Case Studies in Endocrinology

J. Carl Pallais, M.D., M.P.H.
Associate Program Director, Residency Training Program
Senior Physician, Division of Endocrinology

Brigham & Women’s Hospital
October 19, 2017
Disclosures

• None
Topics Covered Elsewhere

- Thyroid
- Diabetes
- Lipids
- Female Reproduction
- Osteoporosis
4 Cases

• Hyperparathyroidism
• Incidental Adrenal Nodule
• 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

*Melmed. 2011*
Circulating Calcium Concentration

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

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

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

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° Hyperparathyrodotism

Additional work-up?
Hyperparathyroidism: Epidemiology

- Common since the introduction of multi-channel autoanalyzers
  - 100,000 new cases/yr
  - ~30 cases/100,000
- Prevalence increases with age
- More common in women (3:1)
  - ~2-3% of postmenopausal women
- Most cases sporadic w/o clear risk factors
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**
- 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

* = New since 2008 guidelines
**Indications for Surgery**

- **Age**
  - < 50 yo

- **Serum**
  - Ca > 1.0 mg/dl above ULN

- **Renal**
  - Crt clearance < 60 ml/min ? ‡
  - 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

* = New since 2008 guidelines

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
Parathyroidectomy

- Tech-99 Sestamibi SPECT suspicious for a R 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
Parathyroidectomy
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
  – Calcimemetic Agents

Bilezekian. JCEM.2014, Khan. JCEM.2009
Case #2

65 yo man with a history of HTN, DM, dyslipidemia, and gout found to have a 2 cm right adrenal mass on a CT done to evaluate RLQ abdominal pain which has since resolved.

He is currently on lisinopril, HCTZ, and metoprolol for his HTN which is marginally controlled.

Approach to the adrenal incidentaloma
Adrenal “Incidentaloma”

- Adrenal mass >1 cm
- Incidentally discovered during radiographic evaluation
- Increasing in incidence because of widespread use of abdominal imaging
Prevalence of Adrenal Nodules

- Autopsy ~ 6%
  » Young. 2000
- Abdominal CT ~ 4%
  » Bovio.2006
- Prevalence increases with age
  - 20-30 yo ~ 0.2%
  - 40-50 yo ~ 3%
  - >70 yo ~ 7%
  » Kloos.1995
EVALUATION

• IS IT FUNCTIONAL?

• IS IT MALIGNANT?
Adrenal Physiology

- **CORTEX**
  - Glomerulosa – Aldosterone
  - Fasciculata – Cortisol
  - Reticularis – DHEA

- **MEDULLA**
  - Chromaffin - Epinephrine
Functional Adrenal Incidentalomas

• Cortisol secreting adenomas
  – ~5% of incidentalomas
  – May have subclinical Cushing’s w/o typical findings of hypercortisolemia

• Pheochromocytomas
  – ~3% of adrenal incidentalomas
  – 60% of pheochromocytomas discovered incidentally as adrenal masses
    • Only ~50% of incidentally discovered pheos had HTN

• Aldosterone secreting adenomas
  – ~1% of incidentalomas
  – Most with HTN
Initial Evaluation

• History and physical
• Hormonal testing
• Radiographic phenotype
Cushing’s (+/-Subclinical)

History and Physical
- Moon facies, plethora
- Central obesity, subclavicular, dorsocervical fat pads
- Depression, emotional lability
- HTN
- Fungal infections
- *Easy bruising
- *Violaceous, wide striae
- *Proximal muscle weakness

Laboratory Findings
- *Hypokalemia
- Hyperglycemia/DM
- Leukocytosis with relative lymphopenia
- Osteopenia/osteoporosis
Pheochromocytoma

History and Physical
- Pounding headaches
- Palpitations
- Perspiration
- Pressure abnormalities
  • HTN / Orthostasis
- Pallor
- Paroxysmal or persistent spells
- “Phever”
- Plugging= constipation
- Anorexia
- Anxiety, tremor
- Lid lag

Laboratory Findings
- Hemoconcentration w elevated Hct
- Hypercalcemia
- Hyperglycemia
Hyperaldosteronism

History and Physical

- HTN
- +/- symptoms of hypokalemia
  - Muscle weakness / cramping
  - Paresthesias
  - Palpitations
  - Polyuria / polydipsia

Laboratory Findings

- *Hypokalemia ( <70% )
  - May result in insulinopenia → hyperglycemia
- Metabolic alkalosis
Hormone Evaluation

