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Bone and Mineral Metabolism

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May 2025

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Disclosures

- I have nothing to disclose

Outline

- Minerals – Homeostasis and Disorders
  - ➢Hormones
    - PTH
    - Vitamin D
    - FGF 23
  - ➢Organs
    - Intestine
    - Kidney
    - Bone
- Bone – Physiology and Disorders

	Content Categories	Initial Certification and In-Training	Maintenance of Certification (MOC)
1.	Carbohydrate Metabolism	16%	16%
2.	Bone and Mineral Metabolism	8%	8%
3.	Thyroid Hormones (Thyroxine [T4] and Triiodothyronine [T3])	13%	14%
4.	Adrenal Disorders	12%	12%
5.	Pituitary/Hypothalamus	10%	10%
6.	Growth	12%	14%
7.	Reproductive Endocrine System	12%	12%
8.	Other Hormones	3%	3%
9.	Lipoproteins and Lipids	3%	3%
10.	Multiple endocrine neoplasia and polyglandular autoimmune disease	2%	2%
11.	Methods and Biological Principles	4%	2%
12.	Core Knowledge in Scholarly Activities	5%	4%

New outline 5%

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Mineral Homeostasis

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Minerals – Calcium

- Structural role in hard tissues (bone and teeth); important regulatory role in metabolic and signaling pathways
- In circulation: 50% ionized; 50% bound to albumin and other anions
- Serum albumin levels
  - ↓ 1 mg/dL Albumin = ↓ 0.8 mg/dL Ca, normal iCa level
- Serum pH (pH 7.4 = 1.15-1.35 mmol/L iCa)
  - AlkaLOsis (high pH): LOW iCa

Minerals – Phosphate

- Structural role in hard tissues (bone, teeth)
- Key intracellular component and cofactor in signaling pathways
  - Phosphorylation of proteins, lipids, ATP, backbone of nucleic acid
- In blood:
  - 84% ionized (phosphoric acid or inorganic phosphate),
  - 10% protein bound, 6% complexed with cations
- Soft tissues contain 10-fold more phosphate than calcium

Age	mg/dl	mmol/L
0-9 days	4.5-9	1.45-2.91
10 days to 2 years	4-6.5	1.29-2.1
3-9 years	3.2-5.8	1.03-1.87
10-15 years	3.3-5.4	1.07-1.74
>15 years	2.4-4.4	0.78-1.42

Harriet Lane

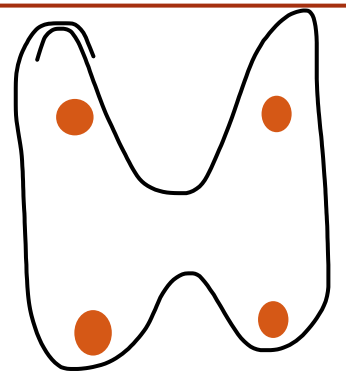
Minerals - Magnesium

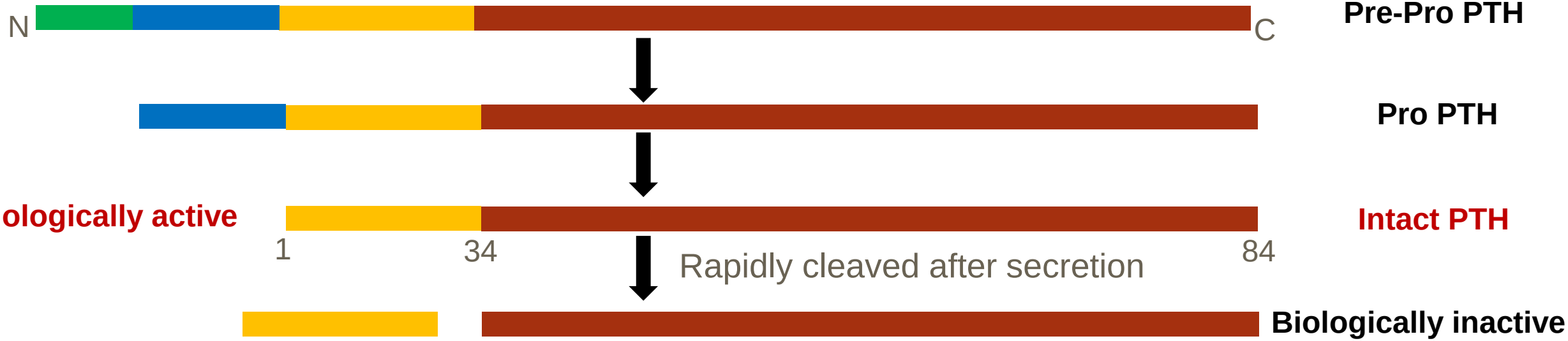
- Most intracellular – bone, muscle, soft tissue
- Bound to ATP, nucleotides, enzyme complexes, crucial for enzymatic reactions
- Important for PTH secretion and action

