Endocrinology

Umm…What is that?
And what do I do about it?

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Disclosures

I have no relevant relationships with ineligible companies to disclose within the past 24 months.

Educational Objectives

- Have an understanding of common endocrinology disorders
- Recognize signs and symptoms
- Order appropriate labs and imaging
- Recommend correct treatment and monitoring
- Know when to refer to endocrinology

34 YO female presents with the following symptoms….diagnosis?

- Tired
- Gaining weight
- Feeling more depressed
- Brain fog

A Busy mom….but wait, maybe that's not all!

Hypothyroidism

- Inadequate production of thyroid hormone
- When thyroid hormone levels are low -> cell metabolism altered

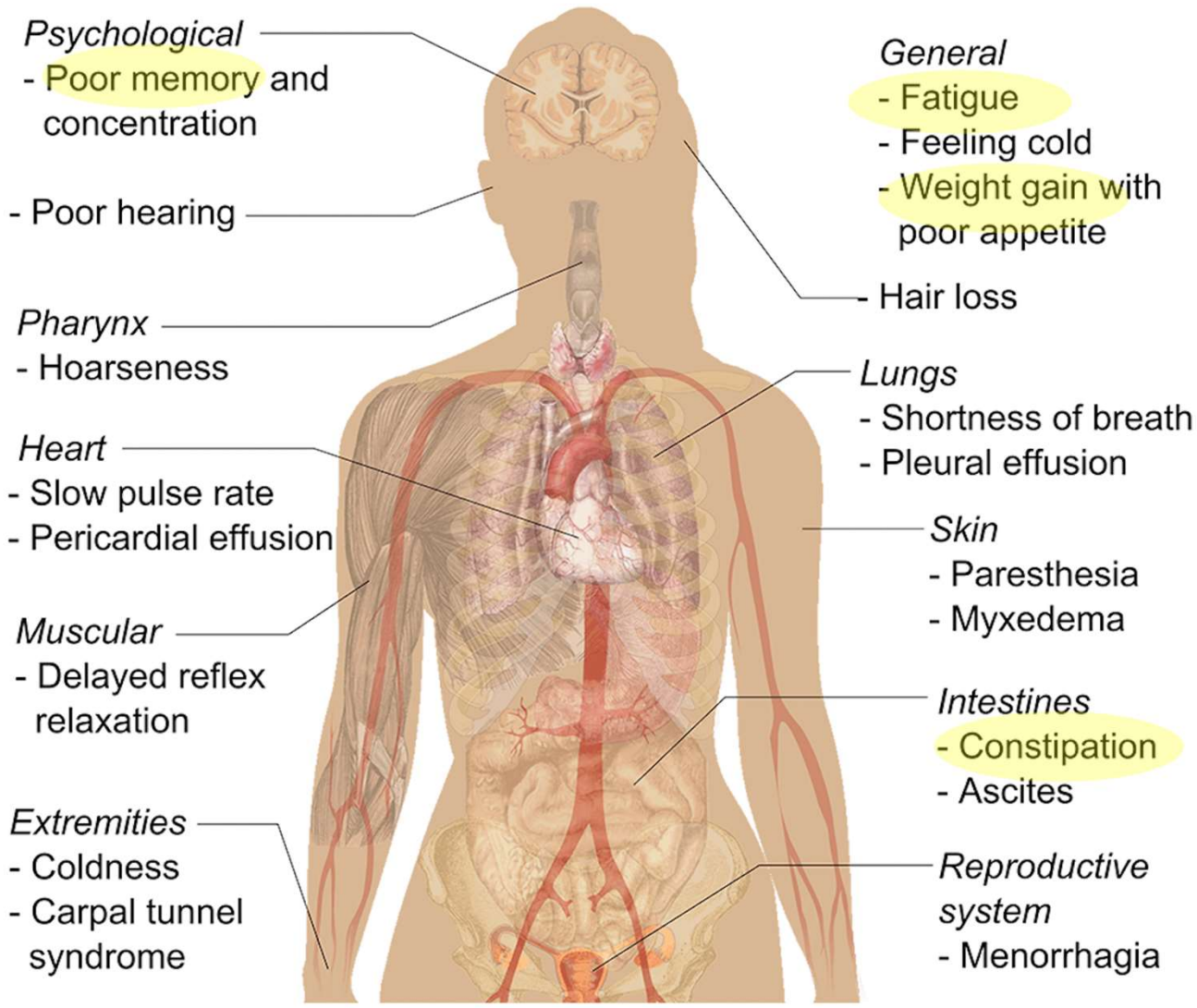


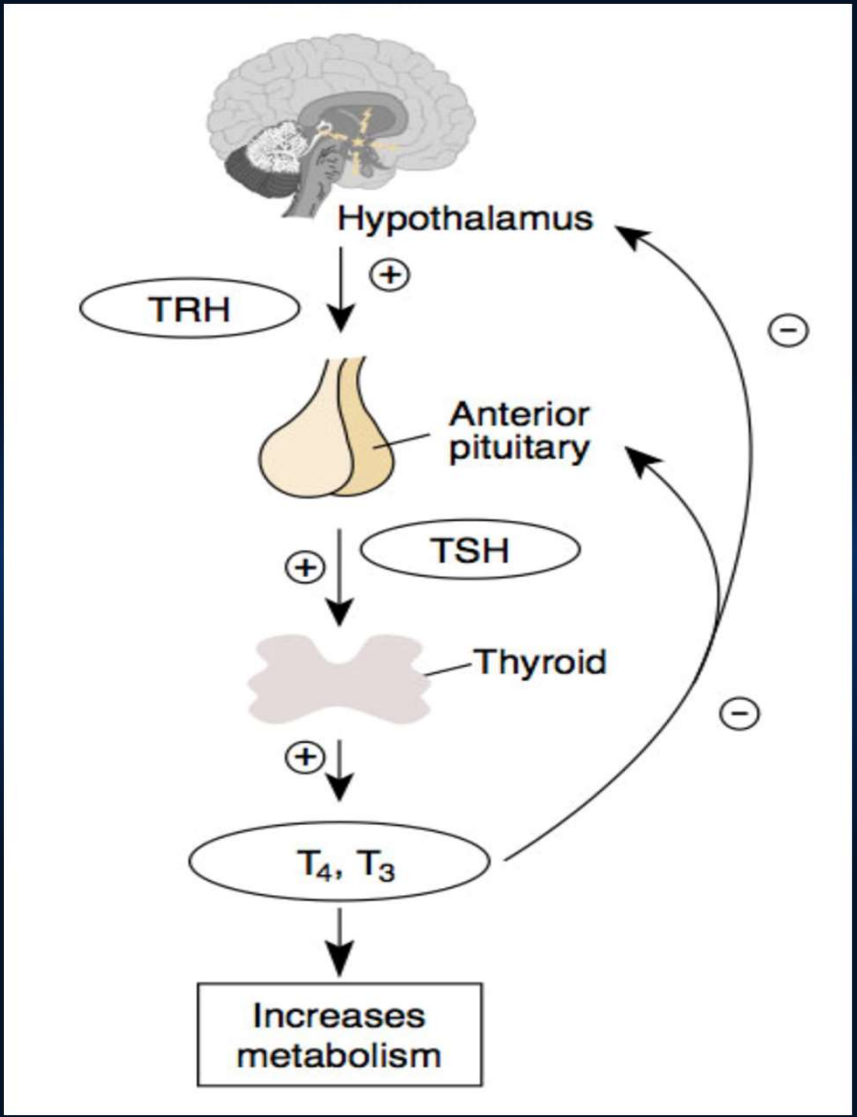
Image via: Wikipedia.org

Labs

- TSH
- Free T4
- T3 measurements are of little use
- rT3 is of no use
- Thyroid Peroxidase (TPO) antibodies
  - Not necessary for diagnosis, Elevated in 90% of patients with chronic autoimmune thyroiditis
  - Positive TPO with normal TSH is NOT Hypothyroidism
- Thyroglobulin antibodies (TG)

Type	TSH	Free T4
Primary Hypothyroidism	Elevated	Low
Subclinical Hypothyroidism	Elevated	Normal
Secondary Hypothyroidism	Normal or Low	Low

Hypothalamic Pituitary Thyroid Feedback Axis



Hill MA. (2019). Two Web Resources Linking Major Human Embryology Collections Worldwide. *Cells Tissues Organs (Print)* , , 1-10. PMID: 30673660 DOI.

Causes of Primary Hypothyroidism

Autoimmune mediated thyroiditis (Hashimoto's)	Positive antithyroid antibodies; other autoimmunity
Postablative	Following RAI ablation, surgery
Transient thyroiditis	Hypothyroid phase usually transient
Drugs	Lithium (5–15%), amiodarone (7–22%), Alemtuzumab, valproic acid, TKIs (27%), checkpoint inhibitors (1.5%–10.8%), IFN-γ.
Infiltrative disease	Hemochromatosis, amyloidosis, sarcoidosis, scleroderma, leukemia, cystinosis – RARE
Genetic	Thyroid agenesis/dysgenesis, dyshormonogenesis
Head and neck radiation	History of treatment of head and neck cancer
Neoplasia	Primary or metastatic (very rare)

Okosieme, OE, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nature reviews endocrinology. 2018.