• 1 mg Dexamethasone Suppression
  – Preferred as subclinical Cushing’s may have nl 24h UFC
  – Abnormal if post suppression cortisol > 5 ug/dl (? 1.8 ug/dl)

• Plasma Fractionated Metanephrines
  – Plasma metanephrines
    • Sensitivity >96%, specificity 75-89%
  – 24 h urine metanephrines & catecholamines
    • Sensitivity 91%, specificity 98%

• If HTN, Plasma Aldosterone Concentration / Plasma Renin Activity (PAC / PRA)
  – Abnormal if PAC/PRA ratio > 20 AND PAC > 10 ng/dl
  – Can be done on any BP meds EXCEPT spironolactone, eplerenone, and amiloride

Tsagrikis.2006; Gorges.1999; Sawka.2003; Young.2007; Funder.2016
Confirmatory Testing

If initial hormone testing is abnormal, need confirmatory testing [REFER]

- **Cushing’s Syndrome**
  - 24h Urine Free Cortisol, midnight salivary cortisol, ACTH

- **Pheochromocytoma**
  - 24h Urine metanephrine, I\(^{\text{123}}\)MIBG

- **Hyperaldosteronism**
  - Aldosterone suppression test
    - NS IV or 3 day salt load
  - +/- Adrenal vein sampling

If adrenal nodule confirmed to be hyperfunctional → SURGERY

Young.NEJM.2007; Androulakis. JCEM.2014; Lim. JCEM.2014
Evaluation Algorithm

Hormonal Testing *(DST, metanephrines, PAC/PRA)*

- **Positive results**
  - Confirmatory testing
  - Confirmation of autonomous secretion of cortisol, aldosterone, or catecholamines
    - Consider: Surgery

- **Negative results**
  - Lack of autonomous secretion of cortisol, aldosterone, or catecholamines
  - Imaging phenotype
Radiographic Phenotype

- **High fat content = Adenoma**
  - **CT**
    - low attenuation (<10 HU)
    - Rapid washout of contrast (>50% washout in 10', >60% in 15'')
  - **MRI**
    - signal loss on out-of-phase images in chemical shift MRI (lipid sensitive mode)

- **Low fat content**
  - **CT**
    - Increased attenuation (prominent vascularity)
    - Delayed washout of contrast
  - **MRI**
    - high signal intensity in T2 imaging

---

**Adenoma**

- 3.6 cm
- -18 HU
- >60% washout

**Pheochromocytoma**

- 4.5 cm
- 40 HU
- <50% washout

**Malignancy**

- 7.5 cm
- 30 HU
- <50% washout

Predictors of Malignancy

• Cancer history
  – History of cancer (esp. lung, breast, kidney, GI)
    • 20-50% of adrenal masses are mets (often bilaterally)
  – No known cancers
    • >85% represent benign tumors

• Size of Mass (if no h/o CA)
  – <4 cm - ~ 2% malignant (adrenal cortical CA)
  – >6 cm - ~ 25% malignant (adrenal cortical CA)

• Radiographic Phenotype
  Good
  smooth
  homogenous
  <10HU, ↑washout
  Slow growth (<1cm/yr)
  Bad
  irregular
  heterogeneous
  > 30 HU, ↓washout
  rapid growth (>1cm/yr)

Evaluation Algorithm

Hormonal Testing (DST, metanephrines, PAC/PRA)

Positive results
- Confirmatory testing
  - Lack of autonomous secretion of cortisol, aldosterone, or catecholamines
  - Imaging phenotype

Negative results
- Confirmatory testing
  - Confirmation of autonomous secretion of cortisol, aldosterone, or catecholamines

Consider:
- Surgery
- Growth ≥1 cm
- Autonomous hormonal secretion

Benign appearance
- Unenhanced CT attenuation ≤10 Hounsfield units
- CT contrast-medium washout ≥50% at 10 min

Consider:
- Repeating imaging at 6, 12, and 24 mo
- Repeating hormonal testing annually for 4 yr
- Surgery if mass is ≥4 cm in diameter

Suspicious appearance
- Unenhanced CT attenuation >10 Hounsfield units
- CT contrast-medium washout <50% at 10 min

Consider:
- Fine-needle aspiration biopsy if metastatic disease or infection suspected
- Surgery
- Close follow-up (e.g., repeating imaging at 3 mo)
Case # 2