  **Hypermagnesemia suppresses PTH secretion

Parathyroid Hormone (PTH)

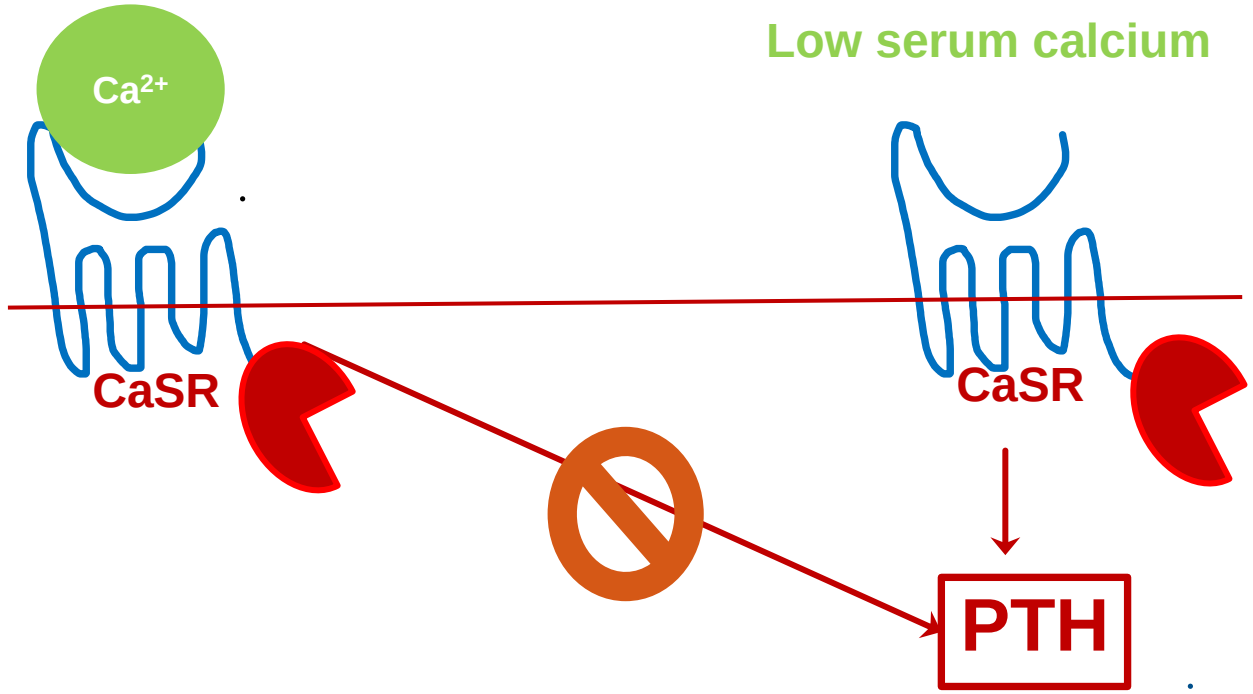
- Endodermal lining of 3rd and 4th pharyngeal pouches
- Principal (chief) cells secrete PTH
- 84 amino acid polypeptide; short $t_{1/2}$ <5 minutes