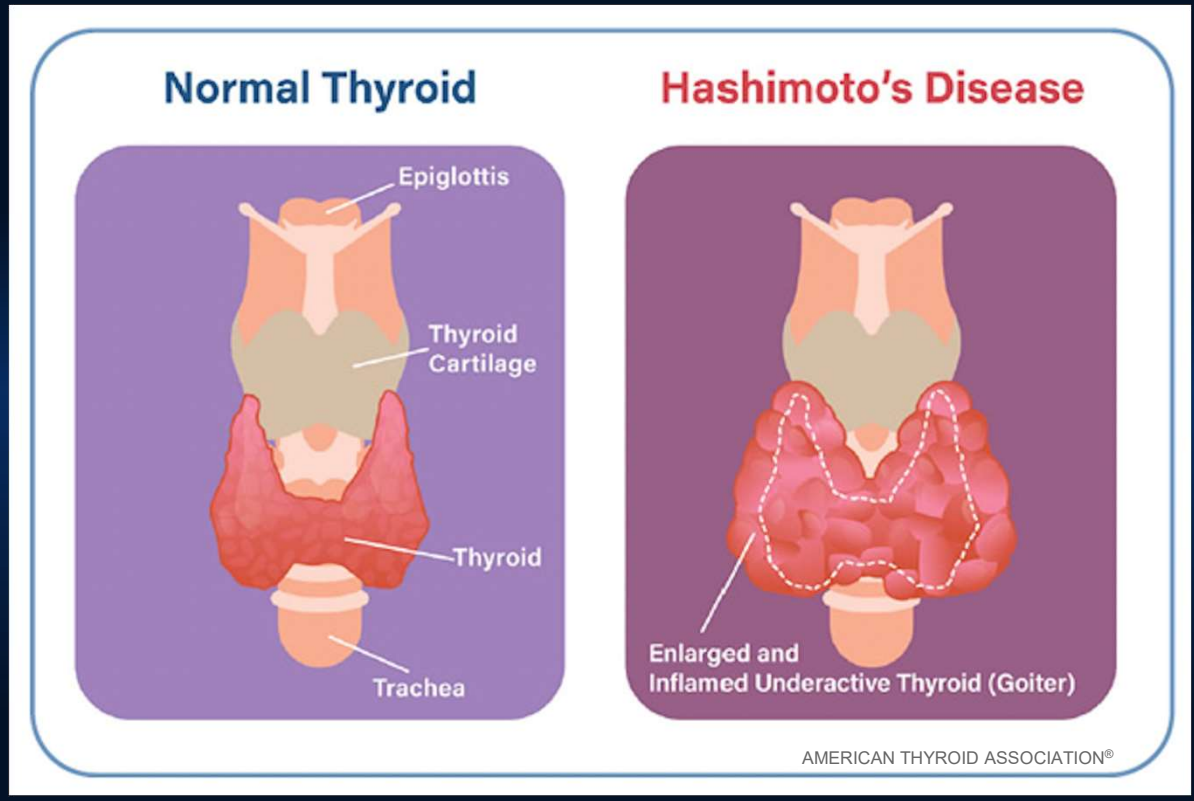
What is Hashimoto's

- **Autoimmune disorder**

➡ TPO and/or Tg antibodies develop

➡ causes inflammation of the thyroid gland

  - Goiter
  - Trouble making enough T4 (hypothyroidism)



Hashimoto thyroiditis – precipitating factors

Most common cause of hypothyroidism in the US
Most common in women, but can also affect men
More common in older, but can occur at any age

Genetic susceptibility

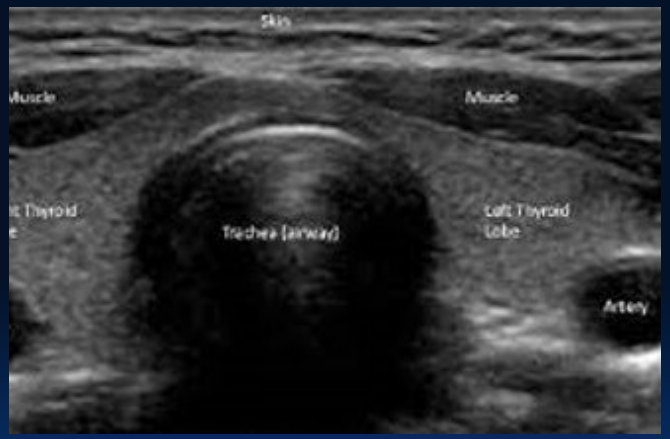
Thyroid injury:
Infection, Radiation, Drugs

Stress (physical or psychological)

Pregnancy

High Iodine intake

Normal Thyroid Ultrasound



Heterogeneous echotexture in chronic thyroiditis

Imaging

- Thyroid ultrasound is NOT necessary for diagnosis
- If performed, may show evidence of autoimmune thyroiditis

Tan GH, Gharib H. Thyroid incidentalomas: Management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Annals of Internal Medicine. 1997.

Treatment of hypothyroidism

- Goal: Normal TSH
- Drug of choice is T4
  - Levothyroxine
- Initial Dose
  - 1.6mcg /kg (Predicted full dose)
  - Start low and work up to full dose for young/healthy patients
  - Older patients/CAD/Hx afib, start *LOW* (25-50mcg)

Brito JP, et al. Comparative Effectiveness of Generic vs Brand Name Levothyroxine in Achieving Normal Thyrotropin Levels. JAMA. Netw open .2020.

Taking LEVOTHYROXINE Correctly

- Empty stomach
- Ideally at the same time every day
- Wait 30 - 60 minutes before eating or other medications
- If taking at night, wait at least 4 hours after eating or any medication
- MVI, Ca, Iron interfere with absorption if taken within 4 hours
- Missed dose - take 2 pills the next day

Monitoring

- After Initiation of T4
  - TSH typically repeated in **6 weeks**

- If repeat TSH is **HIGH**
  - Ensure adherence to dose/timing
  - Typically increase the dose 10-20%
  - Repeat TSH in 6 weeks

- If repeat TSH is **LOW**
  - Typically decrease dose 10-20%
  - Repeat TSH in 6 weeks

Maintenance Dosing

- Check TSH every 6-12 months
- Sooner if:
  - Pregnancy
  - Weight change of 10%
  - New RX of interfering med (including OCPs)

When to refer to Endocrinology

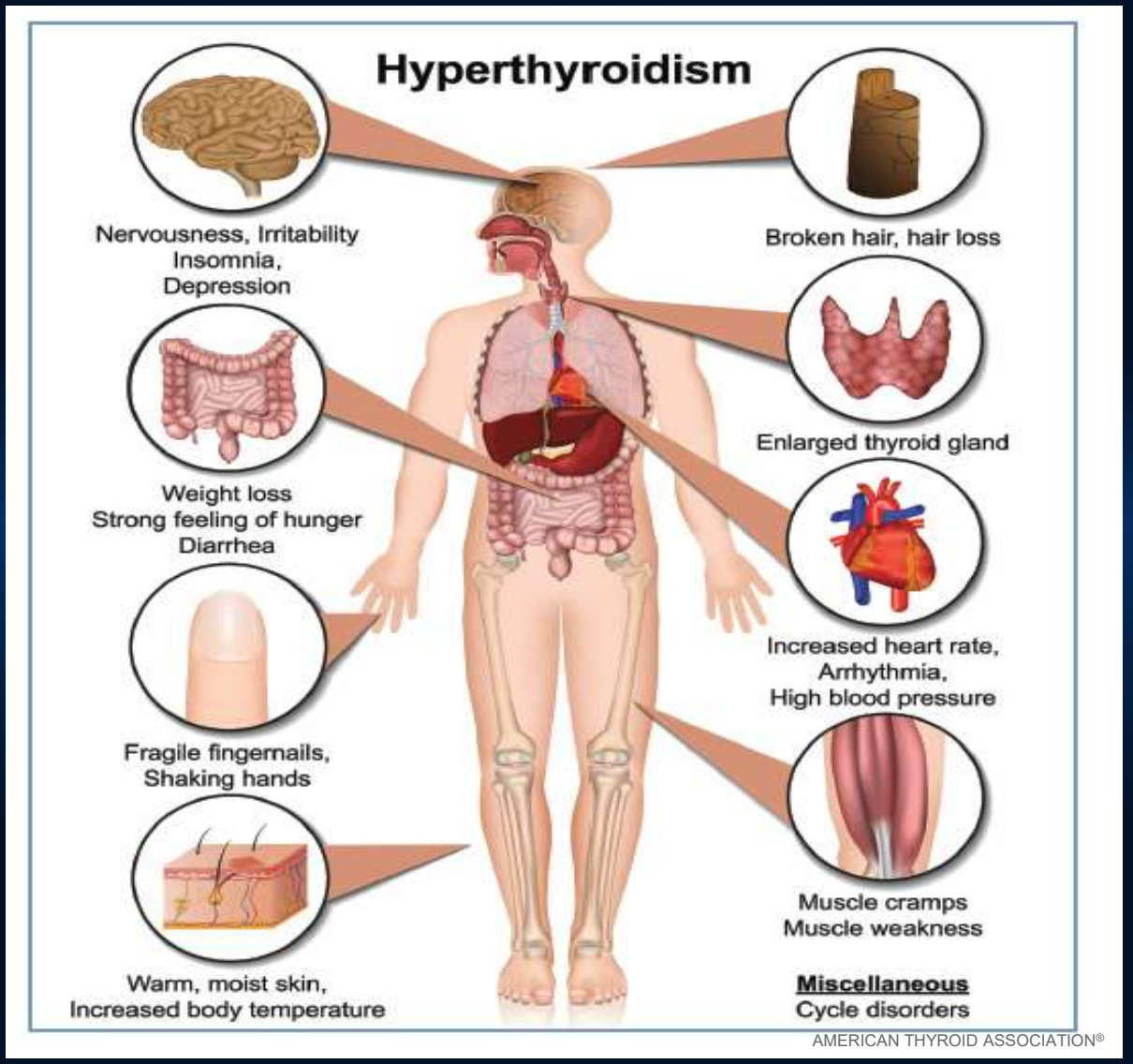
- Numerous medication dose changes
- Suspected malabsorption
  - Patients requiring doses far higher then 1.6mcg/kg
- Pregnant patients (Patients pre-pregnancy who aren’t controlled)

Hyperthyroidism

Excess production of thyroid hormone

Symptoms

- Anxiety/emotional lability
- Palpitations
- Heat intolerance
- Increased BM freq
- Sweating
- Weight loss
- Weakness



Physical Exam Findings

- Tremor
- Tachycardia
- Rapid speech/restlessness
- Lid lag/exophthalmos
- Skin: warm, moist, Plummer’s nails, alopecia/vitiligo
- Goiter/thyroid nodules/painful thyroid

