Case Studies in Endocrinology

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Disclosures

- None

3 Cases

- Hyperparathyroidism
- Hyperprolactinemia
- Male Hypogonadism

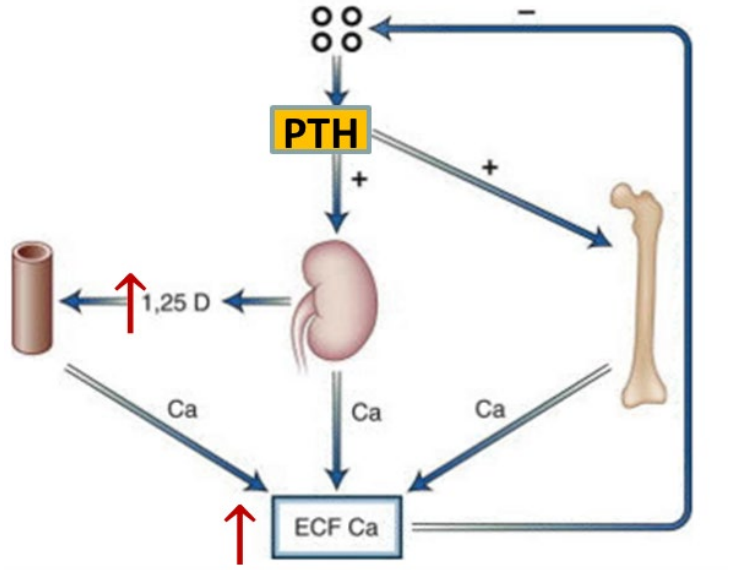
Case #1

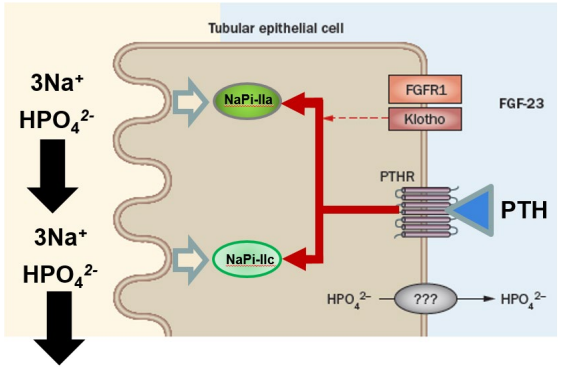
67 yo woman with a history of HTN and hypothyroidism found to have a calcium of 11.1 mg/dL (nl < 10.5) on routine labs prior to a screening colonoscopy

Approach to hypercalcemia in the office setting

Calcium Regulation

- Primary regulator of Ca is PTH
- PTH increases serum Ca
  - Bone
    - –↑mobilization of Ca
  - Kidney
    - –↑ calcium reabsorption
    - –↑ 1 alpha hydroxylase
  - GI
    - –↑ dietary Ca absorption
- PTH decreases serum phos





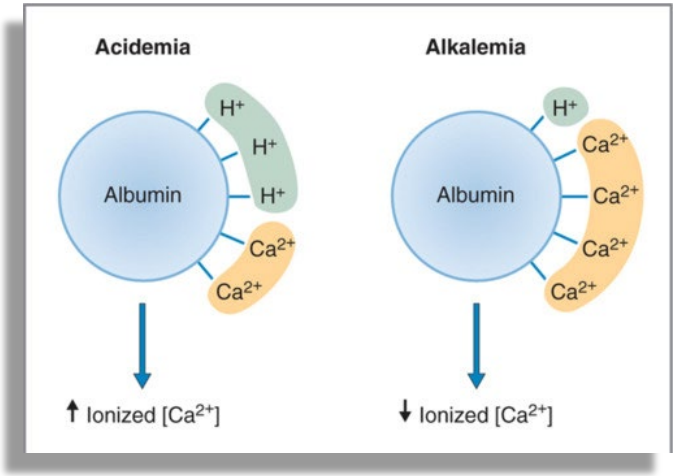
Baia.Nature Rev Nephrol.2015.

Circulating Calcium Concentration

- Only ~50% of circulating calcium is ionized
  - 10% bound to inorganic anions (phos, etc.)
  - 40% bound to Albumin

$$[Ca]_{corrected} = [Ca]_{measured} + 0.8(4 - [Alb])$$

- Percentage bound is determined by pH
  - Acidosis- ↓ bound , ↑ free
  - Alkalosis- ↑ bound, ↓ free

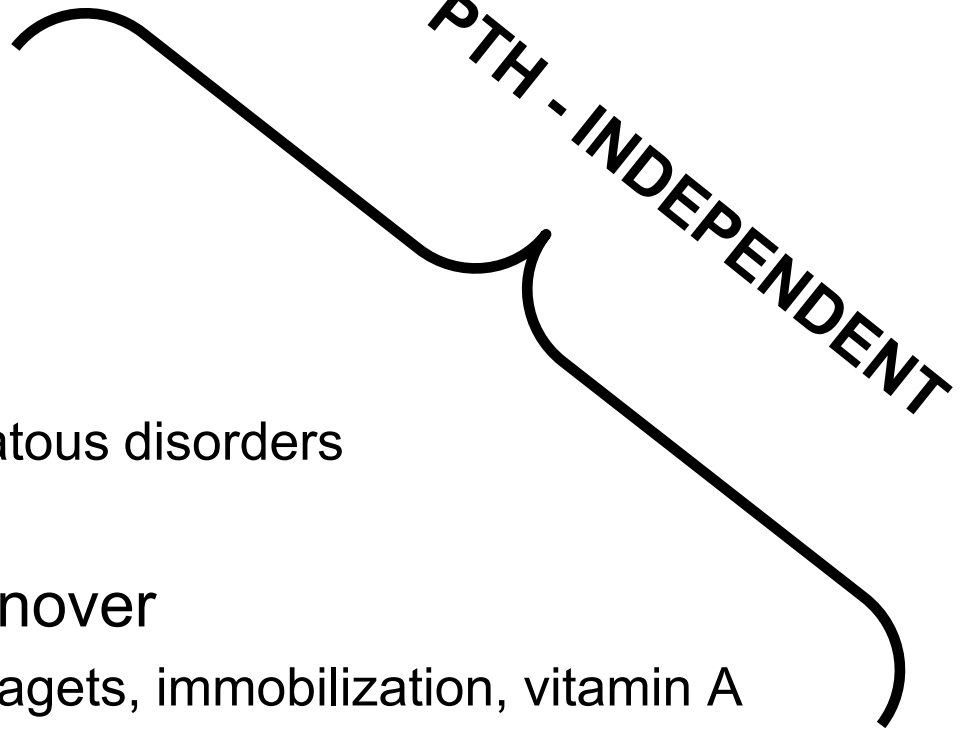


Costanzo.Physiology.2010.

Causes of Hypercalcemia

- #1= PTH-dependent

- #2= Malignancy
- Others
  - Milk-Alkali
  - Vitamin D excess
    - Sarcoid, granulomatous disorders
    - Excess intake
  - Increased bone turnover
    - Hyperthyroidism, Pagets, immobilization, vitamin A



PTH – Dependent Hypercalcemia

- Adenoma (85%)
- Hyperplasia (15%)
  - Spontaneous
  - MEN I & IIA, Jaw Tumors Syndrome
  - Tertiary hyperparathyroidism
- Rare
  - Carcinoma
  - Ectopic PTH
    - Lung, Ovarian, Thymus CA, PNET, Islets Tumor
  - FHH/NSHP/AHH
    - Abnormal Ca-sensing receptor
  - Meds- Lithium

Normocalcemic Primary Hyperparathyroidism

Initial Evaluation

- Calcium, albumin (+/- ionized Ca)
- Phosphate
- PTH

If PTH suppressed:

- 25-OH vit D;1,25 $(OH)_2$ vit D; PTHrP; TSH; ACE; Alk phos +/- bone scan
- Imaging studies-CA, granulomatous dz

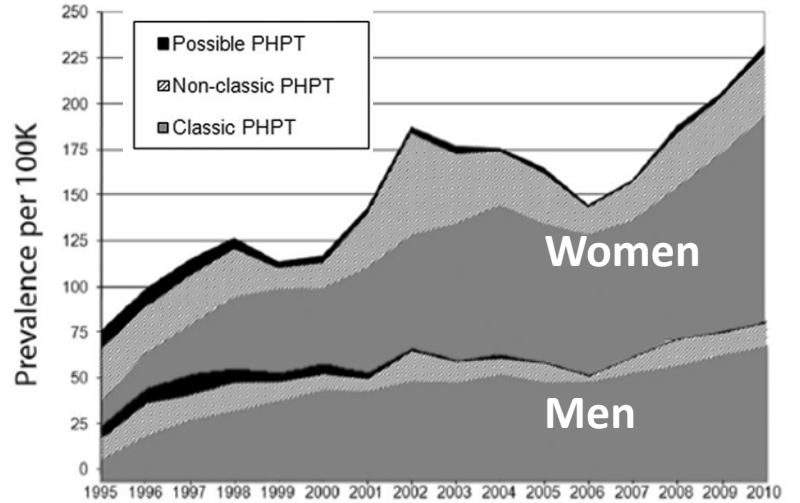
Case #1 Labs

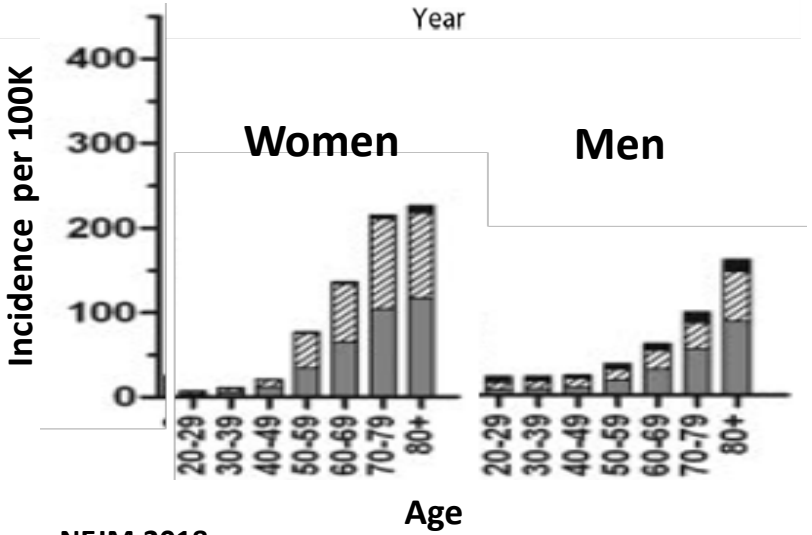
- Repeat calcium 10.9 mg/dl *(nl <10.5)*
- Albumin 3.6 g/dl
- Phosphate 2.2 mg/dl *(nl >2.5)*
- PTH 105 pg/ml *(nl <60)*

Diagnosis = 1° Hyperparathyrodism

Epidemiology of 1^{o} Hyperparathyroidism

- Prevalence
  - Increased 6 fold since 1970s
  - Women > Men
    - 233 vs 85 per 100K
    - ~1/50 postmenopausal F
- Incidence
  - ~100K new dx/yr
  - Increased with age
    - Age ↑ gender difference





Yeh.JCEM.2013, Insogna.NEJM.2018

Hyperparathyroidism: Symptoms (Then & Now)

- Bones
  - Osteitis fibrosa cystica, pseudogout, **fractures**→ osteopenia/osteoporosis
- Stones
  - Staghorn kidney, stones, DI → **stones**
- Groans
  - Pancreatitis, PUD → constipation, Abd pain
- Psychiatric Overtones
  - Stupor, delirium → fatigue, depressed mood

Asymptomatic incidental finding

Additional Work-Up

Serum

- **25-OH vitamin D**

Renal

*= New since 2008 guidelines

- **Creatinine & eGFR**
- ***24h urine calcium and creatinine****
  - ***R/O hypocalciuria & R/In hypercalciuria***
  - ***Stone risk profile****
- ***Abdominal imaging (U/S, X-ray, CT)****

Skeletal

- **Bone density & *vertebral spine frx****
  - **DXA (spine, hip, & *distal 1/3 radius*)**
  - ***DXA-VFA or Dedicated spine imaging***

Pallais. NEJM.2004; Bilezikian.JBoneMinerRes.2002, JCEM 2009,*JCEM 2014.

