# Alternative Medicine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
<th>Clinical Pearls</th>
<th>Adverse/DDI</th>
</tr>
</thead>
</table>
| Dyslipidemia  | Fish Oil/ Omega-3 Fatty Acids    | **Decreases hepatic secretion of VLDL and increases VLDL clearance, lowers TGs (does NOT affect LDL)**  
500 mg qd for primary prevention or 1000 mg for secondary prevention; 1-4 g of DHA and EPA  
Lowering of TGs by ~30% with statins  
Can decrease fishy taste by freezing or using enteric coating  
Limit fish intake to 12 oz/week in pregnancy (mercury risk); avoid shark, swordfish, and tilefish  
*Treatment option for patients who can’t take niacin due to gout or flushing reaction*  
Potentiates antiHTN drugs  
Krill oil (per Dr. Oz): might be alternative to fish oil, but data is still being collected | Fishy taste  
GI side effects  
Increase risk of bleeding with anticoagulants  
Interactions with “G” herbs: ginger, garlic, ginkgo, ginseng |
| Fiber         |                                  | **If 51% whole grain → can say that reduces risk of heart disease**  
Blond Psyllium (10-12 grams)  
Oat Bran | Not discussed |
| Niacin        |                                  | **Dose of 1200-3000 mg/day may lower LDL and TG, and increase HDL, but no significant decrease in all cause mortality**  
Can give aspirin before to avoid flushing | Side effects: flushing, increase uric acid (gout), increase blood sugar, headache  
Monitor LFTs due to hepatotoxicity risk |
| Plant Sterols and Stanols | Inhibits about 50% of intestinal cholesterol absorption (decrease TG and LDL, no effect on HDL)  
Can be found in butters and juices  
800 mg-6 g doses (2 g optimal) | Diarrhea and steatorrhea  
Takes 2-3 wks to be effective and only effective as long as you take it  
Interactions with beta carotene and Vit. E and Zetia | Diarrhea  
Increased risk of bleeding with anticoagulants (discontinue 2-3 weeks prior to surgery)  
Interactions with “G” herbs: ginger, garlic, ginkgo, ginseng |
| Flaxseed      | Good source of linolenic acid  
40-50 g/d to decrease LDL (no effect on HDL; oil form not effective)  
Take with water | GI upset, heartburn, flatulence  
Many DDIs  
- Herbs: Coenzyme Q10, niacin, Kava, and St. Johns Wort  
- Food: EtOH, grapefruit, and food  
- Drugs: CYP3A4, cyclosporine, gemfibrozil  
- Monitor: CK, LFT, serum cholesterol | |
| Red Yeast Rice| Active ingredient resembles a statin (inhibits HMG CoA reductase)  
May contain Citrinin (renal toxicity) | **GI upset, heartburn, flatulence**  
**Many DDIs**  
- Herbs: Coenzyme Q10, niacin, Kava, and St. Johns Wort  
- Food: EtOH, grapefruit, and food  
- Drugs: CYP3A4, cyclosporine, gemfibrozil  
- Monitor: CK, LFT, serum cholesterol | |
| Calcium       | 800-1200 mg/d increases weight loss | Belching, flatulence | |
| Hoodia Gordonii | Raspberry flavored yogurt drink that causes weight loss | Nausea and skin issues | |
| Ephedra       | Significant weight loss | Dizziness, N/V, palpitations, HTN, MI, arrhythmias, sudden death  
**DO NOT RECOMMEND! Risk outweighs benefit** | |
| Bitter Orange | Was created in response to ephedra ban: contains 1-6% of synephrine (related to ephedrine) and often also contains caffeine | Dizziness, N/V, palpitations, HTN, MI, arrhythmias, sudden death  
**DO NOT RECOMMEND! Risk outweighs benefit** | |
| Orlistat (Alli) | Inhibit pancreatic and gastric lipases (decreases fat absorption by 30%); take pill with each fatty meal (take with multivitamin)  
FDA approved for long term weight loss | HA, oily spotting, fecal urgency, steatorrhea (can take fibers to decrease side effects); liver related events (liver failure/damage)  
DDIs: anticoagulants, amiodarone, levothyroxine, and vitamins | |
| Aside on Diets | Atkins (low carb, high protein)  
Macrobiotic (low fat, restrict fluid intake)  
Ornish (only 10% calories from fat, F/V)  
South Beach  
Zone (40% carb, 30% protein, 30% fat)  
Vegetarian  
Mediterranean (whole grains, F/V, olive oil for fat, seafood, wine with each meal)  
Others (Weight Watchers, Jenny Craig) | |
| Diabetes | Chromium | • May reduce oxidative stress  
• May reduce blood glucose, HbA1c, FFA | • HA, insomnia, irritability, mood changes & sleep disturbance  
• Vomiting, diarrhea, & hemorrhage  
Interactions:  
• Herbs: bilberry, brewer yeast, iron, Vit. C & zinc  
• Drugs: insulin, levothyroxine, NSAIDs & corticosteroid |
| Alpha-lipoic acid | • Improvement in insulin resistance; no effect on HbA1c  
• Antioxidant | • DDIs with garlic, ginseng, psyllium, DM drugs, and chemo |
| Vanadium | • Stimulates glycogenogenesis, inhibits lipolysis | • GI upset, tongue discoloration (green tongue)  
• Interactions with “G” herbs: ginger, garlic, ginkgo, ginseng  
• DDIs with anticoagulants and antiplatelets |
| Dietary/Culinary Herbs | • Bitter Melon  
• Cassia Cinnamon (caution in liver dz)  
• Magnesium (100 mg/d may lead to 15% decrease in T2DM risk)  
• Prickly pear cactus  
• Stevia (sweetener)  
• Chia (“superfood”)  
• Fruit (blueberries, grapes, apples) | |
| Hypertension | Garlic | • Allicin is the active ingredient; inhibits hepatic cholesterol synthesis; relaxes smooth muscle (vasodilation=decrease BP); also used for dyslipidemia  
• Need about 1 raw clove (4g) per day  
• Odorless product does NOT have allicin (active ingredient) | • Halitosis, body odor, heartburn, GI upset  
• DDIs: anticoagulant/antiplatelet; CYP3A4 and CYP2E1  
• Herb DDIs: ginger, ginkgo, and vitamin E  
• GI upset, heartburn, appetite loss  
• DDIs with anticoagulants  
• May artificially increase T4/T8 levels |
| Coenzyme Q-10 | • Used for CHF (not strong evidence), preventing myopathy (no evidence) | |
| Pomegranate | • Juice may decrease systolic BP (conflicting data)  
• Antioxidants (.2-1% polyphenols) → more than green tea or wine | • Rare: angioedema  
• Herbs DDIs: Co Q-10, fish oil, stinging nettle  
• Drugs DDIs: ACEIs |

**Notes**
- **Complementary Medicine:** used together with Western medicine
- **Alternative Medicine:** therapy used instead of Western medicine
- (Complementary and Alternative Medicine): Using therapies that are proven safe and effective and adopting them into conventional health care
- 72% of patients don’t report CAM use to health care providers; mostly used by ages 50-59 (esp women) and American Indian populations
- Most often used for pain, especially back pain
- **Dietary Supplement and Health Education Act (DSHEA) of 1994**
  - Evaluate vitamins, herals, etc more like food rather than medication → products can’t be on same shelf as OTC drugs
  - Grandfathered in any supplement on market prior to 1994
- **White House Commission on CAM Policy (WHCCAMP)**
  - Need more research to increase knowledge about CAMs
  - Educate health care providers
- **Labeling**
  - Must state that product has not been approved by FDA and must say that it is not intended to diagnose, treat, cure or prevent disease
  - Structure/function label
- **Good Manufacturing Practices (GMPs):** more stringent regulation of records, quality, testing, production, etc
- **Independent Supplement Seals of Approval**
  - Good Manufacturer Practices, Consumer Labels, United States Pharmacopoeia (government), National Sanitation Foundation
- **Tips:** start low dose; use caution in pregnancy, elderly, children, serious disease or chronic disease
- Go to [www.naturaldatabase.com](http://www.naturaldatabase.com) for summary of supplement data
## Hypothalamus, Pituitary & Hormones

### Anterior Pituitary (Adenophysis)

<table>
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<tr>
<th>Hypothalamic Hormone</th>
<th>Receptor &amp; Signaling</th>
<th>Associated Anterior Pituitary Hormone &amp; Function</th>
<th>Clinical Correlates</th>
</tr>
</thead>
</table>
| TRH Thyrotropin Releasing Hormone | • Act on Thyrotrophs 
• Gq=Hydrolysis of membrane phosphotidylinositol | INCREASE TSH 
• Glycoprotein hormone 
• Important for metabolism/basal metabolic rate | • HYPER-TSH 
○ Thyroid hormone resistance 
○ Tumor (very rare)=thyrotropinoma (goiter, tremor, weight loss, heat intolerance, hair loss, diarrhea + mass effects) 
○ Diagnose: elevated free T4 and non-suppressed TSH; pituitary MRI |
|                      |                      | INCREASE Prolactin 
• Polypeptide hormone that promotes mammogenesis, lactogenesis and galactopoiesis 
• Estrogen potentiates mammogenesis; progesterone inhibits lactogenesis and galactopoiesis 
• Short half life (20-30 min) 
• Cytokine (JAK/STAT) Receptors | • HyperPRL: amenorrhea, decrease in libido, inhibition of GnRH 
○ Physiologic: pregnancy, suckling, sleep 
○ Pharmacologic: estrogens (OCPs), antipsychotics, antidepressants, antiinemics, opiates 
○ Pathology: pituitary stalk interruption, hypothyroidism, prolactinoma 
  ▪ Prolactinoma: most common functional pituitary adenoma (30-40%); more in females 10:1 and median age is 34 yrs 
  ○ Diagnose: Random high PRL level (usu >100-150 ng/mL with prolactinomas) and pituitary MRI |
|                      |                      | INCREASE LH 
• Glycoprotein hormone | • HypoPRL is rare, usu accompanied general decrease in pituitary function 
○ Failed lactation in females, nothing in men 
○ Diagnose: low basal PRL level |
| GnRH Gonadotropin Releasing Hormone | • Act on Gonadotrophs 
• Gq=Hydrolysis of membrane phosphotidylinositol | INCREASE FSH 
• Glycoprotein hormone | • HyperGonadotropin 
○ Hypergonadotrophic hypogonadism 
○ Gonadotrope adenomas: majority are silent but mass effects of tumor (HA, nerve palsies, vision loss) 
○ HYPOgonadotropin 
  ○ Hypogonadotropic hypogonadism: females may have oligo/amenorrhea, decreased libido, loss of bone mass, hot flashes 
  ○ Diagnose: low FSH/LH, pituitary MRI, IHC analysis of tissue |
| CRH Corticotropin Releasing Hormone | • Act on Corticotrophs 
• G-protein (Gs= increase cAMP) | INCREASE ACTH 
• Cleaved from POMC 
• Cortisol fxn: gluconeogenesis, breakdown fat and protein → most is bound to transcortin (10-15 % bound to albumine) → burst before waking and decreases thru day | • HYPOcortisol 
  ○ ACTH-dependent (~75%): corticotrope adenoma (Cushing’s dz) or Ectopic Cushing’s (ACTH/CRH tumors) 
  ○ ACTH-independent (~25%): adrenal adenoma, adrenal carcinoma, nodular hyperplasia 
○ HYPOcortisol 
  ○ Primary AI → will have high ACTH which stimulates melanocortin=darker skin 
  ○ Secondary i.e. from tumor resection for Cushing’s or opioids or pituitary dz but most commonly from high glucocorticoid steroid use 
  ○ Presents: fatigue, anorexia, nausea, weight loss, hypotension and hypoglycemia, orthostatic dizziness, altered mentation, scant axillary/pubic hair (DHEA-S dependent) |
| GHRH Growth Hormone Releasing Hormone | • Act on Somatotrophs 
• G-protein (Gs= increase cAMP) | INCREASE GH 
• Stimulated by: sleep, ghrelin/arginine, hypoglycemia 
• Inhibited by: obesity, FFAs, chronic glucocorticoids, hyperglycemia 
• Direct: Stimulates gluconeogenesis (diabetogenic), increase lipolysis, and increase protein synthesis/muscle mass 
• Indirect: GH (with insulin) releases IGF which is a powerful mitogen 
• Half life is ~20-45 min | • HyperGH: 
  ○ Excess before puberty= Gigantism 
  ○ Excess after puberty= Acromegaly 
○ HypoGH: 
  ○ Adult Growth Hormone Deficiency (GHD): 
    ○ Aside: functional hypoGH when GH is normal but GH receptors/IGF are not 
  ▪ Laron’s dwarfish (nl GH but bad receptors) 
  ▪ African pygmies (nl GH but abnl IGF) |
<table>
<thead>
<tr>
<th>Somatostatin/GIH</th>
<th>Decrease GH</th>
<th>Not discussed</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH Inhibiting Hormone</td>
<td>Act on Somatrophs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G-protein (Gi= decrease cAMP)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease TSH</td>
<td>Not discussed</td>
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<thead>
<tr>
<th>PIH (Dopamine) Prolactin Inhibiting Factor</th>
<th>Decrease Prolactin</th>
<th>Can be dysregulated in prolactin producing tumors; with D2 antipsychotics</th>
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<tbody>
<tr>
<td></td>
<td>Act on Lactotrophs</td>
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<tr>
<td></td>
<td>D2 Dopamine receptor (Gi= decrease cAMP)</td>
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### Posterior Pituitary (Neurophysis)

