Endocrine review

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This review does not include diabetes, thyroid disorders & dyslipidemia

(Those are available as separate talks)

Pituitary disorders

Causes of hyperprolactinemia

- Prolactinoma
- Drugs:
  - antipsychotics, SSRI, estrogen, methyldopa, metoclopramide, domperidone, verapamil
- Pituitary/hypothalamic tumors or disorders
- Hypothyroidism
- CKD
- Chest wall injury
- Idiopathic

Manifestations of hyperprolactinemia

- Oligomenorrhea
- Amenorrhea
- Infertility (can occur with normal menses)
- Galactorrhea
- Erectile dysfunction (in men)
- Headache

Evaluation of high prolactin

- Are there symptoms?
- Always do TSH, serum creatinine
- How high is the prolactin level?
  - > 200 is suggestive of prolactinoma
  - Mild increase (21 -40) can be due to: physical or emotional stress, meal, breast stimulation
  - If mild increase, repeat test fasting
- If repeated prolactin is still high, do MRI pituitary with contrast

Evaluation of high prolactin

- If there is a suspicion of a drug effect:
  - History is very important
    - **Relation of high prolactin to starting the medication**
  - Stop the drug if possible
  - If not possible, switch to another medication with similar action
  - Consult psychiatrist before stopping antipsychotic medications
  - Check prolactin after 3 days

Evaluation of high prolactin

- **Do NOT start treatment before doing MRI**

1)If MRI showed pituitary lesion:

  - **If prolactin is > 200**
    - Suggestive of prolactinoma
  - **If prolactin 20-200:**
    - Still can be prolactinoma
    - Or pituitary tumor

Evaluation of high prolactin

1) If MRI is **NORMAL**:

- Rule out other causes
- If no cause is found:
  - **Idiopathic hyperprolactinemia**
  - Can try treatment if there are symptoms
  - If no symptoms: no treatment is needed

Prolactinoma

- **Size <1 cm = microprolactioma**
- **Size ≥1 cm = macroprolactinoma**

When to treat high prolactin?

1) Symptoms of hypogonadism (amenorrhea, oligomenorrhea, infertility, erectile dysfunction)
2) Neurologic symptoms due to the size of the tumor (impaired vision or headache)
3) Macroadenoma or if the tumor extends outside the sella, or elevates optic chiasm, or invades cavernous or sphenoid sinuses
4) Disturbing galactorrhea

Treatment of hyperprolactinemia

- **Dopamine agonists:**

  1) Bromocriptine

  - Low cost
  - Start 1.25 mg at bedtime
  - ↑ after 1 week to 1.25 mg bid
    - After breakfast, after dinner
  - Switch to cabergoline if intolerance or inadequate response

Treatment of hyperprolactinemia

2) Cabergoline

- 1st choice
- More effective than bromocriptine
- Less side effects than bromocriptine
- Higher cost
- Start by 0.25 mg twice weekly at bedtime
- Safe in pregnancy
- If using >2 mg/week, consider cardiac echo monitoring for valve disease

Follow up after treatment of hyperprolactinemia

- Advise the patient to **stop** treatment if she gets pregnant
- Check prolactin after 1 month
- Assess symptoms (menses, headaches,…)
- Assess for side effects (nausea, dizziness)
- If intolerance or resistance to bromocriptine, switch to cabergoline

Follow up after treatment of hyperprolactinemia

- Increase drug dose according to prolactin level
- Target is prolactin level and ↓ symptoms
- Decreasing tumor size is NOT the target

1) If normal prolactin:

- Continue same dose of medication
- Gonadal function may take **few months** to return

Follow up after treatment of hyperprolactinemia

2) If prolactin is still high :

- Increase dose of medications
  - Bromocriptine up to 5 mg bid
  - Cabergoline 1.5 mg twice/week (higher dose can be used)
- Continue same dose once prolactin is normal
- Some patients will have no symptoms with mildly high prolactin. Can keep same dose

Prolactinoma: when to do surgery?

1. Intolerance to medical therapy
2. Inadequate response to medical therapy
3. Pituitary apoplexy (hemorrhage) with neurological deficits

Endocrine society guideline. J Clin Endocrinol Metab 2011;96:273.

Evaluation of a sellar mass

When would a sellar mass be discovered?

- With neurologic symptoms (visual disturbance, diplopia, headache)
- As an incidental finding on MRI or CT scan done for other reason
- During evaluation of hormonal abnormalities

Causes of a sellar mass

- **Pituitary adenoma** (most common)
- **Physiologic enlargement of the pituitary:** pregnancy, primary hypothyroidism, primary hypogonadism
- **Benign tumors:** craniopharyngioma meningioma
- **Malignant tumors**: germ cell tumor, CNS lymphoma, metastatic (mostly from breast and lung cancer).
- **Hypophysitis:** most commonly in postpartum women
- **Others:** cyst, abscess, arteriovenous fistula of the cavernous sinus

Pituitary adenomas

- <1 cm = microadenomas
- ≥1 cm = macroadenomas
- Adenomas can arise from any type of cell of the anterior pituitary
- Adenomas can cause increased secretion of the hormone(s) produced by that cell and/or decreased secretion of other hormones due to compression of other cell types

Classification of pituitary adenomas

1) Gonadotroph adenomas: usually present as non-functioning sellar masses
2) Thyrotroph adenomas: may present as clinically non-functioning sellar masses or hyperthyroidism
3) Corticotroph adenomas: usually cause Cushing's disease or it may be rarely clinically silent
4) Lactotroph adenomas: cause hyperprolactinemia which leads to hypogonadism in females and males
5) Somatotroph adenomas: cause acromegaly or it may be clinically silent

Evaluation of a sellar mass

- Serum prolactin (lactotroph adenomas)
- Insulin-like growth factor-1 (IGF-1) (somatotroph adenomas)
- Plasma ACTH and 24-hour urinary free cortisol (corticotroph adenomas)
- If gonadotroph or thyrotroph adenoma is suspected: LH, FSH, free T4, TSH, alpha subunit
- If the mass is ≥1 cm, do evaluation for hyposecretion

Incidentally discovered pituitary mass (pituitary incidentaloma)

1) If the mass is ≥ 1 cm:
   - Hormonal work up as described in previous slide (prolactin, IGF-1, ACTH, 24-hour urinary free cortisol)
   - If gonadotroph or thyrotroph adenoma is suspected: LH,FSH, free T4, TSH, alpha subunit
2) If the mass is <1 cm:
   - If no clinical features to suggest pituitary abnormalities:
     - Only check serum prolactin

Causes of hypopituitarism

1) Pituitary infarction (Sheehan' syndrome)
2) Tumors (pituitary or hypothalamus)
3) Infiltrative lesions: (hypophysitis, hemochromatosis)
4) Surgery for pituitary tumors
5) Radiation therapy for CNS & nasopharyngeal malignancies
6) Traumatic brain injury
7) Infections (TB meningitis, HIV)
8) Stroke
9) Empty sella
10) Genetic mutations

Features of hypopituitarism

- Depends on affected hormone
- Pituitary hormones:
  - FSH, LH (gonadal function)
  - ACTH (adrenal function)
  - TSH (thyroid function)
  - Prolactin
  - Growth hormone
- Most affected initially:
  - Gonadal & GH
  - Then ACTH, TSH
  - Not always

Features of hypopituitarism

- ↓ FSH, LH: hypogonadism
  - Irregular menses, amenorrhea, infertility, hot flashes, ↓ energy, ↓ libido
- ↓ ACTH: adrenal insufficiency
- ↓ TSH: hypothyroidism
- ↓ Prolactin:
  - Failure to lactate after delivery
- Growth hormone:
  - ↓ energy

Diagnosis of hypopituitarism

1) LH, FSH:

- If normal menses, no tests needed
- If symptoms, check LH, FSH, testosterone in men

2) ACTH:

- See next slides

3) TSH:

- Check TSH & Free T4
- TSH may be low or normal but low Fee T4

4) Prolactin: not useful

5) GH:

- IGF-1

Diagnosis of adrenal insufficiency

- AM (8-9 am) cortisol <3 mcg (83 nmol) highly suggests adrenal insufficiency:
  - ♦ Repeat to confirm
  - ♦ ACTH level (if available):
    - High = primary insufficiency
    - Normal or low = secondary insufficiency
- AM cortisol ≥18 mcg (497 nmol) is normal and no need for ACTH stimulation test
- AM cortisol >3 & <18 mcg: do ACTH stimulation test

Diagnosis of adrenal insufficiency

- **ACTH (Cosyntropin, Synacthen) stimulation test:**
  - ♦ Baseline serum cortisol
  - ♦ Give ACTH 250 micrograms IV bolus
  - ♦ Then check cortisol after 30 & 60 minutes
  - ♦ Can be done at any time of the day
  - ♦ Can use IM if IV is not possible
  - ♦ Normal: peak serum cortisol ≥18 μg (497 nmol)

Diagnosis of adrenal insufficiency

- **<u>If patient is acutely sick:</u>**
  - ♦ Start treatment; do not wait for results
  - ♦ If test will delay treatment, start treatment then do the test later when the patient is stable
- **<u>Plasma aldosterone & renin: (in primary disease)</u>**
  - ♦ Low aldosterone and high renin in primary disease

Treatment of hypopituitarism

1) LH, FSH:

A) Women:

- If no pregnancy desired: estrogen/progestin
- If pregnancy desired: gonadotropins

B) Men:

- If no fertility desired: testosterone
- If fertility desired: gonadotropins

Treatment of hypopituitarism

2) ACTH: see next slides

3) TSH:

- Thyroxine
- Follow Free T4
- Keep Free T4 in upper half of normal

4) GH:

- Not generally treated

Treatment of adrenal insufficiency

- All patients (1^{ry} & 2^{ry}) require **<u>glucocorticoids</u>**:

  - Hydrocortisone (15-25 mg/d) divided in 2-3 doses/day (depends on patient's weight)

    10 am, 5 pm or 15 am, 5 pm or 15 am, 10 pm

- Some will feel fatigue at night or morning: give 3 doses
  - 10 am, 5 afternoon, 5 evening
  - or 15/5/5
- Slow-release form (once daily at am) available

Alternative treatment of adrenal insufficiency

- Prednisone or Prednisolone (2.5-7.5 mg/d) 1-2 times/day
  - Use if patient is not compliant with multiple daily doses
  - or in those with late-evening or early morning symptoms

    that are not relieved by three-times daily hydrocortisone

Monitoring of treatment for adrenal insufficiency

- Symptoms (energy level, headache, dizziness)
- Watch also for symptoms/signs of high dose (increased weight, puffy face)
- Clinical (weight, postural BP, edema)
- Hormonal monitoring is **not** recommended

Glucocorticoids potency

- 20 mg Hydrocortisone =
- 5 mg Prednisone/Prednisolone =
- 4 mg Methylprednisolone =
- 0.75 mg Dexamethasone

Male Hypogonadism

- Primary (testicular): ↓ Testosterone, ↑ FSH/LH → testicular pathology

- Secondary (pituitary/hypothalamic): ↓ Testosterone, NL or ↓ FSH/LH

MRI pituitary & hypothalamus

Male hypogonadism

- A decrease in testosterone and/or sperm production
- **Primary:**
  - Disease of the testes
  - Low testosterone and/or sperm count
  - High FSH and/or LH
- **Secondary:**
  - Disease of the pituitary or hypothalamus
  - Low testosterone and/or sperm count
  - Normal or low FSH and/or LH

Endocrine Society guideline. J Clin Endocrinol Metab 2018;103:1715.

