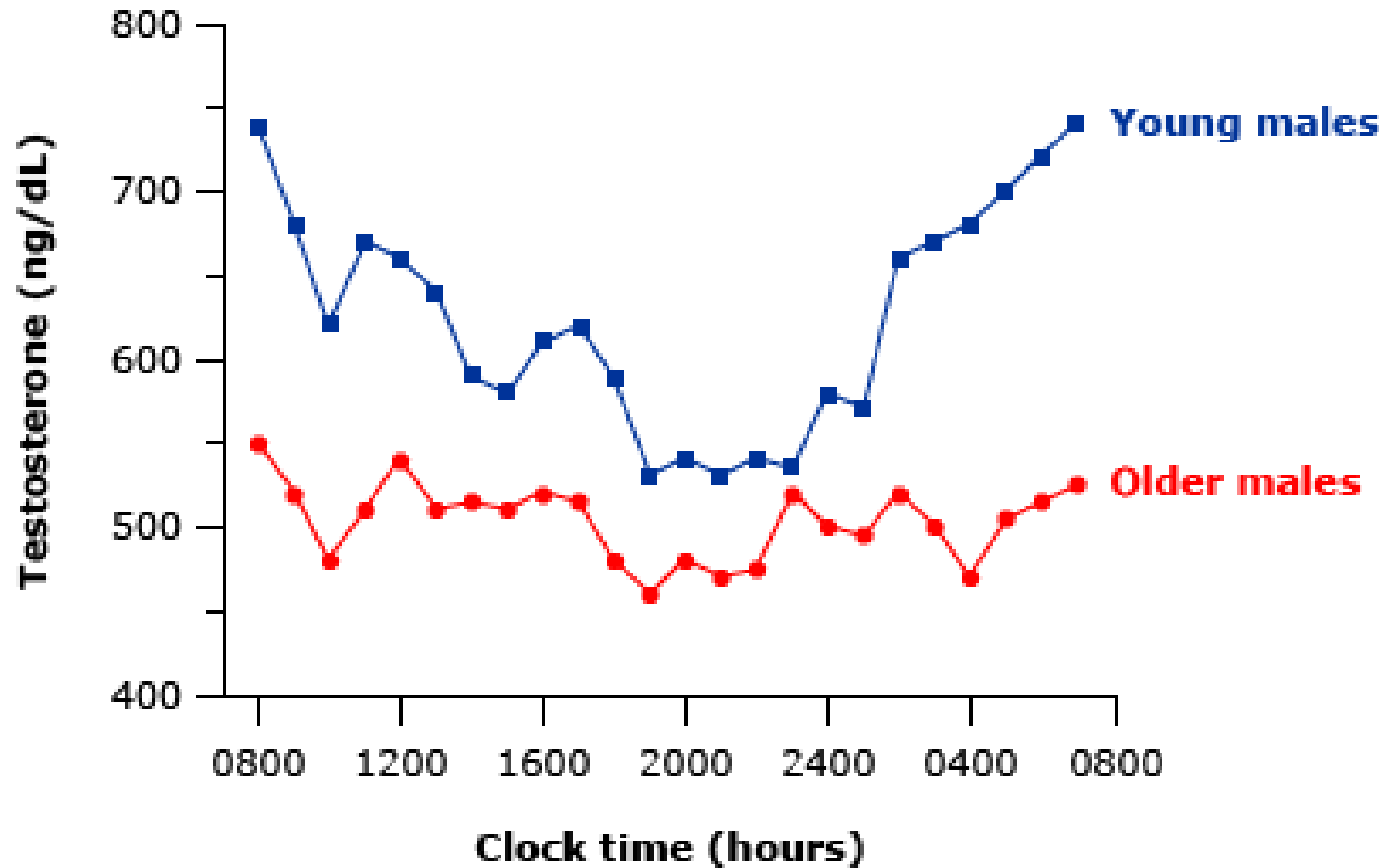
Eating reduces testosterone levels

Use a reliable reproducible lab

# Testosterone Screening Caveats

- Day to day variations
  - Endocrine society recommends measure total testosterone concentrations on 2 different mornings.
- Use reliable reproducible assay
  - Use an assay that is certified by an accuracy-based standardization or quality control program
- For men with low SHBG or testo levels near lower normal measure free testo
  - Avoid immunoassays
  - Measure with equilibrium dialysis or calculate by using total testosterone, SHBG and albumin concentrations.
- Avoid testing during acute illness or when on short term medications such as gluco-corticosteroids or opioids.