#### Hypothalamic Hormone Function & Signaling

<table>
<thead>
<tr>
<th>ADH Antidiuretic Hormone/Vasopressin</th>
<th>SIADH: inappropriate ADH release</th>
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</thead>
<tbody>
<tr>
<td>Secreted from magnocellular cells as prohormone in response to increase in plasma osmolarity or decrease in BP</td>
<td>Hallmark: inappropriately concentrated urine in setting of hypo-osmolality and hyponatremia</td>
</tr>
<tr>
<td>Acts on renal tubule/collection ducts to increase water resorption (increase aquaporins) and increase BP</td>
<td>One of the most frequent causes of hyponatremia (esp in hospitalized pts)</td>
</tr>
<tr>
<td>Two kinds of ADH Receptors</td>
<td>Presents with hyponatremia (&lt;135 leading to mental sx i.e. anorexia, N/V, HA, Sz, coma), hypotonic blood (osmolality &lt; 275 mOsm/kg), concentrated urine, (&gt;100 Osm); euvolemic status (no edema, JVD), exclusion of other causes of euvolemic hypoosmolality (hypothyroidism, hypocortisolism)</td>
</tr>
<tr>
<td>V1 (Gq= increase DAG, IP3; activate PLC) → vasopressive action</td>
<td>Treat underlying dz; can range from H2O restriction to V2 antagonists to hypertonic saline (severe hyponatremia)</td>
</tr>
<tr>
<td>V2 (Gs= increase cAMP) → regulates GFR in kidney</td>
<td>Diabetes Insipidus (low ADH or ADH insensitivity): hypotonic polyuria</td>
</tr>
<tr>
<td>Coiled bilingual cells</td>
<td>Hallmark is voluminous (&gt;40 ml/kg/d) dilute urine</td>
</tr>
<tr>
<td>Causes: Central DI, Nephrogenic DI, pregnancy, psychogenic polydipsia</td>
<td>Causes: Central DI, nephrogenic DI, congenital AVP mutation, inflammatory/infectious diz, trauma</td>
</tr>
<tr>
<td>Nephrogenic → pathology originating from the kidney (kidneys bad, won’t respond to dDAVP treatment)</td>
<td>Post-op DI: Triphasic response → DI-SIADH-DI</td>
</tr>
<tr>
<td>Can be congenital (X-linked recessive V2 receptor gene), from drugs (demiclocycline, lithium, amphotericin B), hypokalemia or hyper calcemia, infiltrative dz (sarcoid), or sickle cell</td>
<td>Phase 1: DI from axonal shock/decreased ADH release (1-5 d)</td>
</tr>
<tr>
<td>Neurogenic → pathology arising from nervous system (kidneys good, so will respond to dDAVP treatment)</td>
<td>Phase 2: SIADH from degenerating neurons/excessive AVP release (6-11)</td>
</tr>
<tr>
<td>Pituitary tumor, congenital AVP mutation, inflammatory/infectious diz, trauma</td>
<td>Phase 3: DI from depleted ADH stores and if &gt;80% AVP neuronal cell death</td>
</tr>
<tr>
<td>Permanent DI is uncommon complication with an experienced neurosurgeon</td>
<td>Isolated second phase (just SIADH after surgery) is common (~25%)</td>
</tr>
<tr>
<td>Can lead to dehydration if no water access or impaired thirst response</td>
<td>Can respond to ADH replacement (dDAVP)</td>
</tr>
<tr>
<td>Diagnose: polyuria with 24 hr urine (normalized creatinine); assess urine and plasma osmolality, can do water deprivation test, pituitary imaging</td>
<td>Excessive sedation, renal insufficiency, and other electrolyte disturbances</td>
</tr>
<tr>
<td>Exclude hyperglycemia, renal insufficiency, and other electrolyte disturbances</td>
<td>Water deprivation test: fluid restrict to stimulate ADH release → then measure Uosm, Posm, serum Na, and urine output</td>
</tr>
<tr>
<td>After dDAVP, neurogenic DI will resolve but not nephrogenic</td>
<td>Treatment: first line is dDAVP (nasal, oral, parenteral; longer half life than ADH and no vasopressor effect); second line is (IV or IM ADH/vasopressin)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Oxytocin</th>
<th>Not discussed</th>
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</thead>
<tbody>
<tr>
<td>Secreted from magnocellular cells as prohormone during childbirth</td>
<td></td>
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<tr>
<td>During sexual intercourse</td>
<td></td>
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<tr>
<td>In response to suckling by infant during breastfeeding</td>
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Oxytocin
### Hormones Classified by TYPE

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptides</td>
<td>Oxytocin, ADH, Angiotensin, TRH, GRH AND Proteins</td>
</tr>
<tr>
<td>Insulin, Glucagon, GH, ACTH, Prolactin, TSH</td>
<td></td>
</tr>
</tbody>
</table>

### Hormones Classified by FUNCTION

<table>
<thead>
<tr>
<th>Function</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water/Mineral Metabolism</td>
<td>Vit. D, Aldosterone, ADH</td>
</tr>
<tr>
<td>Regulation of Energy Metabolism</td>
<td>Insulin, Glucagon, Cortisol</td>
</tr>
<tr>
<td>Regulation of Reproduction</td>
<td>Estrogen, Testosterone, Progesterone</td>
</tr>
<tr>
<td>Regulation of Growth</td>
<td>GH, Testosterone, Estrogen</td>
</tr>
</tbody>
</table>

### Measuring Hormone Levels
- **1) Bioassays** (using exogenous systems i.e. cell lines to measure activity; measures functional capacity of hormone but is time/resource intensive)
- **2) Immunooassays** (i.e. Radioimmunoassay and ELISA measure antibody binding to hormone; measures absolute level of hormone and is cheaper/faster)
- **Hormone deficiency is assessed by a stimulation test**
- **Hormone excess is assessed by a suppression test**
- **Note:** for steroid hormones, where the majority of hormone is bound/inactive, you may measure the precursor hormone (i.e. measuring TSH when determining levels of thyroxin) AND target gland hormones (i.e. T4, T3) to get a better idea of hormone levels

### Types of disorders
- **Primary** or **Peripheral** (defect in target organ) vs **Central** (secondary=pituitary, tertiary=hypothalamus defect)

### Anterior Pituitary (adenohysis)
- Derived from Rathke’s pouch; includes pars tuberalis, pars intermedia, and pars distalis
- Secretion: Hypothalamus secretes hormones into median eminence → hormones travel through portal system to anterior pituitary → allows for 1) easy access to hypothalamic hormones because outside of blood-brain barrier and 2) hormones arrives relatively undiluted
- If lose ant pit (panhypopit): GH lost first, then LH/FSH, ACTH, TSH, PRL

### Posterior Pituitary
- Derived from neural tissue from evagination of the diencephalon; consists of median eminence, infundibulum, and pars nervosa
- Posterior pituitary hormones are synthesized in supraoptic nucleus and paraventricular nucleus, which have 2 cell types (magnocellular, which terminate in pars nervosa and parvocellular, which end in median eminence and influence anterior pituitary secretion)

### HYPOpituitarism (deficiency of 1+ hormones)
- Some are genetic but majority (75%) are acquired lesion and/or treatments (i.e. tumors, brain damage, apoplexy)
- For anterior pituitary: first lose GH lost first, then LH/FSH, ACTH, TSH, PRL → treat with end organ hormone replacement (i.e. levothyroxine for TSH; except PRL, no good formulation)
- For tumors that metastasize to the pituitary, ADH-deficiency is common finding
- Apoplexy: syndrome of headache, vision changes, ophthalmoplegia and altered mental status caused by sudden hemorrhage or infarction of pituitary gland
  - Occurs in 10-15% of pituitary adenomas; subclinical disease is more common
  - Diagnose with pituitary MRI or CT
  - Treatment: emergent surgery; stress dose steroids for suspected adrenal insufficiency

### Regulation of Hormone Levels

<table>
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<tr>
<th>Regulation</th>
<th>Example</th>
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<tr>
<td><strong>Diurnal/circadian pattern</strong></td>
<td>Provides regulation by controlling timing and peaks of pulses</td>
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<tr>
<td><strong>Pulsatile</strong></td>
<td>Hormonal effect can also be regulated by altering expression of hormone receptors (i.e. downregulating hormone receptor if the hormone is chronically high)</td>
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</tbody>
</table>

### Notes
- **Dopamine and Epi** are secreted similarly to peptides and proteins (see below)
- **Note:** Dopa and Epi are secreted similarly to peptides and proteins (see below)
- **Steroid (cholesterol) derivatives:** Testosterone, Cortisol, Estrogens, Aldosterone, Vit. D, Progesterone
  - **Production:** Steroids (lipophilic=membrane permeant) are not stored in cell, but immediately released into blood → bound to carrier protein in bloodstream with ~1-5% existing in free/active form → thus the half lives are much longer (hrs-days)
  - **Signaling:** Steroid receptors are nuclear → once the steroid binds the receptor, the complex binds hormone responsive elements (HRE) and activates transcription of specific genes
- **Peptides**
  - **Production:** pre-prohormone is synthesized on ribosomes (rough ER) → cleaved to prohormone and targeted to Golgi for packaging into vesicles → cell secretes hormone via Ca-dependent exocytosis → hormone travels as free hormone (except GH, prolactin, insulin-like growth factor) in bloodstream → half life of hormone dependent on proteases in the blood
  - **Signaling:** depending on the hormone, there is a change in 2nd messengers which can have immediate (i.e. increase Ca, exocytosis, channel opening, etc) and long term effects (gene regulation)
    - **G-protein receptors:** Gi (decrease cAMP), Gi (decrease cAMP), and Gq (increase DAG and IP3; activate PLC)
    - **Cytokine (JAK/STAT) receptors:** activation of JAK tyrosine kinase, which phosphorylates STAT transcription factors → GH and Prolactin
    - **EGF Family (Tyrosine Kinase) receptors:** binding of hormone cause autophosphorylation and activation of receptor → Insulin, IGF-1

### Treatment of disorders
- **Incidence**
  - 15% of pituitary adenomas; subclinical disease is more common
- **Apoplexy**
  - Syndrome of headache, vision changes, ophthalmoplegia and altered mental status caused by sudden hemorrhage or infarction of pituitary gland
  - Occurs in 10-15% of pituitary adenomas; subclinical disease is more common
  - Diagnose with pituitary MRI or CT
  - Treatment: emergent surgery; stress dose steroids for suspected adrenal insufficiency
# Growth Hormone

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<th>Concept</th>
<th>Information &amp; Description</th>
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| **GH Function and Regulation** | • Polypeptide hormone that is fundamental for postnatal growth  
  • Can be alternatively spliced, the 191 aa chain is most important  
  • Half life is ~20-45 min  
  • **Stimulated by:** sleep, ghrelin/arginine, hypoglycemia  
  • **Inhibited by:** obesity, FFAs, chronic glucocorticoids, hyperglycemia  
  • **Direct effects:** Counter-regulatory hormone that stimulates gluconeogenesis (diabetogenic), increase lipolysis (increase hormone sensitive lipase=inc FFA), and increase protein synthesis/muscle mass  
  • **Indirect effects:** GH (when combined with insulin) releases Insulin-like Growth Factor (IGF) which is a powerful mitogen=promotes growth  
  • Increases long bone growth, muscle mass, and fat storage (inhibit lipolysis) → this insulin-like action antagonizes that of GH  
  • IGF-I is made in liver and increases slowly from birth to puberty  
  • Acts at EGF Family (tyrosine kinase) of receptors → initiates IRS I & II binding → MAP kinase or PI3 kinase pathways (recall how this resembles insulin signaling)  
  • Note that GH has to be accompanied by high insulin so that there is enough energy to promote growth (i.e. growth will NOT happen in fasting state when GH is high and insulin is low) |
| **Measurement** | • Difficult to accurately interpret direct GH levels (normally fluctuates quite a bit)  
  • Measure GH secretion by exercise or high doses of arginine or clonidine (but take several measurement throughout the day, since the levels fluctuate)  
  • Can also measure IGF as proxy |
| **HYPER-GH** | • Excess before puberty=**Gigantism**, diabetes, cardiac hypertrophy (lifespan ~20 yrs) and inhibition of GnRH  
  • Excess after puberty=**Acromegaly**  
  • 3-4/million; middle aged onset (~44 yrs) but delayed diagnosis (8 yrs)  
  • Diagnose with elevated IGF-I (make sure that levels are compared to age/gender match since these change over lifetime); may also do OGTT or GH levels  
  • MRI since majority of cases due to pituitary adenoma (and 80% of those are MACROadenomas) → 95% assoc with benign pituitary adenoma  
  • Clinical signs: interdental teeth spacing, skin tags, bigger hands/feet, sweating, headaches, joint pain  
  • CV complications: HTN, valve disease, arrhythmias, cardiac hypertrophy (not as much as in gigantism)  
  • Diabetes  
  • 2-3 fold increased mortality  
  • Dopamine agonists (i.e. bromocriptine) can decrease GH in acromegaly |
| **HYPO-GH** | • Adult Growth Hormone Deficiency (GHD):  
  • Increased fat, decreased muscle mass/bone strength, increased cholesterol, inc CRP, impaired energy and mood → actual medical treatment is relatively uncommon  
  • Diagnose: with insulin induced hypoglycemia but CONTRAINDICTED in elderly, sz, CAD → second best test is GHRH-ARGinine but no longer used in US → Now use arginine and glucagon stimulation tests  
  • If the setting of multiple pituitary def, a low IGF-1 level is diagnostic  
  • **Aside: Functional GH deficiency, where GH is normal but GH receptor/IGF-1 is not**  
  • Laron’s dwarfism (normal GH but bad receptors)  
  • African pygmies (nl GH but abnl IGF)  
  • Many other syndromes (i.e. Turners, Prader Willi, etc) associated with GH deficiency |
| **Treatment** | • Can now use recombinant GH therapeutically, but very expensive (many approved uses i.e. in Prader-Willi, Turner’s etc, but still controversial for idiopathic short stature and other conditions)  
  • Beware of OTC or GH supplements found in stores → many are fraudulent and highly abused (also note that any advertised oral GH is not effective) |
## Pituitary Imaging & Pathology

<table>
<thead>
<tr>
<th>Concept</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Basics of MRI</strong></td>
<td>- MRI images three properties of protons in magnetic fields</td>
</tr>
<tr>
<td></td>
<td>o Proton density</td>
</tr>
<tr>
<td></td>
<td>o T1 relaxation rate: tendency to align with magnetic field</td>
</tr>
<tr>
<td></td>
<td>o T2 relaxation rate: loss of magnetization</td>
</tr>
<tr>
<td></td>
<td>- No ionizing radiation → electromagnetic fields in radiofrequency range</td>
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<tr>
<td></td>
<td>- Contrast agent detects “leaky capillaries” → i.e. can indicate angiogenesis in a tumor</td>
</tr>
<tr>
<td></td>
<td>- Can be obtained in any plane</td>
</tr>
<tr>
<td></td>
<td>- MRI is standard (CT only if there is an MRI contraindication) for pituitary imaging</td>
</tr>
<tr>
<td><strong>Pituitary study</strong></td>
<td>- High Res sagittal and coronal pre and post contrast T1 images</td>
</tr>
<tr>
<td></td>
<td>- High Res coronal T2 images</td>
</tr>
<tr>
<td></td>
<td>- First time studies usually include whole brain for associate or incidental pathology</td>
</tr>
<tr>
<td><strong>Highlights of NORMAL Anatomy</strong></td>
<td>1. Anterior Pituitary Gland: Enhances (no BBB), Low T2</td>
</tr>
<tr>
<td></td>
<td>- Secretes: Prolactin, GH, ACTH, LH, FSH, TSH</td>
</tr>
<tr>
<td></td>
<td>2. Intermediate (Septum) Usually slightly brighter on T2</td>
</tr>
<tr>
<td></td>
<td>3. Posterior Pituitary Gland (sometimes bright on T1, does not fat saturate)</td>
</tr>
<tr>
<td></td>
<td>- Secretes: Oxytocin, Vasopressin</td>
</tr>
</tbody>
</table>