Causes of primary male hypogonadism

- Congenital abnormalities (e.g. Klinefelter syndrome)
- Infections (e.g. mumps)
- Radiation
- Drugs (cyclophosphamide, cisplatin, ketoconazole, Glucocorticoids)
- Trauma
- Testicular torsion
- Autoimmune damage
- Chronic systemic illnesses (cirrhosis, CKD, AIDS)
- Idiopathic

Causes of secondary male hypogonadism

- Congenital (e.g. Isolated gonadotropin deficiency)
- Hyperprolactinemia
- Glucocorticoid, GnRH analogs
- Critical illness
- Chronic systemic illness
- Opiates
- Diabetes mellitus
- Disease of pituitary/hypothalamus:
  - Tumors, infiltrative diseases, infections, trauma, surgery or radiation in the sellar region

Clinical features of male hypogonadism

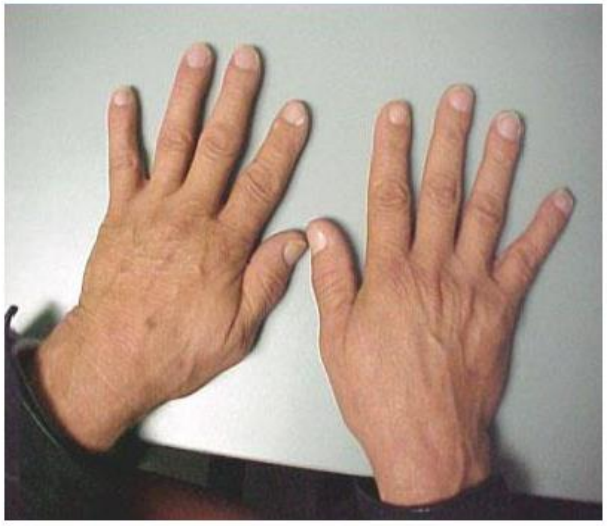
- Decreased energy
- Decreased libido (sexual desire)
- Decreased muscle mass
- Decreased body hair
- Hot flashes
- Gynecomastia
- Infertility

Acromegaly facts

- Excessive secretion of growth hormone
- If it occurs before fusion of the epiphyseal growth plates is called **gigantism** (leads to ↑ height)
- Commonest cause: pituitary adenoma
- Clinical features are due to high levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)

Clinical features of acromegaly

- Headaches
- Visual disturbances
- Fatigue
- Tissue over-growth:
  - Enlarged jaw (macrognathia)
  - Enlarged, swollen hands and feet
  - Enlarged nose and frontal bones
  - Enlarged tongue (Macroglossia)
  - Thick skin, skin tags
  - Enlarged cartilage: arthropathy
  - Enlarged thyroid, heart, liver, lungs, kidr



Clinical features of acromegaly

- Hypertension, left ventricular hypertrophy, cardiomyopathy
- Heart failure, valvular heart disease
- Sleep apnea
- Neuropathy
- Diabetes mellitus
- Hypogonadism
- Colonic polyps, colonic diverticula
- Malignancies (colon, stomach, esophagus, melanoma)
- Increased mortality

Diagnosis of acromegaly

1) High serum insulin-like growth factor-1 (IGF-1)

2) Confirm diagnosis by 75-gram OGTT (oral glucose tolerance test):

- Measure serum growth hormone (GH) at 30, 60, 90, 120 minutes (normally GH levels are suppressed)
- GH > 1 microgram/L (1 ng/mL) confirms the diagnosis

3) Once biochemical diagnosis confirmed: do MRI pituitary

4) If MRI is normal: suspect hypothalamic cause or ectopic GH

- Measure serum GHRH & do chest and abdominal CT scans

Endocrine society guideline. J Clin Endocrinol Metab 2014;99:3933

Treatment of acromegaly

- **Surgery (for pituitary tumor):**
  - For most patients
- **Medical therapy:**
  - If adenoma does not appear to be fully resectable
  - Patients who refuse or are not candidates for surgery
  - Persistent disease after surgery (biochemical or radiological)
  - Generally using somatostatin analog (octreotide, lanreotide)
  - Cabergoline for mild disease
  - Pegvisomant (GH receptor antagonist) can be used if no response to above. (needs monitoring of liver enzymes)

Endocrine society guideline. J Clin Endocrinol Metab 2014;99: 3933

Female reproductive disorders

Menopause

- Menopause is cessation of menses
- Occurs generally at age 51 years
- Average age 45-55 years
- If indicated: [Menopausal Hormone Therapy (MHT)]

  - Estrogens (alone if no uterus)

  - Progesterone with estrogen if uterus is intact to prevent endometrial hyperplasia and cancer

North American Menopause Society guidelines. Menopause 2017;24:728.

Effects of menopausal hormone therapy (MHT)

- ↑ CAD: (only with combined therapy)
- ↑ Stroke:
  - CAD & stroke occurred mainly in ladies **age ≥60 or if menopause duration >10 years**
- Cancer: - ↑ Breast Ca.
  - No difference in endometrial or ovarian cancers
  - ↓ Colorectal Ca.
- ↑ DVT/PE
- ↓ Osteoporotic fractures
- ↓ risk of type 2 diabetes
- No effect on cognition or Alzheimer's disease

Pinkerton J. N Engl J Med 2020;382:446.

Polycystic ovary syndrome (PCOS)

- One of the commonest causes of hirsutism and infertility

1) <u>Diagnosis in adults:</u>

- **Rotterdam criteria: (2 out of 3)**

  1) Menstrual abnormality

  2) Signs of hyperandrogenism (clinical or biochemical)

  3) Polycystic ovaries on ultrasound

  ** Exclusion of other disorders that can result in menstrual abnormality and hyperandrogenism

International PCOS network. Fertil Steril 2018;110:364
Endocrine Society guideline. J Clini Endorinol Metab 2013;98:4565

Features of PCOS

- **Menstrual abnormality:**
  - Oligomenorrhea**:** less than 9 periods in a year
  - Amenorrhea: no periods for ≥3 consecutive months
  - Anovulation: can occur with a normal period
- **Hyperandrogenism**:
  - Clinically: hirsutism, acne, male-pattern hair loss
    Or biochemically: mildly high testosterone
- **Ovarian appearance on ultrasound**:
  - Presence of ≥12 follicles in either ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL) without a cyst or dominant follicle)

Diagnosis of PCOS in adolescents

1) Menstrual abnormality

2) Signs of hyperandrogenism (clinical or biochemical)

- Ovarian morphology on ultrasound is NOT used for the diagnosis

International PCOS network. Fertil Steril 2018;110:364
Endocrine Society guideline. J Clini Endorinol Metab 2013;98:4565

Laboratory evaluation of PCOS

- Total testosterone
- TSH
- Prolactin
- 17-hydroxyprogesterone (to rule out congenital adrenal hyperplasia)
- Other tests as clinically indicated

**** (high LH:FSH ratio is not helpful for diagnosing PCOS)**

PCOS associations

- Infertility
- Obesity
- Insulin resistance:
  - Prediabetes & type 2 diabetes
- Dyslipidemia
- Fatty liver
- Sleep apnea
- Endometrial hyperplasia (& possibly cancer)
- Depression, anxiety
- During pregnancy: GDM, preterm delivery, pre-eclampsia

Treatment of PCOS

- **General measures:**
  - Weight loss (using lifestyle changes and, if necessary, medications and bariatric surgery) to improve hyperandrogenism and insulin resistance
  - Hair removal measures (shaving, chemical depilatory agents, bleaching, waxing, Eflornithine cream, or laser)
  - Treatment of acne (same as in patients without PCOS)

Treatment of PCOS

1) Ladies not seeking pregnancy:

- Weight loss
- Oral contraceptives [combined (estrogen + progestin)]
- Metformin
- Antiandrogens (spironolactone, cyproterone, finasteride)
- Gonadotropin-releasing hormone agonists