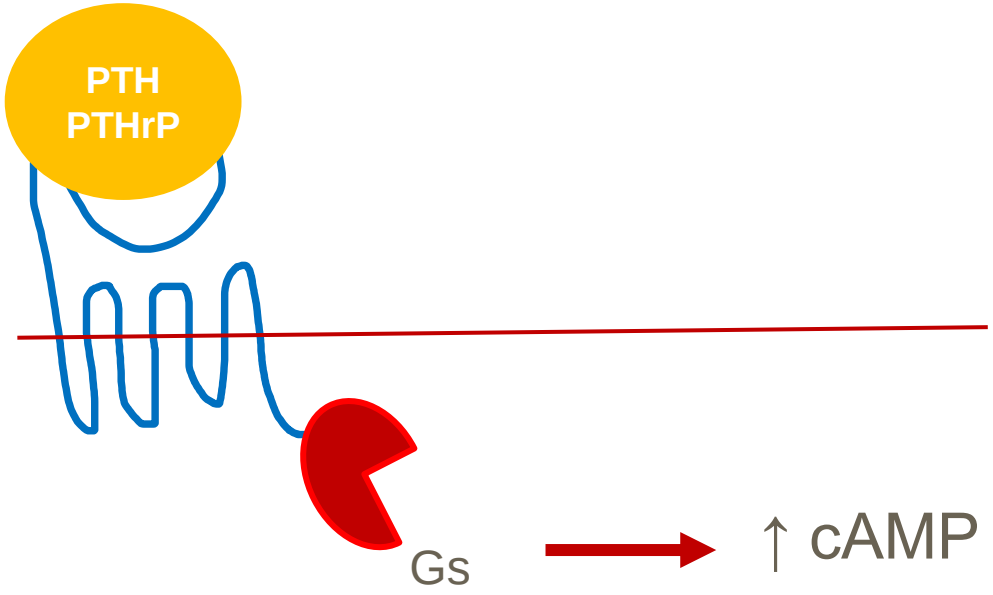


Receptor and Signaling

Calcium Sensing Receptor (CaSR)



PTH/PTHrP Receptor



Measurement of plasma and urinary cAMP is a measure of PTH activity

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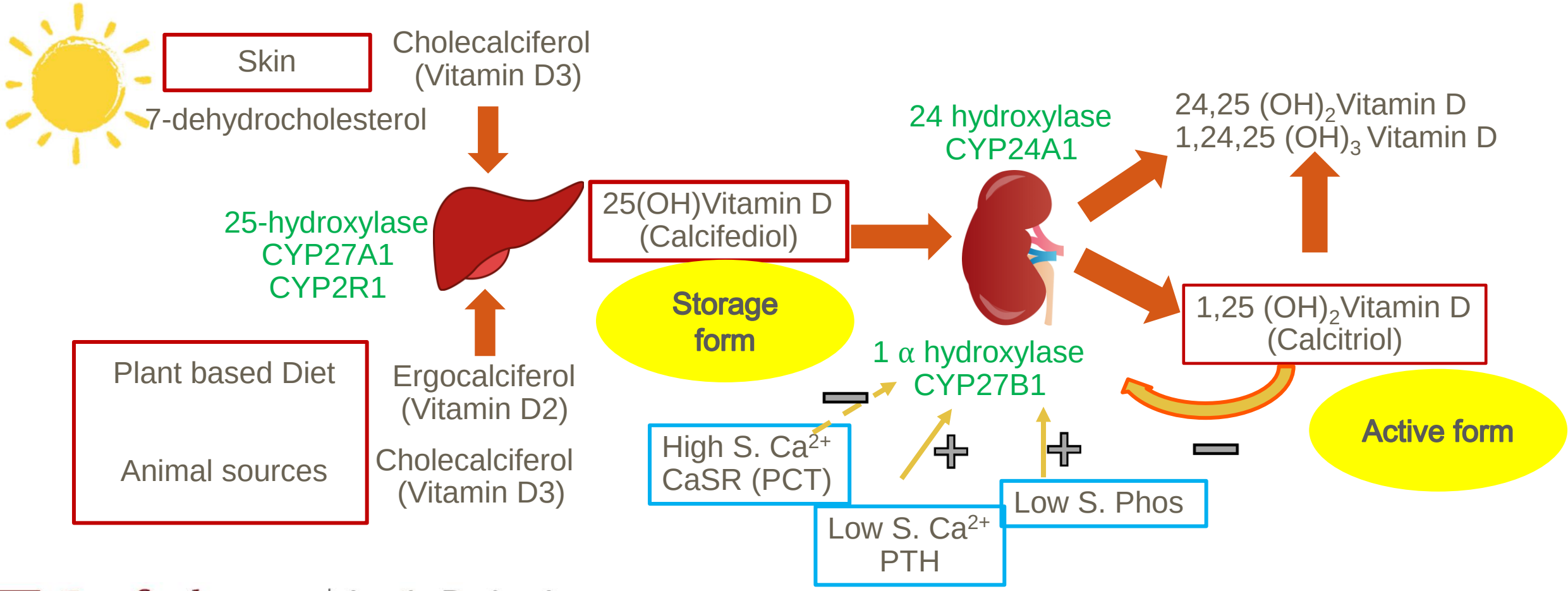
Vitamin D