### PATHOLOGY Key Points

- Pituitary adenomas are most common pathology → Adenomas recapitulate embryonic lineage i.e. Corticotroph neoplasms secrete ACTH
  - GnRH (non-secreting) and prolactinomas are most common
- Less than 5% are familial, the majority are sporadic (put another way, end organ failure or hyperplasia does NOT cause adenomas)
  - Four genes associated with familial: MEN1, CDKN1B, PRKAR1A, AIP → also in familial, will have other tumors and early onset
- Clinical Presentation: (usually middle-aged adults, but can occur at any age)
  - Hormone hypersecretion: acromegaly, Cushing’s, amenorrhea, galactorrea
  - Mass effect: headache, vision loss → bilateral temporal hemianopsia is classic visual deficit due to mass effect at optic chiasm, nerve palsies, pituitary hormone dysfunction
- ALMOST ALL ARE WHO GRADE I (staging is done by radiologists, not pathologists)
- Almost never get posterior pituitary dysfunction i.e. do NOT cause diabetes insipidus
- Reticulin stain is single most informative histochemical stain for adenomas and distinguishes tumor from normal tissue
- Size is not correlated with outcome → nuclear pleomorphism is uncommon in pituitary adenomas but have no prognostic significance → mitoses are rare in MICROadenomas, occasional in MACROadenomas
  - MICROadenoma (<1 cm)
  - MACROadenoma (>1 cm)
  - Giant macroadenoma (>4 cm)
- Many of the larger tumors are non-secreting i.e. patients don’t have any hypersecretion systemic symptoms, which allows the tumor to grow until patient feels symptoms of mass effect
**Pituitary apoplexy**
- Due to fact that these tumors are highly vascularized → vascular complications
- Apoplexy= “stroke like”
- Syndrome of headache, vision changes, ophthalmoplegia and altered mental status caused by sudden hemorrhage or infarction of pituitary gland
- Occurs in 10-15% of pituitary adenomas; subclinical disease is more common
- Diagnose with pituitary MRI or CT
- Treatment: emergent surgery; stress dose steroids for suspected adrenal insufficiency

### Treatment

**Goals**
- Control growth and mass effects
- Preserve pituitary function
- Prevent recurrence
- Control hormone hypersecretion especially GH because of cardio issues

**Surgery (first line) is well-tolerated**
- Types of surgery: transnasal microscopic approach, transnasal endoscopic approach (more invasive, but have a wider view)
- Most common surgically resected tumors are 1) non-secretors (Gonadotropin) 2) GH tumors, and 3) ACTH tumors → recall that GnRH and prolactinomas are most common overall but prolactinomas DO NOT undergo surgery (just DA medication therapy)
  - 1. Non-secretors (Gonadotroph cell tumor) → present with mass effects and make FSH/LH → >80% are MACROadenomas and can be resolved with surgery alone
  - 2. ACTH tumors: majority are MICROadenomas and can have devastating effects despite being small → Cushing’s
    - This is a basophilic tumor; will require inferior petrosal sampling
    - Aside: can have ACTH hyperplasia (rare) usually due to ectopic CRF secretion
  - 3. GH tumors: >80% are MACROadenomas
    - If not 100% resected, can have some hyperGH → still have symptoms and affects lifespan
    - Goal is to get <1 ng of GH, where lifespan will resemble controls
    - Treat with somatostatin after surgery if still have hypersecretion after surgery
    - There are subtypes of GH adenomas (sparsely granulated) that are not as somatostatin responsive

**Risks**
- Infection risk is 1-2%! Usually chronic sinusits, occasionally meningitis
- Post-op spinal fluid leakage is 1% (require placement of spinal drain with increased hospital stay)
- Diabetes insipidus → treat with DDAVP
- Injury to optic nerves, carotid artery, normal pituitary gland

**After surgery**
- MRI
- Check hormone levels (make sure not deficient)
- During hospitalization, may develop triphasic post-op response DI-SIADH-DI (DI=dehydration, hyponatremia; SIADH=hyponatremia)

**Medications:**
- Prolactinomas → use dopamine agonists instead of surgery, have to use medication lifelong → very common incidental finding on autopsy → size correlates with serum PRL
- GH secreting tumors → use somatostatin to mediate any residual hyperGH
- Radiation (if can’t undergo surgery); not used as much anymore
- Can develop hypopituitarism years after radiation

**Aside: because there are so many structures intersecting in sellar region there are many other things that can occur (see below) but the majority (85%) are pituitary adenomas**
- Hyperplasia: enlarged pituitary
- Rathke Cleft Cyst → causes a bright T1 signal (derived from pars intermedia, one cyst, can undergo squamous metaplasia but rarely becomes a neoplasm)
- Lymphocytic hypophysitis (classically in young women during late pregnancy/early postpartum; autoimmune disorder; looks like adenoma on imaging, can only be distinguished on biopsy)
- Craniopharyngioma (rim calcifications) → WHO Grade I, usu in kids, difficult to remove surgically; has cystic and solid nature
  - Adenomatous (usu kids)
  - Papillary (usu adults)
- Meningioma (dural based mass)
- Infiltrative Germinoma
- Clivus cordoma
- While not a mass in the sellar region, a syndrome affecting the pituitary Sheehan’s syndrome: ischemic necrosis due to blood loss and hypovolemic shock during and after childbirth
<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug Class</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>Uses</th>
<th>Side Effects/Adverse</th>
</tr>
</thead>
</table>
| **Growth Hormone Deficiency** | Recombinant GH Somatropin | Recombinant peptide that confers same action as physiologic IGF-1 (promote growth) | Half-life: 25 min, peak 2-4 hrs, lasts 36 hrs IM | Replacement therapy in deficient children  
                               |                          | 119 aa peptide that confers same action as physiologic GH (promoting growth, stimulating IGF) |                      | Daily SC or 3x/wk IM  
                               |                          |                              |                      | Controversial in kids with idiopathic short stature  
                               |                          |                              |                      | Poor growth from Turner’s, Prader-Willi, renal insufficiency  
                               |                          |                              |                      | GH deficiency in adults  
                               |                          |                              |                      | Wasting or cachexia in AIDS patients  
                               |                          |                              |                      | Patients on TPN  
                               |                          |                              |                      | I illicit/not recommended use in sports and “anti aging”  
                                                                                   |                      | benefits outweighed by increased risk of adverse events |                                      |
| **Nephrogenic Diabetes Insipidus** | Recombinant IGF-1 Mecasermin | Recombinant peptide that confers same action as physiologic IGF-1 (promote growth) | Not discussed | Give if growth hormone insensitive (i.e. mutation in GH receptor like Laron dwarfism) | Take with carb to avoid hypoglycemia |
| **Growth Hormone Excess**     | Somatostatin Analogs     | Inhibit GH release via Gi protein receptor (decrease cAMP)  
                               |                          | Octreotide: half-life of 90 min, lasts 12 hrs, admin SC every 6-12 hrs or IM every month  
                               |                          | Lanreotide: SC every month | Octreotide: oral  
                               |                          | Also has effects on GI (decrease motility), reducing insulin/glucagon, and interfering with TRH |                      | For acromegaly and gigantism; long acting analog is preferred  
                               |                          |                              |                      | Medication follows surgical resection in cases of GH excess due to pituitary adenoma  
                               |                          |                              |                      | Other uses: octreotide is used to control of bleeding from esophageal varices (liver disease) and GI hemorrhage |                                  |
|                             | Dopamine Agonist Antagonist | Binds D2 receptors, which somewhat inhibits GH secretion | Oral | Second line (Cabergoline is preferred) – not as effective for GH, but has advantage of oral admin |                                                |
|                             | Cabergoline Bromocriptine | Mutated GH molecule made to extend half life and competitively inhibit GH receptor | 1 SC dose/day | Cabergoline is preferred agent (more effective/selective for D2, less side effects) |                                                |
|                             | Pegvisomant               |                              | Second line |                                                      |                                                |
| **Hyperprolactinemia**       | Dopamine Agonists         | Binds D2 receptors, which inhibits PRL secretion and reduces prolactinoma size | Oral | Cabergoline is preferred agent (more effective/selective for D2, less side effects) |                                                |
|                             | Cabergoline Bromocriptine |                              |                      |                                                      |                                                |
| **Central Diabetes Insipidus** | ADH Analog Desmopressin (DDAVP) | ADH analog that has vasoconstrictive (V1=Gq receptor) and antidiuretic (V2=Gs receptor) | Nasal: 1-2/day  
                               |                          |                              | Oral: 2-3/day  
                               |                          |                              | Half-life: ~2 hrs | Inadequate ADH secretion (Central DI)  
                               |                          |                              |                      | Drugs inducing Diabetes Insipidus: Lithium, demeclocycline  
                               |                          |                              |                      | Other: IV desmopressin also used in nocturnal enuresis, von Willebrand’s, and hemophilia  
                                                                                   |                      |                                                      |                                                |
|                             | Chlorpropamide           | 1st gen sulfonylurea that potentiates ADH action | Not discussed | For pts that are DDAVP intolerant | Hypoglycemia |
| **Diabetes Insipidus Drugs-Induced** | Thiazide Diuretics Hydrochlorothiazide | Paradoxically reduces polyuria – not completely understood buy antidiuretic effects parallels ability to cause natriuresis | Not discussed | Inadequate ADH action (Nephrogenic DI)  
                               |                          |                              |                      | Thiazides and indomethacin used as combo therapy | Not discussed |
|                             | NSAIDS Indomethacin      | Inhibit PG synthesis (PGs reduce ADH acvity) | Not discussed |                                                      |                                                |
| **SIADH**                    | V2 Receptor Antagonists  | Inhibits V2 receptor, thus inhibiting the antidiuretic effects of ADH | Tolvaptan: oral, expensive  
                               | Tolvaptan, Conivaptan |                          | Convivaptan: IV  
                               |                          |                          | Both are CYP3A4 metabolized | Incomplete suppression of ADH under hypoosmolar conditions (from many causes i.e. tumors, pulm dz, CNS trauma, infection)  
                               |                          |                          |                      | hyponatremia  
                               |                          |                          |                      | Drugs inducing SIADH: SSRIs, haloperidol, TCAs | Rapid correction of hyponatremia can lead to cerebellar pontine myelinolysis  
                               |                          |                          |                      | CYP3A4 interactions |
Adrenals

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Description &amp; Function</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids</strong>&lt;br&gt;Cortisol</td>
<td>▪ Important for stress response → glucose mobilization  &lt;br&gt;  ▪ Increases gluconeogenesis (counters insulin)  &lt;br&gt;  ▪ Increases proteolysis in muscle to provide aa for gluconeogenesis  &lt;br&gt;  ▪ Net increase in lipolysis → increased FFAs  &lt;br&gt;  ▪ Varies with time of day (surge of cortisol around time of waking)  &lt;br&gt;  ▪ 90% is protein bound (75% to CBG, 15% to albumin) and 10% is free  &lt;br&gt;  ▪ Half-life is 60-70 minutes; metabolized in liver to water soluble form for excretion  &lt;br&gt;  ▪ Regulation (HPA axis)  &lt;br&gt; ▪ CRH (hypothalamic) → ACTH (pituitary) → cortisol (adrenals)  &lt;br&gt; ▪ 1. CRH binds Gs-protein receptor = increase cAMP → release of ACTH in Ca-dependent manner (POMC transcription is also activated)  &lt;br&gt; ▪ 2. ACTH binds Gs-protein receptors in zona fasciculata → increase cAMP → increases cortisol secretion AND increases proliferation and biosynthetic enzymes in all zones AND increases pregnenolone secretion AND increases LDL uptake (increases cholesterol for hormone synthesis)  &lt;br&gt; ▪ 3. Plasma cortisol feeds back to inhibit CRH and ACTH (cortisol is primary regulator of ACTH) → the negative feedback can be overridden by the effects of chronic stress</td>
<td>▪ When GCs are chronically high (high catabolism)  &lt;br&gt; ▪ Prolonged proteolysis → muscle weakness is hallmark  &lt;br&gt; ▪ Thinning of skin, easy bruising → cortisol decreases fibroblasts=decreased collagen  &lt;br&gt; ▪ Osteoporosis (cortisol opposes Vit. D and decreases calcium absorption)  &lt;br&gt; ▪ Centriportal adipose deposition to trunk, face (“moon facies”), “buffalo hump”  &lt;br&gt; ▪ Polycythemia (cortisol promotes RBC production)  &lt;br&gt; ▪ Increases heart rate, increases ejection fraction  &lt;br&gt; ▪ Permissive effects (potentiates effects of other hormones): Paracrine effect on medulla → stimulate PNMT increasing the production of epi to norepi  &lt;br&gt; ▪ Anti-inflammatory: cortisol inhibits Phospholipase A2, which is needed for LT/PG formation from arachidonic acid → can use as anti-inflammatory but not if there are wounds or active injuries; recommended for short term  &lt;br&gt; ▪ Decreased immune function (cortisol decreases T-cell function and proliferation)  &lt;br&gt; ▪ Amenorrhea/hirsutism in women</td>
</tr>
<tr>
<td><strong>Mineralcorticoid</strong>&lt;br&gt;Aldosterone</td>
<td>▪ Maintaining salt balance (absorb Na, secrete K+ and H+)  &lt;br&gt; ▪ Half-life is ~20 minutes; metabolized in liver to a more water soluble form that can be excreted  &lt;br&gt; ▪ Regulated by the renin-angiotensin system  &lt;br&gt; ▪ Renin is secreted by JGA of kidney in response to low Na or low volume → converts Angiotensin I to Ang II, which stimulates aldosterone secretion and is a pressor</td>
<td></td>
</tr>
<tr>
<td><strong>Sex Steroids</strong>&lt;br&gt;DHEA&lt;br&gt;DHEA-S</td>
<td>▪ Vary with cortisol secretion → stimulated by ACTH  &lt;br&gt; ▪ Large increase in adrenal androgens at puberty  &lt;br&gt; ▪ Adrenal androgens are less potent in males (because majority of androgens are coming from gonads) but are the primary source for females</td>
<td></td>
</tr>
<tr>
<td><strong>Layers of adrenals</strong> (adrenals are located at the upper poles of the kidney)</td>
<td>▪ Zona Glomerulosa (outer) → aldosterone  &lt;br&gt; ▪ Zona Fasciculata → cortisol  &lt;br&gt; ▪ Zona Reticularis → sex steroids  &lt;br&gt; ▪ Medulla (inside; neural crest in origin) → catecholamines (especially epinephrine) from chromaffin cells  &lt;br&gt; ▪ Rate limiting step is tyrosine hydroxylase (tyrosine to DOPA)  &lt;br&gt; ▪ Splanchnic nerve (preganglionic sympathetic) releases ACh, which stimulates epi release → increase glycoegenolysis and gluconeogenesis and lipolysis  &lt;br&gt; ▪ Aside: ACh binds nicotinic (ligand-gated cation channel → fast) and muscarinic (Gq-protein → a little slower, but still fast) receptors  &lt;br&gt; ▪ Epi (and norepi) bind alpha and beta-adrenergic receptors  &lt;br&gt; ▪ Beta receptors are Gs-protein (increase CAMP)  &lt;br&gt; ▪ Alpha 1 receptors are Gq (activate PLC) and alpha 2 are Gi (decrease CAMP)  &lt;br&gt; ▪ In fetus, the adrenals are proportionally bigger and there is an additional fetal zone that is important source of estrogen synthesis (this zone disappears after birth)</td>
<td>▪ All the hormones secreted from adrenal are derived from cholesterol; the precursor is pregnenalone (from cholesterol via 20,22 desmolase) which goes to 17-prenenolone, which can go to DEA  &lt;br&gt; ▪ Pregnenalone → aldosterone (requires 21-hydroxylase, a mutation in which is a common congenital defect)  &lt;br&gt; ▪ 17-prenenolone → cortisol (requires 21-hydroxylase, a mutation in which is a common congenital defect)  &lt;br&gt; ▪ DEA → sex steroids  &lt;br&gt; ▪ Specific enzymes are in each zone of adrenals → drives production of specific hormones in each zone</td>
</tr>
</tbody>
</table>