# Diurnal pattern of testosterone release



# Conditions when free testosterone may be recommended

## Decreased SHBG

- Obesity
- Diabetes especially uncontrolled
- Use of glucocorticoids
- Nephrotic syndrome
- Untreated hypothyroidism
- Acromegaly
- Progesterone therapy

## Increased SHBG

- Aging
- HIV
- Cirrhosis/hepatitis
- Hyperthyroidism
- Anticonvulsant use
- Estrogen therapy

# Hypogonadism

## Primary

- Elevated LH/FSH
- Decreased testosterone and/or sperm count
- Sperm production impaired to a greater degree than Leydig cell function
- Inability to restore sperm production

## Secondary

- Normal or low LH/FS
- Decreased testosterone and/or sperm count
- Sperm production impaired to a similar degree as testosterone production
- Treatment with LH/FSH/HCG could restore sperm production

# Primary vs Secondary Illness

## Primary Hypogonadism

- Klinefelter's Syndrome
- Cryptorchidism/anorchia
- Chemotherapy induced or testicular radiation/orchidectomy
- Orchitis (Mumps)
- Trauma/Torsion
- Androgen deprivation (leuprolide)
- ESRD

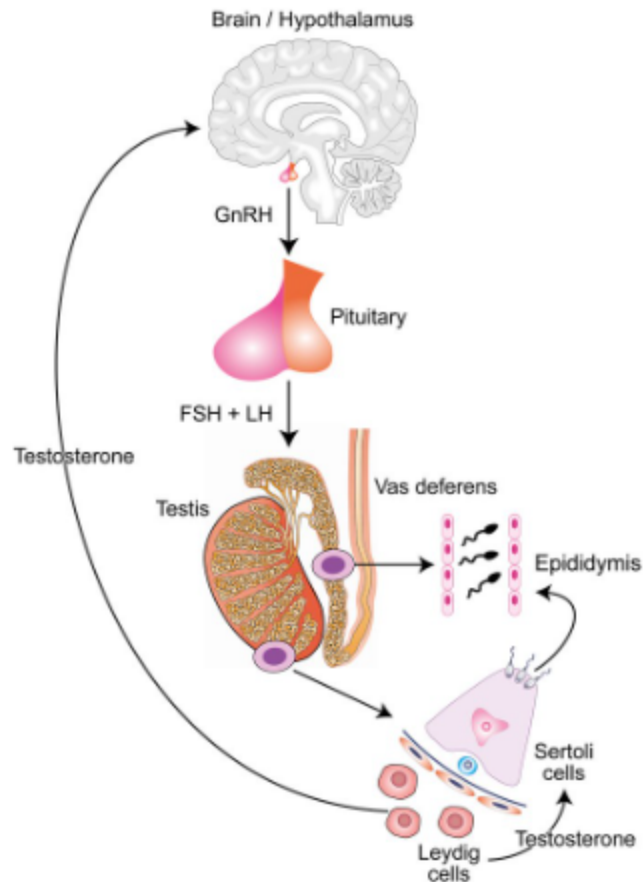
## Secondary Hypogonadism

- Pituitary tumor/hyperprolactinemia
- Hemochromatosis
- Idiopathic loss of LH/FSH
- Opioids/ETOH, Marijuana
- Anabolic steroid use/abuse
- Systemic illness
- Severe obesity/nutritional deficiency
- Organ failure
- Comorbid illness.