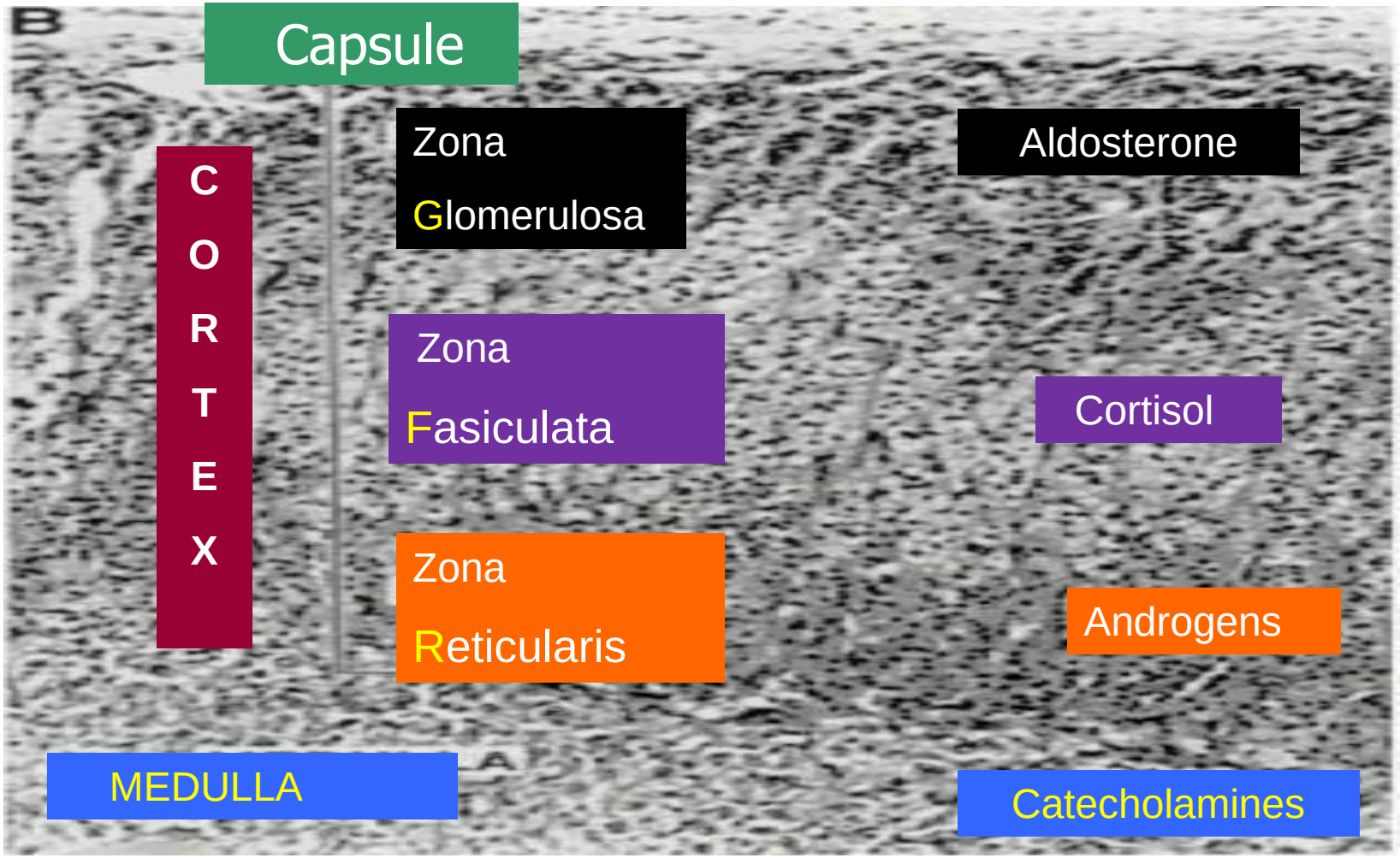
Treatment of PCOS

2) Women seeking pregnancy:

- Weight loss
- Clomiphene
- Letrozole
- Metformin
- Gonadotropins
- In vitro fertilization

Adrenal disorders

Histology of the Adrenal gland



When to suspect adrenal insufficiency?

- Symptoms not explained by other tests
- Presence of autoimmune diseases such as:
  - Type 1 DM
  - Hypothyroidism
  - Vitiligo
- Acutely ill patients with volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain

Manifestations of Adrenal insufficiency

- **Early stage:**
  - Fatigue, dizziness
  - Anorexia, weight loss
  - Abdominal pain
  - Nausea, vomiting
  - Fever
  - Hyperpigmentation
  - Depression, anxiety
  - Loss of libido (women)

Adrenal crisis

- **Late presentation of adrenal insufficiency:**
  - Weakness
  - Abdominal pain
  - Fever
  - Hypotension
  - Confusion
  - Coma

Laboratory findings in adrenal insufficiency

- Hyponatremia
- Hyperkalemia
- Metabolic acidosis
- Hypoglycemia
- Anemia
- Hypercalcemia

Causes of adrenal insufficiency

- **Primary**
  - Disease of the adrenal gland. “Addison’s disease “
  - Cortisol and mineralocorticoid deficiency
- **Secondary**
  - Interference with ACTH (pituitary gland)
  - Cortisol deficiency
- **Tertiary:**
  - Interference with CRH (hypothalamus)
  - Cortisol deficiency

Causes of primary adrenal insufficiency

- Autoimmune (most common)
- Destructive:
  - TB
  - Fungi
  - HIV
  - Metastasis, sepsis, emboli, infarction
  - Hemorrhage (anticoagulation, coagulopathy)

Causes of secondary adrenal insufficiency

- Part of hypopituitarism
- Isolated ACTH deficiency
- Autoimmune
- Traumatic brain injury

Causes of tertiary adrenal insufficiency

- Sudden withdrawal of high-dose glucocorticoids:
  - They decrease CRH
- Cure of hypercortisolism (Cushing's syndrome)
- Hypothalamic lesions: (tumors, sarcoidosis), cranial radiation

Diagnosis of adrenal insufficiency

- AM (8-9 am) cortisol < 3 μg (83 nmol) highly suggests adrenal insufficiency:
  - ♦ Repeat to confirm
  - ♦ ACTH level (if available):
    - High = primary insufficiency
    - Normal or low = secondary insufficiency
- AM cortisol ≥ 18 mcg (497 nmol) is normal and no need for ACTH stimulation test
- AM cortisol > 3 & < 18 mcg: do ACTH stimulation test

Diagnosis of adrenal insufficiency

- **ACTH (Cosyntropin, Synacthen) stimulation test:**
  - ♦ Baseline serum cortisol
  - ♦ Give ACTH 250 micrograms IV bolus
  - ♦ Then check cortisol after 30 & 60 minutes
  - ♦ Can be done at any time of the day
  - ♦ Can use IM if IV is not possible
  - ♦ Normal: peak serum cortisol ≥ 18 μg (497 nmol)

Diagnosis of adrenal insufficiency

- **If patient is acutely sick:**
  - ♦ Start treatment; do not wait for results
  - ♦ If test will delay treatment, start treatment then do the test later when the patient is stable
- **Plasma aldosterone & renin: (in primary disease)**
  - ♦ Low aldosterone and high renin in primary disease

Treatment of adrenal insufficiency

- All patients (1ry & 2ry) require **glucocorticoids**:

  - Hydrocortisone (15-25 mg/d) divided in 2-3 doses/day (depends on patient's weight)

    10 am, 5 pm or 15 am, 5 pm or 15 am, 10 pm

- Some will feel fatigue at night or morning: give 3 doses
  - 10 am, 5 afternoon, 5 evening
  - or 15/5/5
- Slow-release form (once daily at am) available

Alternative treatment of adrenal insufficiency

- Prednisone or Prednisolone (2.5-7.5 mg/d) 1-2 times/day
  - Use if patient is not compliant with multiple daily doses
  - or in those with late-evening or early morning symptoms

    that are not relieved by three-times daily hydrocortisone

Monitoring of treatment for adrenal insufficiency

- Symptoms (energy level, headache, dizziness)
- Watch also for symptoms/signs of high dose (increased weight, puffy face)
- Clinical (weight, postural BP, edema)
- Hormonal monitoring is **not** recommended

Mineralocorticoids treatment in primary adrenal insufficiency

- Patients with aldosterone deficiency:
  - Should received mineralocorticoid replacement
  - Fludrocortisone (50-100 micrograms/day)
- Monitoring:
  - Clinical assessment (salt craving, postural hypotension, edema)
  - Blood electrolytes

Glucocorticoids potency

- 20 mg Hydrocortisone =
- 5 mg Prednisone/Prednisolone =
- 4 mg Methylprednisolone =
- 0.75 mg Dexamethasone

Cushing’s syndrome

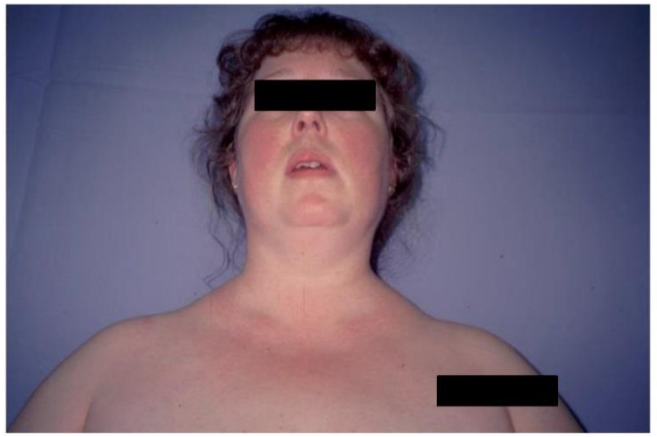
Clinical features of Cushing's Syndrome

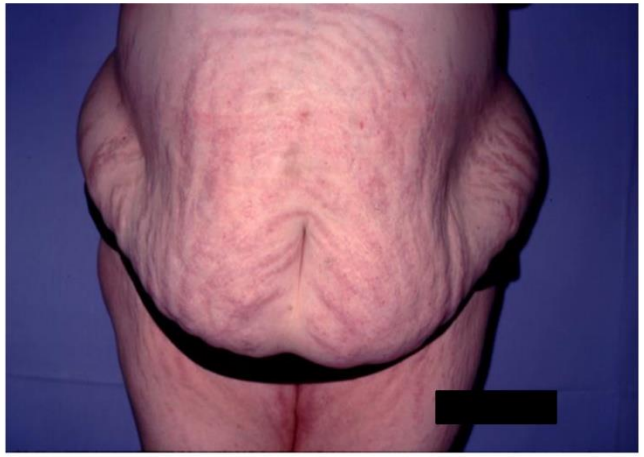
- Weight gain
- Skin infections
- Fatigue
- Mood changes
- Depression
- Decreased libido
- Hirsutism