**Fetal zone**: important source of estrogen synthesis, disappears after birth.
# Adrenal Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>General Info</th>
<th>Clinical Presentation</th>
<th>Diagnostics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenal Insufficiency</strong></td>
<td>PRIMARY AI</td>
<td>• Can be autoimmune (70-80% i.e. Addison’s), infectious (TB, 10-20%), hemorrhage, infiltrative (sarcoïd, amyloidosis), tumor, post-op, metabolic</td>
<td>• Vitiligo, pigmentation (primary only) because high ACTH will act on melanocortin receptors to darken skin</td>
<td>Serum cortisol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• &lt; 3 ug/dl baseline</td>
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<td></td>
<td></td>
<td></td>
<td>• &lt; 20 ug/dl after 250 ug Cosyntropin</td>
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<td></td>
<td></td>
<td></td>
<td>• &lt; 18 ug/dl baseline after 1 ug Cosyntropin</td>
</tr>
<tr>
<td></td>
<td>SECONDARY AI (Pituitary or Hypothalamic defect)</td>
<td>• Defect in CRH release from hypothalamus OR defect in ACTH release from pituitary. In addition to the same causes of primary AI, secondary AI can also be caused by GC’s (supraphysiologic doses for &gt; 3 wks), opioids, post-op surgery for Cushing’s Disease</td>
<td>• Fatigue, weakness, myalgias, anorexia, salt craving, dizziness, abd pain, etc.</td>
<td>Serum cortisol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• &lt; 3 ug/dl baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• &lt; 20 ug/dl after 250 ug Cosyntropin</td>
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<td></td>
<td></td>
<td>• Cosyntropin Stimulation Test is more accurate if AI &gt; 3 wks</td>
</tr>
<tr>
<td><strong>Primary Aldosteronism (Conn Syndrome)</strong></td>
<td>Normally, aldo is responsible for salt balance</td>
<td>• Who to screen: HTN patients with o Spontaneous or diuretic induced hypokalemia o Severe HTN (&gt;160/100) o Resistant HTN (&gt;2 drugs) o HTN onset before 20 yrs o Adrenal Incidentaloma o APA more likely in &lt; 40 yrs</td>
<td>• Hypokalemia, hypercalcaemia</td>
<td>Screening Test: Morning blood sample</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Plasma Aldo/Plasma Renin Activity (PA/PRA) &gt;20 (high aldol, low renin) and PA &gt; 15 ng/dl</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Medication restriction: Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Abnormal HTN is from primary aldosteronism</td>
<td>Clinically characterized by difficult to control HTN and hypokalemia</td>
<td></td>
<td>Confirmationary Test</td>
</tr>
<tr>
<td></td>
<td>Two main types from lecture</td>
<td>• Oral Salt Loading/High Na diet: After 3 days, the 24 hr urine aldosterone &gt; 12 ug</td>
<td>• Oral: Aldosteronism (Spironolactone, Eplerenone) PLUS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Aldosterone Producing Adenoma (APA) accounts for 34% (adenomas are most common incidental finding) o Idiopathic hyperaldosteronism (IHA) accounts for 60% Statistics from small group</td>
<td>• IV Saline Infusion: PA &gt; 10 ng/dl</td>
<td>• HTN Meds (Thiazides, CCBs, ACEIs, ARBs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Causes of primary hyperaldosteronism (Conn’s)</td>
<td>• Medication restriction: Spironolactone Imaging:</td>
<td></td>
<td>Medical management ONLY for IHA</td>
</tr>
<tr>
<td></td>
<td>o 70% are bilateral hyperplasia o 25% are adrenomas o 5% are carcinoma, GC remedial</td>
<td>• CT is best</td>
<td>• Aldo Antagonists (Spironolactone, Eplerenone) PLUS</td>
<td></td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td>Tumor causing hypercatecholamine secretion</td>
<td></td>
<td></td>
<td>Surgery option for APAs</td>
</tr>
<tr>
<td></td>
<td>Accounts for &lt;1% of HTN ➔ risk of HTN crises</td>
<td>• Who to screen: HTN patients with o Triad (HA/spell, sweating, palpitations), o Severe HTN (&gt;160/100) o Resistant HTN (&gt;2 drugs) o Familial syndrome</td>
<td>• Plasma Metanephrines &gt; .5 nmol/L</td>
<td>• Pre-op: Aldo Antagonist (Spironolactone, Eplerenone)</td>
</tr>
<tr>
<td></td>
<td>Rules of 10:</td>
<td>May get additional symptoms if extra-adrenal (i.e. in bladder, will have urinary symptoms) and up to 2% may be extra-abdominal</td>
<td>• Urine Normetanephrines &gt; 200 ug/dl</td>
<td>• Then give: Beta-blockers</td>
</tr>
<tr>
<td></td>
<td>o 10% are malignant o 10% are familial o 10% are bilateral o 10% in kids o 10% calcium o 10% are extra-adrenal Familial Syndromes (genetic testing for all):</td>
<td></td>
<td>• Best for High RiskPts (i.e. family hx, mass): plasma metanephrines</td>
<td>• OR give calcium channel blockers (alone)</td>
</tr>
<tr>
<td></td>
<td>MEN Type 2A/2B (Ret receptor)</td>
<td></td>
<td>False positives: levodopa, ETOH, TCADs, acetaminophen, physical stress, renal failure</td>
<td>Surgery (adrenalectomy)</td>
</tr>
<tr>
<td></td>
<td>Von-Hippel Lindau, Neurofibromatosis Type 1</td>
<td></td>
<td>Imaging</td>
<td></td>
</tr>
</tbody>
</table>
Cushing's Syndrome

HYPERcortisolism = Cushing’s SYNDROME

- **Endogenous**
  - Most (75-80%) are pituitary origin=Cushing’s DISEASE i.e. from ACTH adenoma or ectopic cortisol/ACTH tumors (high cortisol, high ACTH, normal aldosterone)
  - Adrenal origin (20-25%) i.e. adrenal adenoma, adrenal carcinoma, nodular hyperplasia (high cortisol, low ACTH, high aldosterone)
  - Note that other lectures/small group state 80% of endogenous causes are pituitary tumors, 10% are ectopic adenomas and that 10% (not 20-25%) are adrenal in origin
  - Exogenous origin (steroid therapy): high cortisol, low ACTH, normal aldosterone

  - Synthetic GCs: dexamethasone (most potent), prednisone, hydrocortisone, triamcinolone

- **Exogenous**
  - Fatigue, weakness, HA, easy bruising, facial plethora, “moon facies,” striae, “buffalo hump,” central obesity, thin skin, hirsutism, proximal muscle weakness, irregular menses
  - Conditions with high cortisol that are not Cushing’s: pregnancy, depression, alcoholism, severe obesity, poorly controlled DM

- Screening Tests
  - High 24 hr urine cortisol
  - High bedtime salivary cortisol
  - Cortisol >1.8 ug/dl with 1 mg Dexamethasone suppression test
  - Use high dose 8 mg Dexamethasone to distinguish between pituitary (will suppress) and ectopic (won’t suppress) adenomas

- Confirmatory differential: check plasma ACTH
  - Low ACTH= adrenal tumor
  - Normal/high ACTH=pituitary tumor
  - High/very high=ectopic ACTH (may cross react with mineralocorticoid receptor=hypokalemia)

- Imaging: pituitary MRI, chest CT, abdominal CT
  - Inferior petrosal sinus sampling (can determine the laterality of the pituitary tumor)

- CRF Stimulation Test will increase cortisol in pituitary adenoma but not in ectopic or adrenal tumor

- High DHEA-S suggests pituitary tumor, whereas low/nl DHEA-S suggests adrenal tumor

- Surgery to remove tumor
  - Cortisol synthesis inhibitors
  - Cortisol receptor blockers

Adrenal Incidentaloma

- Frequent finding on abdominal imaging (5-15%)
  - Usually benign, usually > 6 cm
  - Causes: adrenal adenoma, carcinoma, metastases, pheochromocytoma, myelolipoma, nodular adrenal hyperplasia

- Determine cancer risk: measure size and assess growth over time
  - Determine if hormonally active
    - Cortisol: Dexamethasone suppression
    - Aldosterone: plasma ald and renin
    - Androgens: testosterone & DHEA-S
    - Catechols: plasma metanephrines

- Imaging:
  - CT: Hounsfield Units (represents lipid composition)
    - High HU= benign
    - Low HU= malignant
  - MRI
  - FDG-PET (FDG uptake proportional to malignancy potential)

- Surgery if
  - >4.5 cm
  - progressive growth
  - hormone secretion

- Monitor if
  - <4.5 cm
  - no hormone secretion

Notes
- Normal adrenal glands: upside-down “V”
  - Normal body size is 5-8 mm; normal limb size is 2-3 mm
  - CT is best imaging modality for all adrenal pathology, except pheochromocytoma (abdominal MRI)
### GLUCOCORTICOIDS

<table>
<thead>
<tr>
<th>Class</th>
<th>Kinetics</th>
<th>Mech</th>
<th>Uses</th>
<th>Adverse</th>
</tr>
</thead>
</table>
| **Glucocorticoids**<br>See below for key points for each drug | Route:  | Anti-inflammatory effects | GENERAL | Glucocorticoid Side Effects:<br>- CH₂O → increased glucose = diabetes-like<br>- Protein → increase amino acids = muscle wasting and connective tissue deterioration<br>- Fat → increase fatty acids = centripetal fat deposition<br><br>**Mineralcorticoid Side Effects**<br>- Known as "salt retaining" effects<br>- Increased Na⁺ → increase BP<br>- Increased water → edema<br>- Increased K⁺ and H⁺ secretion → hypokalemia and metabolic alkalosis<br><br>**Adverse Effects** (high dose, sustained therapy)<br>- Iatrogenic Cushing’s syndrome (too much GC, get extreme GC side effects)<br>- HPA axis suppression (insuff response to stress)<br>- Mood disturbance (initial euphoria, then psychic letdown when dose reduced; insomnia)<br>- Impaired wound healing (due to catabolism of collagen/fibroblasts)<br>- Increased susceptibility to infection<br>- Possible with very large doses<br>- Osteoporosis via direct (decrease in osteoblasts) and indirect (dec. Ca absorption)<br>- Posterior capsular cataracts (esp in children receiving prolonge asthma treatment)<br>- Skin atrophy / loss of collagen support<br>- Growth retardation in kids<br>- Peptic ulceration |<br>- Oral (pro-drug; prednisone, cortisone) has ketone on carbon 11 → must be metabolized to active OH<br>- Topical (cortisol aka hydrocortisone) is already active<br>- IA (prednisolone=activated prednisone)<br>- Metabolism<br>- Liver: 11beta-HSD1 is activating (ketone=OH)<br>- Kidney: 11beta-HSD2 is inactivating (OH → ketone) which protects kidney from unreg MC activity<br>- IN fetus, 11-betaHSD1 is not functional but mom’s placental 11beta HSD2 is active<br>- Dosing<br>- Alternate day schedule can reduce adverse effects (b/c anti-inflammatory effect outlasts suppressive effect on HPA axis)<br>- Terminate administration if take GCs longer than week | 1. Inhibiting Phospholipase A₂ (no production of arachidonic acid from phospholipids)<br>2. Inhibit COX2: Effect is downregulation of PG, TX, LT, LX (all eicosanoids)<br><br>**Immunosuppressive**<br>1. Suppress T-cell activation<br>2. Suppress cytokine production<br>3. Prevent mast cell and eosinophils from releasing mediators (histamine, PG, LT)<br><br>**Cushing’s Syndrome (Hypercortisolism)**<br>- If due to tumor, surgery is preferred<br>- **Synthesis inhibitors:** Ketoconazole<br>- Glucocorticoid receptor antagonist: Milopristone<br>- **Congenital Adrenal Hyperplasia**<br>- Lack of cortisol suppression = increased ACTH<br>- Can be accompanied by deficiency<br>  - 21-hydroxylase def: inc androgens and dec MC=HYPOTension<br>  - 17alpha-hydroxylase def: no androgens, inc MC=HYPOTension<br>  - 11beta-hydroxylase: inc androgens and inc MC=HYPOTension<br><br>**Pheochromocytoma**<br>- Pre-op Management<br>  - First give: Alpha blockers (Phenoxybenzamine, Prazosin, Terazosin, Doxazosin)<br>  - Then give: Beta-blockers (Metoprolol)<br>- Calcium channel blockers (alone i.e. nifedipine)<br>- Surgery (adrenalectomy)<br>- Physiologic replacement (has equal GC and MC activity) and in emergencies<br>- Oral and Parenteral |<br>- Prednisone<br>- Most common oral agent (activated to prednisolone via first pass in liver; NO topical effect)<br>- GC:MC is 13:1 |<br>- Methyprednisone<br>- Best if want parenteral admin (Solu-Medrol) but can also use orally (Medrol)<br>- No better than oral prednisone in acute exacerbation of asthma<br>- Minimal MC action |<br>- Triamcinolone<br>- Potent systemic agent with excellent topical activity<br>- No MC activity |<br>- Dexamethasone<br>- Most potent anti-inflammatory (does not need to be activated) → mostly used in adults (use hydrocortisone in kids)<br>- Also used in cerebral edema, chemo-induced vomiting<br>- Minimal MC action, greatest suppression of ACTH secretion at pituitary |<br>- Hydrocortisone (cortisol)<br>- Physiologic replacement (has equal GC and MC activity) and in emergencies<br>- Oral and Parenteral

**Prednisone**

- Most common oral agent (activated to prednisolone via first pass in liver; NO topical effect)
- GC:MC is 13:1

**Methyprednisone**

- Best if want parenteral admin (Solu-Medrol) but can also use orally (Medrol)
- No better than oral prednisone in acute exacerbation of asthma
- Minimal MC action

**Triamcinolone**

- Potent systemic agent with excellent topical activity
- No MC activity

**Dexamethasone**

- Most potent anti-inflammatory (does not need to be activated) → mostly used in adults (use hydrocortisone in kids)
- Also used in cerebral edema, chemo-induced vomiting
- Minimal MC action, greatest suppression of ACTH secretion at pituitary
### Thyroid