Indications for Surgery

Age	• **< 50 yo**
Serum	• **Ca > 1.0 mg/dl above ULN**
Renal	• **Crt clearance < 60 ml/min ? ‡** *= New since 2008 guidelines • **Presence *or* ↑ *risk of kidney stones**** • ***24h UCa>400 mg or stones on imaging***

Skeletal	• **Bone density *& vertebral spine frx*↓***
	  • **DXA T<-2.5** (spine, hip, & *distal 1/3 radius)*
	  • ***Frx on DXA-VFA or vertebral imaging***

Relative Indications	– Symptoms – Vitamin D deficiency – Patient preference, poor follow-up

Pallais. NEJM.2004; Bilezikian.JBoneMinerRes.2002, JCEM 2009,*JCEM 2014.

Parathyroidectomy

- Localization
  - U/S
  - Sestamibi Scan
  - 4D-CT
  - Good Surgeon !!!!
- Surgical techniques
  - Neck exploration
  - Minimally invasive
- Complications
  - Hypocalcemia
  - Hungry bone

Case #1 Work-Up

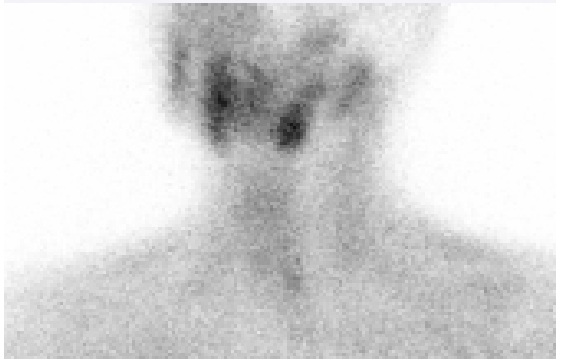
- 67 yo, no h/o fractures or kidney stones
- Labs:
  - Calcium 10.9 mg/dl, (PTH 105 pg/mL)
  - 25-OH vitD – 38 ng/mL (nl>32)
  - (Creatinine clearance > 60 ml/min)
- 24h Urine calcium – 220 mg Ca
- Abd U/S- no kidney stones
- DEXA
  - T:- 2.0 spine, -2.4 fem neck, **-2.7 in hip, -2.8 wrist**
  - VFA: no vertebral frx

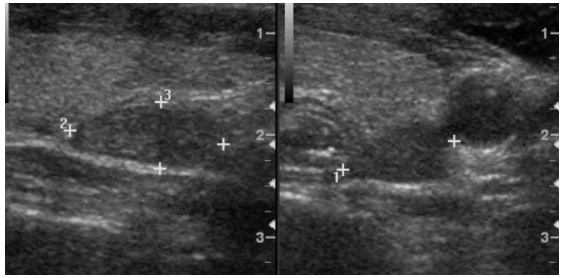
Osteoporosis as indication for surgery

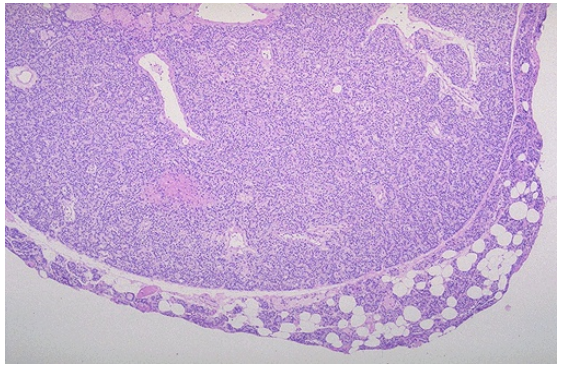
Case #1
Imaging/ Parathyroidectomy

- Tech-99 Sestamibi SPECT suspicious for a L lower parathyroid adenoma
- Neck ultrasound confirmed

- Resection of enlarged gland
  - intraop PTH 112 → 45 pg/ml
- Path- 900 mg gland w little stromal fat c/w adenoma



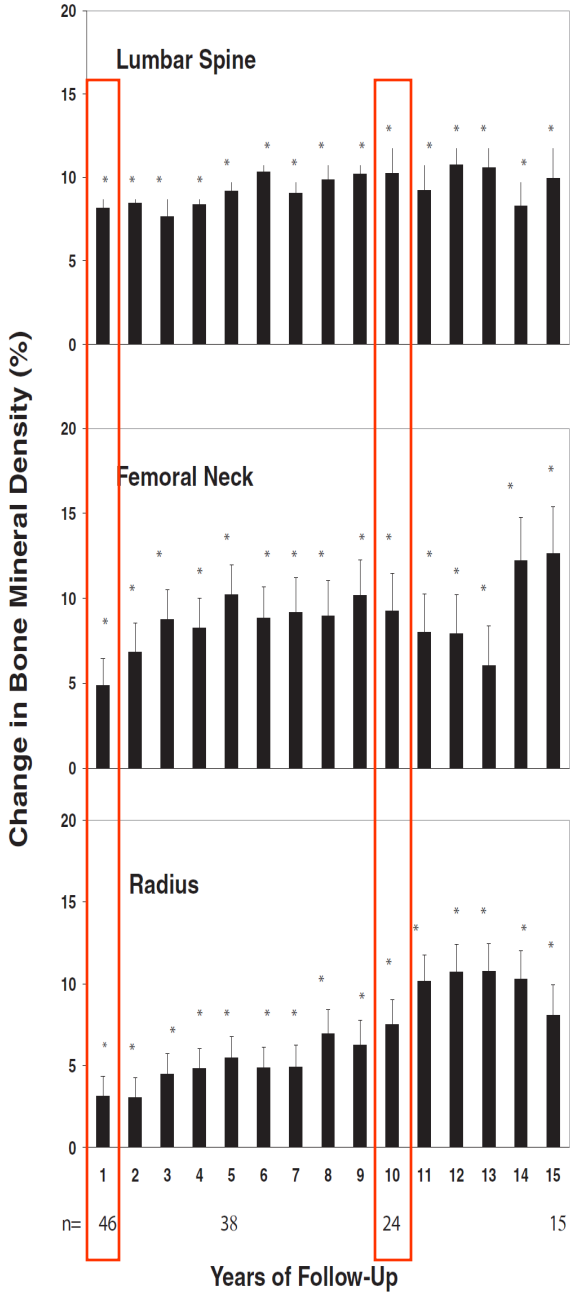




Improvement in BMD

Post-surgical improvement

- Spine
  - 9% after 1 yr
  - 12% after 10 yr
- Femoral Neck
  - 5% after 1 yr
  - 10% after 10 yr
- Radius
  - 3% after 1 yr
  - 7% after 10 yr



Silverberg.NEJM.1999 & JCEM.2009; Rubin.JCEM.2008.

What If…

…BMD had been normal

- If no indications for surgery, monitor:
  - Serum calcium — annually
  - Serum creatinine — annually
  - BMD — every 1-2 yrs*
  - *Vertebral fracture assessment* — *if clinical signs**
  - *Renal stone assessment* — *if clinical signs**
- Biochemical levels did not change significantly in > 10 yr of f/u
- However, accelerated bone loss may occur

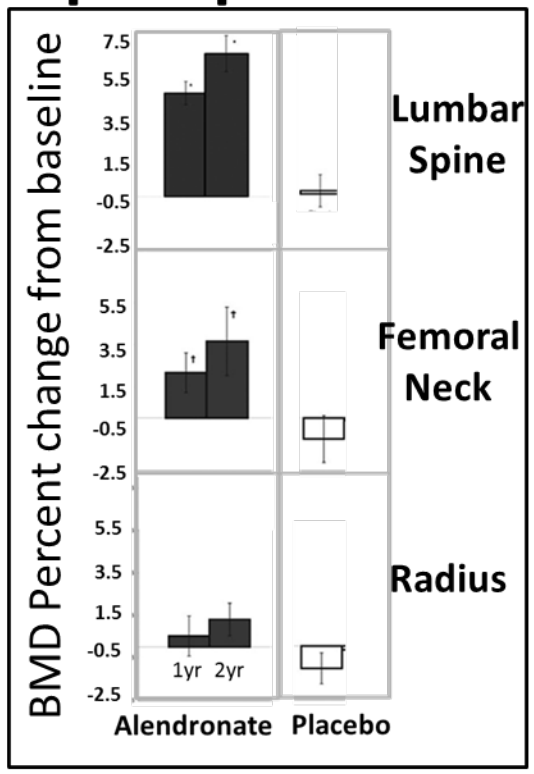
Bilezekian. JCEM.2014*, Khan.JCEM.2009

What If…

…Patient refused surgery

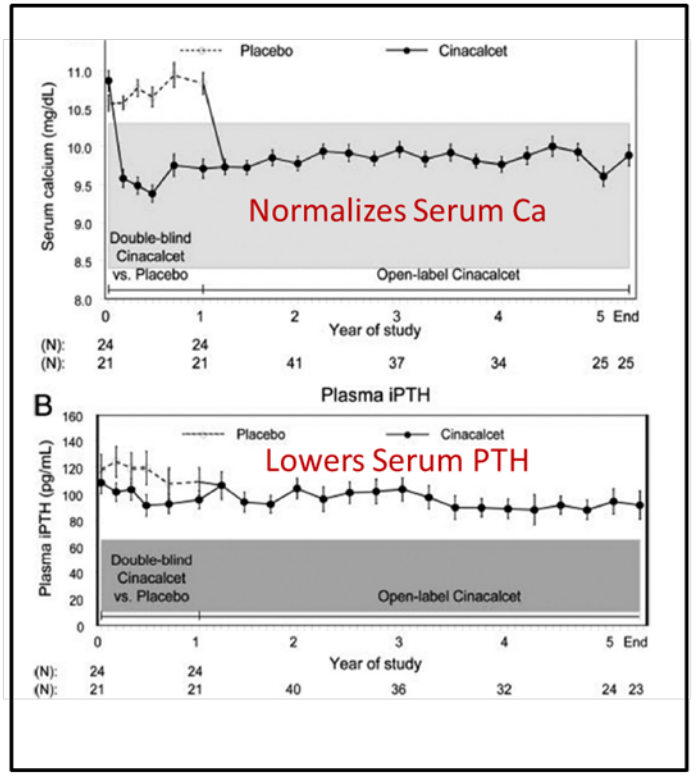
- Available medical therapy include:

Bisphosphonates



Khan.JCEM.2004

Cinacalcet



Peacock.JCEM.2009

Case #2

32yo G2P2 woman with history of anxiety found to have a prolactin level of 56 ng/ml (nl <20) during evaluation of persistent amenorrhea 6 months after she stopped nursing her youngest child.