Nieman LK. Eur J Endocrinol 2015;173:M33

Physical findings in Cushing's Syndrome

- Facial plethora
- Moon facies
- Supra-calvicular fat pads
- Central obesity
- Proximal muscle weakness
- Wide (> 1 cm), purple or red striae
- Spontaneous ecchymoses

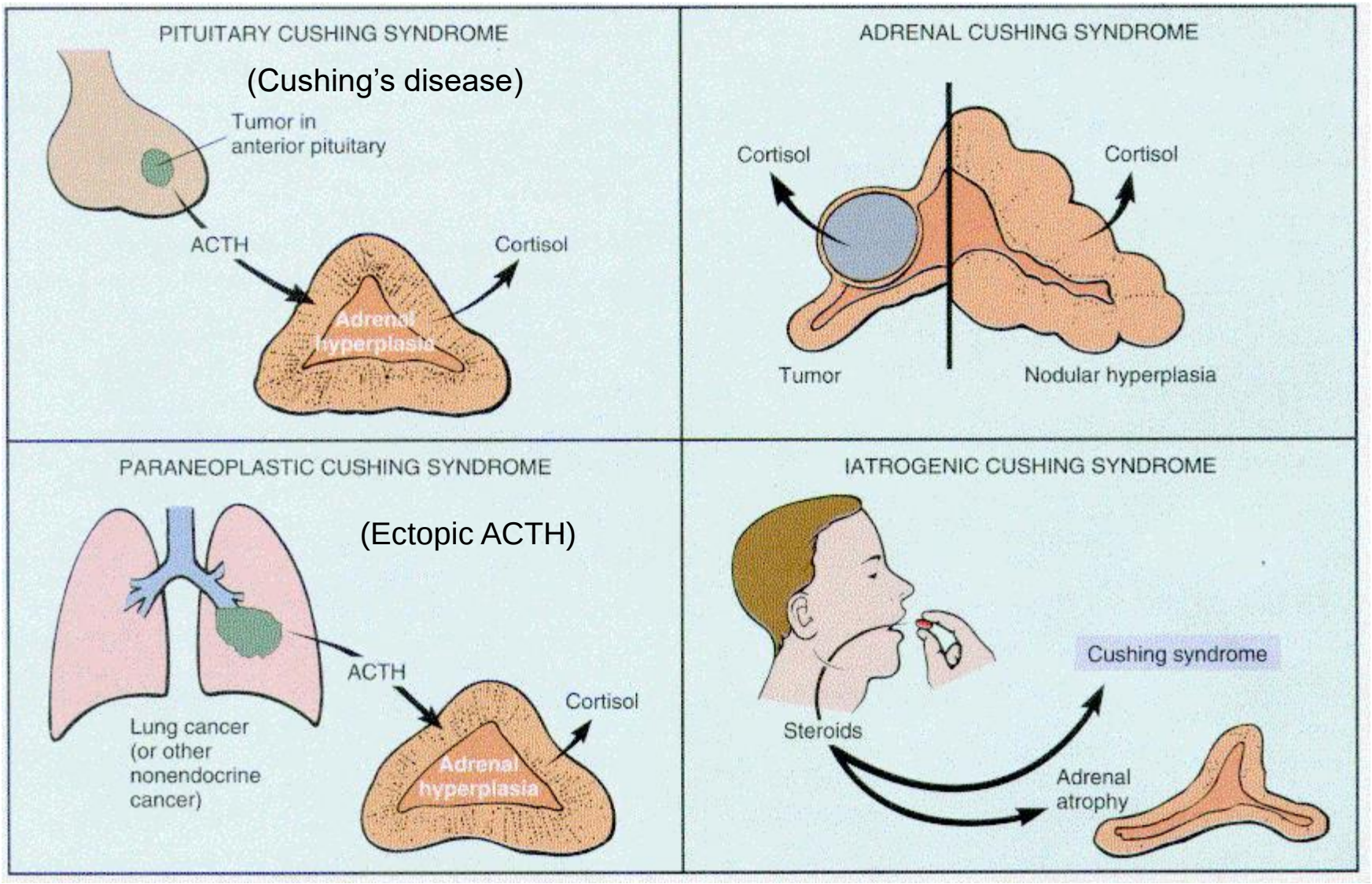




Associations with Cushing's Syndrome

- Hypertension
- Diabetes mellitus
- Osteoporosis
- Hypogonadism
- Poor wound healing
- Kidney stones

Causes of Cushing's syndrome



When to suspect Cushing's syndrome?

- Clinical features of Cushing's syndrome , especially facial plethora, proximal myopathy, striae (>1 cm wide and red or purple), easy bruising
- Unusual findings such as osteoporosis or hypertension in young adults
- Unexplained severe features (resistant hypertension, osteoporosis) at any age
- Adrenal incidentaloma
- **Always take a full history on the use of steroids (oral, inhalers, local, injections)**

Diagnosis of Cushing's syndrome

- The following tests have been used (1 or more):

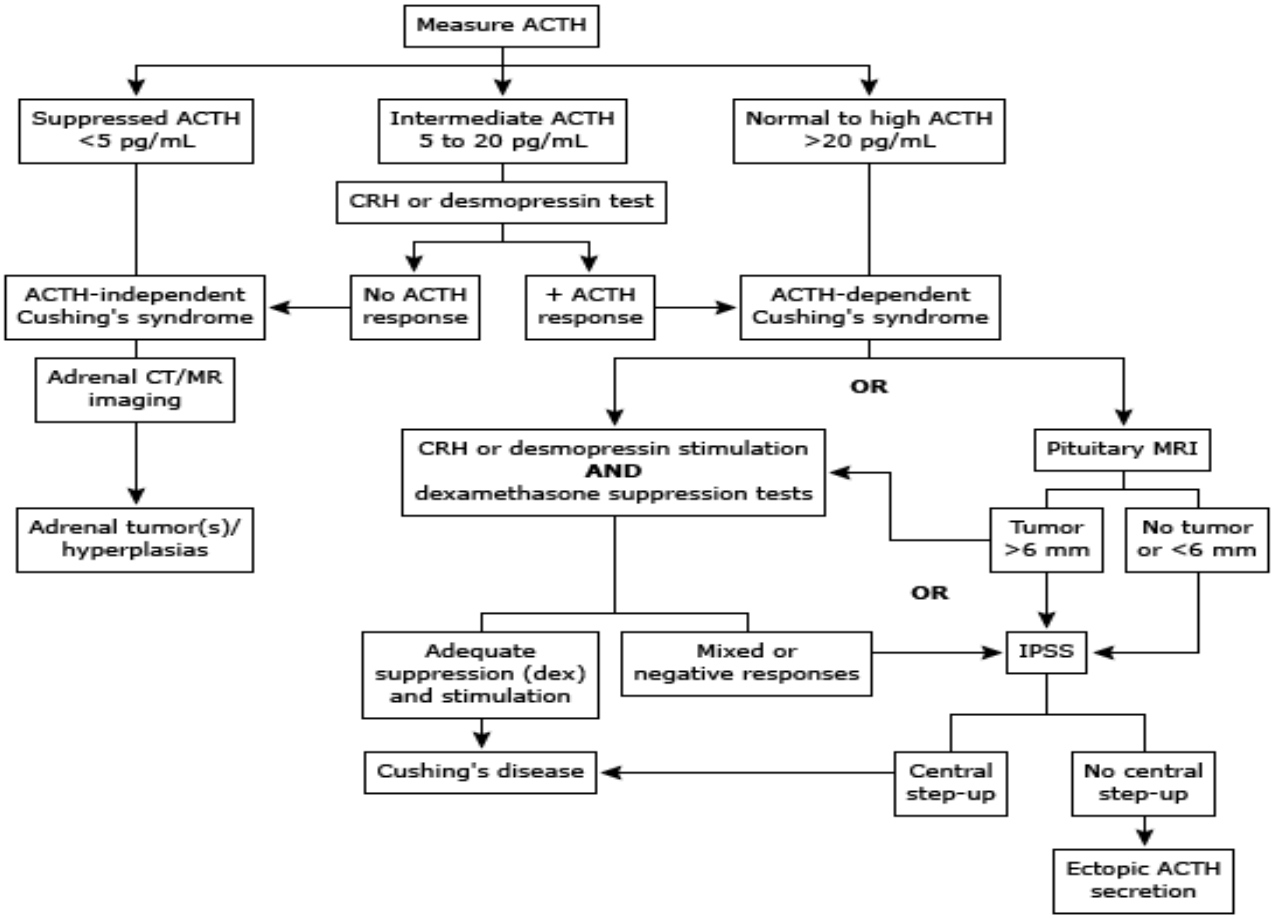
1) 24-hour urinary free cortisol
   - Is usually >3-fold the upper limit of normal to suspect Cushing's

2) Late-night salivary cortisol
   - Different cutoffs depending on the used assay

3) Overnight 1 mg dexamethasone suppression test:
   - 1 mg of dexamethasone orally at 11 PM to 12 AM
   - Check serum cortisol next day at 8 AM [Normal < 50 nmol (1.8 mcg)]

Endocrine Society guidelines. J Clin Endocrinol Metab 2008;93:1526

Establishing the cause of Cushing's syndrome



www.uptodate.com

IPSS: inferior petrosal sinus sampling

Primary aldosteronism

Features of primary hyperaldosteronism

- Hypertension
  - A common cause of secondary HTN
- Hypokalemia
  - Not in all patients
- Metabolic alkalosis
- Mild hypernatremia
- Hypomagnesemia
- Muscle weakness
- Higher rate of cardiovascular morbidity & mortality

Causes of primary hyperaldosteronism

- **Bilateral idiopathic hyperaldosteronism** (or idiopathic hyperplasia [IHA] (60-70%)
- **Unilateral aldosterone-producing adenoma** [APA] (30-40%)
- Unilateral hyperplasia or primary adrenal hyperplasia
- Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism) [GRA]
- Aldosterone-producing adrenocortical carcinomas, ectopic aldosterone-secreting tumors

When to test for primary hyperaldosteronism?