<table>
<thead>
<tr>
<th>Concept</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td></td>
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</table>
- **First endocrine gland to develop**: connected to tongue via *thyroglossal duct* and then descends (completes descent in 7th gestational week); at 12 weeks, thyroid gland can trap iodide and start secreting hormone  
  - Placenta allows small amount of T4 → fetal brain has Type I Diodinase (converts T4 to T3)  
  - Within 30 min of birth, TSH rises to levels of 60-80 uU/ml → which is why screen needs to be at 3-5 days so that results are not confounded by this surge  
- Thyroid is two lobes connected by isthmus located below larynx (supplied by superior thyroid and inferior thyroid arteries)  
- **Functional unit of gland=follicle**  
  - Follicle is a layer of cells surrounding a lumen filled with **colloid** (which contain thyroglobulin TG) → from endodermal pharynx (floor b/w 1st and 2nd pharyngeal arches)  
  - Blood is on basolateral side; Colloid is on apical side  
  - **Parafollicular (C cells)** cells are found between follicles and secrete calcitonin → from neural crest  |
| **Imaging** |  
- **10-40% of normal patients have small pyramidal lobe arising superior to the ishmus, lying in front of thyroid cartilage**  
- **Anatomic Imaging**: to detect or characterize thyroid pathology (i.e. nodules)  
  - **US** (US is usually best) → also best to detect lymph node metastasis and used for real-time guidance for FNA  
  - **CT**: useful to determine lymph node metastasis and evaluating the thyroid bed  
  - **MRI**: useful in identifying infiltrative disease, particularly in post-therapy neck where anatomy is distorted; detection of deep nodal disease  
  - **X-ray not that useful but may reveal incidental thyroid pathology** (i.e. via mass effect on soft tissues or trachea)  
- **Functional Imaging**  
  - **Iodine (123I or 131I) scan** → evaluate level of thyroid function; 131I can also be therapeutic for hyperthyroidism or well-differentiated thyroid cancer  |
| **Synthesis of TH** |  
- **Thyroid Hormone Reactants**: iodide and tyrosine  
  - **Iodide**: from dietary intake  
  - “Iodide trap”  
  - Iodide is cotransported with Na into follicular cell on basolateral side (Na/KATPase on basolateral side maintains driving Na gradient) → As a result, concentration of iodide in the thyroid is 30-40 times that in the serum  
  - **Iodide diffuses to apical side of cell where it is incorporated onto tyrosines on Thyroglobulin (TG) via thyroperoxidase (TPG)** to form moniodotyrosine (MIT) and diiodotyrosine (DIT) on TG → process known as *organification*  
  - Then 2 DITs (T4) or 1DIT + MIT (T3) couple to form iodothyronines (also occurs via thyroperoxidase)  
  - **Thyronine** = backbone of TH (can be iodinated at 3,5,3’ and 5’ positions)  
  - 3,5,3’ triiodothyronine = T3 (active)  
    - **Half life of 1 day**  
    - TH Receptor has 10x higher affinity for T3 than T4  
    - T3+Receptor complex act on DNA to regulate transcription of different proteins (i.e. Na/KATPase, respiratory enzymes)  
  - 3,5,3’, 5’ tetraiodothyronine = T4 (thyroxine)  
    - **Half life of 7 days** (higher affinity for carrier proteins)  
    - Converted to active T3 via 5’deiodinase (D1I and D2I are activating, D3I is inactivating)  
    - Can inhibit 5’deiodinase with pregnancy, period, starvation, severe illness, stress, and drugs (GCs, propranolol, amiodarone, radiocontrast)  
- Before secretion of TH, TG is endocytosed from colloid into follicular cell and lysosomal enzymes cleave T4 and T3 from TG(T4 is cleaved ~20x in excess of T3) → then T3 and T4 are secreted into the blood from the basolateral side  
- Once in the blood, almost 100% is bound to proteins i.e. TBG, TBPA, and albumin → protein-binding delays, buffers, and prolongs the action of TH  
- **Aside on drugs that inhibit iodination**: decrease TH and increase TSH and cause goiter: thiourea drugs (propylthiouracil-PTU, methimazole)
### Actions of TH

- **TH** is the major regulator of metabolic rate (determined by BMR).
  - Increases of T3 = increases in catabolic activity → *calorigenic effect* (heat producing effect, largely due to increased Na/K ATPase, myosin ATPase, and SR Ca ATPase).
  - Very high T3 can lead to increased fuel consumption, protein breakdown, and muscle wasting (and *calorigenic effect can lead to heat intolerance*).
- TH is necessary for normal fetal and neonatal brain development (proliferation, differentiation, myelinogenesis, neurite outgrowth, synapse formation).
- Congenital hypothyroidism can lead to severe developmental delay (part of neonatal screening can reverse if caught early) → also known as “cretinism”.
- TH (along with GH) are important for normal growth (TH deficiency = stunting).
- TH enhances response to catecholamines (increase number of beta adrenergic receptors) especially in cardiovascular system.

### Regulation of TH

- TRH (hypothalamus) promotes release of TSH (anterior pituitary) via an increase in cAMP/hydrolysis of phosphatidylinositol.
- In thyroid, TSH stimulates iodide pump, thyroperoxidase, and endocytosis of colloid → increases TH synthesis.
- T3 and T4 inhibit TRH (negative feedback).

### Disorders

#### HYPERthyroidism
- **Graves’ Disease** (autoimmune) → most common
- Tumors of pituitary or thyroid
- Excess TH administration

**Signs & Symptoms**
- High BMR
- Hair loss
- Frequent bowel movements
- Nervousness/palpitations/tachycardia
- Pretibial Myxedema, Exophthalmos, lid retraction, diplopia (Graves)
- Heat intolerance
- Muscle weakness
- Hyperreflexia
- Goiter (distinguishes between hyperfunction and excess TH administration)

#### HYPOthyroidism
- Hashimoto’s thyroiditis (autoimmune) → most common
  - Can also have post-partum thyroiditis
  - Subacute thyroiditis distinguished because it’s *very painful, high T4 and low RIU and high ESR*
- Congenital hypothyroidism (“cretinism”)
- Iodine deficiency (can also have a paradoxical low release of TH in response to very high doses of iodide → Wolff-Chaikoff effect)
- Perchlorate and thiocyanate (found in cabbages and cassava) can competitively inhibit iodide uptake from blood into follicular cell
- **Drugs that inhibit iodination** = cause goiter: thiourea drugs (propylthiouracil-PTU, methimazole)

**Signs & Symptoms**
- Low BMR, bradycardia
- Lethargy, weakness, slow speech
- Myxedema
- Constipation
- Cold intolerance
- Goiter, Hoarseness
- Hypermenorrhea
<table>
<thead>
<tr>
<th>Disorder</th>
<th>General Info</th>
<th>Clinical Presentation</th>
<th>Diagnostics</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>HYPERthyroidism</strong></td>
<td>Graves’ Disease</td>
<td>• High BMR&lt;br&gt; • Nervousness/palpitations&lt;br&gt; • Tachycardia&lt;br&gt; • Pretibial Myxedema, Exophthalmos, lid retraction (Graves)</td>
<td>• Measure serum TSH first → low or normal TSH&lt;br&gt; • High T4&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
<td>• Antithyroid drugs&lt;br&gt; • Radioactive Iodin&lt;br&gt; • Surgery</td>
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<td></td>
<td>Toxic Nodule Goiter</td>
<td>• Mutation of TSH receptor to be constitutively active&lt;br&gt; • “Hot nodules” → overproduction of T3/T4 (high RAI)</td>
<td>• Measure serum TSH first → low TSH&lt;br&gt; • High T4&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
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<td></td>
<td>Thyroiditis</td>
<td>• Previous viral infection causes leaky membranes of thyroid hormone leaks out&lt;br&gt; • Goiter&lt;br&gt; • Amenorrhea (high T4=low SHBG=increased free estrogens)</td>
<td>• Measure serum TSH first → high TSH&lt;br&gt; • High T4&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
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<td>TSHomea</td>
<td>• Tumor producing TSH</td>
<td>• Measure serum TSH first → low TSH&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
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<td>Thyroid Hormone Resistance</td>
<td>• Receptor mutation&lt;br&gt; • Low metabolism, “bird-like” facies</td>
<td>• Measure serum TSH first → low TSH&lt;br&gt; • High T4&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
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<td></td>
<td>Excess TH Administration</td>
<td>• Usually from overadministration of levothyroxine</td>
<td>• Measure serum TSH first → low TSH&lt;br&gt; • High T4&lt;br&gt; • HIGH Radioactive Iodine Uptake (RAI)</td>
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<td><strong>HYPOTHYROIDISM</strong></td>
<td>Congenital Hypothyroidism</td>
<td>• Baby usually appears normal!&lt;br&gt; • Almost always overlooked&lt;br&gt; • Later on&lt;br&gt; o Large posterior fontanel&lt;br&gt; o Prolonged jaundice&lt;br&gt; o Macroglossia&lt;br&gt; o Hoarse cry&lt;br&gt; o Umbilical hernia&lt;br&gt; o Hypotonia&lt;br&gt; • Assoc congenital heart defects in &lt;5%&lt;br&gt; • Evidence for genetic etiology: More in girls, different incidence in ethnic groups, higher in consanguineous, 2% of affected relative</td>
<td>• Newborn screen at 3-5 days (usually as baby is about to be discharged)&lt;br&gt; Two screening methods&lt;br&gt; In Colorado: First do primary T4 → if T4 is in the lowest 10% of results for that day, TSH will be measured&lt;br&gt; o Abnormal if TSH 20→uU/ml call PCP &amp; do confirmatory labs&lt;br&gt; o If ≤20, not abnormal but can’t rule out&lt;br&gt; • Primary TSH screen (but will miss central hypothyroidism)&lt;br&gt; Measurement of TH can be inaccurate if there are deficiencies/excesses of thyroid binding→can either use measure Free-T4 (expensive) or T3-uptake&lt;br&gt; • T3 uptake: T3 will take up binding sites on proteins that are not occupied by T4 and the remaining T3 is taken up by resin → results are reported as uptake by resin&lt;br&gt; o Low T4 and low (resin) uptake = hypothyroid&lt;br&gt; o Low T4 and high (resin) uptake= TBG deficiency&lt;br&gt; Interpreting results&lt;br&gt; • Low T4, high TSH=congenital hypothyroidism&lt;br&gt; • Low T4, low TSH, normal FT4 (or low resin T3 uptake) =TBG deficiency&lt;br&gt; • Low T4, Normal (inappropriately) TSH, and low FT4=cental hypothyroidism</td>
<td>• Treat with brand name (preferred for kids) and crust tablets (DON’T &amp; suspension) thyroid supplement&lt;br&gt; • Monitor after 4 wks and for every 3 mos for first three years of life&lt;br&gt; • Need to treat early (&lt;3 weeks) in order to avoid severe developmental delay</td>
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<td>• Newborn screen at 3-5 days (usually as baby is about to be discharged)</td>
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### Thyroid Nodules

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Histopathologic Features</th>
<th>Prognosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Hypothyroidism</td>
<td>Deficiency in hypothalamus or pituitary</td>
<td>Low BMR, bradycardia</td>
<td>Thyroid supplement (levothyroxine)</td>
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<tr>
<td>Usually in setting of multiple pituitary hormone deficiency (i.e. septic-optic dysplasia)</td>
<td>Need to evaluate other pituitary hormones and MRI</td>
<td>Low T4</td>
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<tr>
<td>Thyroid Nodules</td>
<td>Growth, pain, cough, voice change, hx of irradiation (3x more risk); family history</td>
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<td>Benign Nodules</td>
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<tr>
<td>Adenoma (benign)</td>
<td>Most common, multifocal, lymphatic spread, well-differentiated, excellent prognosis</td>
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<td>Very common (60%) incidental finding</td>
<td>Frond-like (papillary) appearance on path</td>
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<td>PAPILARY (70%):</td>
<td>Optically clear nuclei, nuclear grooves, nuclear pseudoinclusions, rare or absent mitoses, psammoma bodies (laminar calcifications)</td>
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<td>Follicular/Hürthle (5%):</td>
<td>Very aggressive, older patients (had a thyroid nodule for many years but suddenly grows quickly)</td>
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<td>Anaplastic (&lt;2%):</td>
<td>Three patterns: spindle cells, giant cells, squamous cells</td>
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<td>Medullary (5%):</td>
<td>Necrosis and hemorrhage</td>
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<td>Familial (MEN syndromes)</td>
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<tr>
<td>Thyroid Nodules</td>
<td>RARE: Lymphoma (usu in background of Hashimoto’s; positive LCA lymphoid stain), Sarcoma, Metastatic</td>
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</table>