Approach to the patient with hyperprolactinemia

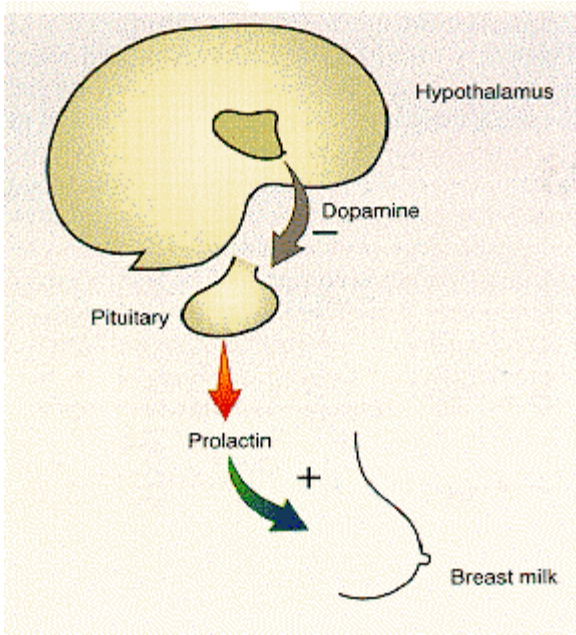
Prolactin Physiology

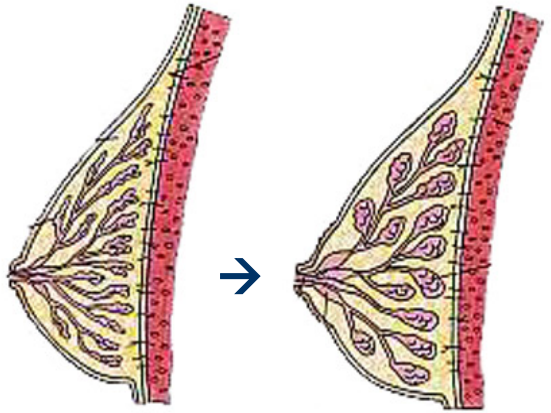
Prolactin secretion from pituitary lactotrophs under tonic inhibitory hypothalamic control

- INHIBITORY SIGNALS
  - –Dopamine
- STIMULATORY SIGNALS

TRH	VIP
Serotonin	GnRH
Histamine	Angiotensin II
Estrogen	Oxytocin

  Breast/chest wall stimulation (spinal afferent)
  Stress, food-insulin, exercise, intercourse, sleep
- Prolactin is released in a pulsatile fashion 4-9 pulses/day w levels rising during late sleep
  - –Levels < 25 ng/ml in women (<20 ng/ml in men)
- Primary function is the regulation of lactation
  - –Prolactin increases in pregnancy (200's ng/ml)
  - –Lactation when estrogen levels fall
    - PRL inhibits LH & FSH secretion





Prolactin

Vance.NEJM.1994; Molitch.EndoMetabClinNorthAm.1992.

DDX of Hyperprolactinemia

- Pregnancy
- Hypothyroidism

- Drug-Induced
- CNS abnormalities
- Prolactinoma

- Other
  - Breast stimulation, chest wall lesions (zoster, etc.), seizure
  - Renal failure, liver dz

Drug-Induced

TABLE 1. **Medications That May Cause Hyperprolactinemia**

- Antipsychotics (neuroleptics)
  - Phenothiazines
  - Thioxanthenes
  - Butyrophenones
  - Atypical antipsychotics
- Antidepressants
  - Tricyclic and tetracyclic antidepressants
  - Monoamine oxidase inhibitors
  - Selective serotonin reuptake inhibitors
  - Other
- Opiates and cocaine
- Antihypertensive medications
  - Verapamil
  - Methyldopa
  - Reserpine
- Gastrointestinal medications
  - Metoclopramide
  - Domperidone
  - Histamine$_2$ receptor blockers?
- Protease inhibitors?
- Estrogens

TABLE 2. **Effects of Psychotropic Medications on Prolactin Levels***

	Increase in prolactin†
Antipsychotics	
Typical	
Phenothiazines	+++
Butyrophenones	+++
Thioxanthenes	+++
Atypical	
Risperidone	+++
Molindone	++
Clozapine	0
Quetiapine	+
Ziprasidone	0
Aripiprazole	0
Olanzapine	+
Antidepressants	
Tricyclics	
Amitriptyline	+
Desipramine	+
Clomipramine	+++
Nortriptyline	–
Imipramine	CR
Maprotiline	CR
Amoxapine	CR
Monoamine oxidase inhibitors	
Pargyline	+++
Clorgyline	+++
Tranylcypromine	±
Selective serotonin reuptake inhibitors	
Fluoxetine	CR
Paroxetine	±
Citalopram	±
Fluvoxamine	±
Other	
Nefazodone	0
Bupropion	0
Venlafaxine	0
Trazodone	0

Aripiprazole

-Partial D2 agonist, may be least a/w ↑ prolactin levels

Molitch.Pituitary.2008, Peuskens.CNS Drugs.2014.

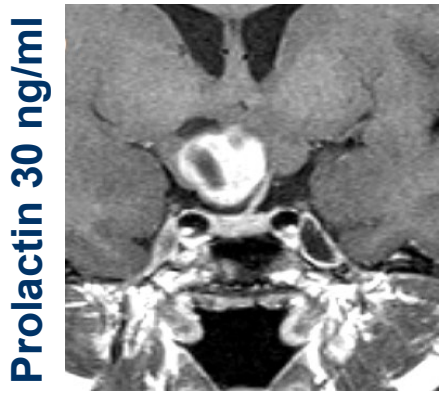
CNS Disorders

Hypothalmic Disorders

- Tumors
  - Craniopharyngiomas
  - Meningiomas
  - Dysgerminomas
  - Gliomas
  - Lymphom
  - Metastatic disease
- Infiltrative dz/infection
  - Sarcoid
  - Tuberculosis
  - Eosinophilic granuloma
- Other
  - Irradiation, trauma

Pituitary Disorders

- Stalk disorders
  - Trauma
  - Tumors
  - Infiltration
  - Arterial aneurysm
- Pituitary Macroadenomas
  - Stalk compression



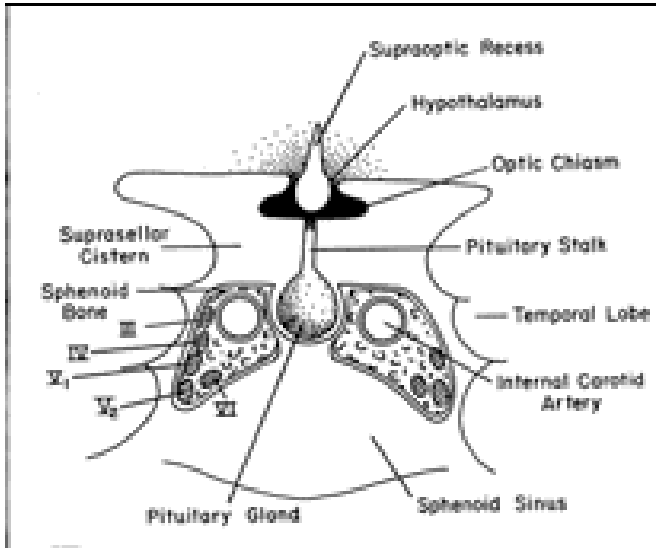
Molitch.Endocrinol Metab Clin North Am.1992.

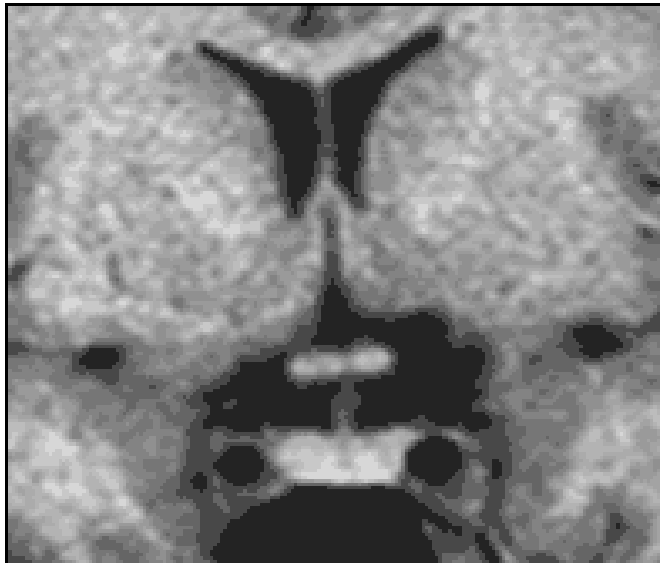
Prolactinoma

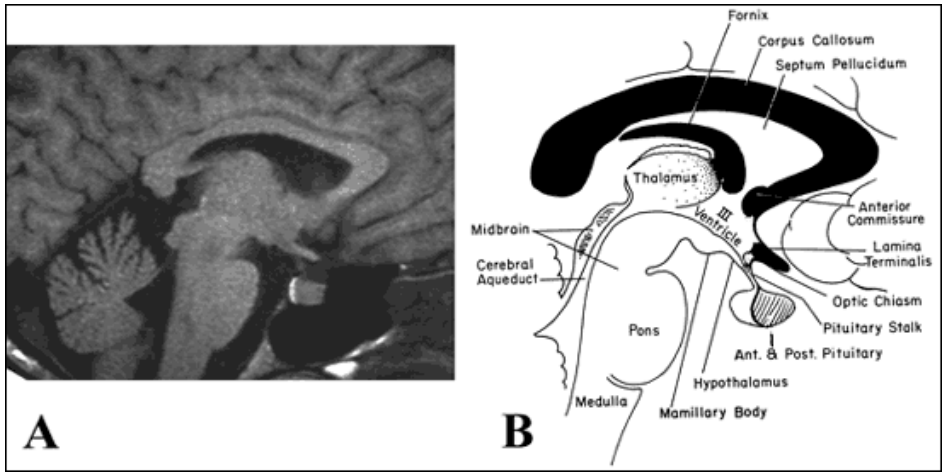
- Benign pituitary adenomas
- Most common hormone secreting pituitary tumor
  - Account for ~40 % of pituitary tumors
- > 90% are small and slow growing
- Tumor size is correlated to prolactin levels
  - Macroadenoma (>1 cm) → PRL usually >200 ng/ml
    - If prolactin < 100-150 ng/ml
      - Non-prolactin tumor w stalk compression
      - Hook effect- assay artifact at very high PRL concentration
  - Idiopathic hyperprolactenemia (<2-3mm)