Skin
Cholecalciferol
(Vitamin D3)
7-dehydrocholesterol
25-hydroxylase
CYP27A1
CYP2R1
25(OH)Vitamin D
(Calcifediol)
Storage
form
24 hydroxylase
CYP24A1
24,25 (OH)2Vitamin D
1,24,25 (OH)3 Vitamin D
1,25 (OH)2Vitamin D
(Calcitriol)
Active form
Plant based Diet
Animal sources
Ergocalciferol
(Vitamin D2)
Cholecalciferol
(Vitamin D3)
1 α hydroxylase
CYP27B1
High S. Ca2+
CaSR (PCT)
Low S. Ca2+
PTH
Low S. Phos

Vitamin D Receptor (VDR)

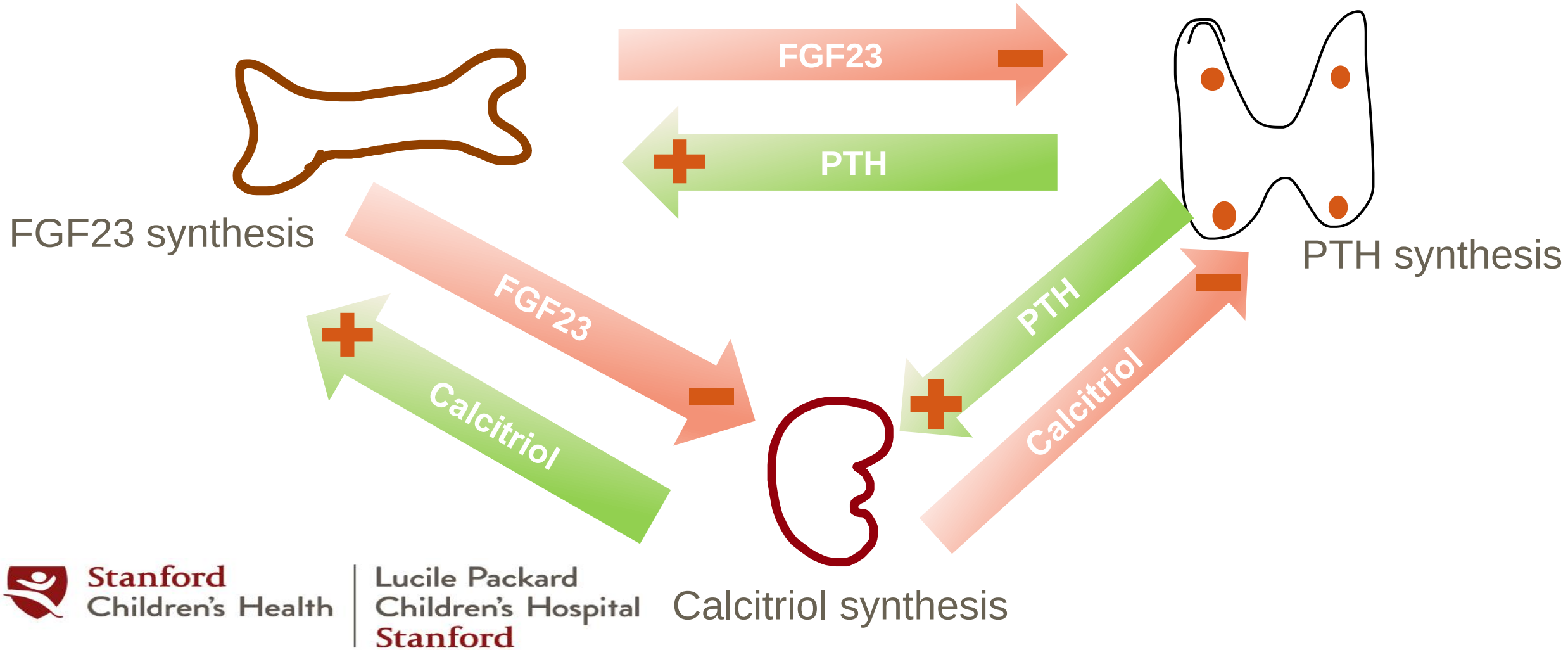
- Nuclear hormone receptor

- Regulates gene expression in target tissues
  - Small Intestine: increases calcium channels and calbindin etc.
  - Bone: sensitizes osteoblasts to PTH
    regulates osteoid production and calcification
  - Kidney: promotes phos reabsorption by PCT (NaPi cotransporters)
  - Parathyroid gland: inhibit PTH gene expression
    stimulate CaSR gene expression