- Resistant hypertension
- When secondary hypertension is suspected
- Hypertension with adrenal incidentaloma
- Hypertension with sleep apnea
- Hypertension and a family history of early-onset hypertension
- All hypertensive first-degree relatives of patients with primary aldosteronism

Diagnosis of primary hyperaldosteronism

1) Screening test:

- Plasma aldosterone concentration (PAC):
  - High or normal
  - ≥10 ng/dL (277 pmol/L)
- Plasma renin activity (PRA) or concentration (PRC):
  - Low
  - [PRA <1 ng/mL/hour] or [PRC < lower limit of normal]
- Ratio (PAC/PRA) or (PAC/PRC):
  - High
  - >20

Endocrine Society guideline. J Clin Endocrinol Metab 2016;101:1889

Diagnosis of primary hyperaldosteronism (2)

2) Confirmatory test:

- Oral sodium loading or saline infusion test

A) Oral sodium loading:

- Sodium normally suppresses aldosterone
- Aldosterone does not suppress in 1^{ry} aldosteronism
- 2 grams sodium chloride tablets three times daily × 3 days
- 24-hour urine sodium [should be >200 mEq (4600 mg) to document adequate sodium loading]
- 24-hour urine aldosterone >12 mcg (33 nmol) confirms primary hyperaldosteronism

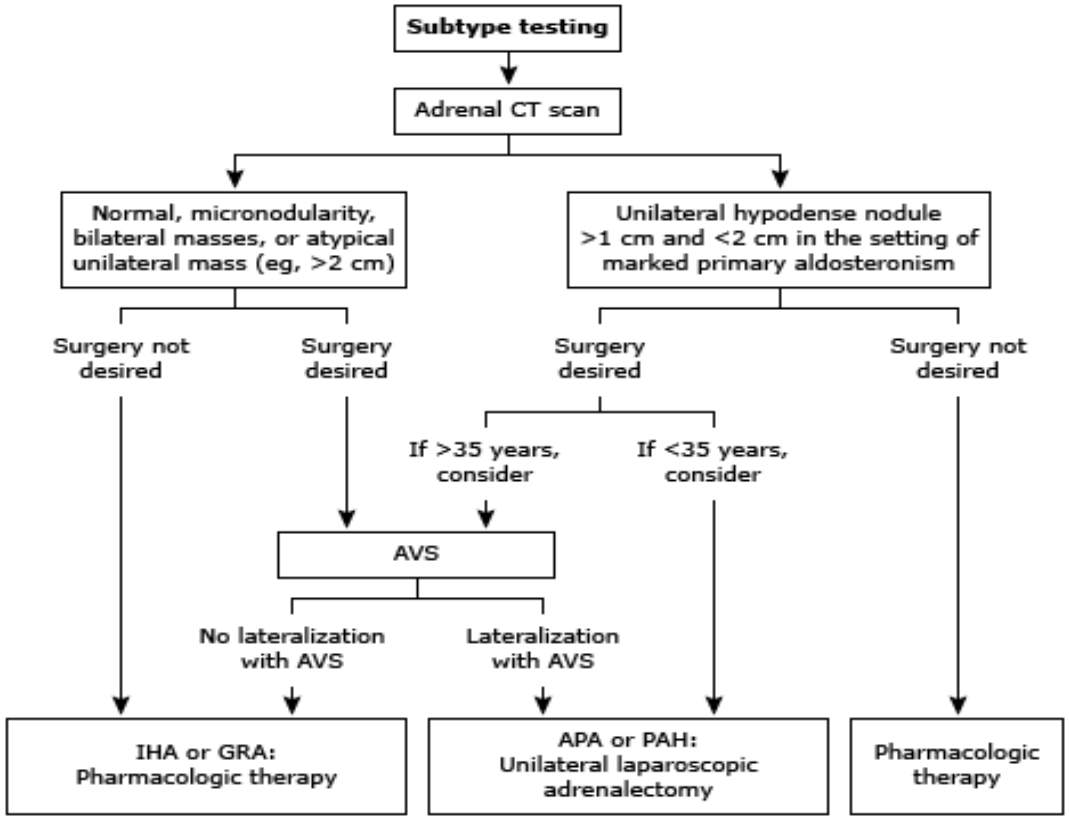
Diagnosis of primary hyperaldosteronism (3)

2) Confirmatory test:

B) **Saline infusion test** :

- Sodium normally suppresses aldosterone
- IV infusion of 2 Liters of isotonic saline over 4 hours (from 8 AM to 12 PM), ideally while the patient is seated
- Plasma aldosterone at end of infusion: > 10 ng/dL (277 pmol/L) confirms primary aldosteronism

Determining the subtype of primary aldosteronism



AVS: adrenal venous sampling; IHA: idiopathic hyperaldosteronism; GRA: glucocorticoid-remediable aldosteronism; APA: aldosterone-producing adenoma; PAH: primary adrenal hyperplasia

www.uptodate.com

pheochromocytoma

Pheochromocytoma

- Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla
- Catecholamine-secreting paragangliomas are tumors that arise from the sympathetic ganglia. Also called "extra-adrenal pheochromocytomas”
- Occurs in 0.2% of cases of hypertension

Associations with pheochromocytoma

- There are several familial disorders that are associated with pheochromocytoma
- All have autosomal dominant inheritance
- **Multiple endocrine neoplasia type 2 (MEN2A & MEN2B)**
- **von Hippel-Lindau (VHL) syndrome**
- **Neurofibromatosis type 1 (NF1)**

Symptoms of pheochromocytoma

- **Triad of: headache, sweating, palpitations**
  - Most patients do not have all the 3 symptoms
  - Headache (up to 90% of symptomatic patients)
  - Sweating (up to 60-70% of symptomatic patients)
- **Other symptoms** may include:
  - Palpitations, tremor, pallor, dyspnea, generalized weakness, panic attack, blurred vision, weight loss, polyuria, polydipsia, constipation
- **Asymptomatic:**
  - During evaluation of an adrenal incidentaloma or on screening for familial disorder or family history

Clinical features of pheochromocytoma

- **Sustained or paroxysmal hypertension:**
  - The commonest sign
  - But 5 to 15% of patients have normal BP
- **Paroxysmal elevations in BP** during diagnostic procedures, surgery, or with drugs (such as beta blockers, tricyclic antidepressants, corticosteroids)
- Orthostatic hypotension, papilledema
- Insulin resistance, hyperglycemia, leukocytosis

When to suspect pheochromocytoma?

- Headache, sweating & palpitations (with or without HTN)
- Hyperadrenergic spells (palpitations, diaphoresis, headache, tremor, or pallor)
- When secondary hypertension is suspected
- Resistant hypertension
- A familial syndrome (multiple endocrine neoplasia type 2, neurofibromatosis type 1 or von Hippel-Lindau)
- A family history of pheochromocytoma
- Adrenal incidentaloma with or without hypertension
- ↑↑ BP response during anesthesia, surgery, or procedure

Interfering medications with testing for pheochromocytoma

- Falsely elevated urinary and/or plasma metanephrines:
  - Acetaminophen
  - Labetalol
  - Sotalol
  - Methyldopa
  - Tricyclic antidepressants
  - Buspirone
  - Phenoxybenzamine
  - MAO-inhibitors, sympathomimetics, cocaine
  - Sulphasalazine
  - Levodopa

Diagnosis of pheochromocytomas

- 24-hour urinary fractionated catecholamines (dopamine, norepinephrine and epinephrine), fractionated metanephrines (metanephrine , normetanephrine) and creatinine
- This is the usual test done in most centers
- Creatinine is done to assure adequate sample
- Values are usually are > 2-3 times upper limit of normal

Endocrine Society guideline. J Clin Endocrinol Metab 2014; 99: 1915

Diagnosis of pheochromocytomas (2)

- **Plasma fractionated metanephrines**
  - Is helpful when it is normal (high sensitivity)
  - But it has a high false positive rate (lower specificity)
  - Suggested if there's high suspicion for pheochromocytoma:
    - A family history of pheochromocytoma
    - A genetic syndrome (such as MEN2)
    - A past history of resected pheochromocytoma
    - An incidentally discovered adrenal mass that has imaging characteristics consistent with pheochromocytoma

Diagnosis of pheochromocytomas: Plasma fractionated metanephrines

- Overnight fast
- Place IV cannula
- Patient stays **supine** for 20 minutes
- Then draw blood
- The cutoffs to exclude pheochromocytoma:
  - Metanephrine <0.3 nmol/L and/or normetanephrine <0.66 nmol/L

What if results are indeterminate?

- For patients with mildly high results
- Repeat testing during symptoms (if they exist)
- Obtain (or repeat) plasma fractionated metanephrines
- Or repeat 24-hour urinary fractionated catecholamines, metanephrines and creatinine
- Re-assess after 6 months

Localization of pheochromocytomas

- This is done only after biochemical confirmation of pheochromocytoma is achieved
- **CT-scan** (preferred)
- **MRI** for:
  - Metastatic pheochromocytoma
  - For detection of skull base and neck paragangliomas
  - Patients with surgical clips that cause artifacts when using CT
  - Patients with an allergy to CT contrast
  - Patients in whom radiation exposure should be limited (children, pregnancy)
  - Patients with known germline mutations
  - Patients with recent excessive radiation exposure

Localization of pheochromocytomas

- If imaging is negative, consider:
  - Re-assess the diagnosis
  - Whole body MRI

    or
  - FDG-PET scan

    or
  - Iobenguane I^{123} scan [also called metaiodobenzylguanidine (MIBG)])]

Treatment of pheochromocytomas

- Surgical resection
- Preoperative management:

1) Alpha-adrenergic blockade:

- Phenoxybenzamine, prazosin, terazosin or doxazosin
- Start 1-2 weeks before surgery
- Adjust per BP

2) Beta-adrenergic blockade:

- Start 2-3 days before surgery
- Never start alone (can lead to unopposed alpha-adrenergic stimulation causing increase in BP)
- Propranolol or metoprolol (adjust per pulse, BP)

Treatment of pheochromocytomas (2)

- **Preoperative management:**

  3) High-sodium diet and fluid intake:

  – To reverse catecholamine-induced blood volume contraction preoperatively

  – To prevent severe hypotension after tumor removal

- **Post-operative management:**

  – Monitor blood pressure, heart rate, and blood glucose

- **Follow up:**

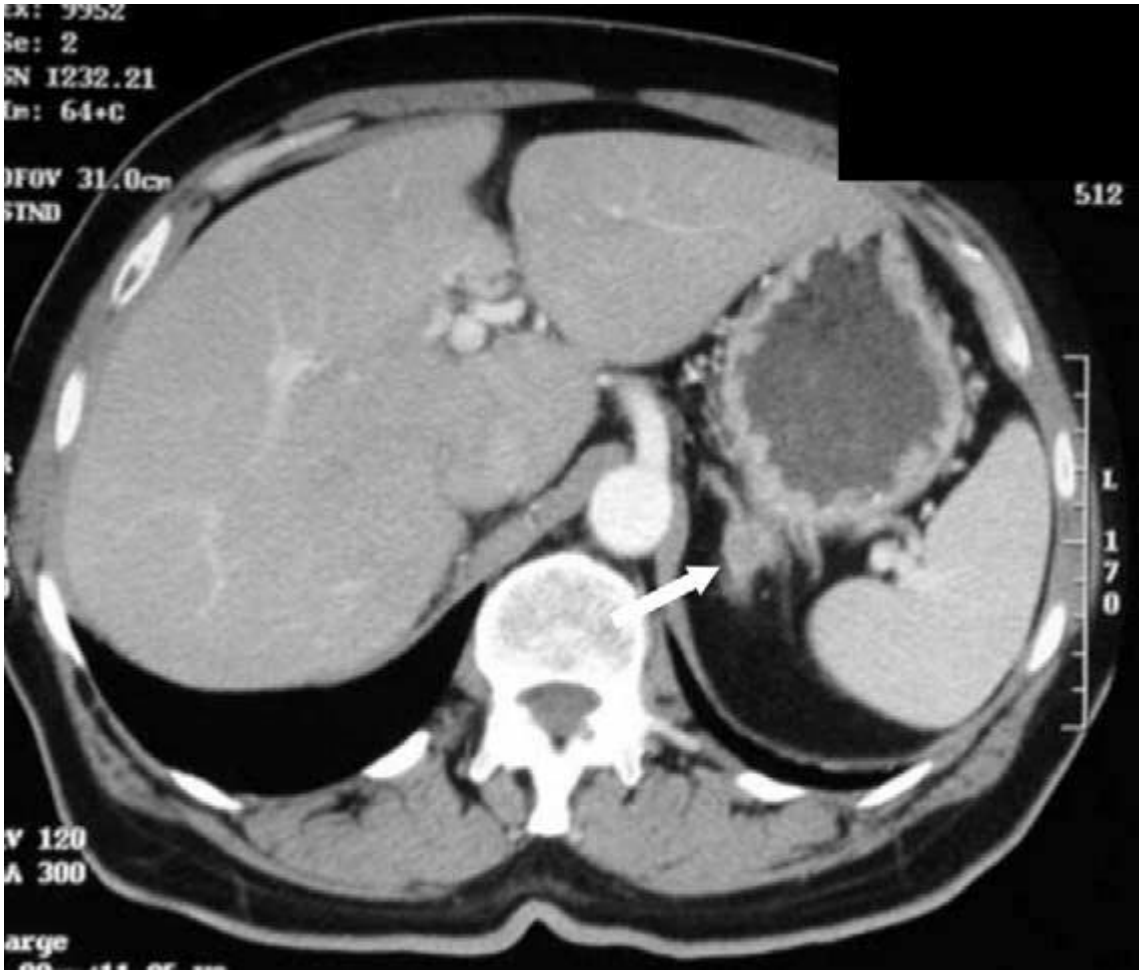
  – Lifelong annual biochemical testing to assess for recurrent or metastatic disease

Case presentation

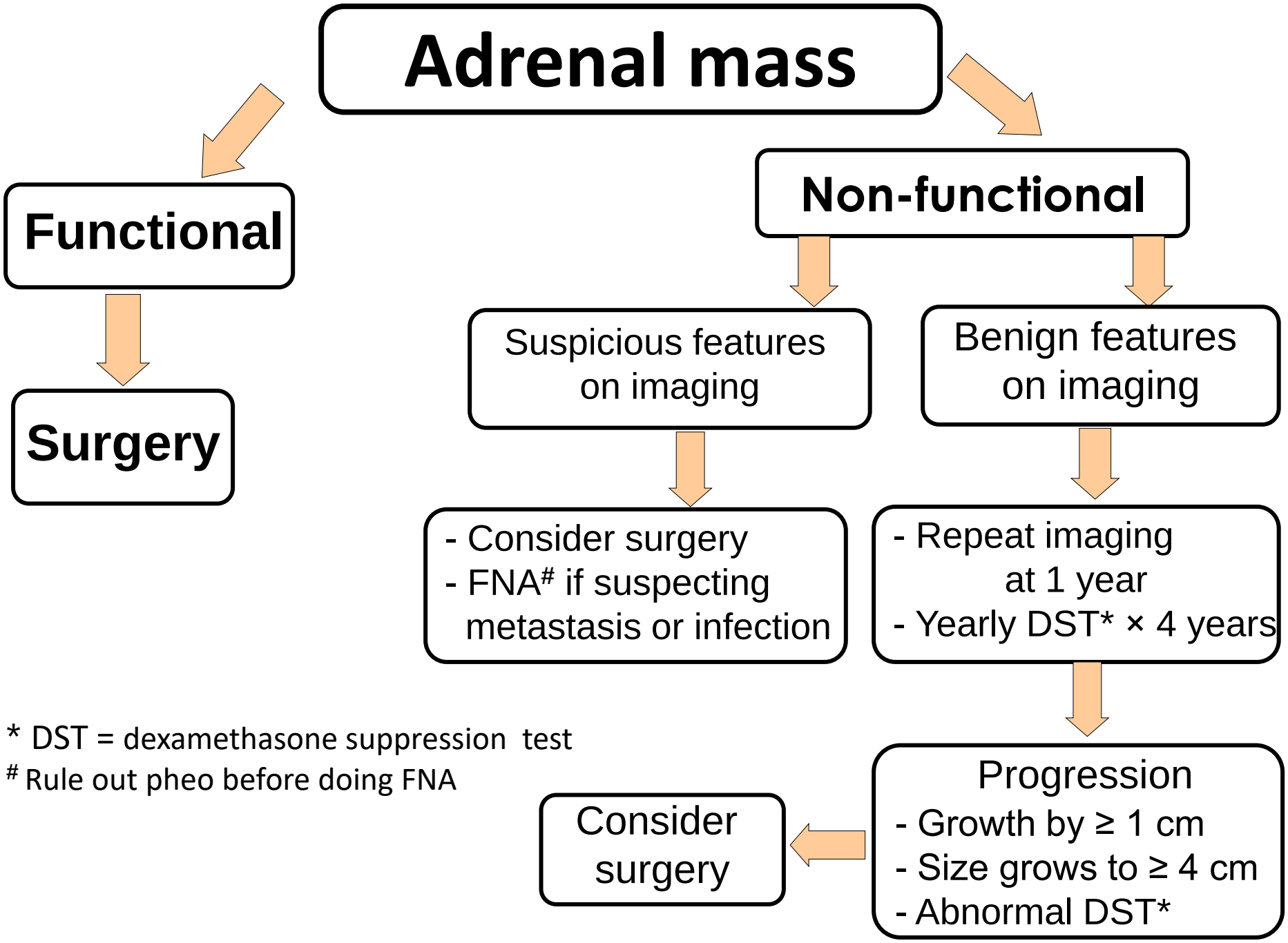
- A 48-year-old woman is evaluated in the surgery clinic for chronic abdominal pain for 6 months
- Her past medical history and family history are not significant
- CT-scan of the abdomen was only significant for a 2.5 cm left adrenal mass
- B.P. 110/72
- Systematic examination was normal
- **How would you approach?**

Incidentally-discovered adrenal mass **(Adrenal incidentaloma)**

- >1 cm in size, discovered on imaging
- Prevalence 4.4%. In elderly: around 10%
- Rule out pheochromocytoma (urine or plasma catecholamines, metanephrines)
- Rule out Cushing's syndrome (usually subclinical; 1-mg dexamethasone suppression test is more sensitive)
- If HTN, rule out primary aldosteronism (serum aldosterone, plasma renin activity)



Left adrenal mass found incidentally on CT-scan



* DST = dexamethasone suppression test

Rule out pheo before doing FNA

Calcium disorders & Osteoporosis

Approach to hypocalcemia

1) Repeat test

2) Check serum albumin

   - Correct calcium if albumin is low
   - Calcium ↓ by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL (10 g/L) ↓ in albumin (normal 4 g/dl)
   - example: calcium 8 mg, albumin 2 g/dL
     - Corrected calcium 8 + (0.8 ×2) = 9.6 mg

3) Can check ionized calcium, but expensive

Causes of hypocalcemia

- Post-surgical (thyroid, parathyroid surgery)
- Autoimmune hypoparathyroidism
  - Can be isolated
  - Or with chronic mucocutaneous candidiasis + adrenal insufficiency (polyglandular syndrome type 1)
- Vitamin D deficiency
- Pseudohypoparathyroidism (PTH resistance)
- Acute or chronic kidney disease
- Acute pancreatitis
- Tumor lysis syndrome
- Hypomagnesemia, hyperphosphatemia
- Acute illness, sepsis

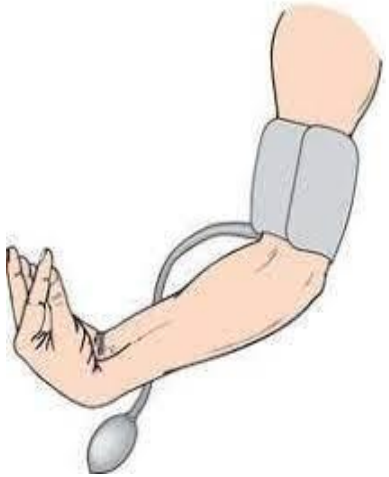
Manifestations of hypocalcemia

- Perioral numbness
- Paresthesia of hands and feet
- Muscle cramps & pains
- Carpopedal spasm
- Laryngospasm
- Seizures (focal or generalized)
- Fatigue, irritability, anxiety, depression
- Some have no symptoms