Pituitary Anatomy

- Anterior pituitary
  - Lactotrophs- laterally
- Vessels
- Cavernous sinus
- Cranial nerves
- Chiasm
- Sphenoid sinus







Lechan.EndoText.2004. Functional Anatomy of the Pituitary and Hypothalamus

Clinical Presentation

Women

- Amenorrhea/ oligomenorrhea
- Infertility
- Galactorrhea
  - Up to 80%, not all symptomatic
- Tumor effects
  - Rare in women as most tumors are small
- Osteopenia

Men

- Tumor effects
  - HA
  - CN palsy
  - Visual field defects
  - Hypopituitarism
- Hypogonadism
  - Decreased libido
  - Erectile dysfunction
  - Infertility
- Osteopenia
- NOT galactorrhea
  - Exceedingly rare

Schlechte.NEJM.2003; Trouillas.Neuroendocrinology.2019

Initial Evaluation

- History and physical
  - Meds
  - Evidence of secondary causes
  - Mass effect
- Labs
  - Repeat prolactin (+/- serial dilutions)
  - hCG, TFTs, BUN/Crt, LFTs
  - +/- other pituitary function tests
    - IGF-1, LH, FSH, gonadal steroids, cortisol
- Imaging studies
  - MRI with gadolinium better than I+ CT
    - If macroadenoma → formal visual field testing

Case # 2

- No physiologic or known secondary causes, no other symptoms besides amenorrhea
- Exam unremarkable except for expressive galactorrhea
- Laboratory Tests
  - Repeat PRL 70 ng/ml
  - hCG negative
  - BUN/Crt, LFT's, TSH, FT4, IGF-1 all WNL
  - LH, FSH, and estrogen suppressed
- MRI showed a **5 mm pituitary adenoma** not impinging on chiasm
- Not interested in further fertility

Indications for Treatment

- Macroadenoma or tumor growth
- Hypogonadism
- Infertility
- Symptoms
  - Galactorrhea
  - Hirsutism

Conservative monitoring is an option for pts not interested in fertility & no other indication

Klibansky.NEJM.2010, Melmed. JCEM.2011

Treatment Options

- Dopamine agonists
  - Bromocriptine
  - Cabergoline
- OCP
  - If small microadenoma in pt not desiring further fertility and whose only indication for trx is amenorrhea
- Surgery
  - Unable to tolerate medical tx, unresponsive to tx (persistent chiasmal compression, ↑ tumor size), apoplexy
  - High recurrence rate
- XRT
  - More definitive but higher risk of panhypopituitarism

Melmed. JCEM.2011

Bromocriptine vs Cabergoline

- Cabergoline is easier to administer
  - Cabergoline has a longer half life (can be dosed weekly)
  - Bromocriptine has more side effects
    - Nausea, vomiting (50%)
    - HA (20%)
    - Orthostasis (20%)

    Nasal Congestion
    Constipation
    Fatigue, anxiety

- Cabergoline more effective
  - PRL normalization (80% vs 60%)
  - Pts achieving >50% tumor shrinkage (96% vs 64%)
  - Persistently normal PRL after trx d/c'ed (60% vs 33%)
  - Cabergoline effective for tx of bromocriptine resistant tumors

- Bromocriptine may be preferred when fertility is an issue
  - More experience w bromocriptine in pregnancy

Gillam.2006; Webster.NEJM.1994; Schlechte.NEJM.2003; Melmed.JCEM.2011; Huang.EndoMetClinNA.2019

Case # 2

- Treatment
  - Dopamine agonist [or OCP]
- Follow-up
  - Prolactin- yearly
  - MRI
    - If clinical evidence of tumor expansion
    - If considering trial off dopamine agonists
      - After > 2yrs of uninterrupted treatment
      - Persistently normal prolactin measures

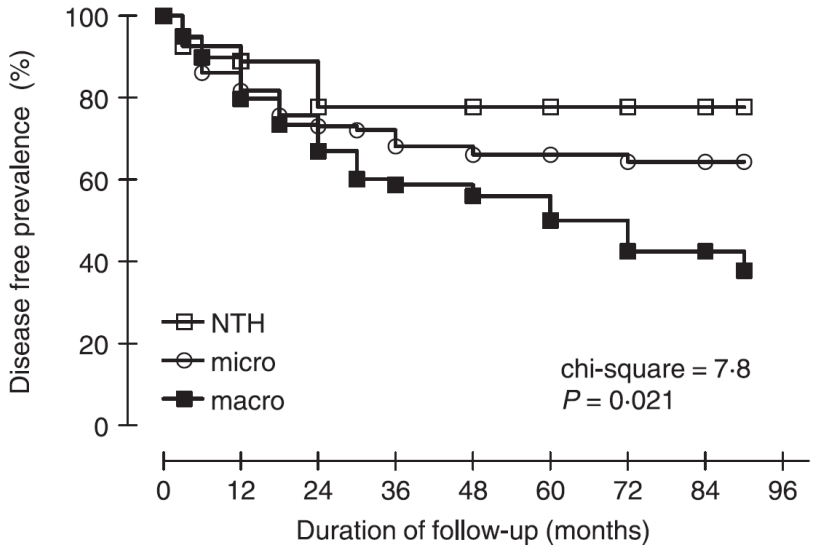
Cabergoline Withdrawal

If initial adenoma < 2cm AND PRL has normalized, tumor shrank by >50%, & no evidence of cavernous sinus invasion, can attempt to d/c cabergoline after 2 yrs of trx

- Long-term remission possible based on tumor size

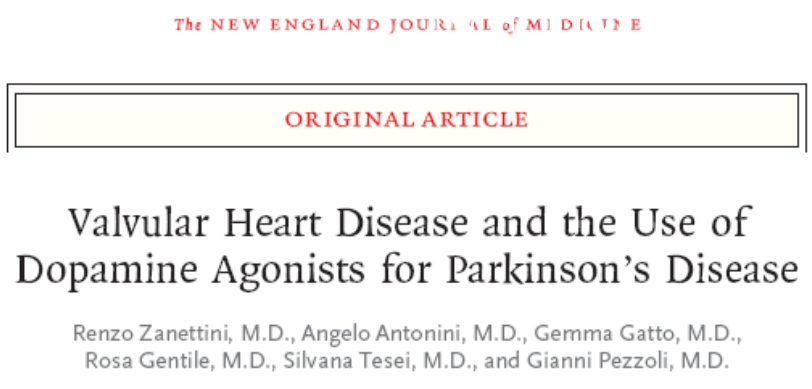
  Before TX:
  - Non-tumoral ~ 75%
  - Microprolactinoma ~ 66%
  - Macroprolactinoma ~ 50

  After TX:
  - No remnant tumor ~80%
  - Remnant tumor ~50%
- Renewed tumor growth was not seen 5 yrs after cabergoline w/d



Colao.NEJM.2003 & Clin Endo.2007, Melmed.JCEM.2011.

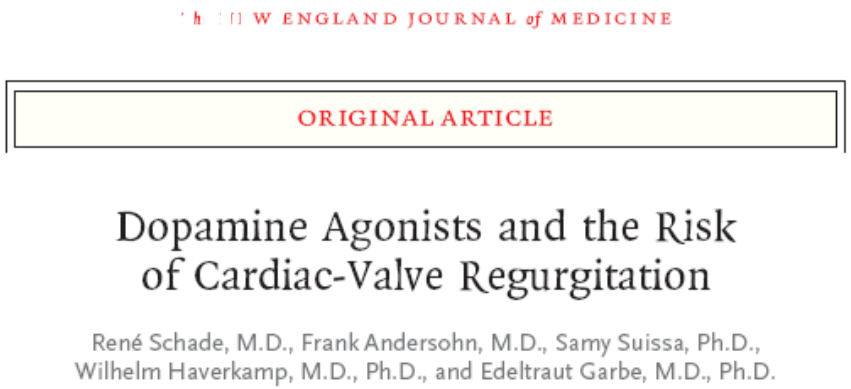
Additional Consideration


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D., Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.


THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D., Ph.D.

- Long-term use of cabergoline for ↑ prolactin a/w TR but of unclear clinical significance
  - Mod TR in cabergoline vs controls: 54% vs 18%
- Use lowest dose of cabergoline to normalize prolactin & consider withdrawal trial depending on response

Colao.JCEM.2008; Kars.JCEM.2008; Melmed.JCEM.2011; Vroonen.Neuroendocrinology.2019

Case #3

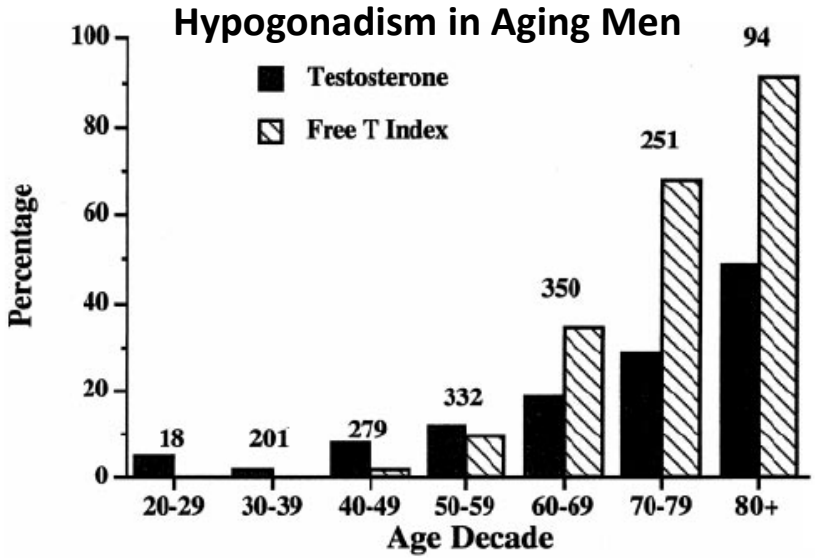
58 yo man with a history of DM, HTN, and dyslipidemia was found to have an afternoon testosterone level of 185 ng/dl (nl >270) after complaining of erectile dysfunction, diminished libido, and decreased energy.