### Hypothyroidism (continued)

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Histopathologic Features</th>
<th>Prognosis</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Thyroid Nodules</td>
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<tr>
<td>Benign Nodules</td>
<td>Often post-partum (Ab to thyroid during pregnancy); NOT painful</td>
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<tr>
<td>Malignant Nodules: (Use Bethesda system)</td>
<td>Note the initial phase is HYPERthyroid, followed by a HYPOTHYROID recovery phase</td>
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<tr>
<td>Silent Thyroiditis (recovery phase)</td>
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<td>NOT painful (unlike subacute thyroiditis)</td>
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<tr>
<td>Antibodies to thyroid</td>
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<tr>
<td>Subacute Thyroiditis (recovery phase)</td>
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<tr>
<td>Distinguished because it’s very painful Note that the initial phase is HYPERthyroid, followed by a HYPOTHYROID recovery phase</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>More females, very common; less in Hispanic and African-American populations compared to Caucasian</td>
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<td>THYROID:</td>
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<tr>
<td>Thyroid supplementation (levothyroxine)</td>
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<tr>
<td>Thyroid nodules</td>
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<tr>
<td>Thyroid nodules for many years but suddenly grows quickly</td>
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<td>Papillary Cancer: RET/PtC</td>
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<td>RET/PtC rearrangement</td>
<td>pathway</td>
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<td></td>
<td>normally inhibited</td>
<td>always on=growth</td>
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<td></td>
<td>Follicular:</td>
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<td></td>
<td>Ras mutation</td>
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<td>Poorly differentiated cancers usually from p53 mutations</td>
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### Notes
- HYPERthyroid: 4-5x more prevalent in women, increases with age
- Hypothyroid: More females, very common; less in Hispanic and African-American populations compared to Caucasian
- Stimulating TSH in the setting of Adrenal Insufficiency can be fatal
- Start steroids first
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>General Info &amp; Mech</th>
<th>Kinetics &amp; Uses</th>
<th>Adverse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs for HYPOthyroidism</td>
<td>Levothyroxine Synthroid</td>
<td><strong>First line, preferred treatment</strong>&lt;br&gt;Low cost, synthetic T4&lt;br&gt;Advisable to use the same product since there can be variability between formulations&lt;br&gt;Check hormone levels after 6 wks of treatment</td>
<td><strong>Should be taken on empty stomach with water for best absorption</strong> (impaired by metal ions, cipro, sucralate, dietary fiber, soy)&lt;br&gt;<strong>Once daily dosing: Narrow therapeutic index</strong>&lt;br&gt;○ Adults: start 50-100 mcg and uptitrate&lt;br&gt;○ Infants/children require more T4/kg&lt;br&gt;○ Low dose for elderly (may reveal subclinical cardiac disease)&lt;br&gt;○ Increased dose in pregnancy</td>
<td><strong>Caution in patients with cardiac disease!</strong>&lt;br&gt;<strong>For severe untreated HYPOthyroid (Myxedema Coma) → IV T4 (large loading dose + daily dose) +/- hydrocortisone to prevent adrenal crisis</strong>&lt;br&gt;<strong>Excessive T4 can cause toxicity resembling hyperthyroid</strong>&lt;br&gt;○ Kids: restless, insomnia, accelerated bone growth/maturatiom&lt;br&gt;○ Adults: anxiety, heat intolerance, palpitations/tachycardia, tremors, weight loss, increased bowel movements → can exacerbate subclinical cardiac disease**&lt;br&gt;<strong>DDI: will increase adrenergic effects of sympathomimetics (i.e. epinephrine) or decongestants</strong></td>
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<td>Levothroid&lt;br&gt;Unithroid&lt;br&gt;Generics (many)</td>
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<td>Iodotope&lt;br&gt;Radioactive Iodine (¹³¹Iodine) Iodotopoe</td>
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<td>Liothyronine&lt;br&gt;Cytomel</td>
<td><strong>Synthetic T3</strong>&lt;br&gt;NOT recommended for routine replacement b/c of short half life → add on therapy once optimized levothyroxine therapy&lt;br&gt;Used in T3 suppression test</td>
<td><strong>Short half life</strong>&lt;br&gt;<strong>Greater fluctuation in plasma levels between doses</strong></td>
<td><strong>Avoid cardiac disease</strong></td>
</tr>
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<td></td>
<td>Liothyronine&lt;br&gt;Cytomel</td>
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<td></td>
<td>Synthroid&lt;br&gt;Thyrolar&lt;br&gt;Thyroid Strong</td>
<td><strong>4:1 T4/T3 combination</strong>&lt;br&gt;More expensive</td>
<td><strong>T4/T3 ratio doesn’t provide advantage for final concentration; rarely required or recommended</strong></td>
<td><strong>May cause increased incidence of low TSH and increased markers of bone turnover</strong></td>
</tr>
<tr>
<td></td>
<td>Leoxyl&lt;br&gt;Levothroid&lt;br&gt;Soy&lt;br&gt;Thyrolar&lt;br&gt;Soy&lt;br&gt;Thyroid Strong</td>
<td></td>
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<tr>
<td>Thyroid USP</td>
<td>Thyroid Strong</td>
<td><strong>Porcine thyroid extract</strong></td>
<td><strong>NOT recommended</strong></td>
<td><strong>Variable T4/T3 ratio (unexpected toxicities)</strong>&lt;br&gt;<strong>Protein antigenicity; product instability</strong></td>
</tr>
<tr>
<td></td>
<td>Methimazole&lt;br&gt;Propylthiouracil (PTU)</td>
<td><strong>Block iodine organization</strong>&lt;br&gt;Takes ~ 1 month for effects to be seen&lt;br&gt;Leave gland intact but 60-70% relapse&lt;br&gt;Can give beta-blocker (propanolol) for symptomatic relief until hyperthyroid has resolved (blocks T4 → T3 conversion)&lt;br&gt;Methimazole is preferred because of dosing and less risks</td>
<td><strong>PTU absorption is incomplete (50-80%) and methimazole (100%)</strong>&lt;br&gt;Crosses placental barrier → caution in pregnancy (PTU is safer) but thionamides are treatment of choice in pregnancy&lt;br&gt;Short half lives, but drugs accumulate in thyroid for longer action (PTU=3x/day; methimazole=1x/d)&lt;br&gt;<em>Best for mild disease, small gland, or younger patients</em>*</td>
<td><strong>Most common: pruritic rash, gastric intolerance, arthralgias</strong>&lt;br&gt;<strong>Most dangerous: agranulocytosis (obtain CBC if have fever or sore throat)</strong>&lt;br&gt;<strong>PTU hepatotoxicity is rare but severe enough to raise concerns about routine use</strong>&lt;br&gt;<strong>These drugs only work in thyrotoxicosis (high RIU), not in other causes of hyperthyroid</strong></td>
</tr>
<tr>
<td>Drugs for HYPERthyroidism</td>
<td>Iodides&lt;br&gt;SSKI&lt;br&gt;Lugol’s solution</td>
<td><strong>High doses of iodine inhibit hormone synthesis</strong>&lt;br&gt;Occur rapidly, thus can be useful in thyroid storm</td>
<td><strong>Rarely used alone today but may be useful in thyroid storm or to decrease size and vascularity of hyperplastic gland prior to surgery</strong></td>
<td><strong>Variable effects, rebound effects when withdrawn, may worsen existing hyperthyroidism</strong>&lt;br&gt;<strong>Can delay onset of thionamide therapy so initiate iodine after thionamide therapy</strong></td>
</tr>
<tr>
<td></td>
<td>Radioactive Iodine (¹³¹Iodine) Iodotopoe</td>
<td><strong>Beta-radiation causes slow inflammatory process that destroys gland over wks-mos</strong>&lt;br&gt;<strong>Effective, low expense, not painful</strong></td>
<td><strong>Preferred in patients &gt;21</strong>&lt;br&gt;<strong>Oral, rapidly absorbed</strong></td>
<td><strong>Contraindicated in pregnancy</strong>&lt;br&gt;<strong>Slow onset and time to peak (2-6 months)</strong>&lt;br&gt;<strong>10% require second dose</strong>&lt;br&gt;<strong>Radiation thyroiditis can lead to CV complications</strong>&lt;br&gt;<strong>May worsen ophthalmopathy</strong>&lt;br&gt;<strong>80% develop hypothyroidism → need levothyroxine</strong></td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery</td>
<td><strong>Treat with antithyroid drugs until euthyroid (6 wks) before surgery</strong>&lt;br&gt;Can be utilized in 2nd trimester of pregnancy if needed</td>
<td><strong>Treatment of choice for large gland but used less today because of radioactive iodine</strong></td>
<td><strong>850-60% develop hypothyroidism</strong>&lt;br&gt;<strong>Risks of anesthesia and parathyroid/recurrent laryngeal nerve damage</strong></td>
</tr>
<tr>
<td>Drugs for Thyroid Storm</td>
<td>Beta Blockers AND Hydrocortisone</td>
<td>Goals of therapy are to</td>
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</tbody>
</table>
|                         | Symptoms: fever, flushing, sweating, tachycardia/afib, delirium, coma | o Control symptoms  
|                         | Propanolol blocks T4→T3 reaction to control CV complications | o Inhibit release of preformed hormone  
|                         | Sodium iodide IV (or KI oral) slow release of hormone | o Block synthesis/ T4→T3 conversion  
|                         | PTU can block synthesis (but NOT methimazole) |  
|                         | Hydrocortisone protects against shock, blocks T4→T3, and may modulate the immune response that leads to thyrotoxicosis |  

**NOTES**
- Thyroid hormones are consistently in top 10 of most frequently prescribed drugs
- Hypothalamus-Pituitary-Thyroid Axis
  - **Activated:** by circadian rhythms, prolonged cold exposure, acute psychosis → pituitary simulated by hypothalamic TRH
  - **Inhibited:** by stress → pituitary inhibited by somatostatin, dopamine, and glucocorticoids
- DDIs
  - **Estrogens/SERMs/Tamoxifen** INCREASE hormone binding to protein; **Salicylates and anti-sz med** DECREASE binding
  - **Drugs** that DECREASE 5’-deiodinase (T4→T3): GCs, Beta-Blockers, PTU at high doses
  - **Conditions** that DECREASE 5’-deiodinase (T4→T3): illness, calorie deprivation, malnutrition, fetal/neonatal period
Starred Items from Endocrine Dysfunction and Psych Lecture (thanks Sarah Tietz!)

- Thyroid Receptors are located throughout the brain. High concentrations of T3 receptors are found in the amygdala and hippocampus.
- These receptors, in turn, influence neural activity. The effects of thyroid dysregulation on brain function are variable at different stages of life.
- Interactions of the thyroid and neurotransmitter systems, primarily NE, SHT and DA, help regulate mood and behavior.
- Iodine deficiency is a common cause of hypothyroidism world-wide
- Some post-partum moodiness & depressions may be secondary to thyroid disease.
- ~40% of clinically hypothyroid patients have symptoms of depression.
- Forgetfulness, fatigue, mental slowness, inattention, emotional lability. May mimic dementia.
- Perceptual changes: alterations of taste, hearing, and vision.
- Psychosis (myxedema madness), delusions, visual & auditory hallucinations typically develop after physical symptoms, often after a period of months or years.
- Symptoms are usually reversed with return to euthyroid state, although severe hypothyroidism can result in irreversible dementia when not treated in time.
- A significant number of people have asymptomatic chronic autoimmune thyroiditis; 8% of women (10% of women over age 55 years, 20% >60) and 3% of men develop subclinical hypothyroidism.

- In Subclinical hypothyroidism
  - Increased serum TSH may be the first abnormality to appear in subclinical hypothyroidism.
  - Progression to clinical hypothyroidism occurs in about 3% to 18% of patients per year.
- Subclinical hypothyroidism a risk factor for:
  - Depression.
  - Treatment resistant depression.
  - Is often found in rapid cycling bipolar disorder.
- Partial response to depression treatment:
  - Treat until patient is back to pre-depressed state. In partial response look for clinical and sub-clinical hypothyroidism, is the patient taking the right drug at the right dose for a long enough time?
- Graves’ Disease
  - Increased risk of Graves in autoimmune diseases: type 1 diabetes, rheumatoid arthritis, and vitiligo. Stress may potentiate autoimmune response.
  - Sx: wt loss, tremor, palpitations, atrial fibrillation, sweating, proptosis, anxiety (60%), depression (30-70%), insomnia, diarrhea, weakness
  - Elderly: less obvious symptoms: confusion, dementia, apathy, depression
  - Other causes: *beware of supplements e.g. Kelp, other seaweed.
- President Bush – Grave’s Dz = His first symptoms were atrial fibrillation, severe fatigue, hand-tremors and a mild goiter.
- Diabetes:
  - *Depression is 2-3 x more common in diabetics than general population. Results in poorer glycemic control, increased diabetic complications.
  - Increased type 2 diabetes in bipolar disorder: Some due to increased obesity in bipolar patients, some iatrogenic due to mood stabilizer weight gain.
  - *Sleep loss → increased ghrelin → weight gain → diabetes/obstructive sleep apnea which worsens sleep loss (and increases risk of depression.)
- Increased Cortisol (Cushing’s, etc)
  - *Psychiatric symptoms common in hyper-adrenalism and may appear before physical signs.
  - *Depression most common, but anxiety, hypomania /mania, psychosis, and cognitive dysfunction all occur.
- Hyper/hypo parathyroidism
  - Mild-to-moderate hypercalcemia (10-14 mg/dL): depression, apathy, irritability, lack of initiative, and lack of spontaneity.
  - Severe hypercalcemia (>14 mg/dL) can result in delirium, psychosis, catatonia, or lethargy, and may progress to coma.
  - Hypocalcemia, patients may experience anxiety, paresthesias, irritability, and emotional lability.
  - Severe Hypocalcemia: Mania, psychosis, tetany, and seizures occur in severe hypocalcemia.
  - Therefore, Psychosis may occur in a patient with severe hypercalcemia or hypocalcemia.
- Addison’s disease: primary (adrenal destruction) or iatrogenic (suppression of ACTH by corticosteroid therapy).
  - *Psychiatric symptoms: apathy, anhedonia, fatigue, depression.
- Acromegaly:
  - *Obstructive sleep apnea is common

True / False
- Kelp, bladderwrack (seaweed) can cause sx of hyperthyroidism  T
- High concentrations of T3 receptors are in the amygdala and hippocampus  T
- Iodine deficiency is a rare cause of hypothyroidism world-wide F
- Subclinical hypothyroidism = risk factor for depression and treatment resistant depression.  T
- Insomnia is common in hypothyroidism but not Graves’ disease F
- Atrial fibrillation & anxiety can be precipitated by excessive seaweed intake T
- Psychosis is not a symptom of steroid treatment  F
- Hypercalcemia may precipitate depression, apathy, irritability, and lack of spontaneity T
- Acromegaly is a risk factor for obstructive sleep apnea T
- It is likely that Graves disease is not found more frequently in the presence of autoimmune diseases  F
# Growth Charts

## Concept
- **Overview**
  - Poor growth may be the first and only sign of underlying health problems → consequences of missed diagnoses can have permanent consequences in development
  - Should be measured at birth, 2 d, 4 d, 1, 2, 3, 6, 9, 12, 15, 18, and 24 months and every year until 21 → plotted on growth charts
  - 1-2 yrs are supine measurements vs 2-20 yrs
  - WHO is gold standard (for breastfed infants; CDC includes formula-fed)

## Measurements
- **Height**
  - Height below 2 SD (3% is 1.9 SD for age and gender OR height more than 2 SD below the midparental target height)
    - Genetic potential formula (general rule: boys are 5 inches taller than females)
      - For boys: average of dad’s height and mom’s height+ 5 in (plus or minus 3 inches)
      - For girls: average of mom’s height and dad’s height-5 in (plus or minus 3 inches)
  - Dwarfism: height below 3 SD
  - Midget: dwarf with normal body proportions
    - While these terms are still used, avoid as they are derogatory
  - Abnormal growth velocity: slow linear growth velocity or dropping across two major centile lines on growth chart
  - Skeletal maturation: can make height prediction using height and bone age
    - Not accurate in children with growth disorders and may be confounded by tempo of puberty → may help in differentiating causes of short stature
  - Body proportions
    - Upper: lower body ratio starts at 1.7 and fall to 1.0 by ten years of age
    - Arm span is shorter than height in boys before 10/11 and girls 10-14 → then arm span exceeds height (avg male=5.2> ht; avg female is 1.2 cm>ht)
  - Screening labs: CMP, CBC, UA, karyotype (esp girls), TSH & T4, IGF-1
    - For nutritional growth retardation: also get ESR, TTG (celiac Ab), and IgA

## Causes

### NORMAL Constitutional short stature
- Constitutional short stature ("late bloomer")
  - Growth deceleration during first 2 years of life followed by normal growth paralleling lower percentile curves
  - Skeletal maturation delayed
  - Catch up growth achieved by late puberty and delayed fusion of growth plates
  - Polygenic trait (positive in about 60-80%)
  - Ask women about when period started and ask boys if they grew in height more after high school vs before/during
  - Approach
    - Reassurance of normal growth pattern
    - Can treat boys with testosterone if bone age >11-12 yrs to avoid compromising final height
    - Can treat girls with estrogen but not common

### Familial short stature
- Normal growth velocity and heights are within normal limits for parent’s heights
  - Initially will have decrease in growth rate between 6 and 18 mos
  - May have tubular bone alterations (i.e. brachydactyly syndromes, SHOX haplosufficiencies)
  - Make sure that the family is short not just the parents (because parent may have undiagnosed pathology)

### Nutritional
- Zn, Fe Deficiency
- Anorexia
- IBD, Celiac, CF

### Chromosome defects
- Turner’s Syndrome
  - Haploinsufficiency of SHOX genes
  - Most common sex chromosome abnormality of female (affects 3% of concept, but many to do not come to term); 1/2000 live births
  - Caused by complete or partial absence of one of the X chromosomes
  - Virtually all exhibit short stature; final ht is ~ 20 cm less than target
  - Girls are not generally GH deficient, but GH therapy significantly improves growth (earlier the better)
  - Clinical findings may be subtle so diagnosis is often delayed and some girls are never diagnosed
  - Other findings: cardiac defects (bicuspid aortic valve, coarctation), renal (horseshoe kidney), ovarian insufficiency, hypothyroidism/celiac, otitis media hearing loss, non-verbal learning disability