# Illness associated with hypogonadism

- Pituitary masses
  - Prolonged high dose glucocorticoid steroid or opiates
  - Weight loss associated with HIV
  - ESRD
  - Mod/severe COPD
  - Infertility
  - Osteoporosis/fragility fracture in young men
  - Type 2 Diabetes
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- Avoid testing in acute/subacute illness.

# Diagnosing hypogonadism



Repeat 8 am  
testosterone

- I usually perform with LC/MS
- Or via equilibrium dialysis

Serum  
LH/FSH

- Primary hypogonadism with elevated LH/FSH
- Secondary hypogonadism with normal or low LH/FSH

# Diagnosing hypogonadism

## Elevated LH/FSH

- Obtain karyotype to diagnose Klinefelter's syndrome

## LH/FSH low or inappropriately normal

- Measure prolactin
- Measure iron studies
  - Ferritin if indicated
- Consider other anterior pituitary assessment
- Pituitary MRI
  - Younger men
  - LH/FSH low
  - Symptoms of pituitary adenoma
  - Hypopit/hyperprolactinemia

# 34 year old Army guy

- Already on testosterone from outside provider after 1 lab
- History of TBI's with blast trauma from military service (blown up more than once in his vehicle)
- Chronic headaches
- Has not fathered kids
- On exam, testes 12 ml bilaterally, no masses
- Discussed risks of therapy, symptoms, signs, agreed to stop testosterone for 3 months

# 34 year old Army guy 3 months off testosterone

- Total testosterone (LC/) fasting 8 am 150
- Free testosterone (LC/MS) 30 (45-135)
- LH low 1.2
- FSH low 2.4
- Prolactin mildly increased 24
- Ferritin WNL
  
- Thyroid, adrenal, Na, IGF-1 WNL
  
- Do we have primary or secondary hypogonadism?
- What do you want to do next?

# 34 year old Army guy with hypogonadotropic hypogonadism

- Pituitary MRI reveals small pituitary, small stalk, no masses
- Suspected TBI related pituitary/hypothalamic injury
- Low LH/FSH from either direct pituitary trauma or hypothal which also would explain slightly elevated prolactin
- Decreased FSH results in loss of sperm production and decreased testicular volume
- Initiated back on testosterone replacement therapy
  - Monitoring of other pituitary hormones going forward.

# Routine testosterone screening

- Endocrine society recommends against routine screening of asymptomatic patients
  - Benefits and adverse events in asymptomatic patients unclear
- Special populations with high chance of low testosterone
  - Pituitary mass/radiation
  - Opioid/glucocorticoid use
  - Withdrawal from anabolic steroid abuse
  - HIV associated weight loss
  - Infertility
  - Osteoporosis
  - Low libido

# Testosterone screening

- Significant assay variability

Quoted testosterone of 280-300 low normal reference range

- Certified reproducible labs
- Recommend use your local reference range with a lab that is LC/MS or equilibrium dialysis for best accuracy.

# Treatment of hypogonadism

- Endocrine society recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of low testosterone.
- Recommend use of testosterone replacement therapy
  - But not: Clomiphene has been used in hypogonadotropic hypogonadism, but has not been studied for efficacy or safety in randomized trials. Off label.
- Recommend against testosterone therapy:
 

• Men planning fertility near term	Elevated HCT	Uncontrolled CHF
• Breast cancer	Untreated OSA	MI/CVA <6 mo
• Prostate cancer	Severe prostate symptoms/PSA>4	Thrombophilia

# Treatment

- Prostate cancer risk
  - Shared decision making with patient ages 55-69 with at least 10 yrs of life expectancy  
Risk/benefit discussion with patient and prostate screening.
  - Reassess prostate cancer screening 3 mo and 12 mo after therapy initiation
  - Higher risk men (African Americans and 1<sup>st</sup> degree relative) screening starting at age 40.
- Thereafter, follow routine screening guidelines