Approach to the patient with androgen deficiency

"Andropause"

Several cross-sectional and longitudinal studies have demonstrated a decline in serum testosterone with age

- Testosterone levels ↓ at a fairly constant rate
  - average ↓ 3.2 ng/dl / year
    Baltimore Longitudinal Study of Aging
- Increased frequency of testosterone values in the hypogonadal range with aging



Harman. 2001

Harman.JCEM.2001, Feldman.JCEM.2002, Morley.Metabolism.1997

Who Has Androgen Deficiency?

Endocrine Society Clinical Practice Guideline:

We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency

AND

unequivocally and consistently low serum testosterone levels

Bhasin.JCEM.2018.

Challenges

We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency AND unequivocally low serum testosterone levels

- Signs and symptoms are non-specific
  - Common with age
  - Often seen in patients with normal testosterone levels
- Many barriers in determining what constitutes “unequivocally low” testosterone levels

Androgen Deficiency

Clinical findings depend on age of onset

- Fetal- hypospadias, microphallus, cryptorchidism
- Prepubertal-incomplete sexual maturation
- Adulthood- regression of sexual function, infertility, hot flashes

Most signs and symptoms in adult onset are non-specific

<u>More reliable features</u>

- Abnormal sexual development
  - Prepubertal testes
  - High pitched voice
  - Eunuchoid proportions
- ↓ virilization
- Azoospermia
- New gynecomastia
- Hot flashes
- Fragility fracture

<u>Less reliable features</u>

- Mild anemia
- Decreased energy
- Decreased aggressiveness
- Depressed mood
- Decreased muscle/strength
- Impaired memory
- Increased adiposity

Impaired sexual function*, ↓ libido*,
↓ spontaneous erections*

Pallais. 2007, *Wu.2010, Bhasin.2018.

Signs and Symptoms of Sexual Dysfunction are Common

- High prevalence of sexual problems even in young men(<60 yo)
  - By age 40, 40% of men reported some level of impaired sexual function

Wu. NEJM.2010; Laumann. JAMA.1999

- There is a waning in sexual function and libido with each decade

Massachusetts Male Aging Study (Feldman.1994, Araujo.2004)

- Decline in sexual function is associated with co-morbid conditions

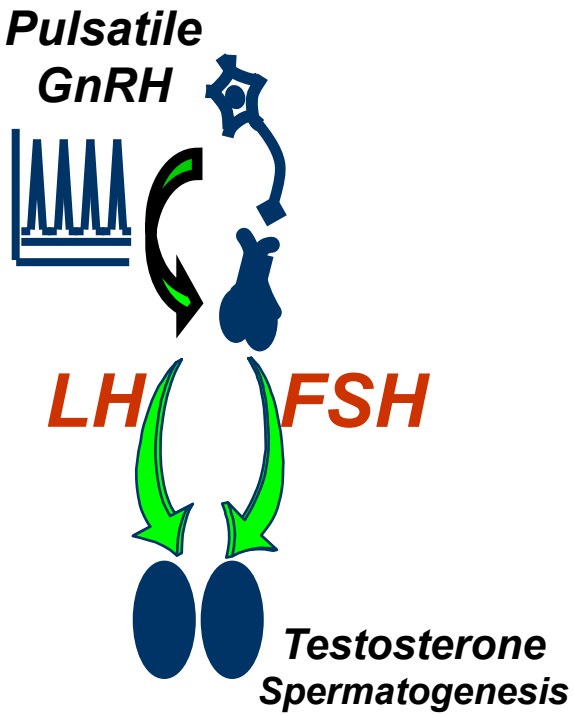
Health Professional Follow-up Study (Bacon.2003)

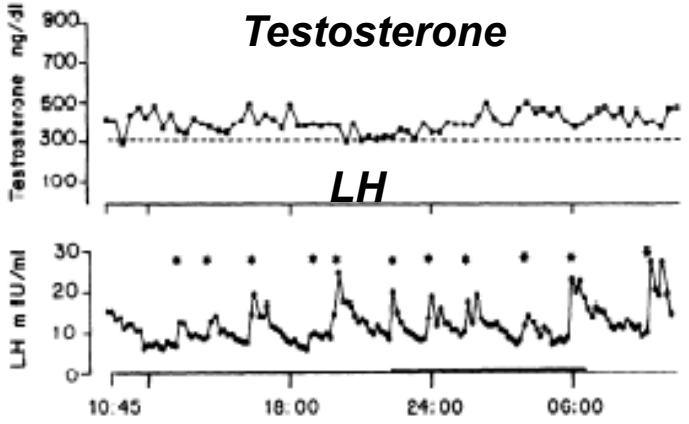
Challenges in Testosterone Measurements

- Physiologic variations
  - Pulsatile secretion
  - Circadian variation
  - Protein binding
- Technical challenges
  - Tissue conversion and intracellular receptors
- No established physiologic testosterone threshold to guide therapy or confirm the diagnosis of androgen deficiency
  - Only population norms
- Effect of medicines and co-morbid conditions

Normal Physiology

- Hypothalamic-Pituitary-Gonadal (HPG) Axis
  - GnRH
  - LH, FSH
  - Testosterone, gametogenesis
- Pulsatile gonadotropin secretion
  - ~10-12 pulses/d
  - Significant fluctuations in testosterone levels (can be >50%)
- Circadian variation
  - Morning > evening
  - ~20% of normal subjects with testosterone levels occasionally dropping into the "hypogonadal" range in a 24h period





Spratt.AmJPhysiol.1988.

Circulating Testosterone

- Protein binding
  - "Bioavailable" testosterone is non-SHBG bound fraction
    - ~55% tightly bound to SHBG
    - ~45% weakly bound to Albumin
    - ~1-3% free

    } ***Bioavailable***

- Several factors alter SHBG levels

Conditions that ↑ SHBG	Conditions that ↓ SHBG
Aging	Obesity
Hepatitis	Nephrotic syndrome
Hyperthyroidism	Hypothyroidism
HIV	Acromegaly
Estrogen	Androgens
Anticonvulsants	Insulin
GH deficiency	Glucocorticoids
	Progestins
	Familial

Klee.MayoClinProc.2000, Bhasin.JCEM.2018.

Testosterone Measurements

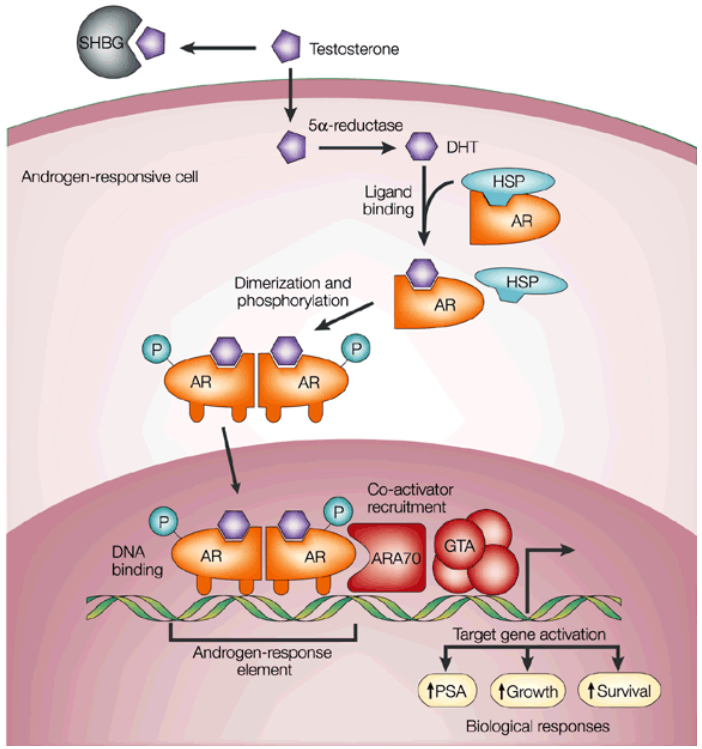
- Reliable assays for free or bioavailable testosterone are not widely available
  - Commonly available free testosterone measurements are **not very reliable**
  - Can estimate bioavailable androgens from total testosterone and SHBG concentration
- **Normative ranges** in healthy young men **vary** among laboratories & assays

30% of pts in the mildly hypogonadal range have normal levels on repeat measurement

Bhasin.JCEM.2006, Rosner.JCEM.2007, Antonio.JCEM.2016, Bhasin.JCEM.2018.

Additional Limitations

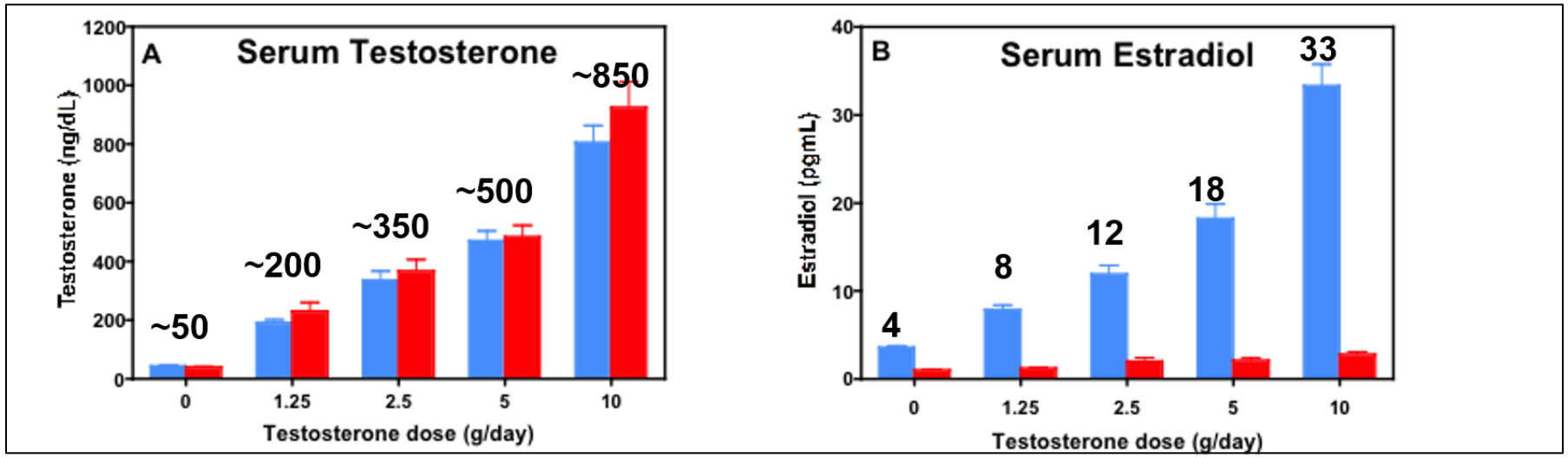
- Testosterone is a pro-hormone
  - Enzymatic conversion in tissue
    - Dihydrotestosterone *(5αReductase)*
    - Estrogen *(Aromatase)*
    - Inactivated *(3αReductase)*
- Affect is mediated through intracellular receptor
- No clear physiologic threshold for hypogonadism has been established



Feldman.Nature Reviews Cancer.2001, Winters.NIDA.1990.