Labs

- TSH is **LOW**
  - Check T4 Free and T3 Total
- Check CMP, CBC
- TRAb (Thyrotropin Receptor Ab)

Causes of Hyperthyroidism

Graves' disease	Too much hormone	Subacute/painful thyroiditis	Toxic multinodular goiter
Solitary Toxic nodule	Hyperemesis graviduram	Amiodarone	IV Contrast with Iodine

Low TSH – Non-thyroidal causes

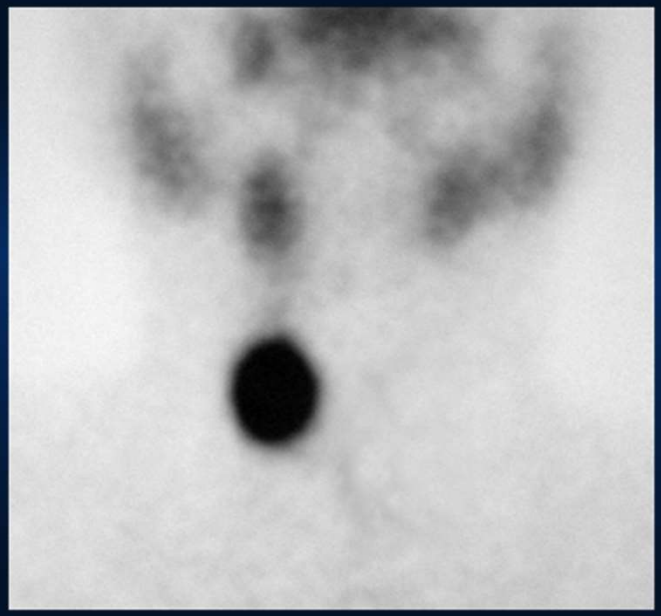
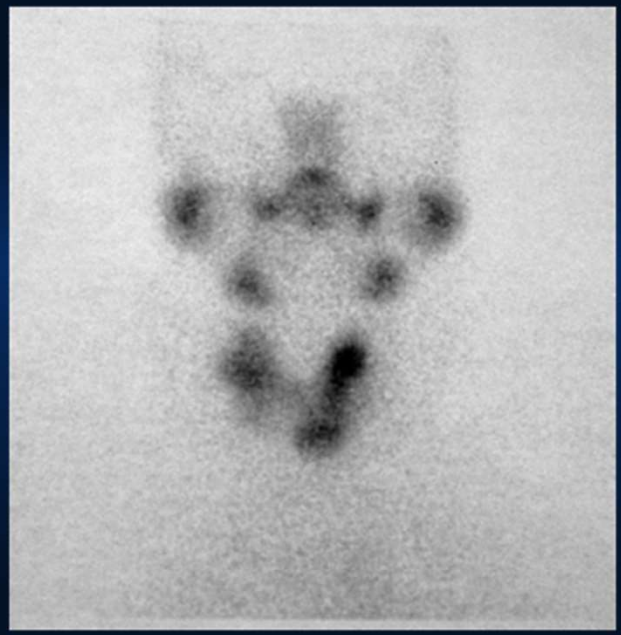
- Sick euthyroid
- Pituitary/Hypothalamic dysfunction
- Supplements that contain surreptitious T4
- Biotin use interferes with lab assay
  - Must not take Biotin for at least 2 days before TSH test.

Imaging

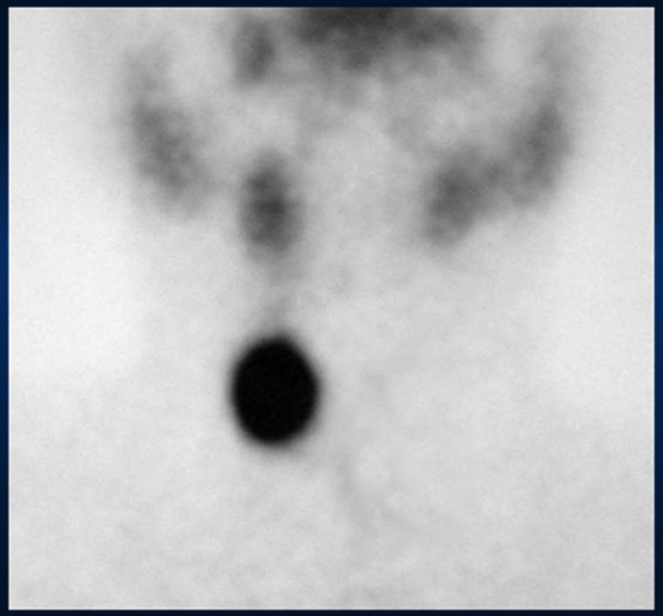
- If TRAb is positive -> Graves' Disease
  - No imaging
- If TRAb is negative -> consider thyroid US to assess for nodules and radioiodine uptake scan

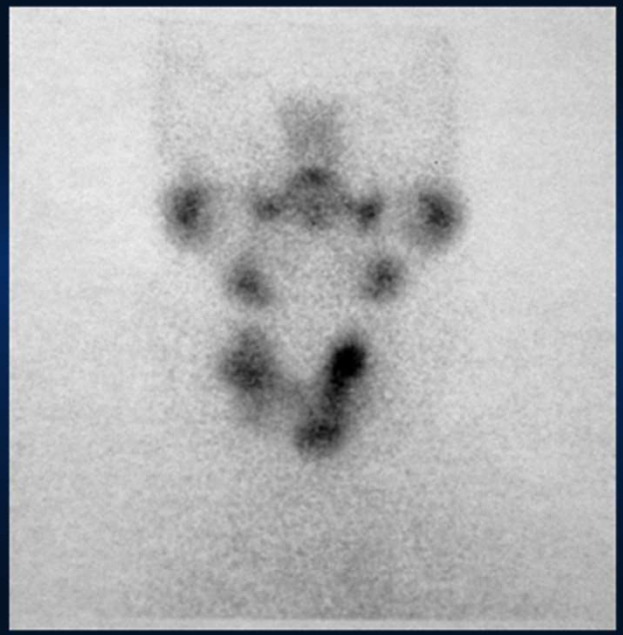
Radioiodine Uptake Scan – I 123

- High Uptake
  - Graves' Disease (diffuse uptake) – Not necessary if TRAb +
  - Toxic multinodular goiter (patchy uptake)
  - Toxic adenoma
- Low Uptake
  - Iodine induced thyrotoxicosis (Rare)
  - Thyroiditis - Inflammation and destruction of thyroid tissue
  - Factitious thyrotoxicosis/Extrathyroidal source of thyroid hormone
- Contraindicated in Pregnancy and Breastfeeding

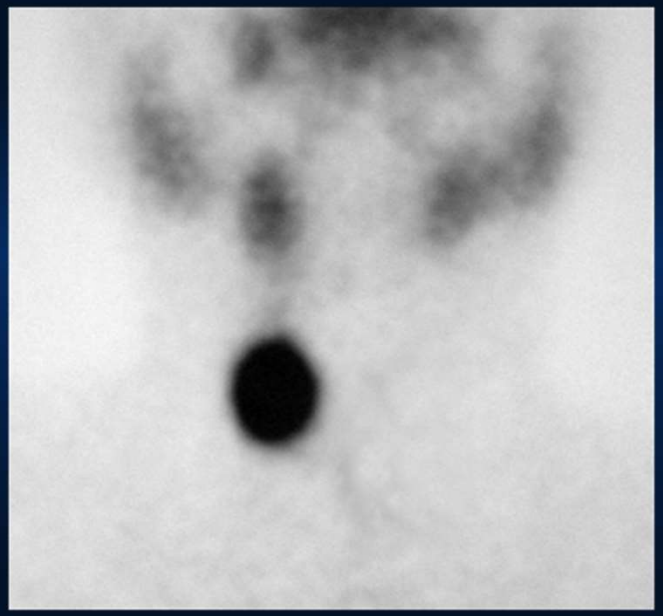
Graves’

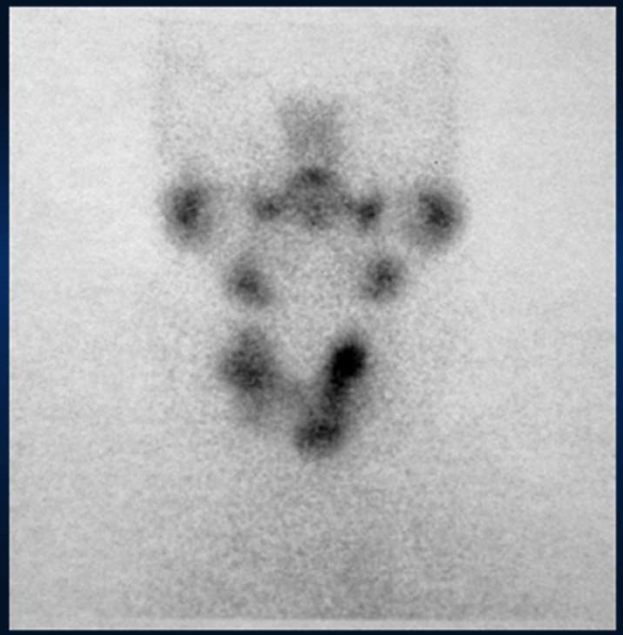




Graves’