Physical examination

- **Trousseau's sign**:

  induction of carpal spasm by inflation of a sphygmomanometer above systolic blood pressure for 3 minutes

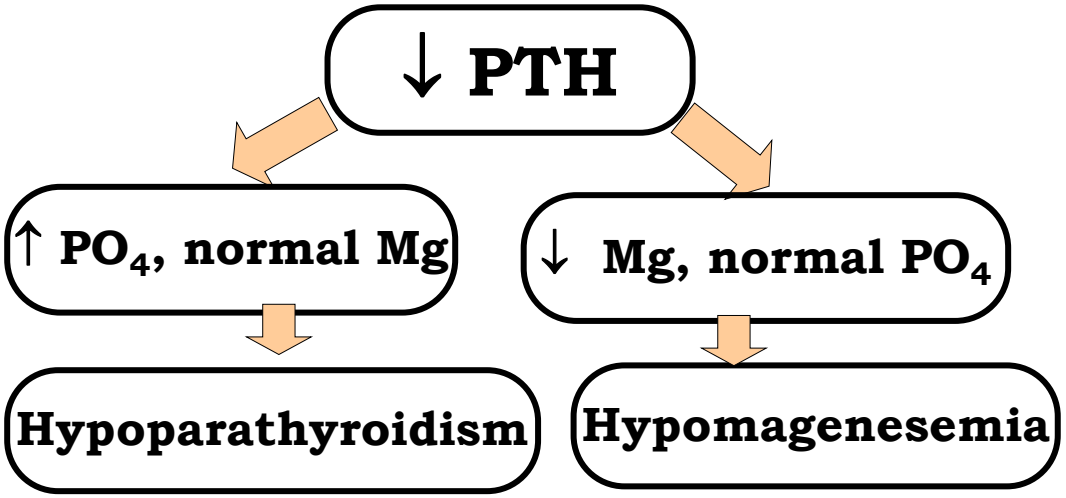


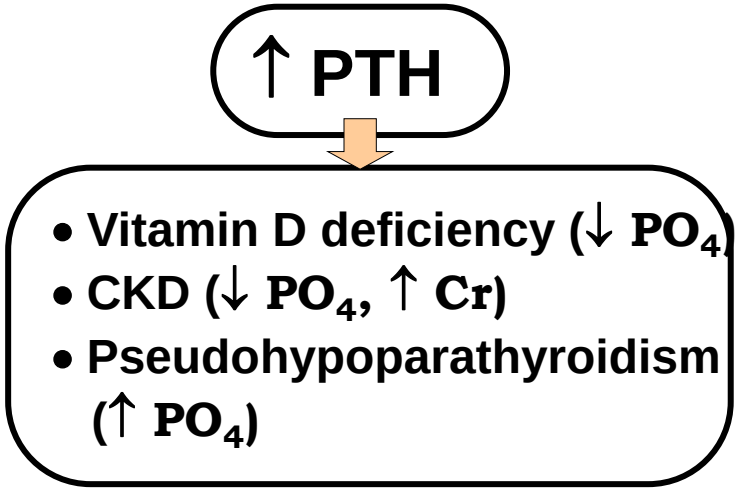
- **Chvostek's sign**:

  contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear (may occur in normal persons)

Work up of hypocalcemia

- **PTH**, creatinine, 25-OH vitamin D, magnesium, phosphorus





Evaluation of hypocalcemia

	PTH	Phosphorus	Magnesium	25-OH vit D	creatinine
Hypoparathyroidism	↓	↑	Normal	Normal	Normal
Pseudohypoparathyroidism	↑	↑	Normal	Normal	Normal
Hypomagnesemia	Normal or ↓	Normal	↓	Normal	Normal
Vitamin D deficiency	↑	↓ or normal	Normal	↓	Normal
Chronic kidney disease	↑	↑	Normal or ↑	Normal	↑

Treatment of hypocalcemia

1) Acute symptoms or very low calcium (< 7 mg):

- IV calcium
- Check magnesium and potassium (replace if low)

2) Chronic treatment:

- Oral **elemental** calcium 1-2 grams/day
  - Ca carbonate = 40% elemental calcium (1250 mg = 500 mg)
  - Ca citrate = 21% elemental calcium
  - Ca lactate = 13%
- Vitamin D:
  - Calcitriol 0.25 to 2 mcg /day (higher doses can be used)
  - Or Alfacalcidiol (one alpha) 0.25 to 2 mcg/day (may need ↑)

3) Target calcium is low normal (8 to 8.5 mg)

Case presentation

- A 52-year-old lady is referred because of high serum calcium
- She only reports occasional joint pains
- No medications
- Past history: none

  Family history: hypertension & DM with mother
- Exam: BP normal. No abnormalities
- Calcium 11.2 mg (8.5-10.5), CBC & creatinine normal, TSH normal
- **How would you approach?**

Causes of hypercalcemia

VITAMIN-TRAP

Vitamin intoxication (D, A)

Immobilization

Thiazide, Theophylline, Tamoxifen, Lithium

Addison's disease, **A**cromegaly

Milk-alkali syndrome

Inflammation/infection (TB, sarcoidosis, fungal)

Neoplasia (kidney, lung, breast, MM, esophagus, lymphoma, leukemia..)

Thyrotoxicosis

Rhabdomyolsis

AIDS

Parathyroidism (1^{ry},3^{ry})

Pheochromocytoma

Parenteral nutrition

FHH:
Familial hypocalciuric hypercalcemia

Evaluation of high calcium

- Repeat calcium & check PTH

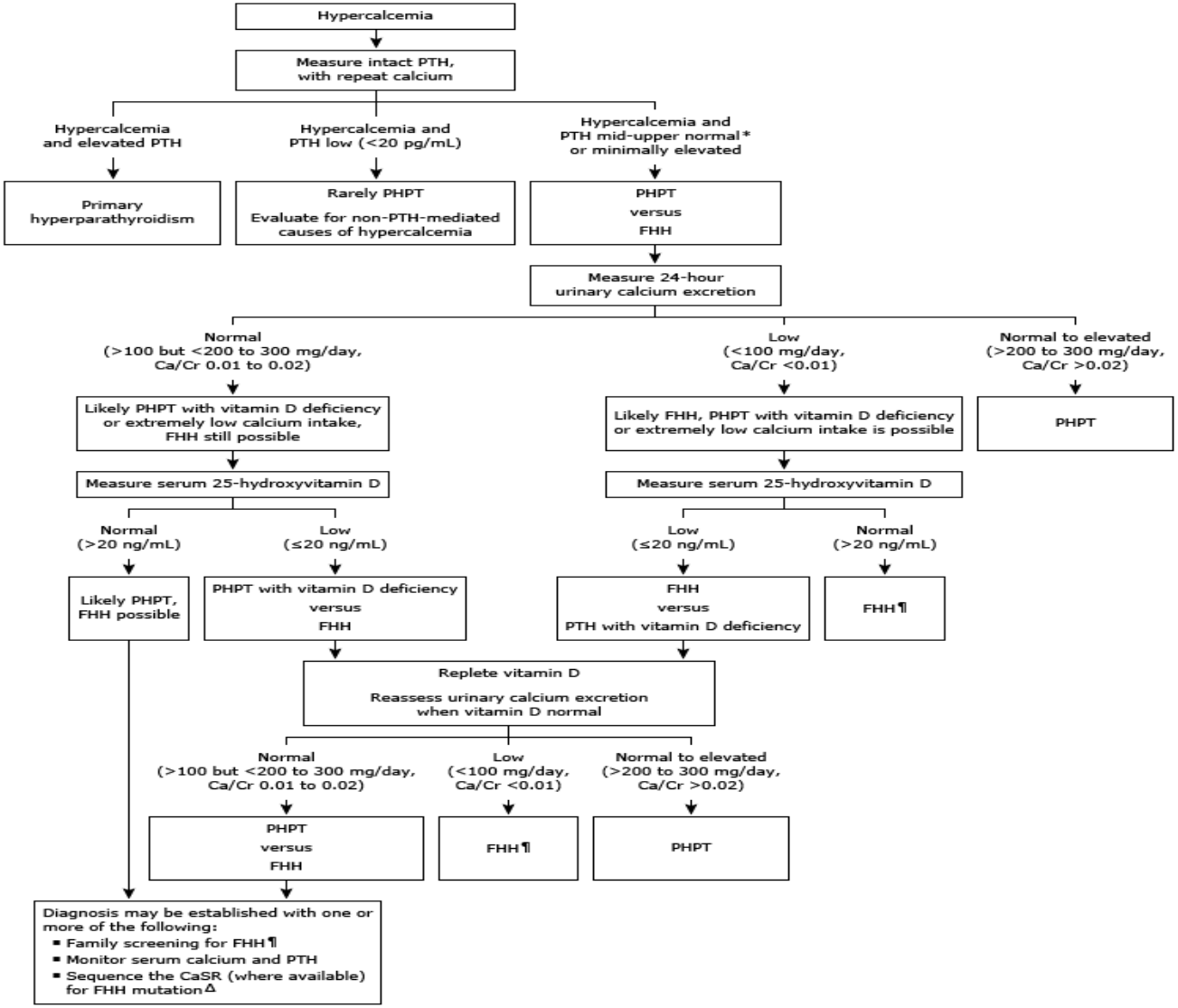
1) **High PTH**
   - Primary hyperparathyroidism (PHPT)
2) **Upper normal or slightly high:**
   - PHPT (likely)
   - FHH (less likely)
3) **Low-normal or low:**
   - Non-parathyroid causes

Approach to hypercalcemia

1) High PTH:

- Mostly caused by a parathyroid adenoma
- Evaluation:
  - Serum creatinine, eGFR
  - 24-hour urine calcium
  - Bone density (including the distal third of the radius)
  - Renal ultrasound to detect stones
  - Serum 25-OH vitamin D

Diagnosis of primary hyperparathyroidism



PTH: parathyroid hormone; PHPT: primary hyperparathyroidism; FHH: familial hypocalciuric hypercalcemia; Ca/Cr: calcium/creatinine ratio; CaSR: calcium-sensing receptor.