### Down Syndrome
- Prader-Willi Syndrome (GH deficient)
- Noonan syndrome (abnormal GH post-receptor signaling)
<table>
<thead>
<tr>
<th>Endocrine</th>
<th></th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothryroid:</strong></td>
<td></td>
<td><strong>Skeletal dysplasias</strong></td>
</tr>
<tr>
<td>o Many of the clinical features seen in adults are lacking in children</td>
<td></td>
<td>o Skeletal abnormalities: short stature, increased carrying angle, short neck, micro or retrognathia</td>
</tr>
</tbody>
</table>
| o Causes: primary hypothyroidism (high TSH, low T4), central hypothyroidism (low T4, inappropriately normal TSH) | | **IUGR/SGA**  
**Intrauterine Growth Restriction/Small for Gestational Age** |
| o TH is very potent stimulator of linear growth (even more than GH) | | o SGA= Less than 2 SD for birth weight or length |
| **GH Deficiency:** | | o Hypothesis of pathophys: fetal response to prolonged nutritional deficiency late in gestation may be to prematurely reset to a slow growth rate with a degree of resistance to GH, IGF-1, and insulin |
| o GH deficiency symptoms: decreased muscle, increased subcutaneous trunk fat, face immature for age, prominent forehead/depressed midface, small phallus in males, other midline facial defects, may have hx of prolonged jaundice and/or hypoglycemia in newborn period | | o Can be due to maternal influences (infection, deficiencies, uterine abnormalities, smoking, EtOH, drugs), placental (previa, abruption, infarcts, structural, multiple gestation), fetal (chromosome abnormalities, metabolic, infections, malformations) |
| o Evaluation: | | o Most healthy infants born SGA achieve catch-up height by age 2 (most growth during first 6 mos) |
| ▪ Bone age | | o ~10-15% of children born SGA remain short as adult; final height may also be compromised by early puberty |
| ▪ IGF-1 (IGFBP-3 in infant), however it’s low in underweight regardless of GH status | | o GH treatment approved if have NOT caught up on growth by 2 yrs, may increase final height an average of 3 in  
should not be given without appropriate nutritional intake |
| ▪ Stimulation testing (don’t draw random GH level)  
clonidine, arginine, glucagon, L-dopa (check levels every 30 min for 1.5 hrs) | | **Metabolic** |
| ▪ MRI of pituitary | | **Chronic Diseases** |
| o GH therapy has been progressively approved for more and more conditions (renal insufficiency, SHOX def, Turner’s, Prader-Willi, etc) and is also used off-label for things like CF, IBD, GC-induced growth retardation (difficult to get these covered by insurance) | | **Psychosocial deprivation** |
| o Lots of ethical questions about when GH should be used and who should pay and dangers of side effects (slipped capital femoral epiphysis, pseudotumor cerebri, long term risks?) | | **Drugs (GCs, stimulants)** |
## Calcium & Phosphate Metabolism

<table>
<thead>
<tr>
<th>Concept</th>
<th>Information</th>
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<tr>
<td><strong>Function</strong></td>
<td><strong>Calcium</strong></td>
</tr>
<tr>
<td><img src="image.png" alt="Image" /></td>
<td>o <strong>Structural role (99%, 1.7% of body weight):</strong> major constituent of mineral matrix of bone; reservoir for maintenance of plasma calcium&lt;br&gt;o <strong>Biochemical role (1%):</strong> excitation-contraction coupling; stimulus-secretion coupling, blood clotting, membrane excitability, cellular permeability → most common signal transmitter in body&lt;br&gt;o <strong>Must be maintained within narrow limits 8-10 mg/dl (stated as 8.5-10.5 by another lecturer)</strong>&lt;br&gt;o <strong>Balance of IN (diet, absorption, resorption in kidneys, bone mobilization) and OUT (via feces, filtered out by kidneys, bone formation) in blood compartment</strong>&lt;br&gt;o <strong>Also a rapid exchange for up to 20 g/day</strong> (in lecture notes; cited as 10 g/day by lecturer) between ECF and labile bone (mediated by osteocytes)&lt;br&gt;o <strong>Ca is found in three major compartments</strong>&lt;br&gt;  - Bone (99%) → in the form of hydroxyapatite&lt;br&gt;  - Intracellular compartment (30 g) → free cytosolic Ca is ~50-100 nM in resting cells and is maintained by intracellular buffers, ER stores, ATP linked Ca pump, and Na/Ca antipporter&lt;br&gt;  - Extracellular fluid (2.5 mM) in blood and interstitial fluid → about half is free and filterable by kidney, ~40% is bound to albumin, ~10% as bicarb and phosphate salts (can also be filtered by kidney)&lt;br&gt;  - Kidney filters ~10 g/d of calcium and about 98% is reabsorbed&lt;br&gt;</td>
</tr>
<tr>
<td><img src="image.png" alt="Image" /></td>
<td>o <strong>Structural role:</strong> also a component of mineral matrix of bone&lt;br&gt;o <strong>Biochemical role:</strong> common intracellular buffer, required for phosphorylation reactions&lt;br&gt;o <strong>Must be maintained between 3-4 mg/dl</strong>&lt;br&gt;o <strong>Balance of IN (diet, absorption, resorption in kidneys, bone mobilization) and OUT (out via feces, filtered out by kidneys, bone formation) in blood compartment</strong>&lt;br&gt;o <strong>FGF23</strong> (growth factor in kidney) decreases serum level of phosphate and inhibits Vit. D</td>
</tr>
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</table>

### Hormones Regulating Calcium and Phosphate Homeostasis

<p>| Parathyroid Hormone | Produced by parathyroid and increases plasma calcium (via Gs mechanism) → short term regulator&lt;br&gt;o In BONE: rapid effect-increased efflux of labile bone calcium only (primary effect) AND slow effect-increased bone remodeling releasing Ca and phosphate (usually pathological)&lt;br&gt;o In KIDNEY: increased Ca resorption in distal tubule, decreased phosphate reabsorption, increased synthesis of 1,25 (OH)2 Vitamin D (active)&lt;br&gt;o In GI TRACT: indirect action via Vitamin D to enhance Ca absorption&lt;br&gt;  - Ca absorption is passive in duodenum, jejunum, ileum (via Ca gradient)&lt;br&gt;  - Active in duodenum (Vit D dependent Ca absorption): Absorb Ca via TRPV6 on brush border, transported to basolateral side via transcellular proteins, and pumped into blood via PMCA transporter on basolateral side → all three types of transporter proteins are regulated by Vit D&lt;br&gt;  - Limited “up-regulation” of Ca absorption to compensate for low Ca intake → amount of absorption allowed is proportional to dietary Ca intake&lt;br&gt;  - PTH has complex effects on calcium and phosphate levels → net action is to increase serum Ca and decrease serum phosphate&lt;br&gt;  - While PTH normally increase bone resorption (to increase serum Ca), low and intermittent doses of PTH stimulates bone formation (pharm implications)&lt;br&gt;  - Regulation of PTH secretion via calcium sensor&lt;br&gt;  - At normal/high Ca levels, Ca is bound to and stabilizes a Gq-protein coupled receptor → no signaling&lt;br&gt;  - At low levels of Ca, Ca is not bound to receptor → triggers signaling through receptor (activates PLC) and subsequent PTH release&lt;br&gt; |
| Calcitonin | Released by parafollicular C cells in response to high Ca and certain GI hormones (gastrin, CCK, secretin, glucagon)&lt;br&gt;Decreases efflux of labile bone (can be useful therapeutically in slowing down high turnover bone disorders) → inhibits bone resorption to decrease serum Ca and P&lt;br&gt;Increases rate of storage of acute calcium load (short term regulation) |
| Vitamin D | Important long-term regulation of calcium and phosphate stores → induces Ca-binding protein synthesis, induces RANK-L, decreases Ca &amp; P excretion&lt;br&gt;Synthesis and secretions&lt;br&gt;  - 1. 7-dehydrocholesterol in skin converted to Vitamin D3 (inactive) via sunlight&lt;br&gt;  - 2. Hydroxylated in liver to 25-OH Vitamin D3 (inactive)&lt;br&gt;  - 3. Hydroxylated again in kidney to 1,25 (OH)2 Vitamin D3 (active, also known as calcitriol)&lt;br&gt;    - 25-OH Vitamin D3 (inactive) → 1,25 (OH)2 Vitamin D3 (active) via 1-hydroxylase&lt;br&gt;    - 1,25 (OH)2 Vitamin D3 (active) → 24,25 (OH) Vitamin D (active) via 24-hydroxylase&lt;br&gt;    - 1,25 (OH)2 Vitamin D (active) is mostly transported bound to transcalfiiner&lt;br&gt;    - 1,25 (OH)2 Vitamin D (active) interacts with nuclear receptor in GI tract to influence transcription of proteins, one of which is a calcium binding protein → mobilizes bone to increase Ca and phosphate&lt;br&gt;  - 1.25 (OH)2, Vitamin D (active) negatively feeds back on 1-hydroxylase&lt;br&gt;  - High PTH or low phosphate → increases 1 hydroxylase and decreases 24 hydroxylase → increases Ca and phosphate absorption via cAMP mechanism&lt;br&gt;ASIDE: Estrogen promotes bone formation (decreases osteoclasts and increases OPG) and Glucocorticoids promote resorption (increase PTH, increase RANK-L) |</p>
<table>
<thead>
<tr>
<th>Dietary Intake</th>
<th><strong>RDAs</strong> (actual intake is pretty good for most individuals, with the exception of adolescent females)</th>
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<tbody>
<tr>
<td></td>
<td>o 1-3 yrs: 700 mg/d</td>
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<td>o 4-8 yrs: 100 mg/d</td>
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<td></td>
<td>o 9-18 yrs: <strong>1300 mg/d</strong> → note that is NOT different for pregnant/lactating teens because they will be absorbing a greater percentage of their dietary Ca</td>
</tr>
<tr>
<td></td>
<td>o 19-50 yrs: 1000 mg/d → note that is NOT different for pregnant/lactating women because they absorb a greater percentage of their dietary Ca</td>
</tr>
<tr>
<td></td>
<td>o 19-50 yrs: 1000 mg/d</td>
</tr>
<tr>
<td></td>
<td>o 51-70 yrs: 1200 mg/d (men) and 1000 mg/d (women)</td>
</tr>
<tr>
<td></td>
<td>o &gt;70 yrs: 1200 mg/d</td>
</tr>
<tr>
<td><strong>Sources</strong></td>
<td>o Dairy (about 75% of daily Ca intake)</td>
</tr>
<tr>
<td></td>
<td>o Salmon, tofu, fortified soy milk, fortified rice drink</td>
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<tr>
<td></td>
<td>o Note that greens like spinach, collard greens, broccoli may be high in Ca but also have oxalic/phytic acids that impair Ca absorption</td>
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<tr>
<td><strong>Supplements</strong></td>
<td>o Calcium carbonate (i.e. TUMS): provides about 500 mg Ca, best absorbed with meals, least lead</td>
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<td>o Calcium citrate malate: less % of Ca compared to Ca-carbonate, but best absorbed between meals</td>
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<td></td>
<td>o There is increased risk of MI with high supplement use</td>
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<tr>
<td><strong>Ca absorption is enhanced in pregnancy, adolescence, lactose, gastric acidity, dietary protein</strong> → NOT enhanced by bone mineral depletion</td>
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<tr>
<td><strong>Ca absorption is impaired by Vit D deficiency, steatorrhea, oxalic acid, phytates, gastric alkalinity</strong> (esp gastric achlorhydria in elderly)</td>
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<tr>
<td><strong>Ca absorption in lifetime</strong></td>
<td>o Average healthy adult ~25%</td>
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<tr>
<td></td>
<td>o Infants 40-60% (because of highly lactose diet)</td>
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<tr>
<td></td>
<td>o Early puberty ~34%</td>
</tr>
<tr>
<td></td>
<td>o Pregnant ~50%</td>
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<tr>
<td></td>
<td>o May decrease in elderly (decreased Vit D, decreased gastric acidity)</td>
</tr>
<tr>
<td><strong>Other dietary impacts on Ca absorption</strong></td>
<td>o Increased Na intake decreases Ca absorption (saw decreased bone turnover with DASH diet and decreased urinary Ca)</td>
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<tr>
<td></td>
<td>o Increased protein intake increases Ca absorption AND increases urinary Ca → net effect is neutral or positive absorption</td>
</tr>
<tr>
<td></td>
<td>o Mg deficiency can decrease PTH function</td>
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<tr>
<td></td>
<td>o Oxalic acid and phytic acid decrease Ca absorption</td>
</tr>
<tr>
<td></td>
<td>o Caffeine may increase urine Ca (negligible)</td>
</tr>
<tr>
<td></td>
<td>o Vegetarian diet (decreases urine Ca)</td>
</tr>
<tr>
<td></td>
<td>o Vitamin C: cofactor in collagen synthesis</td>
</tr>
<tr>
<td></td>
<td>o Vitamin K: cofactor with osteocalcin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium Deficiency</th>
<th><strong>Rare</strong> in adults because of massive bone reservoir of Ca</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>High risk groups for Ca deficiency</strong> → maintenance of serum Ca is at expense of bone Ca, thus development of deficiency ins a long-term, silent process</td>
</tr>
<tr>
<td></td>
<td>o Premature infants</td>
</tr>
<tr>
<td></td>
<td>o Adolescents</td>
</tr>
<tr>
<td></td>
<td>o Elderly, especially peri-menopausal women</td>
</tr>
<tr>
<td></td>
<td>o Post-bariatric surgery</td>
</tr>
<tr>
<td></td>
<td>o Also consider in pregnant women, renal disease, hypoparathyroid</td>
</tr>
<tr>
<td><strong>Preventing osteoporosis</strong></td>
<td>o Achieve peak bone mass in adolescence</td>
</tr>
<tr>
<td></td>
<td>o Meet nutrient needs (Ca, Vit D, Vit K, protein)</td>
</tr>
<tr>
<td></td>
<td>o Maintain ovulation and regular menses</td>
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<tr>
<td></td>
<td>o Weight-bearing exercise</td>
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<tr>
<td></td>
<td>o Avoid smoking, EtOH, excess Na, steroids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone Remodeling/ Turnover</th>
<th><strong>Osteoclasts</strong> secrete acids/proteolytic enzymes to break down bone, creating an erosion cavity → PTH and Vit D3 promote osteoclast activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>o RANK-L ligand is expressed on osteoblasts (in response to Vit D, PTH, ILs) and binds RANK receptor on osteoblasts to stimulate osteoclast activity</td>
</tr>
<tr>
<td></td>
<td>o OPG osteoprotoerin opposes RANK-L to decrease osteoclast activity (OPG is a <em>“decoy molecule”</em> that binds RANK-L receptor and competitively inhibit RANK-L)</td>
</tr>
<tr>
<td></td>
<td><strong>Osteoblasts</strong> secrete osteoid (high affinity for Ca and phosphate) to increase formation of bone matrix → osteoblasts that become embedded in bone=osteocytes that act as mechanoreceptors</td>
</tr>
<tr>
<td></td>
<td><strong>Every 10 yrs, full turnover of entire skeleton</strong></td>
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<tr>
<td></td>
<td><strong>Ca ingestion is very important in childhood (but also maintaining throughout life) for Ca accretion in bone</strong> → 30-50% of bone mass is created during 10-20 yrs (especially early puberty) AND by the time you are 30, can accrue bone any longer (have reached lifetime bone mass potential)</td>
</tr>
<tr>
<td></td>
<td><strong>Bone formation:</strong> mesenchymal condensation into cartilage → becomes vascularized → primary ossification center (osteoblasts/clasts) → secondary ossification centers</td>
</tr>
<tr>
<td></td>
<td>o <strong>Cortical bone:</strong> more rigid, stiff</td>
</tr>
<tr>
<td></td>
<td>o <strong>Trabecular bone:</strong> higher osteoclast/blast activity; more spongy → absorbs force</td>
</tr>
<tr>
<td>Disorder</td>
<td>General Info</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------</td>
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</tbody>
</table>
| **Hypercalcemia**     | Primary Hyperparathyroidism  
• Due to adenoma (85%) or hyperplasia (15%) or carcinoma (<1%)  
• 90% sporadic but 10% familial  
  o Familial hyperparathyroidism-AD  
  o MEN 1 (mutation in **men** gene): pituitary tumors, pancreatic islet tumors, parathyroid hyperplasia → "3 Ps"  
  o MEN 2A (Ret gene mutated): medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia  | > 50% are asymptomatic  
• "Bone, Stones, Groans, and Moans" → skeletal, kidney, GI, & psychiatric disease  
• Arthritis, muscle weakness  
• Band keratopathy  
• HTN  
• Anemia  
• Can lead to brown tumor  | High PTH or inappropriately normal  
• Elevated serum Ca (also be sure to take urinary Ca to distinguish from familial hypocalcemic hypercalcemia, which will have low urine Ca)  
• Decreased serum phosphate (high PTH increase P excretion)  
• High serum chloride (high PTH stimulates Cl resorption)  | Surgery  
• Recommended if  
  o Ca > 1 mg/dl above normal  
  o Creatinine clearance < 60 ml/min  
  o BMD T-score <-2.5 or fragility fractures  
  o Kidney stones  
  o < 50 yrs  
• If adenoma → remove 1 gland  
• If hyperparathyroidism → remove 3.5 glands (remaining gland tissue is relocated to arm → it will continue growing, but will be easier to access surgically in arm)  
  Calcimetic Drugs  
  Bisphosphonates (protect bone from bone loss)  
  Calcium and Vitamin D & monitor Ca, creatinine, BMD  |
| **Hypercalcemia**      | Tumor types: lung (esp squamous cell), breast (only when metastasis to bone), head and neck, kidney, bladder, pancreatic, ovarian, multiple myeloma, lymphoma  
• Tumors usually release PTH-related peptide (PTH-RP, most common and binds/activates PTH-receptor), TGF-beta, TNF, IL-1, IL-6, RANK L, Vit D3, etc.  | Polydypsia, polyuria, nausea, vomiting, confusion, coma  
• Elevated serum Ca  
• Decreased serum PTH  
• Increased serum PTH-RP  
• Low chloride/phosphate ratio (<30) as opposed primary hyperPTH  |  |  |
| **Other Causes**       | 5% of hypercalcemia fall into this category → majority due to primary hyperparathyroidism and malignancy  
• Secondary hyperparathyroidism (from some condition causing low Ca, high phosphate, or low Vit D)  
• Granulomatous disease  
• Vit D intoxication or Vit A intoxication  
• Hyperthyroidism  
• Thiazide diuretics  
• Milk-alkali syndrome  
• Immobilization  
• Adrenal insufficiency or Acute renal failure  |  |  |  |
| **Hypocalcemia**       | Rickets (kids) & Osteomalacia (adults)  
• Impaired bone mineralization (inadequate Ca and/or phosphate) → soft weak bones  | Bowing of weight bearing bones (long bones), flaring ends of long bones  
• Fractures and pseudofractures (Milkmans fractures, Loosers lines)  
• Osteomalacia: pain (long bones) deformities, fractures  
• Rickets: pain (long bones), deformities, muscle weakness, short stature, delayed epiphyseal calcification  
General hypocalcemia symptoms  
• Paresthesias  
• Muscle cramps and weakness  
• Chvostek's sign (facial nerve spasm when tap facial nerve)  
• Trousseau's sign (hand spasm with blood pressure cuff)  | Low serum and urine Ca  
• Low phosphate  
• High alk phos  
• High PTH  
• Measure 25, OH Vit D. to distinguish between different disorders (reflects Vit D stores and low value diagnostic of Vit deficiency)  |  
| **Vitamin D Disorders** | Acquired Vit D deficiency: poor intake, malabsorption, inadequate sunlight  
• Acquired Vit D3 deficiency: renal disease, hypoPTH  
• Congenital 1 Alpha Hydroxylase Deficiency ("Vit D dependent Rickets Type 1")  
• Congenital Vit D Receptor Deficiency ("Vit D dependent Rickets Type 2")  |  |  |  |
| **Phosphate Disorders** | Acquired hypophosphatemia: poor intake, renal phosphate wasting  
• Congenital Hypophosphatemia Rickets ("Vitamin D Resistant Rickets" accounts for 95% of Rickets): also has renal phosphate wasting and impaired Vit D3  |  |  |  |
| **Calcimetic Drugs**   | Bisphosphonates (protect bone from bone loss)  
• Calcium and Vitamin D & monitor Ca, creatinine, BMD  |  |  |  |
### Hypoparathyroidism (continued)