- Obese, HTN, DM but no other suggestive clinical findings (nl K+, etc)
- Hormonal Testing
  - DST, metanephrines, Aldo/Renin all WNL
- Adrenal Protocol CT
  - 2 cm, homogenous, smooth borders
  - -5 HU, > 60% washout at 15 minutes

DX= Benign Adrenal Adenoma

- Follow-up
  - Yearly hormonal tests x 4 yrs
  - F/U imaging to confirm lack of growth
Case #3

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

DDX of Hyperprolactinemia

• Pregnancy
• Hypothyroidism

• Drug-Induced
• CNS abnormalities
• Prolactinoma

• Other
  – Breast stimulation, chest wall lesions (zoster, etc), seizure
  – Renal failure, liver dz
### Table 1. Medications That May Cause Hyperprolactinemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Increase in prolactin†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotics (neuroleptics)</strong></td>
<td>Phentolamine</td>
<td>+</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Phenothiazines</td>
<td>+++</td>
</tr>
<tr>
<td>Typical</td>
<td>Butyrophenones</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Thioxanthenes</td>
<td>+++</td>
</tr>
<tr>
<td>Atypical</td>
<td>Risperidone</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Molindone</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Tricyclics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Clomipramine</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>Maprotiline</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>Amoxapine</td>
<td>CR</td>
</tr>
<tr>
<td><strong>Monoamine oxidase inhibitors</strong></td>
<td>Paroxetine</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Clorgyline</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Tranylcypromine</td>
<td>±</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>Fluoxetine</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>±</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Nefazodone</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td>0</td>
</tr>
</tbody>
</table>

### Aripiprazole

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

Hypothalamic Disorders
• Tumors
  – Craniopharyngiomas
  – Meningiomas
  – Dysgerminomas
  – Gliomas
  – Lymphoma
  – 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

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 with stalk compression
      - Hook effect- assay artifact at very high PRL concentration
  - Idiopathic hyperprolactinemia (<2-3mm)

Molitch.1992.; Schlechte.NEJM.2003
Pituitary Anatomy

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

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amenorrhea/oligomenorrhea</td>
<td>• Tumor effects</td>
</tr>
<tr>
<td>• Infertility</td>
<td>– HA</td>
</tr>
<tr>
<td>• Galactorrhea</td>
<td>– CN palsy</td>
</tr>
<tr>
<td>– Up to 80%, not all symptomatic</td>
<td>– Visual field defects</td>
</tr>
<tr>
<td>• Tumor effects</td>
<td>– Hypopituitarism</td>
</tr>
<tr>
<td>– Rare in women as most tumors are small</td>
<td></td>
</tr>
<tr>
<td>• Osteopenia</td>
<td>• Hypogonadism</td>
</tr>
<tr>
<td></td>
<td>– Decreased libido</td>
</tr>
<tr>
<td></td>
<td>– Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>– Infertility</td>
</tr>
<tr>
<td></td>
<td>• Osteopenia</td>
</tr>
<tr>
<td></td>
<td>• NOT galactorrhea</td>
</tr>
<tr>
<td></td>
<td>– Exceedingly rare</td>
</tr>
</tbody>
</table>
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 # 3

• 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/Cr, 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
Case # 3

- **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

• 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

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

Who Has Androgen Deficiency?

Endocrine Society Clinical Practice Guideline

“We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels”
Challenges

“We recommend making the diagnosis of androgen deficiency only in men with consistent symptoms and signs 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

<table>
<thead>
<tr>
<th>More reliable features</th>
<th>Less reliable features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal sexual development</td>
<td>Mild anemia</td>
</tr>
<tr>
<td>Prepubertal testes</td>
<td>Decreased energy</td>
</tr>
<tr>
<td>High pitched voice</td>
<td>Decreased aggressiveness</td>
</tr>
<tr>
<td>Eunuchoid proportions</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>↓ virilization</td>
<td>Decreased muscle/strength</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>Impaired memory</td>
</tr>
<tr>
<td>New gynecomastia</td>
<td>Increased adiposity</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Fragility fracture</td>
</tr>
<tr>
<td>Impaired sexual function*, ↓ libido*, ↓ spontaneous erections*</td>
<td></td>
</tr>
</tbody>
</table>