* Inappropriately normal given hypercalcemia

¶ Assess for a family history of asymptomatic hypercalcemia, especially in young children.

Δ Refer to UpToDate topic on hyperparathyroidism for details.

Indication for surgery in primary hyperparathyroidism

- Serum calcium >1.0 mg (0.25 mmol) over upper limit of normal
- Osteoporosis (spine, hip, femoral neck, or distal 1/3 radius)
- Vertebral fracture
- eGFR <60 mL/min
- 24-hour urinary calcium >400 mg/day (>10 mmol)/day
- Kidney stones
- Age < 50 years
- If follow up is not desired or possible

Insogna K. N Engl J Med 2018;379:1050
Bilezikian JP, et al. J Clin Endocrinol Metab 2014;99:3561

Follow up if no surgery

- Patients who refuse or are not candidates for surgery
- Monitor the following:
  - Serum calcium every year
  - Bone density every 1-2 years (spine, hip, radius)
  - Spine imaging if height loss or symptoms of a vertebral facture
  - Serum creatinine, eGFR annually
  - If history or suspected kidney stones:

    - 24-hour urine calcium, renal imaging (X-ray, U/S or CT) yearly

Insogna K. N Engl J Med 2018;379:1050
Bilezikian JP, et al. J Clin Endocrinol Metab 2014;99:3561

Medical management of primary hyperparathyroidism

- Deficiencies in vitamin D and dietary calcium worsen hyperparathyroidism
- It is not recommended to limit dietary calcium intake
- Adequate calcium diet (1000-1200 mg/day) & vitamin D (serum 25-hydroxyvitamin D >20 ng)
- Cinacalcet:
  - Mild ↓ PTH, ↓ serum calcium. No effect on bone density
  - Approved for use
- Bisphosphonate:
  - Improves bone density, but no data on fracture

Insogna K. N Engl J Med 2018;379:1050
Bilezikian JP, et al. J Clin Endocrinol Metab 2014;99:3561

Osteoporosis

Osteoporosis

- Low bone mass
- Microarchitectural disruption
- Skeletal fragility
- **This causes ↓ bone strength & ↑ risk of fracture**

Clinical manifestations of osteoporosis

- No symptoms until there is a fracture
- **Vertebral fracture**
  - Commonest manifestation of osteoporosis
  - Mostly asymptomatic
  - Found incidentally on imaging
  - May present as height loss or kyphosis
  - Pain if acute presentation
- **Other fractures:**
  - Hip fractures
  - Distal radius fractures (Colles fractures)

Risk factors for osteoporosis

- Women ≥ 65 years, men ≥ 70 years
- Previous fragility fracture
- Parental history of fracture
- Cigarette smoking
- Excessive alcohol use
- Low body weight (< 58 kg)
- Rheumatoid arthritis
- Long term glucocorticoid therapy
- Secondary osteoporosis

When to screen for osteoporosis?

- Women ≥65 years, men ≥70 years
- Women <65 years, men <70 years if:
  - Low body weight
  - Prior fracture
  - High risk medication use
  - Disease or condition associated with bone loss

International society of clinical densitometry guidelines. www.iscd.org

Diagnosis of osteoporosis

- **Fragility fracture:**
  - Occurs spontaneously or from minor trauma (fall from a standing height)
  - Generally at the spine, hip, wrist, humerus, rib or pelvis

OR

- **T-score ≤ -2.5 :**
  - At any site by bone mineral density

Bone mineral density (BMD)

- Usually measured with dual-energy X-ray absorptiometry (DXA) scan
- Scores are expressed as standard deviations
- T score: bone density compared with young **normal** person
- Z score: bone density compared with **age-matched** person
- Definition of bone density depends on **T SCORE**

  Between 0 and - 1 → **Normal**

  Between -1 and above – 2.5 → **Osteopenia**

  At or below -2.5 → **Osteoporosis**

  At or below -2.5 with fragility fracture → **Established Osteoporosis**
- Z score is low in secondary causes of osteoporsis

Evaluation of osteoporosis

- **History and physical examination:**
  - Smoking, alcohol, physical inactivity, poor nutrition
  - History of a fragility fracture
  - Height and weight
  - Secondary causes of osteoporosis
- **Fracture Risk Assessment Tool (FRAX):**
  - A calculator that estimates the 10-year probability of hip fracture and major osteoporotic fracture for untreated patients aged 40-90 years
  - Region/country specific
  - Information include age, risk factors, femoral neck BMD if available
- **Laboratory evaluation**
  - Biochemistry (electrolytes, calcium, phosphorous, albumin)
  - 25-hydroxyvitamin D
  - Complete blood count

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Kuwait Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 70 Date of Birth: Y: 1950 M: D:
2. Sex: Male / Female
3. Weight (kg): 74
4. Height (cm): 164
5. Previous Fracture: No / Yes
6. Parent Fractured Hip: No / Yes
7. Current Smoking: No / Yes
8. Glucocorticoids: No / Yes
9. Rheumatoid arthritis: No / Yes
10. Secondary osteoporosis: No / Yes
11. Alcohol 3 or more units/day: No / Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear | Calculate

BMI: 27.5

The ten year probability of fracture (%)

without BMD

Major osteoporotic	5.1
Hip Fracture	1.5

Print tool and information

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

00026060

Individuals with fracture risk assessed since 1st June 2011

Causes of secondary osteoporosis

- Endocrine disorders (hyperparathyroidism, hyperthyroidism, hypogonadism, Cushing's syndrome, DM)
- GI disorders (celiac disease, IBD, chronic liver disease)
- Nutritional disorders (vitamin D deficiency, parenteral nutrition)
- Medications (glucocorticoids, cyclosporine, heparin, phenytoin, phenobarbital, GnRH agonists & antagonists)
- Rheumatoid arthritis
- Multiple myeloma, leukemia, lymphoma, sickle cell disease
- Organ transplantation (kidney, liver, bone marrow, lung, heart)

When to consider drug therapy for osteoporosis?

- **Postmenopausal women or men ≥ 50 years with:**
  - History of fragility fracture
  - Osteoporosis
  - High risk with osteopenia:
    - Using FRAX tool
    - Defined as:

      A 10-year probability of hip fracture ≥3.0%

      OR

      A 10-year probability of major osteoporotic fracture ≥20%

Treatment of osteoporosis

- **Lifestyle measures:**
  - Adequate calcium intake (1200 mg/day)
  - Adequate vitamin D intake (800 units/day)
  - Exercise
  - Smoking cessation
  - Avoidance of alcohol use

Treatment of osteoporosis

- **Bisphosphonates:**
  - Mostly recommended as 1st line agent
  - Reduce vertebral & hip fractures (Ibandronate did not ↓ hip fractures)
  - Oral: Alendronate, risedronate (daily or weekly dosing),

    Ibandronate (once monthly)
    - Stay upright for 30-60 minutes after taking the medication
    - Do not use if esophageal disorders, inability to follow the instructions
  - IV: Zoledronic acid (every year), Ibandronate (every 3 months)
  - Not recommended if eGFR <30

Endocrine society guidelines. J Clin Endocrinol Metab 2020;105:587

Treatment of osteoporosis

- **Denosumab:**
  - Inhibits osteoclast formation, ↓ bone resorption
  - Reduced rates of vertebral and hip fractures
  - May be used as an alternative (especially if there is intolerance to bisphosphonates or CKD)
  - Subcutaneous injection once every 6 months
  - There is an increased risk of vertebral fractures after stopping it
  - If denosumab is discontinued, an alternative therapy should be given (usually a bisphosphonate)

Treatment of osteoporosis

- **Anabolic agents:**
  - Generally used for severe osteoporosis:
    - T-score of ≤ -3.5, T-score of ≤-2.5 with a fragility fracture, severe or multiple vertebral fractures
  - Teriparatide, Abaloparatide, Romosozumab
  - Teriparatide & abaloparatide (once daily subcut.) for up to 2 years
  - Romosozumab (once monthly subcut.) for up to 1 year
  - Bisphosphonates are usually given after those agents

Treatment of osteoporosis

- **Selective Estrogen Receptor Modulators (SERMs):**
  - In postmenopausal women with osteoporosis at high risk of fracture
  - Reduce the risk of vertebral fractures (not hip)
  - Reduce the risk of breast cancer
  - Raloxifene, Bazedoxifene (oral)
  - Used if low risk for deep vein thrombosis and for whom bisphosphonates or denosumab are not appropriate or with a high risk of breast cancer

Multiple endocrine neoplasia

Multiple Endocrine Neoplasia [MEN]

- 3 Syndromes: **MEN type 1**

  MEN type 2A

  MEN type 2B

- Inherited as autosomal dominant

- A combination of variable endocrine ± Non-endocrine tumors.

- ***Remember***: *Not necessary to have all tumors in each type*

MEN Type 1

- **Remember the 3 P:**

Hyper**P**arathyroidism

Entero**P**ancreatic tumors (gastrinoma, insulinoma,..)

Pituitary tumors (Prolactin, GH, non-functional,..)

MEN Type 2A

- **Medullary Thyroid Cancer**
- **Pheochromocytoma**
- **Parathyroid tumors**

MEN Type 2B

- Medullary Thyroid Cancer
- Pheochromocytoma
- Mucosal, Intestinal ganglioneuromas
- Marfanoid habitus (tall, slender body with long arms and legs, a reduced upper to lower body ratio, and poor muscle development)

MEN syndromes

- MEN 1: **Parathyroid**
  Pancreas
  Pituitary
- MEN 2A: **Parathyroid**
  Medullary thyroid Cancer
  Pheochromocytoma
- MEN 2B: Medullary thyroid Cancer
  Pheochromocytoma
  Others: Mucosal neuromas, Marfanoid