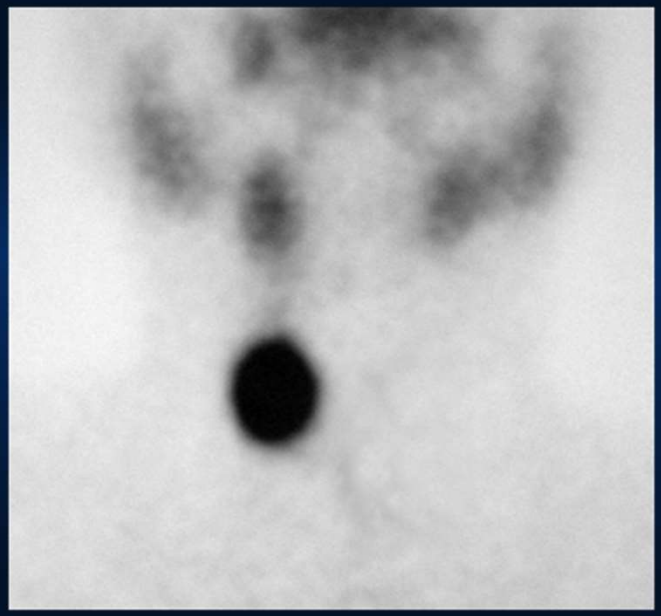
Toxic adenoma



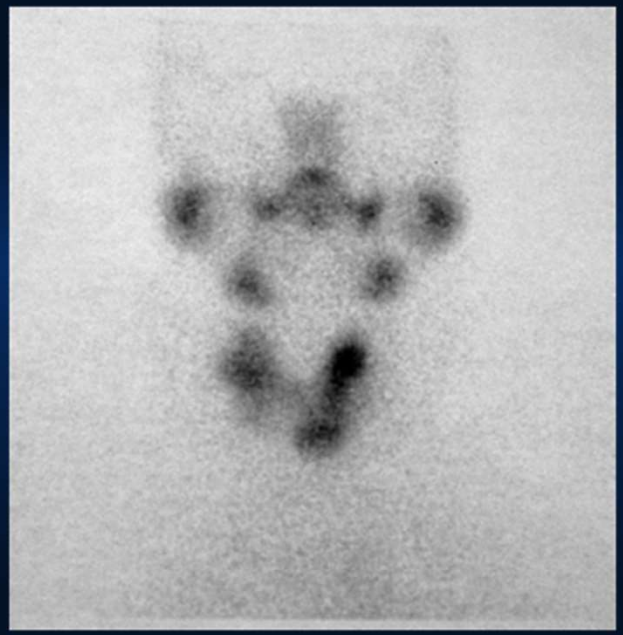


Graves’

Toxic adenoma



Toxic MNG



Graves' disease (most common)

- Autoimmune disease
  - May consist of:
    - Hyperthyroidism
    - Goiter
    - Thyroid eye disease (orbitopathy)
    - Dermopathy (pretibial or localized myxedema)

Graves' disease

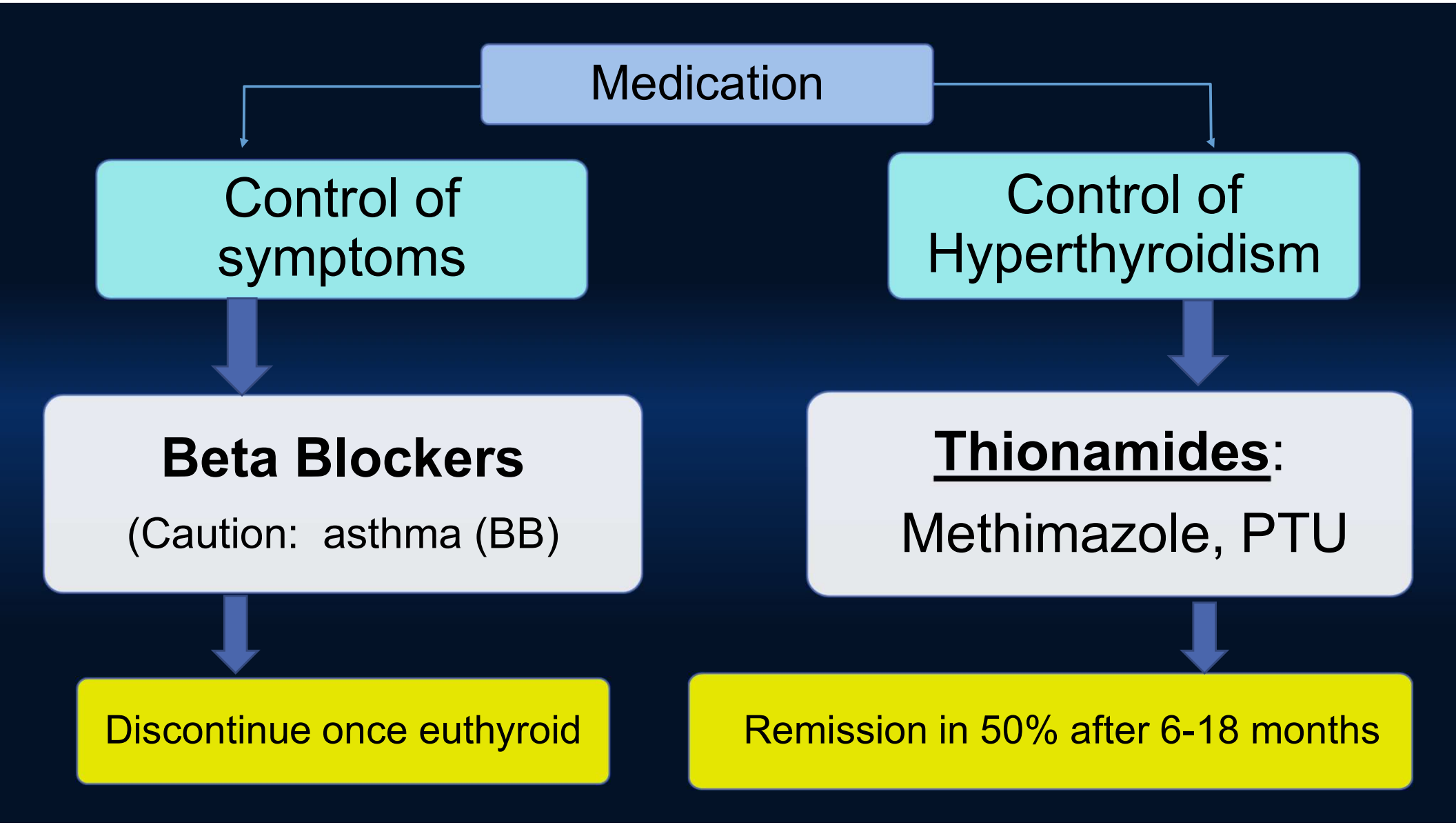
- Labs
  - T4/T3 levels **HIGH**
  - TSH **LOW**
  - TRAb +

Treatment – Graves' Disease

MEDICATION

RAI – I131

THYROIDECTOMY


Medication
Control of symptoms
Control of Hyperthyroidism
Beta Blockers
(Caution: asthma (BB)
Thionamides:
Methimazole, PTU
Discontinue once euthyroid
Remission in 50% after 6-18 months

Methimazole Dosing

- **Free T4 1 - 1.5 X the ULN ->** 5 to 10 mg once daily.
- **Free T4 1.5 - 2 times the upper limit of normal**
  - 10 to 20 mg once daily
- **Free T4 2 - 3 times the upper limit of normal**
  - 20 to 40 mg daily (divided) – i.e. 10mg TID or 15mg BID

Monitoring

- Recheck TSH and FT4 every 4 – 6 weeks
  - T4 levels decrease quicker than TSH.
  - Decrease dose according to T4 level
  - Taper slowly down to maintenance dose
- Check TRAb every 6 months to help determine remission

Thionamide Adverse Reactions

- Common
  - nausea, GI upset, headache, rash, arthralgia.
- Rare
  - agranulocytosis, vasculitis, and hepatitis (more common with PTU)
  - severe sore throat, fever, -> Urgent CBC
  - oral ulcers, jaundice, light-colored stool, dark urine, pruritic rash -> Urgent LFTs
  - Monitor LFTs and CBC with each TFT check

Radioiodine Ablation

- May be a primary treatment for hyperthyroidism
- Secondary option if…
  - Anti-thyroid medication has failed to control hyperthyroidism.
  - Severe adverse events with Thionamides

Surgery - Thyroidectomy

- Patients unable undergo RAI or uncontrolled on meds
  - Pregnant women
  - Those with small children who are unable to comply with restrictions of RAI
  - Severe ophthalmopathy
  - Severely enlarged nodular goiter
- Goal: Euthyroid state prior to surgery (Normal FT4)

Subclinical Hyperthyroidism

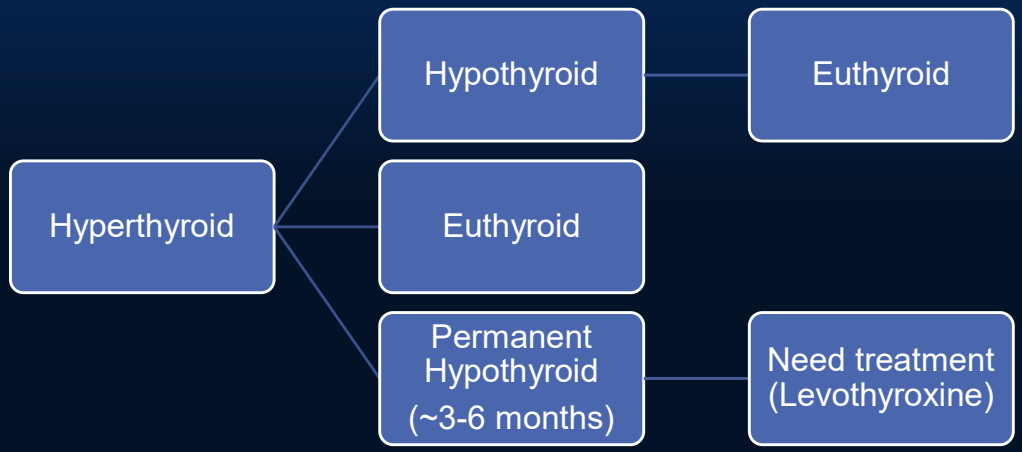
- Most of these patients have no clinical manifestations of hyperthyroidism, and those symptoms that are present are mild and nonspecific.
- Exam: Normal or thyroid enlargement/nodular
- Labs: TSH **LOW** and T4/T3 Normal
- Causes: same as the causes of overt hyperthyroidism
- Evaluate: TRAb, ultrasound, +/- RAI scan

When to Treat

- Subclinical hyperthyroidism associated with an increased risk of atrial fibrillation, coronary heart disease, heart failure and osteoporosis
- Treat if TSH <0.1mU/L for patients with high risk for cardiac or skeletal complications
  - Same treatment as Graves'