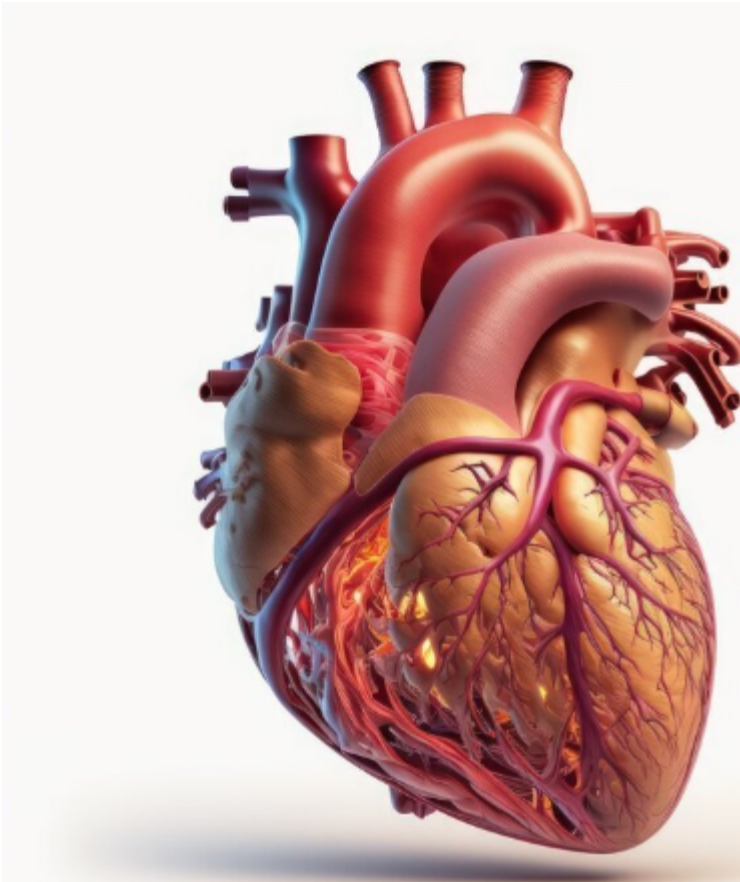
# Testosterone efficacy

- Studies show testosterone therapy induces pubertal changes
  - Consider starting low dose and increasing slowly or refer to peds endo if delayed puberty
- Studies show improvement in libido, erectile function and sexual activity vs. placebo
  
- Testosterone therapy does not improve sexual function and activity in men who do not have low testosterone prior to therapy.
- Testosterone therapy does not improve ED in men with ED without low T.
- Testosterone therapy does not improve ejaculatory function

# Treatment

- Improves well being and depressive symptoms but not if clinical depression is present
  - But no significant improvement in fatigue
- Improves bone strength but no studies show reduction in fracture risk
  - If osteoporosis present use FDA approved option to treat osteoporosis
- Improves muscle strength and intra-abdominal fat
- No change in memory or cognitive function in older men

# Therapy risks



Acne, skin changes, breast tenderness

Low risk of prostate Ca and OSA in young men

Erythrocytosis is most common adverse event

Slight decrease in HDL

No RCT large enough or long enough to show therapy risks of MACE

Low testosterone has been associated with increased cardiovascular mortality as has ED. Likely a marker of overall health

Decreased testicular volume

# Adverse events

## Adverse events for which there is evidence of association with T administration

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Erythrocytosis  
Acne and oily skin  
Detection of subclinical prostate cancer  
Growth of metastatic prostate cancer  
Reduced sperm production and fertility

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## Uncommon adverse events for which there is weak evidence of association with T administration

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Gynecomastia  
Male pattern balding (familial)  
Growth of breast cancer  
Induction or worsening of obstructive sleep apnea

## Formulation-specific adverse effects

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### Intramuscular injections of T enanthate, cypionate, or undecanoate