Fibroblast Growth Factor 23 (FGF23)

- Glycoprotein produced from bone (osteocytes)
- Intact FGF23 is biologically active
  - Cleaved by proteases into N & C terminal fragments (inactive)
- Regulation:
  - Upregulated by ↑ S. Phosphorus and calcitriol
  - Downregulated by PHEX, DMP -1 (by unknown mechanism)
- FGF Receptor (tyrosine kinase receptor) and co-receptor Klotho
  - Promotes phosphorus excretion by kidneys (Degradation of NaPi cotransporter)
  - ↓Calcitriol level

Cross Talk between hormones



Intestine

- Calcium: duodenum and jejunum
  - **Active** (transcellular; epithelial calcium channels TrpV)
  - Passive (paracellular)
  - Dietary sources: dairy products

- Phosphorus: jejunum
  - **Passive** (paracellular)
  - Active (transcellular; NaPi cotransporter)
  - Abundant in western diet

- Magnesium: Passive and active (TRPM 6 channel) absorption

- Calcitriol increases Ca^{2+} absorption and marginally increases PO_4 absorption
- PTH does not have a direct effect, but indirectly via activating 1α hydroxylase

Kidneys

- Calcium:
  - 10 g filtered
  - 200 mg/day loss in urine
  - PCT - passive, paracellular
  - DCT - transcellular reabsorption stimulated by PTH

Thiazides: ↓ calcium excretion

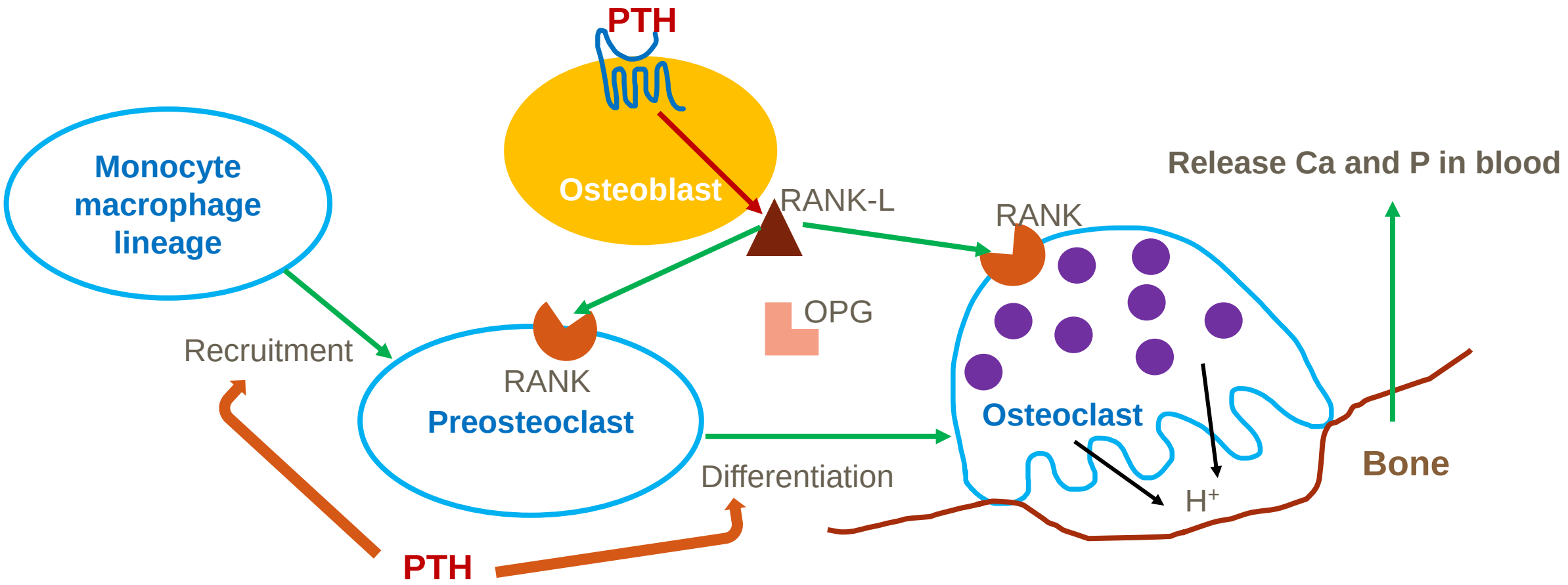
Furosemide and Corticosteroids: ↑ calcium excretion