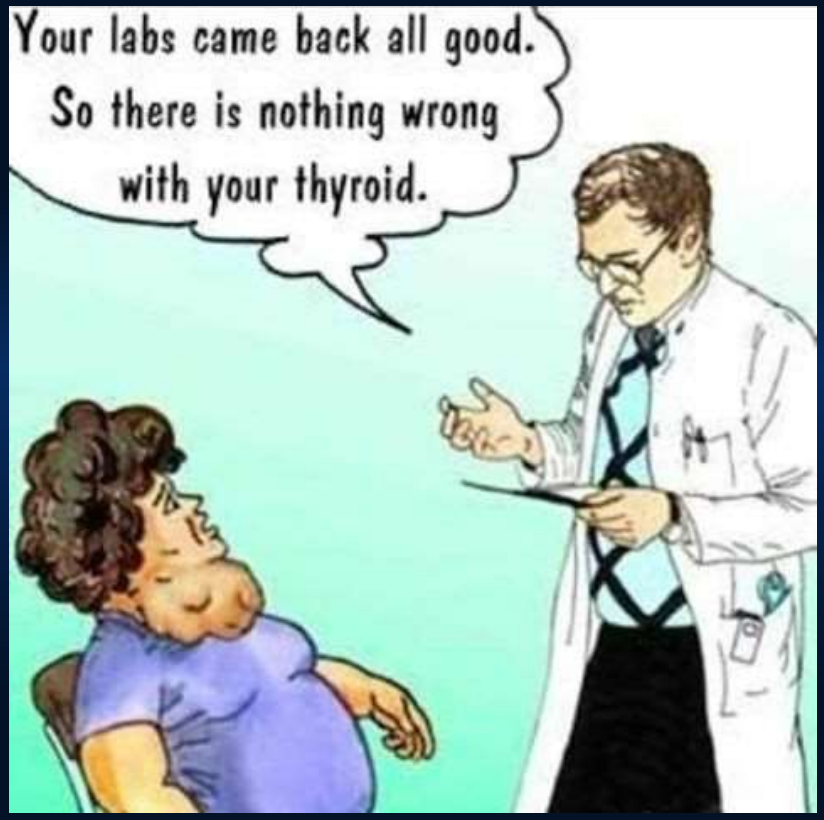
Thyroiditis

- Painless ("silent or lymphocytic") thyroiditis and postpartum thyroiditis - thyroid – temporary inflammation, release of thyroid hormone stores, transient hyperthyroidism.
- Painful thyroiditis is thought to be virus induced. Painful, tender, enlarged thyroid gland. Use NSAIDs or Steroids for symptom relief.
- Not treated with Thionimides – Not a thyroid hormone production problem.



Refer to Endocrinology

- When unable to achieve a euthyroid state despite treatment
- Unable to figure out underlying cause
- Pregnancy



Thyroid nodules

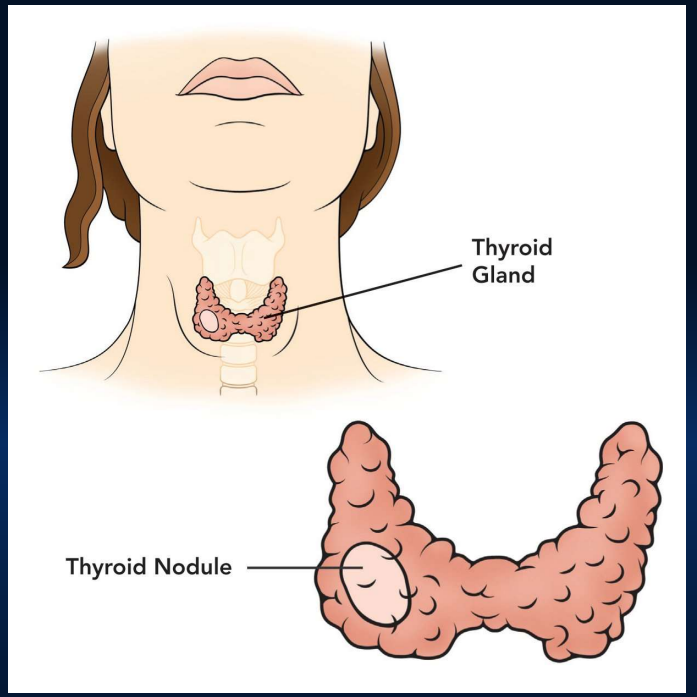
Thyroid nodules are common (up to 50% of adults in US)

-palpable (4-7%)

Palpable and nonpalpable nodules of same size have same malignancy risk

The risk of cancer in a thyroid nodule is small

(~4-6.5%), BUT not insignificant

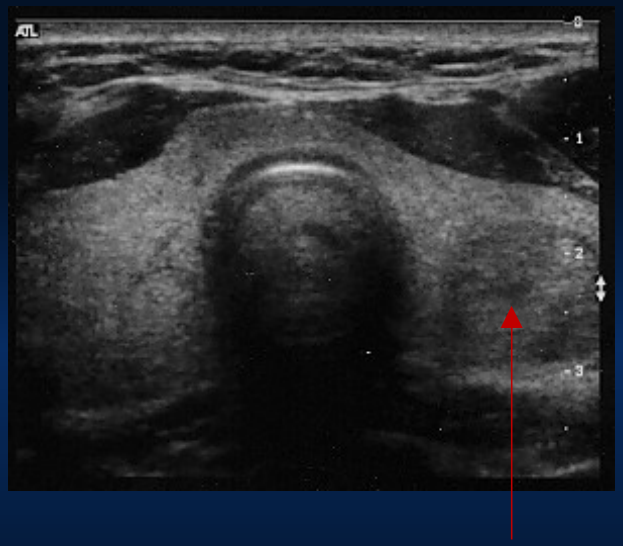


Sign/Symptoms

- Dysphagia
- Dysphonia
- Fullness sensation
- Visible bulge
- Palpable nodule

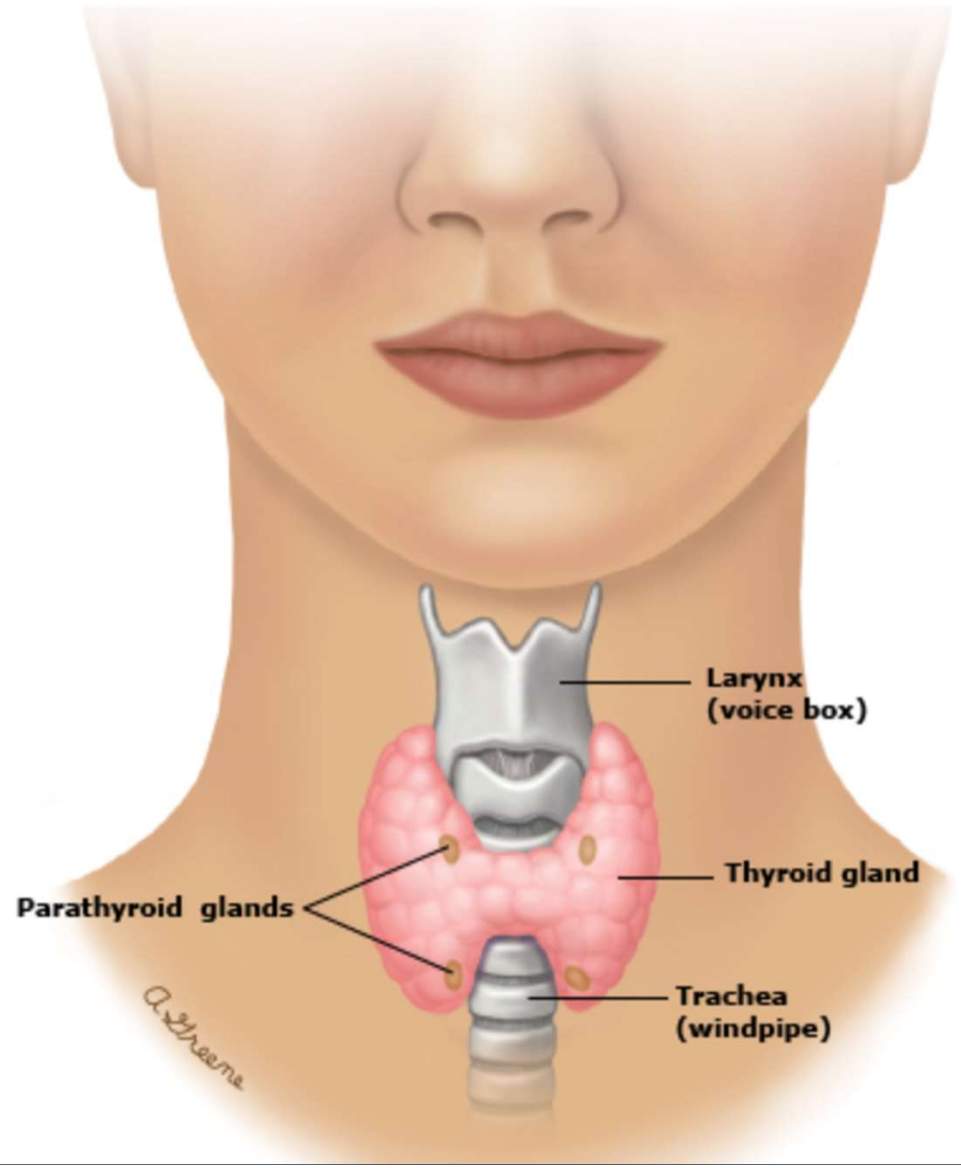
Imaging – Thyroid Ultrasound

- ACR TI-RADS guidelines:
- TR 1 (0 points) and TR 2 (2 points) = no FNA or follow-up
- TR 3 (3 points) = FNA if greater than or equal to 2.5 cm, follow-up ultrasound if 1.5-2.4 cm in 1, 3 and 5 years
- TR 4 (4-6 points) = FNA of greater than or equal to 1.5 cm, follow-up ultrasound if 1.0-1.4 cm in 1, 2, 3 and 5 years
- TR 5 (greater than or equal to 7 points) = FNA if greater than or equal to 1 cm, follow-up ultrasound if 0.5-0.9 cm every 1 year for 5 years.