Fluctuation in mood or libido  
Pain at injection site  
Coughing episodes immediately after the intramuscular injection<sup>a</sup>

### Transdermal patches

Frequent skin reactions at application site

### Transdermal gels and solutions

Potential risk for T transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person)

Skin irritation and odor at application site

Stickiness, slow drying, dripping

### Buccal T tablets

Alterations in taste

Irritation of gums

### Pellet implants

Infection, expulsion of pellet

### T nasal gel

Rhinorrhea, epistaxis, nasal discomfort, nasal congestion, parosmia

### Oral tablets (methylT)—not recommended

Effects on liver and cholesterol<sup>b</sup>

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# TRT preparations

- Injectable testosterone commonly weekly or bi-weekly
- Daily topical gel
- Topical patch, daily
- Intranasal
- Pellets

# Testosterone replacement therapy

T enanthate or cypionate	150–200 mg IM every 2 wk or 75–100 mg/wk	After a single IM injection, serum T concentrations rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	Relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T concentrations that may be associated with fluctuations in symptoms
T transdermal gels: 1%, 1.62%, or 2%	50–100 mg of 1% transdermal gel; 20.25–81 mg of 1.62% gel or 40–70 mg of 2% transdermal gel applied to skin; check package insert for application site and instructions	With appropriate dose, restores serum T and E2 concentrations to the physiological male range; less fluctuation of T concentrations than T enanthate or cypionate	Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable T	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)

# Testosterone replacement therapy

Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men

# Therapy continued

<b>Formulation</b>	<b>Typical Starting Doses</b>	<b>Pharmacokinetic Profile</b>	<b>Advantages</b>	<b>Disadvantages</b>
Nasal T gel	11 mg two or three times daily	Serum T concentrations are maintained in the normal range in most treated men	Rapid absorption and avoidance of first pass metabolism	Multiple daily intranasal dosing required; local nasal side effects, not appropriate for men with nasal disorders

# Oral Therapy

- Methyltestosterone associated with cholestatic jaundice
- Oral testosterone undecanoate: lipophilic absorbed through intestines
  - Increased BP and possible MACE

# Therapy in older men

- Advise against routinely prescribing testosterone in older men (65 and older) with low testosterone concentrations.

2.4 We suggest against routinely prescribing testosterone therapy to all men 65 years of age or older with low testosterone concentrations (1|⊕⊕OO). 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 concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (2|⊕⊕OO)

# Therapy in older men

- Total and free testosterone fall with increasing age.
- Free testosterone decline greater with age due to increased with SHBG in aging.
- Therapy risks:
  - Prostate Ca, increased Hgb, coronary artery plaque volume but similar MACE at 1 year.
  - Many unknown risks
- RCT in older men increased BMD and lean body mass but variable effect on strength, physical or sexual function, energy or mood.
- Trials showed moderate improvement in sexual function and small improvement in walking distance, mood, depressive symptoms. No change in vitality or cognitive function

# Monitoring

- 3-6 mo after initiation
  - Testosterone goal mid normal range
    - Injection: mid interval
    - Gel: 2-8 hrs after application
    - Patch: 3-12 hrs after application
    - Buccal: immediately before or after
    - Pellets: at end of dosing interval
    - Oral undecanoate: 3-5 hrs after ingestion with fat containing meal
    - Injectable undecanoate: end of cycle
- HCT at baseline and 3-6 months
  - HCT over 54% stop therapy
    - Check for OSA
  - BMD baseline and 1-2 yrs after therapy.
  - PSA baseline 3-12 mo after therapy
    - Urological consultation if PSA >4 ng/ml or increases by 1.4 ng/ml in 1 year
    - Detection of prostate nodule on DRE
    - Worsening of BPH symptoms

# Referral

- Patients with secondary disease with signs of pituitary impairment
  - Low LH/FSH
  - Hyperprolactinemia not related to medication side effect
- Klinefelter's disease
- Failure to progress through puberty

# Questions