Hypogonadism in Men (HIM), Hypogonadism with Estrogen Removal(HER)

- Chemical castration with different doses of testosterone add-back (HIM)
  - 0, 1.25, 2.5, 5, or 10 g of testosterone gel
- + Aromatase inhibitor (HER)
  - Evaluate dose-response of various outcomes



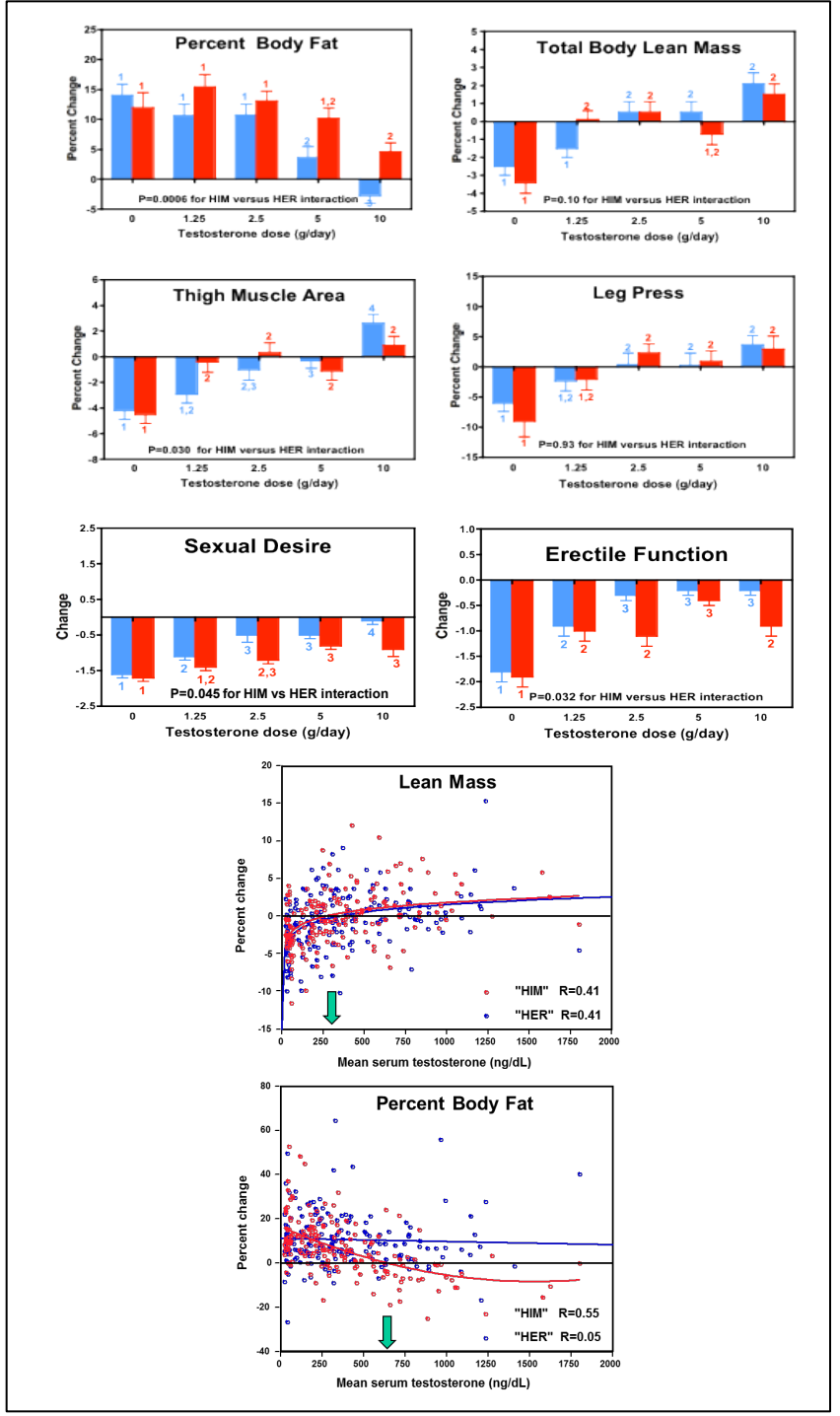
Finkelstein Lee, Burnett-Bowie, Pallais, et al NEJM.2013.

Physiologic Outcomes

Testosterone's effect on many physiologic outcomes were dependent on estradiol levels

- Pure androgenic effects
  - PSA, Hct, lean mass, strength
- Strong estrogen effect
  - ↑ sexual fnx
  - ↓ **body fat**
  - ↓ **bone turnover**

Different outcomes had different testosterone "thresholds"



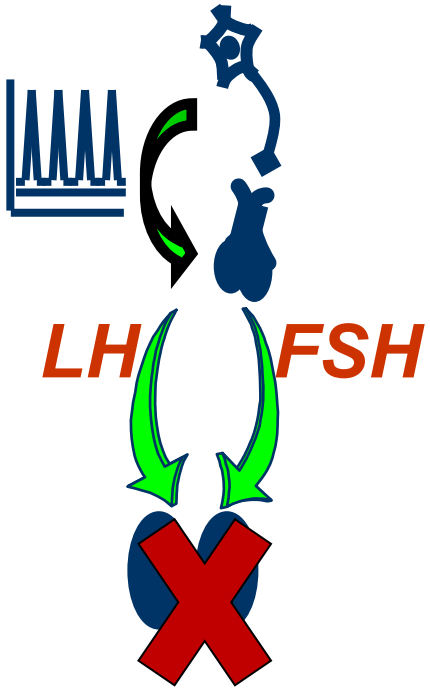
Finkelstein, Pallais et al.NEJM.2013 & unpublished data.

Evaluation

- Morning testosterone & SHBG measurement
  - Confirm by repeating on more than one occasion
- LH & FSH to differentiate between primary and secondary causes
  - Primary- high LH & FSH
  - Secondary- inappropriately low LH & FSH (may within the “normal” range)

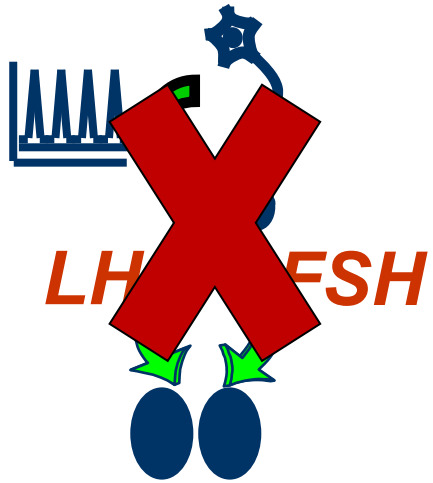
Primary Hypogonadism

- Testicular defect
- High LH, FSH, low testosterone
- Causes
  - Viral orchitis
  - Toxins
    - Radiation, chemotherapy
  - Drugs
    - Alcohol, ketoconazole, spironolactone, metronidazole, etomidate
  - Trauma
  - Systemic diseases
    - Cirrhosis, renal failure, granulomatous dz, HIV
  - Klinefelter Syndrome (47, XXY)



Secondary Hypogonadism (Hypogonadotropic Hypogonadism)

- Central defect
- Inappropriately low LH, FSH, low testosterone
- Causes
  - Hypothalamic or pituitary disorders
    - Tumors, infiltrative diseases, head trauma
    - Hyperprolactinemia
    - Hemochromatosis
  - Functional
    - Acute illness, eating disorders, depression, excessive exercise, AIDS
  - Drugs
    - Glucocorticoids, opiates, MJ, digitalis, exogenous estrogens
  - Idiopathic
    - Anosmic vs normosmic