Thyroid cancer

- Risk Factors
  - Family Hx, Radiation exposure
- Thyroid nodule on exam or incidental from imaging
- Diagnosis via US biopsy - > Refer to surgery and endocrinology
- T4 given post thyroidectomy
- Goal: Keep TSH lower and T4 normal



Parathyroid disease

- Hyperparathyroidism
  - Primary
  - Secondary
  - Tertiary
- Hypoparathyroidism

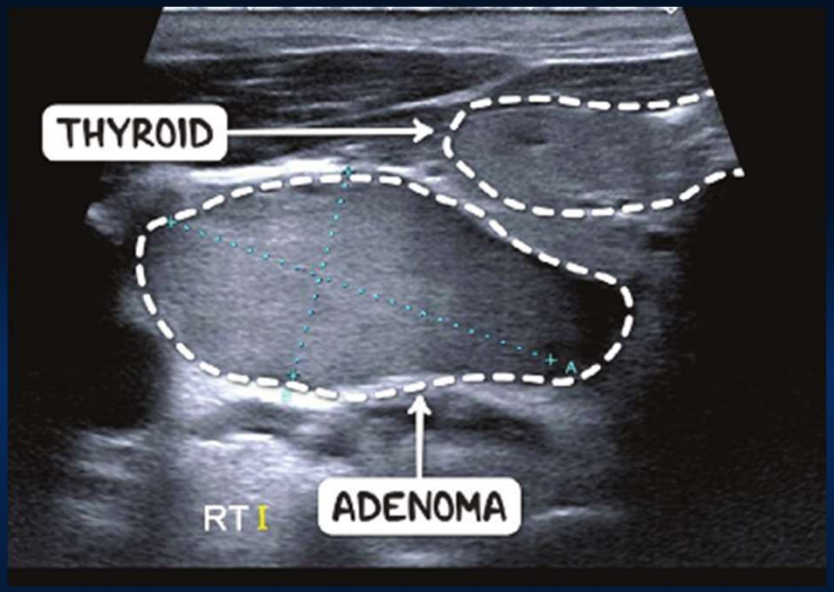
Hyperparathyroidism

- Overproduction of PTH
- Usually asymptomatic
- If symptoms: “bones, stones, abdominal moans, and psychic groans."
- Labs:
  - Elevated serum calcium
  - Elevated PTH
  - Check 24 Hr Urine Calcium, Serum Phos and Vit D

	Serum Calcium	Parathyroid Hormone (PTH)	Serum Phosphate	Serum Vitamin D
Primary Hyperparathyroidism	High	High	Low	Varies
Secondary Hyperparathyroidism	Low	High	High	Low
Tertiary Hyperparathyroidism	High	High	Varies	Low

Imaging

- Ultrasound Neck
  - May show parathyroid adenoma/enlarged gland
- Sestimibi
- 4D CT



Parathyroid adenoma sitting posterior to the right thyroid lobe

Treatment

- Primary Hyperparathyroidism
  - **Refer to Surgery** - > Parathyroidectomy
    - Check serum Calcium and PTH – 6-8 weeks after surgery, 6 month, then yearly
  - Cinacalcet 30mg BID -> For those who can't undergo surgery

    → **Refer to Endocrine**
    - Check PTH and Ca every 2-4 weeks
- Secondary Hyperparathyroidism
  - Dietary phosphate restriction
  - Vitamin D and calcium
  - Calcitriol 0.25mcg 3 times weekly if PTH still high

Hypoparathyroidism

- Underproduction of PTH
- Usually asymptomatic
- Symptoms
  - Mild: paresthesias (perioral, scalp, extremities), muscle cramps
  - Severe: seizures, carpopedal spasms, laryngospasms, arrythmias
- ECG changes
  - Prolonged QT, ST, torsade de pointes, a fib
- Causes: s/p surgery/radiation; Autoimmune, Hereditary

Labs

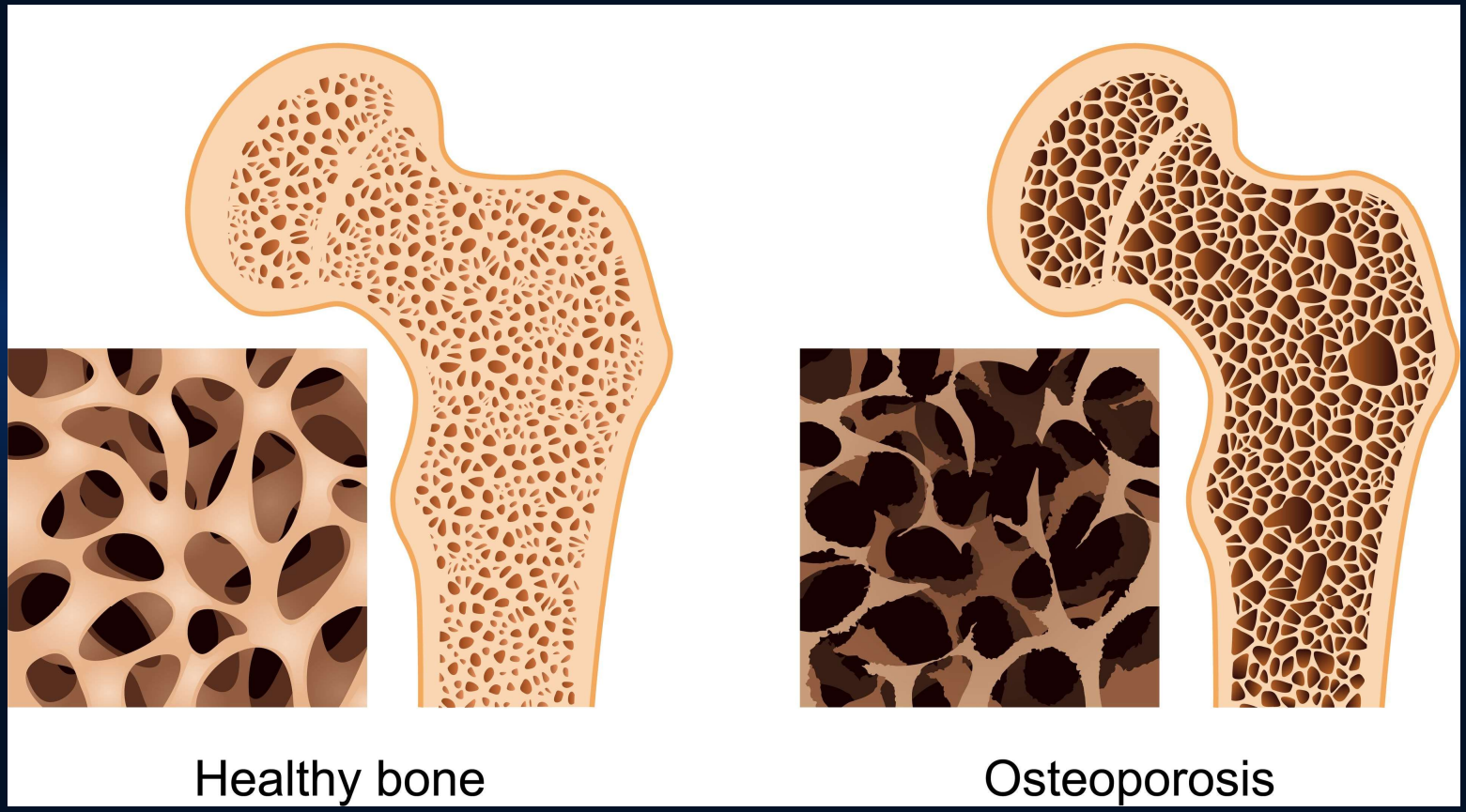
- Low Calcium
- Low PTH
- Hypercalciuria

- Monitor weekly after initiation of treatment

Treatment

- Severe cases
  - IV calcium gluconate
- Mild cases
  - Oral Calcium (1-2g Elemental Calcium daily)
  - Vit D supplement (Calcitriol) Start 0.25mcg BID
- Synthetic PTH only with failed therapy. (Refer to Endo)

Osteoporosis



Osteoporosis is a major public health concern

- More than 10 million Americans have osteoporosis, 43 million have osteopenia
- More than 2 million osteoporosis-related fractures occur each year in the United States, 70% of these occur in women
- For women over 55, costs of caring for osteoporotic fractures exceed the costs of:
  - MI
  - Stroke
  - Breast cancer
  - Mortality after hip fracture is up to 20% in the first year

Indications for Bone Mineral Density Testing

All women 65 years of age or older

All postmenopausal women:

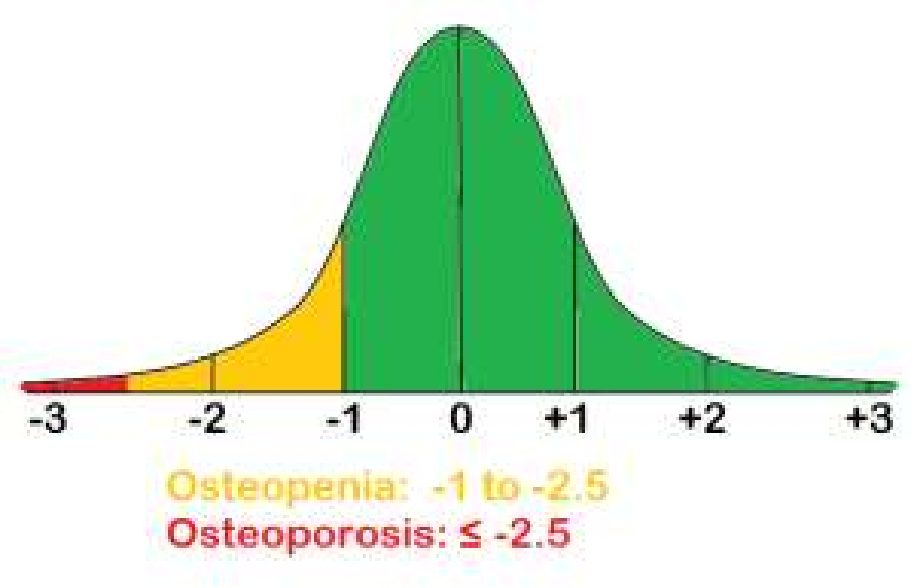
- With a history of fracture(s) without major trauma
- With osteopenia identified radiographically
- Long term systemic glucocorticoid therapy (>3months)