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

Circulating Testosterone

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

- Several factors alter SHBG levels

<table>
<thead>
<tr>
<th>Conditions that ↑ SHBG</th>
<th>Conditions that ↓ SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Obesity</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>HIV</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Androgens</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Insulin</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Progestins</td>
</tr>
<tr>
<td></td>
<td>Familial</td>
</tr>
</tbody>
</table>

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

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

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

Physiologic Outcomes

Testosterone’s effects 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
Diagnostic Gray Zones

- Symptoms
- Testosterone
  - Measurements
  - Levels (± Estrogen)
- Cause and effect vs reverse causation
  - $\downarrow T \rightarrow$ disorder, or
  - disorder $\rightarrow \downarrow T$
  - RCT are rare and of short duration

Photo by Marco Belluci
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 (Hypogonadotropinemic 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
    • MRI
    • Prolactin
    • Pituitary function testing
    • Iron studies
    • ACE-levels
    • Genetic testing / counseling for IHH
  – Consider BMD for any cause of hypogonadism

• Implications for fertility
  – Better success achieving fertility in secondary hypogonadism
Evaluation of Hypogonadism

1. History and physical (symptoms and signs)
2. Morning Total T
   - Normal T
   - Low T #
   - Exclude reversible illness, drugs, nutritional deficiency
     - Repeat T [use free or bioavailable T, if suspect altered SHBG^]
     - LH+FSH
     - SFA [If fertility issue]
     - Follow up

3. Confirmed low T [Low total T ®; or free or bioavailable T®]
   - Low T, low or normal LH+FSH (secondary hypogonadism)
     - Prolactin, iron, other pituitary hormones, MRI [under certain circumstances*]
   - Low T, high LH+FSH (primary hypogonadism)
     - Karyotype [Klinefelter syndrome]
   - Normal T, LH+FSH
Who to treat?

Endocrine Society Clinical Practice Guideline

“We recommend testosterone therapy for symptomatic men with the classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density.”

Bhasin. JCEM. 2010
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

Don’t Treat Men with NORMAL levels!!
Number of Men with Prescriptions for Testosterone by Age

Nguyen. NEJM. 2015
Contraindications for Treatment

- Contraindications
  - Prostate cancer
  - Breast cancer

- Relative contraindications
  - Prostate nodule or induration
  - Unexplained PSA elevation
  - Severe BPH
  - Erythrocytosis (Hct > 50%)
  - Untreated obstructive sleep apnea
  - Unstable CHF
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

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

# T Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=</th>
<th>1&lt;sup&gt;o&lt;/sup&gt; outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>126</td>
<td>↑Hb by 1g/dL</td>
<td>54% vs 15%</td>
</tr>
<tr>
<td>Bone density</td>
<td>211</td>
<td>Quantitative CT (vBMD &amp; finite element analysis)</td>
<td>↑vBMD &amp; estimated strength of spine &amp; hip</td>
</tr>
<tr>
<td>Sexual function</td>
<td>450</td>
<td>Psychosexual daily questionnaire (0-12)</td>
<td>Baseline 1.5; Tx difference 0.6</td>
</tr>
<tr>
<td>Physical function</td>
<td>387</td>
<td>6’ walk test</td>
<td>Not significant</td>
</tr>
<tr>
<td>Vitality</td>
<td>474</td>
<td>Functional Assessment Questionnaire</td>
<td>No change</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>493</td>
<td>Delayed paragraph recall (0-50) &amp; others</td>
<td>No change</td>
</tr>
<tr>
<td>Coronary artery plaque volume</td>
<td>170</td>
<td>Plaque volume by CCTA</td>
<td>↑ plaque volume (40 vs 4 mm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>
Treatment Efficacy

• 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

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

Effects on the Prostate

Composite prostate outcomes higher in T group vs controls
OR 1.8 (p<0.05)

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

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 (2.0-16.8)**

*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 (5 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
  – 30 mg bioadhesive tablets bid / 5.5 mg – 2 pumps tid
    • Mucosal irritation, altered taste

• Testosterone pellets
  – 75 mg pellets- 2-6 pellets implanted sc q 3-6 months
    • Surgical insertion, may extrude spontaneously
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 & evaluate pt for hypoxia and sleep apnea

• If >40-50 yo, **digital rectal exam** & **PSA** at baseline, 3-6 months, and then in accordance to guidelines
  – Refer if: 1) abnl exam, 2) ↑ PSA > 1.4 ng/ml within a yr, 3) PSA velocity >0.4 ng/ml-yr for periods >2 yrs

*Bhasin.JCEM.2010*
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!