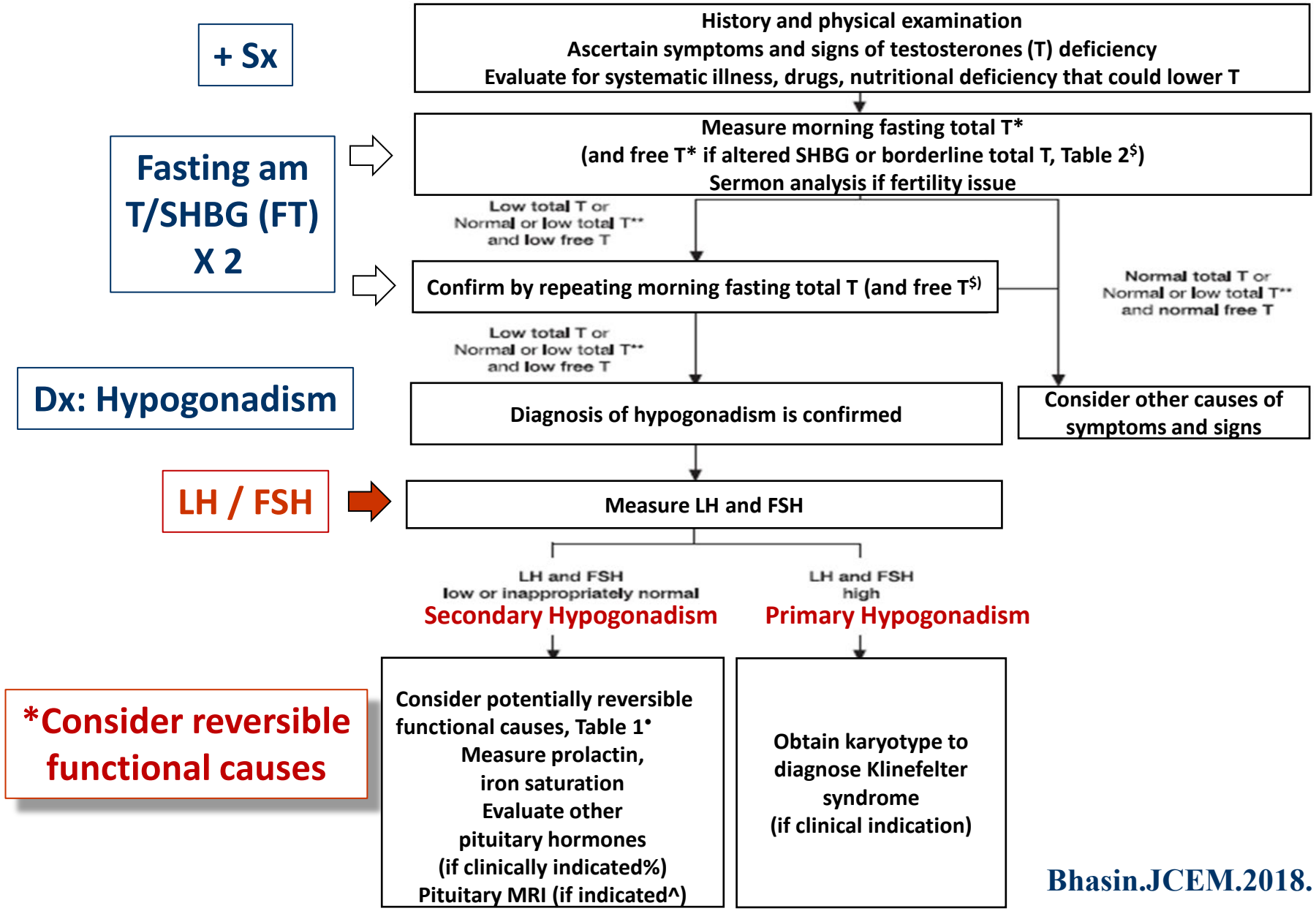


Primary vs Secondary

- Further evaluation
  - Primary
    - Karyotype- including test for mosaic 46,XY/47,XXY
  - Secondary
    - Prolactin
    - Iron studies
    - Pituitary function testing
    - MRI
    - ACE-levels
    - Genetic testing / counseling for IHH
  - Consider BMD for any cause of hypogonadism
- Implications for fertility
  - Better success achieving fertility in secondary hypogonadism

Pallais.Hypogonadotropic Hypogonadism Overview. 2007; Bhasin.JCEM.2018.

Evaluation of Hypogonadism



Bhasin.JCEM.2018.

Functional Hypogonadism

- Caused by conditions that suppress testosterone concentrations but are potentially reversible with treatment of the underlying etiology
  - Hyperprolactinemia
  - Opioids, anabolic steroids, glucocorticoids
  - ETOH, MJ use*
  - Systemic illness*
  - Nutritional deficiencies/excessive exercise
  - Severe obesity, some sleep disorders
  - Organ failure (liver, heart, lung, renal)*
  - Comorbid illness a/w aging*

* Combined 1^{o} & 2^{o} hypogonadism

Bhasin.JCEM.2018.

Who to treat?

Endocrine Society Clinical Practice Guideline

"We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency"

Bhasin.JCEM.2018.

Indications for Treatment

- Established
  - Micropenis
  - Delayed puberty
  - Classic hypogonadism
    - Prepubertal onset
    - Klinefelter
    - Trauma/torsion/tumor
    - Pituitary/CNS injury

FDA approved for these indications

- Controversial
  - Aging
  - Hypogonadism of chronic disease

Limited efficacy & safety data

Don't Treat Men with NORMAL levels!!

Contraindications for Treatment

- Contraindications
  - Prostate cancer
  - Breast cancer

- Relative contraindications
  - Desire for fertility in near term
  - Prostate nodule or induration
  - PSA >4 ng/mL (or >3 if high risk)
  - Severe BPH
  - Erythrocytosis (Hct > 48%)
  - Untreated obstructive sleep apnea
  - Unstable CHF
  - MI or CVA in last 6 mo
  - Thrombophilia

Bhasin.JCEM.2018

Benefits & Side Effects

- Benefits
  - Improved anemia
  - Improved bone density *(no fracture data)*
  - Improved sexual function *(marginally)*
  - Improved body composition *(but not vitality or physical function)*

- Side effects

Spitzer. Nature Reviews.2013; *Basaria.NEJM.2010; *Vigen.JAMA.2013; Bhasin.JCEM.2018.

T Trials:
Effects of Testosterone Treatment on Older Men

- 790 men (12 centers)
  - ≥ 65 yo
  - T < 275 ng/dL
  - **+ Hypogonadal sx's**
    - Sexual dysfunction
    - Difficult walking
    - Low vitality
- Randomized (1yr)
  - T gel
  - Placebo

- Exclusion:
  - Prostate CA or high risk of prostate CA
  - IPSS >19
  - Other causes of ↓T
  - MI/CVA w/i 3mo, unstable angina/CHF, or BP >160/100
  - Severe depression

Snyder.NEJM.2016, Resnick.JAMA.2017, Budoff.JAMA.2017, Roy.JAMA IM.2017, Snyder.JAMA IM.2017.

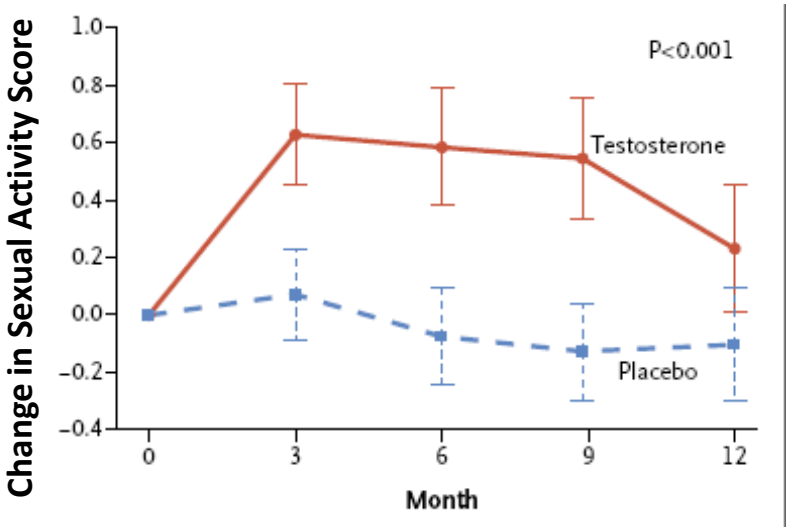
T Trials

Parameter	N=	1^{o} outcome	Results	
Anemia	126	↑Hb by 1g/dL	54% vs 15%	
Bone density	211	Quantitative CT (vBMD & finite element analysis)	↑vBMD & estimated strength of spine & hip	**No frx data**
Sexual function	450	Psychosexual daily questionnaire (0-12)	Baseline 1.5; Tx difference 0.6	**↓Effect after 6mo**
Physical function	387	6' walk test	Not significant	**Not Significant**
Vitality	474	Functional Assessment Questionnaire	No change	
Cognitive Function	493	Delayed paragraph recall (0-50) & others	No change	
Coronary artery plaque volume	170	Plaque volume by CCTA	↑ plaque volume (40 vs 4 mm^3)	**No MI data**

Roy.JAMA IM.2017; Snyder.JAMA IM.2017; Snyder.NEJM.2016, Resnick.JAMA.2017, Budoff.JAMA.2017.

Treatment Efficacy: Sexual Function

- Limited benefit
  - Small improvement in sexual activity index
    - +0.6 vs placebo (out of 12)
- Statistically significant
- Uncertain if clinically significant
  - Effect waned after 6 months
  - PDE5 inhibitor had greater effect
    - IEFF (0-30): Testosterone vs sildenafil
    - +2.64 vs +5.7



Limited generalizability

Healthy bias (80% excluded)

Avg age 72, 90% white

Snyder.NEJM.2016

Benefits & Side Effects

- Benefits
  - Improved anemia
  - Improved bone density *(no fracture data)*
  - Improved sexual function *(marginally)*
  - Improved body composition *(but not vitality or physical function)*

- Side effects
  - Adverse prostate effects
    - Worsening BPH and prostate cancer
  - Cardiovascular events?*
  - Reduced sperm production and fertility
  - Induction or worsening of obstructive sleep apnea
  - Erythrocytosis
  - Gynecomastia
  - Acne and oily skin
  - Male pattern balding

Spitzer. Nature Reviews.2013; *Basaria.NEJM.2010; *Vigen.JAMA.2013; Bhasin.JCEM.2018.

Effects on the Prostate

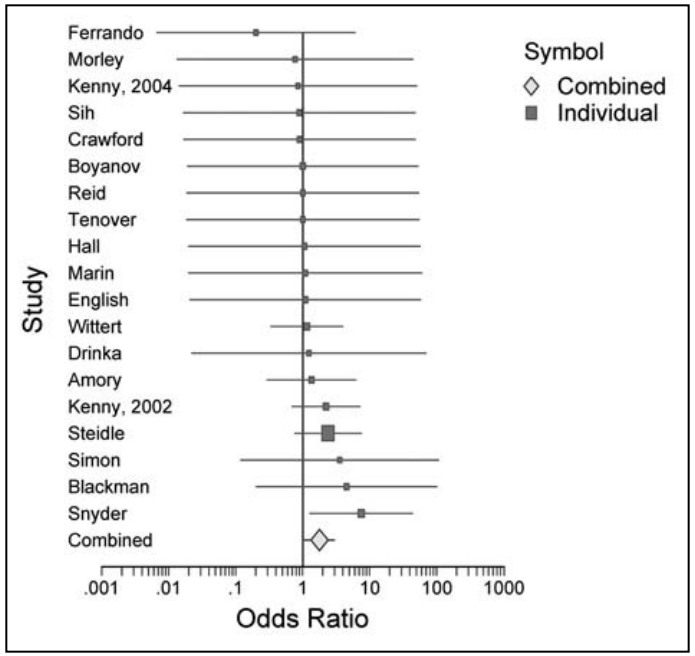
- Moderate increase in prostate volume
- Increase in PSA within the normal range (0.2-0.5 ng/ml)
  - T Trials: 6% of men on T ≥ 1ng/ml vs 2% placebo
- Reviews of variable quality trials *(3mo - 3yr)* have shown conflicting results in the rate of all combined prostate events in testosterone treated group c/t placebo
  - prostate CA, biopsy, PSA>4 ng/ml, ↑IPSS>4
- Insufficient years of follow-up to determine clear effect on prostate cancer

Calof.J Gerontology.2005, Bhasin.JCEM.2010, Fernandez-Balsells.JCEM.2010, Snyder.NEJM.2016.