- **Osteoporosis**
  - Contributes to ~1.5 million bone fractures/year
  - ~25% of women >50 yrs develop osteoporosis
  - ~25% of >50 yrs who have fracture will die within one from fracture related complications
- **Risk factors**
  - Bone Mass Density: 70-80% of peak bone mass is determined by genes
  - Hypogonadism
  - Age; short stature
  - Family history
  - Early menopause
  - Medications (esp corticosteroids)
    - Decreased lifetime Ca intake, low Vit D, low protein intake, low phosphorus, high Na intake
  - Modifiable (smoking, alcohol, lack of weight bearing exercise → muscle mass proportional to bone mass)
- **Paget’s Disease**
  - Idiopathic bone condition characterized by excessive/unregulated bone resorption and formation
  - Combination of genetic predisposition and chronic paramyxovirus infection
    - Genetics:
      - Familial aggregation (15-40%)
      - 18 q linkage, mutation of OPG gene
      - Mutation of SQSTM1/P62 gene in 40-80% of familial Paget’s
  - Environment:
    - High prevalence in US, Western Europe, Australia; low in Asia/Africa
    - Dog ownership
    - Measles
    - Paramyxovirus infection (can get inclusions in osteoclasts)
- **Pain (important), deformity (less common)**
  - Fractures
  - Osteoarthritis
  - **Hypervascularity**
    - Acetabular protrusion
    - Increased risk of osteogenic sarcoma
    - Common sites of involvement: monostotic (one site) or polyostotic (many sites) → pelvis, skull, vertebrae, femur, tibia
  - Neurological symptoms
    - Deafness (compression of CN8)
    - CN compressions by bone
    - Spinal cord compression by hypervascularity
  - **Cardiovascular**
    - Atherosclerosis, aortic stenosis, CHF

### Hypocalcemia

- Fragility fracture is diagnostic → once you’ve had one fragility fracture, have 5x greater risk of future fracture, even if have same bone density
- Low bone mass is not always osteoporosis → can be from many causes i.e. osteogenesis imperfecta, hyperparathyroidy, hyperthyroidy, medications (GC’s, excess TH, anticonvulsants, etc), Cushing’s, many more!
- **Fragility fracture is diagnostic**
  - Bone Mineral Density T-Score
    - > -1 is normal
    - -1 to -2.5 = osteopenia
    - < -2.5 =osteoporosis
    - Score represents standard deviations below peak bone mass
  - **Bone densitometry** used to diagnose osteoporosis
    - Labs to order for low bone mass: Ca, alk phos, creatinine, Vit D, testosterone (in men); TSH, TTG (celiac), 24 hr urine Ca/Na/Creatinine
    - High bone turnover: urine NTX/CTX (bone resorption marker), high serum alk phos (bone formation marker)
  - Can use FRAX Tool (developed by WHO) to evaluate risk of developing osteoporosis (useful to monitor osteoporotic patients)

### Other causes of hypocalcemia

- **Hypoparathyroidism** (only hypocalcemia with low PTH, high serum phosphate → can be autoimmune, post-op, Mg deficiency)
- **Pseudohypoparathyroidism**
  - Inactivating mutation of-G-alpha subunit or downstream signaling molecule PTH-receptor
  - Low Ca, high phosphate, high PTH, short fingers/metacarpals
  - Treat with Ca (1000-3000 mg/d), calcitriol (.25-1 ug/d), thiouze diuretic
- **Hypomagnesemia**
- **Renal failure**
- **Liver Failure**
- **Acute pancreatitis**
- **Hypoprotenemia** (need to correct calcium by adding .8mg/dl for every 1g/L albumin is < 4.0 g/L)

### Prevention and Treatment

- **Calciium**: 1000-1500 mg/d
- **Vit D**: 1000 U/day
- **Exercise**: aerobic and resistance
- **Fall assessment** and prevention
- **Inhibit bone resorption** (Bisphosphonates, denosumab, reloloxifene, calicitin)

### Treatment indications

- Pain, deformity, or fracture
- Weight bearing bone involvement
- Extensive skull involvement
- Neuro involvement
- Impending surgery on pagetic bone
- Immobilization hypercalcemia
- Alk phos > 2x of normal

### Treatment

- **Anti-resorptive agents** (bisphosphonates, calcitomin)
- **Analgesics/NSAIDs**
- **Corrective surgery**

### Labs depend on where in clinical course

- 1. High osteoclastic phase (~10 yrs): high urine NTX/CTX (bone resorption marker)
- 2. High osteoclastic and osteoblastic (~10 yrs): high NTX/CTX and high serum alk phos (bone formation marker) → Paget’s usually diagnosed here
- 3. High osteoblastic (~10 yrs): low NTX/CTX and variable alk pho

### Imaging

- X-ray features are very specific, bone scan (focal areas of intense uptake) is very sensitive
  - Osteolytic lesions (“blade of grass sign” in long bones, resorption front in flat bones)
  - Thickened, disorganized trabeculae
  - Thickened, expanded cortex
  - Expansion of bone size

### Histology

- Increased osteoclasts, increased osteoblast nuclei, increased osteoblasts in periiphery, disorganized bon
### Pharmacology of Calcium Homeostasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>General Info &amp; Mech</th>
<th>Kinetics</th>
<th>Uses</th>
<th>Adverse/Notes</th>
</tr>
</thead>
</table>
| Calcium Repletion and Supplements | - Recommended only if dietary intake insufficient  
  o Adolescents: 1300 mg  
  o 19-50 yrs and men 50-70 yrs: 1000 mg  
  o Men > 70 yrs and women > 50 yrs: 1200 mg | - Calcium carbonate has greatest percentage of calcium (40%)  
  - Take calcium carbonate with meals: calcium citrate between meals | - Severe acute HYPOcalcemia: IV Ca gluconate  
  - Chronic HYPOcalcemia: Ca-carbonate or Ca-citrate | - Well tolerated, some GI upset |
| Loop Diuretics               | - Loop diuretics increase Ca excretion                                             | - Not discussed                                                         | - HYPERcalcemia                                                        | - These patients are often severely dehydrated, so be sure to fluid resuscitate early/aggressively |
| Vitamin D and Analogs        | - Recommended intake  
  o < 70 yrs: 600 IU  
  o > 70 yrs: 800 IU  
  o Safe upper limit of intake is 4000 IU | - Cholecalciferol (D3): preferred agent because of modest cost and efficacy  
  - Ergocalciferol (D2): less efficient than D3 (is what is found in food) → should use D3 instead  
  - Calcifediol - 25(OH)D3: Doesn't require liver hydroxylation, so useful in liver disease patients  
  - Calcitriol - 25(OH)2D3: best for patients with decreased synthesis of calcitriol (i.e. Vit D Dependent Rickets Type 1, chronic renal failure)  
  - Dihydrotachysterol: uses same as calcitriol, just an alternative drug | - GI (heartburn, abdominal pain, diarrhea)  
  - Esophagitis have to stand upright for 30-60 min after admin, no food and full glass of water  
  - Can get severe bone, joint, muscle pain; rarely osteonecrosis of jaw | - Toxicity signs are hypercalciuria and hypercalcemia |
| Bisphosphonates              | - Pyrophosphate analogs that incorporate into bone (high affinity for Ca)  
  - Promote osteoclast apoptosis and inhibit osteoclast function | - 1-10% oral absorption  
  - Not recommend if low GFR  
  - Alendronate/Risedronate are 1x/week  
  - Zoledronate is 1x/year | - First line choice in osteoporosis  
  - Mainstay of hypercalcemia of malignancy treatment  
  - Alendronate/Risedronate are first line, Zoledronate IV is only for pts who can’t tolerate oral | - Related to increased estrogen-like activity: hot flashes, leg cramps, increased risk of thromboembolic disorders |
| SERMs (Selective Estrogen Receptor Modulators) | - Decreases osteoclast activity (induce OC apoptosis) and increase OPG | - Not discussed                                                         | - Second line if patient can’t take bisphosphonates or increased risk for invasive breast cancer  
  - Note that estrogen itself is no longer recommended for osteoporosis (risks> benefits) | - Nausea, HA, dizziness, severe muscle pain  
  - Limit daily Ca to avoid hypercalcemia |
| PTH Analog                   | - Synthetic PTH administered intermittently → increases osteoblastic (bone formation) activity | - Daily subcutaneous admin                                               | - Treatment of severe osteoporosis (expensive) | - Nausea, HA, dizziness, severe muscle pain  
  - Limit daily Ca to avoid hypercalcemia |
| Calcitoxine                  | - Inhibit osteoclast bone resorption                                              | - SQ or nasal spray                                                      | - Used for treatment (NOT prevention) of osteoporosis  
  - Useful if back pain is a problem  
  - May be useful in hypercalcemia | - Nausea, hand-swelling, urticaria cramps  
  - Rhinitis and epistaxis with intranasal admin |
| RANK-L Antibody Denosumab    | - Bind RANK-L and prevent it from stimulating osteoclast activity                | - SQ injections every 6 months                                            | - For patients who are at high risk for fractures or unresponsive to bisphosphonates | - Well tolerated (sometimes flu-like sx) |
| Thiazide Diuretics           | - Thiazides decrease Ca excretion                                                | - Doses usually higher than those for HTN                                | - For hypercalcuria                                                      | - Not discussed |
| Glucocorticoids              | - Decrease Ca absorption, increase Ca excretion                                  | - High dose prednisone, response in 2-5 days                             | - For chronic hypercalcemia                                             | - Refer to Cushing’s effects |

**NOTES**
- Primary osteoporosis  
  - Loss of trabecular bone in postmenopausal women due to INCREASED osteoclast activity  
  - Aging in both men and women due to DECREASED osteoblast activity  
- Secondary osteoporosis (from systemic illness i.e. thyrotoxicosis, Cushing’s syndrome, hyperparathyroidism or drugs i.e. GCS or phenytoin)  
- Non-pharmacological therapy of osteoporosis: 1) increase dietary Ca/Vit D 2) Increase exercise, esp weight bearing exercise and 3) smoking cessation 4) fall assessment and prevention