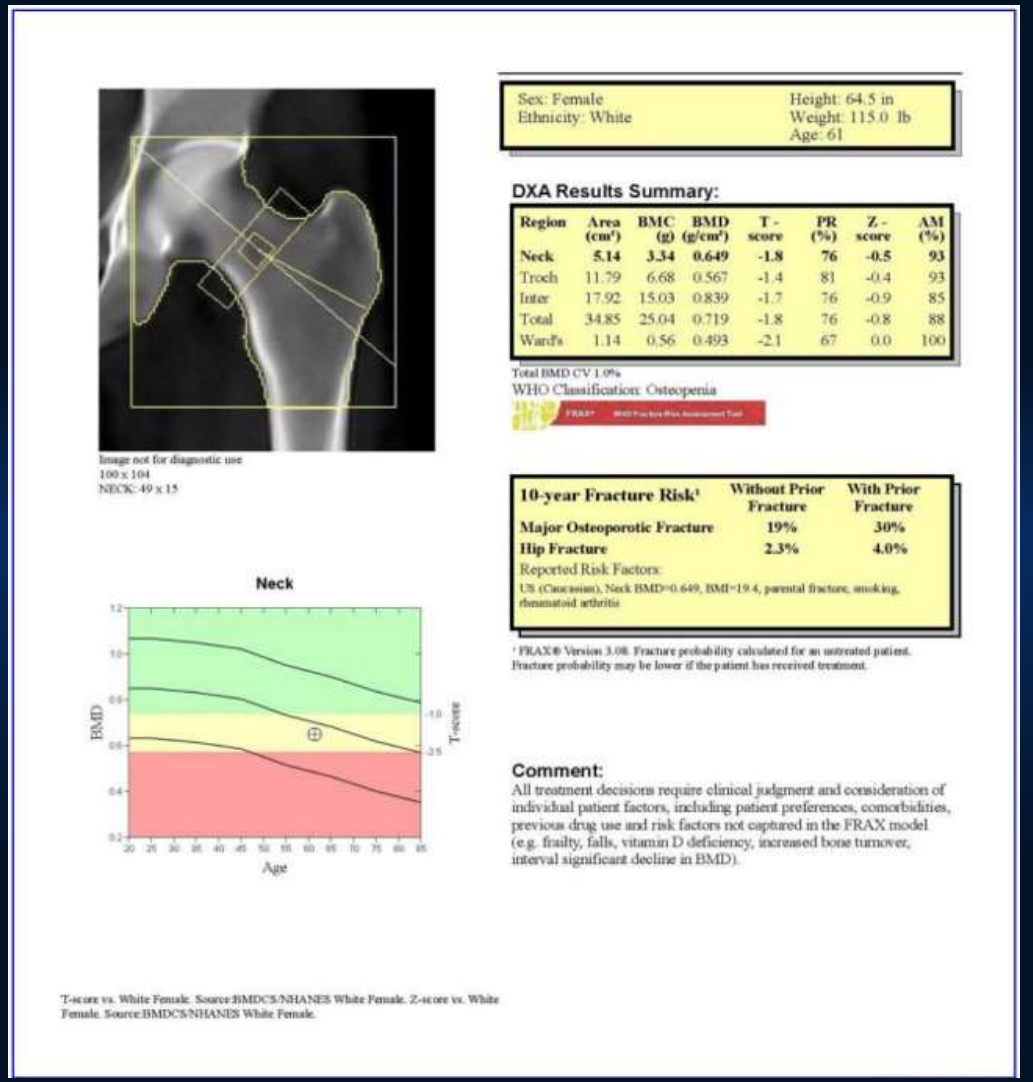
Other perimenopausal or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions

- Low body weight (<127 lb or BMI <20 kg/m2)
- Long term systemic glucocorticoid therapy > 3 months)
- Family history of osteoporotic fracture
- Early menopause
- Current smoking/Excessive alcohol consumption

DEXA scan

T-Score





Sex: Female
Ethnicity: White

Height: 64.5 in
Weight: 115.0 lb
Age: 61

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T-score	PR (%)	Z-score	AM (%)
Neck	**5.14**	**3.34**	**0.649**	**-1.8**	**76**	**-0.5**	**93**
Troch	11.79	6.68	0.567	-1.4	81	-0.4	93
Inter	17.92	15.03	0.839	-1.7	76	-0.9	85
Total	34.85	25.04	0.719	-1.8	76	-0.8	88
Ward's	1.14	0.56	0.493	-2.1	67	0.0	100

Total BMD CV 1.0%
WHO Classification: Osteopenia

Image not for diagnostic use
100 x 104
NECK: 49 x 15

Neck

BMD

T-score

Age

10-year Fracture Risk[1]	Without Prior Fracture	With Prior Fracture
Major Osteoporotic Fracture	**19%**	**30%**
Hip Fracture	**2.3%**	**4.0%**

Reported Risk Factors:
US (Caucasian), Neck BMD=0.649, BMI=19.4, parental fracture, smoking, rheumatoid arthritis

[1] FRAX® Version 3.08. Fracture probability calculated for an untreated patient. Fracture probability may be lower if the patient has received treatment.

Comment:
All treatment decisions require clinical judgment and consideration of individual patient factors, including patient preferences, comorbidities, previous drug use and risk factors not captured in the FRAX model (e.g. frailty, falls, vitamin D deficiency, increased bone turnover, interval significant decline in BMD).

T-score vs. White Female. Source:BMDCS/NHANES White Female. Z-score vs. White Female. Source:BMDCS/NHANES White Female.

Osteopenia vs Osteoporosis

Category	T-score
Normal	-1.0 or above
Osteopenia (Low bone mass)	Between -1.0 and -2.5
Osteoporosis	-2.5 or below
Severe Osteoporosis	-2.5 or below with fragility fracture

Labs

- CMP
- CBC
- 25-hydroxy-vitamin D
- Phosphate
- Magnesium

- PTH
- TSH
- CBC
- Celiac screen
- 24 hour urine
  - Calcium
  - Creatinine
  - Sodium

Treatment: Lifestyle modifications

- Goal: keep musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures
  - Adequate intake of calcium and vitamin D3 in patients with low bone density
    - Vitamin D3 - At least 800-1000 IU (20-25mcg) daily
    - Calcium ~1200mg/day, preferably from dietary sources
  - Minimize falls
    - Weight-bearing, resistance exercise, balance exercises
      - Tai Chi, yoga
  - Avoid tobacco and excessive use of alcohol

Dietary Calcium Sources

Food	Calcium in milligrams
Milk (skim, 2%, or whole; 8 oz)	300
Yogurt (6 oz)	250
Orange juice (with calcium; 8 oz)	300
Tofu with calcium (0.5 cup)	435
Cheese (1 oz)	195 to 335 (hard cheese – higher calcium)
Cottage Cheese (0.5 cup)	130
Ice cream or frozen yogurt (0.5 cup)	100
Soy milk (8 oz)	300
Beans (0.5 cup cooked)	60 to 80
Dark, leafy green vegetables (0.5 cup cooked)	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

Calcium supplements

- **Calcium carbonate** (40% elemental Calcium)
  - Cheap
  - Needs acid to absorb - Can't be on PPI
  - Can find options with 600mg elemental calcium per pill
- **Calcium citrate** (20% elemental Ca)
  - More expensive
  - No need for acid, best for patients on PPIs
  - Can find options with 325mg elemental calcium per pill
  - Split dose if taking >500mg of elemental calcium daily

Pharmacologic Therapy

- **Anti-resorptive Agents**

  ↓ bone resorption

  - **Bisphosphonates**
    - First line
  - **RANK Ligand Inhibitor (Monoclonal Ab)**
    - Use if can't tolerate bisphosphonates
    - Use in CKD patients
  - **SERMs**
    - Benefit for breast cancer

- **Anabolic Agents**

  ↑ bone formation

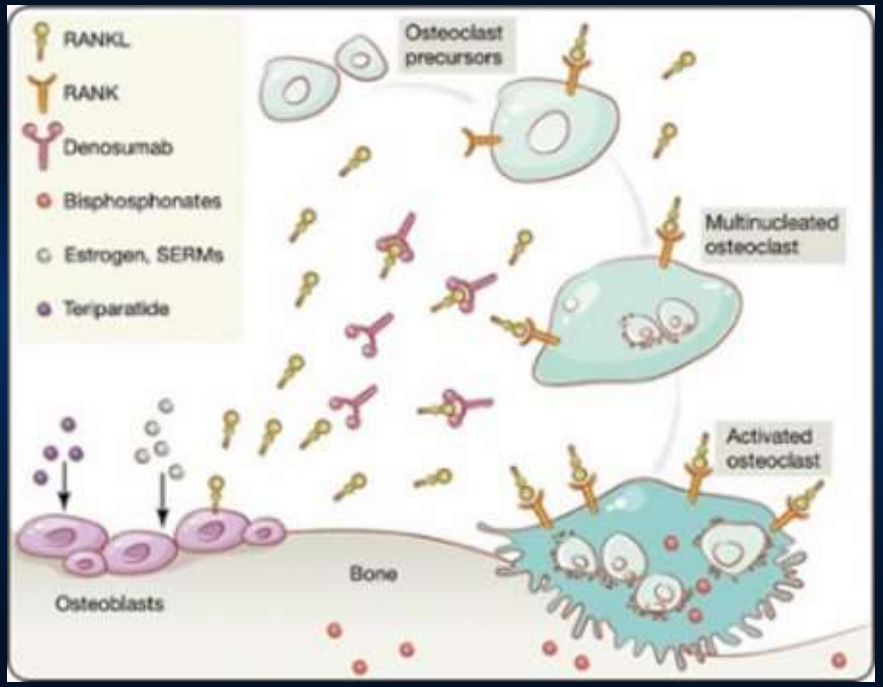
  Use for severe risk (T<- 3.5 or T< -2.5 with fracture)