Effects on the Prostate

Composite prostate outcomes higher in T group vs controls

OR 1.8 (p<0.05)



Calof. J Gerontoloy.2005

RR (CI) T tx Controls

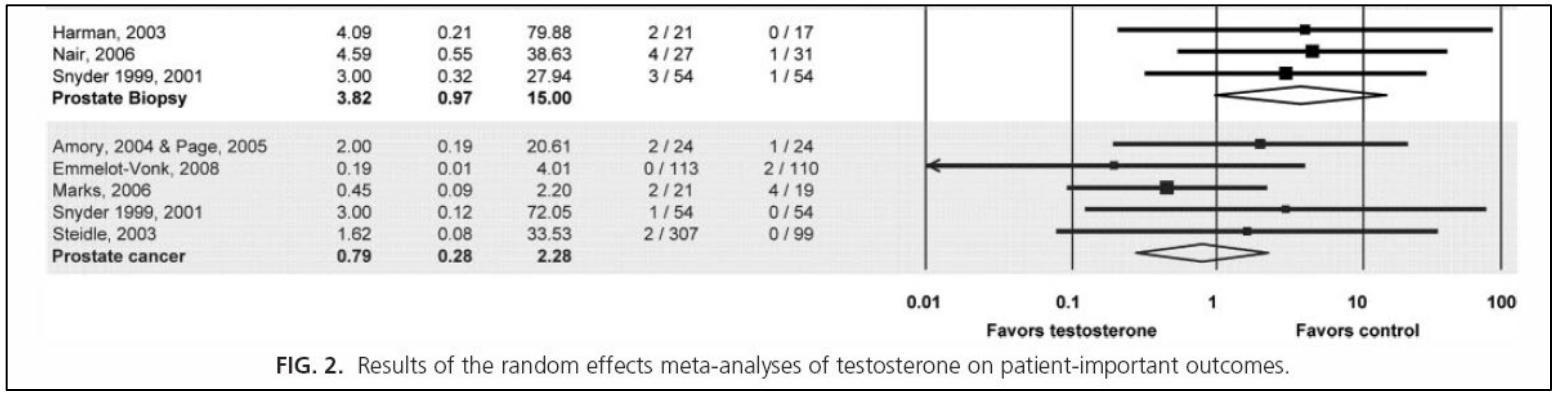


FIG. 2. Results of the random effects meta-analyses of testosterone on patient-important outcomes.

Biopsy

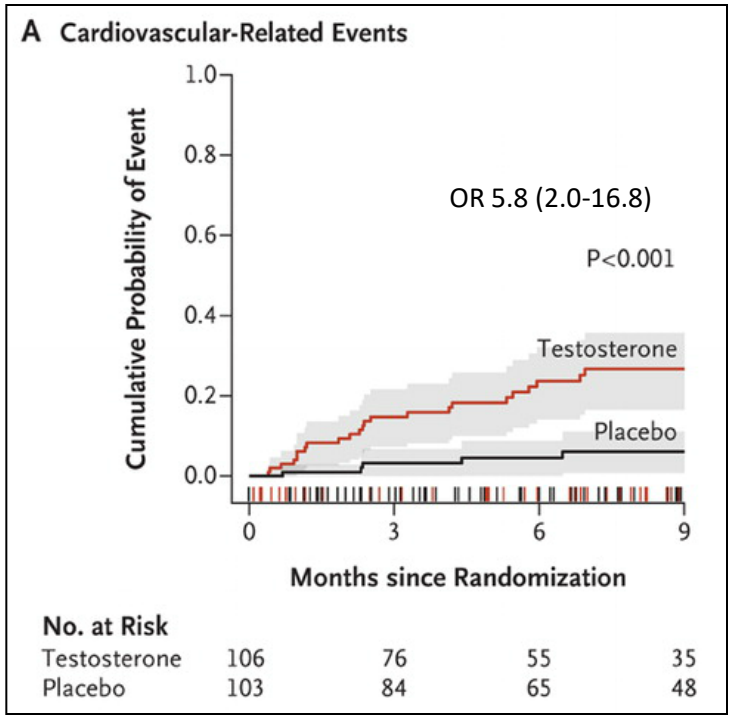
Cancer

Fernandez-Balsells.JCEM.2010.

Cardiovascular Effects

- Testosterone treatment increased the rate of CV events in men with multiple risk factors

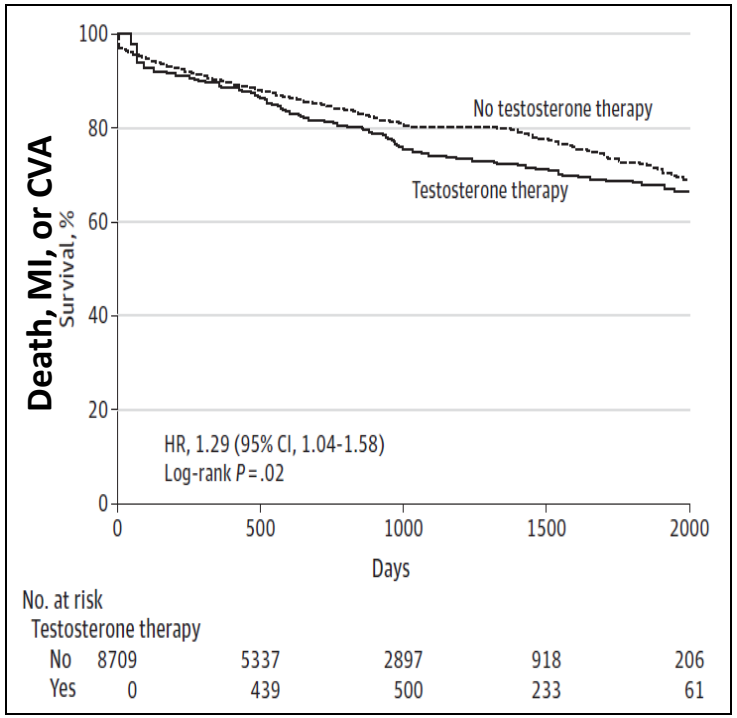
RCT in frail men (avg age 74 yo)



OR 5.8 (p<0.001)

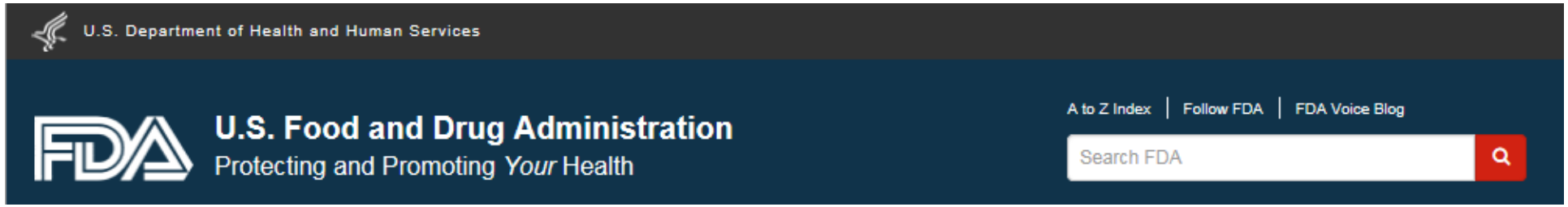
****Basaria.NEJM.2010.***

Observational study s/p cardiac cath



HR 1.29 (p=0.02)

Vigen.JAMA.2013.



- **Drug Safety Communication about possible CV risks *(1/2014)***
  - *"(FDA) is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products."*

- **Label Warning about potential venous blood clots *(6/2014)***
  - *"(FDA) is requiring manufacturers to include a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins."*

- **Caution about treatment of low levels & symptoms due to aging (3/2015)**
  - *"(FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions."*
    - *The benefit & safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if symptoms seem related to low testosterone.*

- **Inform of possible increased risk of heart attack and stroke *(3/2015)***
    - *Label change to reflect possible increased risk of heart attacks and strokes a/w testosterone*

Treatment

- The risk/benefit ratio for testosterone replacement in older men is more difficult to determine than in younger men

- No mortality data available for the long term use of testosterone replacement

Testosterone Formulations

- Intramuscular
  - Testosterone enanthate/cypionate- 100 mg/wk or 200 mg /2 wks
    - Supraphysiologic peak and hypogonadal trough levels
  - Testosterone undecanoate- 750 mg q 10 wks
    - Concern for pulmonary oil microembolism and anaphylaxis
- Transdermal
  - Patch (2-4 mg)- 1 or 2 patches/night
    - Skin irritation
  - 1% /1.62%/2% Gel – ~30-100 mg/d to extremities/trunk/axilla
    - Potential transfer to female partner or child by direct contact
    - Moderately high DHT levels (lowers T:DHT ratio)
- Buccal bioadhesive tablets / Nasal Spray/ **Oral (new)**
  - 30 mg bioadhesive tablets bid / 5.5 mg – 2 pumps tid/ **237 mg bid**
    - Mucosal irritation, altered taste
- Testosterone pellets
  - 75 mg pellets- 2-6 pellets implanted sc q 3-6 months
    - Surgical insertion, may extrude spontaneously

Bhasin.JCEM.2018.

Goals and Follow-Up

- Evaluate for response & side effects at 3-6 months and then annually
- Measure testosterone levels 3-6 months after starting therapy & then yearly
  - Aim for testosterone levels in the mid-nl range
- Check Hct at baseline, 3-6 months, & then yearly
  - Stop tx if Hct>54% until it drops to safe level & restart lower dose; evaluate pt for hypoxia and sleep apnea
- Shared decision making about prostate monitoring (55-69 yo)
  - Digital rectal exam & PSA at baseline, at 3-12 months, and then in accordance to guidelines
  - Refer if: 1) abnl exam, 2) ↑ PSA > 1.4 ng/ml within a yr, 3) PSA >4 ng/ml, 4) worsening BPH

Bhasin.JCEM.2018.

Case # 3

- History & Physical
  - Pt recently started on narcotics for back injury
  - Reported increased stressors at work & home
  - ED was long-standing
    - Had h/o peripheral vascular disease
    - On multiple antihypertensive agents
  - Fatigue temporally correlated to his injury
  - Father and uncle with prostate cancer
  - Obese with BMI 34, no other signs of hypogonadism

- Lab tests normalized after narcotics d/c'ed
  - Repeat morning testosterone measurements
    - T 300-400 ng/dl range with low SHBG levels
  - LH, FSH, & prolactin WNL

Case # 3

- Pt initially disappointed to have “low” T levels
- Discussed
  - Problems related to testosterone measurements (physiologic variations, not a measure of physiologic activity, unclear what constitutes “normal” values)
  - How testosterone levels tend to be lower in obesity (bec of ↓SHBG)
  - Effects of drugs & stress on the HPG axis
  - Likely multi-factorial cause of his ED
  - Potential risk factors with testosterone therapy
- Testosterone replacement not initiated and pt had a good response to tadalafil

Thank You!

Summary

Key points:

- Primary hyperparathyroidism is a common cause of hypercalcemia
- Major causes of persistent hyperprolactinemia include drugs, prolactinomas, and hypothalamic lesion
- Testosterone measurements in men should be interpreted with caution

Next best steps:

- Judicious interpretation of clinical context, laboratory measurements, and imaging studies are necessary for the evaluation and treatment of hypercalcemia, hyperprolactinemia, and male hypogonadism