  - **PTH/PTHrp**
    - Use with achalasia, scleroderma, esophageal strictures
  - **Sclerostin Inhibitor**
    - Use if vertebral fx

Drug Class	Medication	Dose/Timing	Contraindication	Side Effects
Bisphosphonates	Alendronate	1 tab weekly x 5 years	• Uncontrolled GERD (Oral) • Esophagitis (Oral) • CKD (GFR<30) • Hypocalcemia	• **Flu-like reaction** • Arthralgias • Osteonecrosis of jaw (rare) • Atypical Femur fracture (rare)
	Risendronate			
	Ibandronate			
	Zoledronic Acid	**IV infusion** annually X 3 years		
Monoclonal Ab	Denosumab	SubQ Injection every 6 months	• Hypocalcemia	• Increased risk of **rebound fracture** • ONJ/AFF
SERMs	Raloxifene	1 tab daily	• Thromboembolic event hx	• Thromboembolic events • Hot flashes
PTH/PTHrp Analogs	Teriparatide	SubQ injection daily x 2 years	• Paget's dz • Bone mets • Hyperparathyroid	• Dizziness, leg cramps • Hypercalemia
	Abaloparatide			
Sclerostin Inhibitor	Romoszumab	SubQ injection 1x/month x 1 year	• CV event in last year	• ONJ/AFF (rare)

Bisphosphonates

- First Line
- Alendronate, Risendronate, Ibandronate, Zoledronic Acid
- Method of Action:
  - Inhibits osteoclast-mediated bone resorption
  - Decreases mineral release and collagen or matrix breakdown in bone

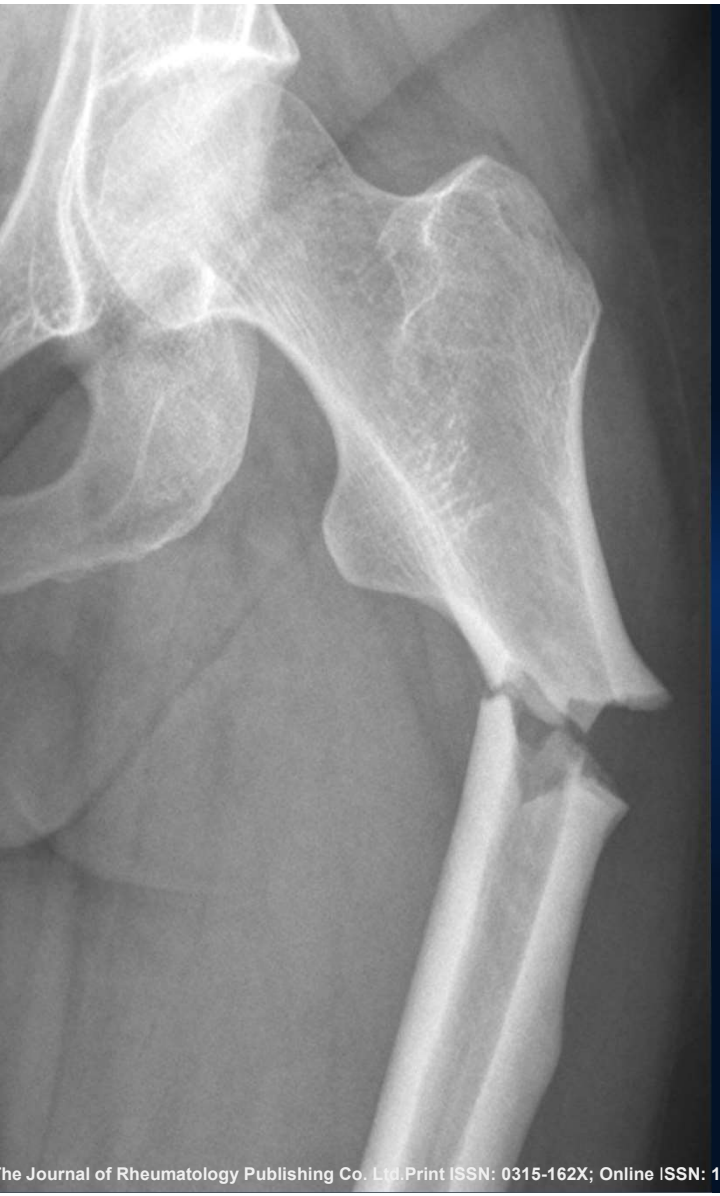


Common adverse side effects

- **Esophageal disease**
  - Needs to be taken on an empty stomach, 30-60 minutes prior to food, sit or stand to avoid esophagitis, reflux symptoms
  - Consider IV if patient has GERD
- For IV zoledronic acid → flu-like symptoms in approximately 25%
  - Severity reduced with hydration and acetaminophen or Ibuprofen

Osteonecrosis of Jaw

- Very low risk (1/10,000 to 1/100,000 patients per year)
- Risk factors:
  - pathologic dental conditions
  - invasive dental procedures
  - poor dental hygiene
  - cancer, chemotherapy, radiation
- Have dental work done prior to initiation of treatment



Atypical Femoral fracture

- Rare - increased risk with long-term therapy
- A prodromal groin or thigh pain in approximately 70% of patients
  - interrupt bisphosphonate treatment while appropriate imaging studies are performed

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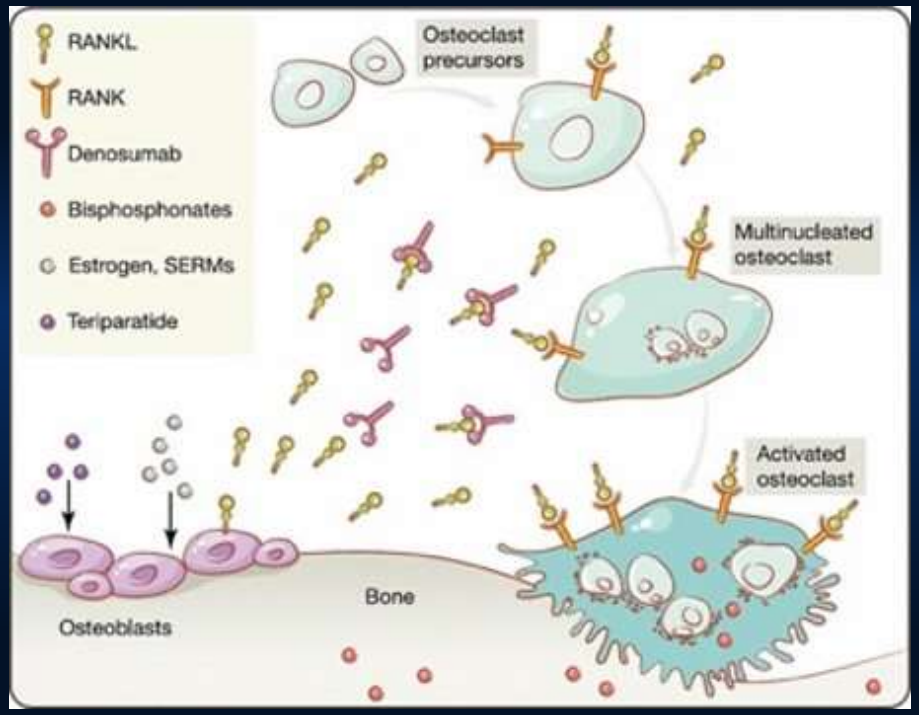
Drug Holiday

- Oral bisphosphonates for 5 years
- IV bisphosphonates for 3 years
- Reduce risk of AFF and ONJ--> But people return from their holidays!
- Fracture risk and BMD should be re-evaluated every 2 to 4 years after discontinuation; or every 1-2 years in high risk patients
- A significant drop in BMD -> Restart osteoporosis therapy
- Duration of holiday can be **2-5 years**

Denosumab

- Monoclonal antibody that targets RANKL
- Binds to RANKL and inhibits its binding to RANK receptor, preventing osteoclast formation
- Decreased bone resorption and increases bone mass



Adverse Effects

- Generally well tolerated
- Most common (>5 % and more common than placebo):
  - Musculoskeletal pain
  - Hypercholesterolemia
  - Cystitis

Rebound fracture

- Vertebral fractures within 3-18 months after discontinuing denosumab therapy
- Rapid increase in bone turnover as the medication wears off
- Doses every 6 months - No delay
- If denosumab is discontinued, administering an alternative therapy (typically IV bisphosphonate) to prevent rapid bone loss is advised
- There is **NEVER** an indication for a denosumab holiday

Candidates for Anabolic therapy

- Severe osteoporosis
  - T-score of -3.5 or below even in the absence of fractures
  - T-score of -2.5 or below plus a fragility fracture
- Unable to tolerate or have contraindications to bisphosphonate therapy
- Fracture and/or loss of BMD in spite of compliance with other osteoporosis therapies

Anabolic Therapy

- **Abaloparatide**
  - MOA: Synthetic peptide analog of human PTHrp
  - Increase in bone mineral density and bone strength at vertebral and/or nonvertebral sites
- **Teriparatide**
  - MOA: Recombinant human PTH
  - Stimulates osteoblast function, increases calcium absorption and renal tubular reabsorption of calcium
  - Lead to increased bone mineral density, bone mass, and strength

Adverse events

- Teriparatide
  - Dizziness and leg cramps
- Abaloparatide
  - Nausea, postural hypotension, dizziness, headache, and palpitations
  - Hypercalcemia
  - Osteosarcoma

Treatment plan

- Anabolic therapy benefits are quickly lost after discontinueation
- A course of teriparatide or abaloparatide (up to 2 years) should be followed by a bisphosphonate, raloxifene, denosumab, or HRT
- Repeat DEXA scan every 1-2 years

Questions

Please feel free to contact me with questions

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