- Phosphorus:
  - Most reabsorbed by PCT (active transcellular; NaPi cotransporter)
    - downregulated by PTH, FGF23
    - upregulated by 1,25 $(OH)_2$ Vitamin D

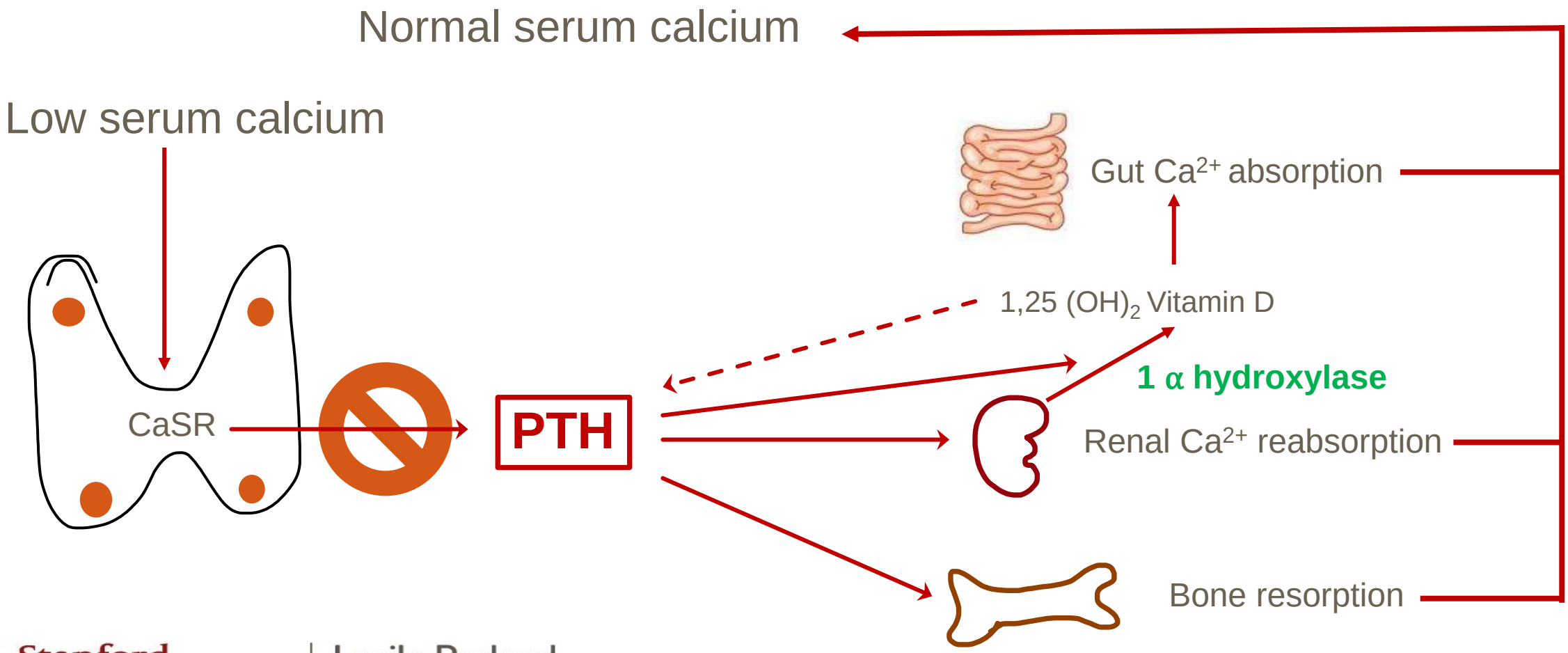
- Magnesium:
  - During magnesium depletion, kidney conserves magnesium
  - During hypermagnesemia, kidney losses increase likely via CaSR

PTH increase magnesium reabsorption

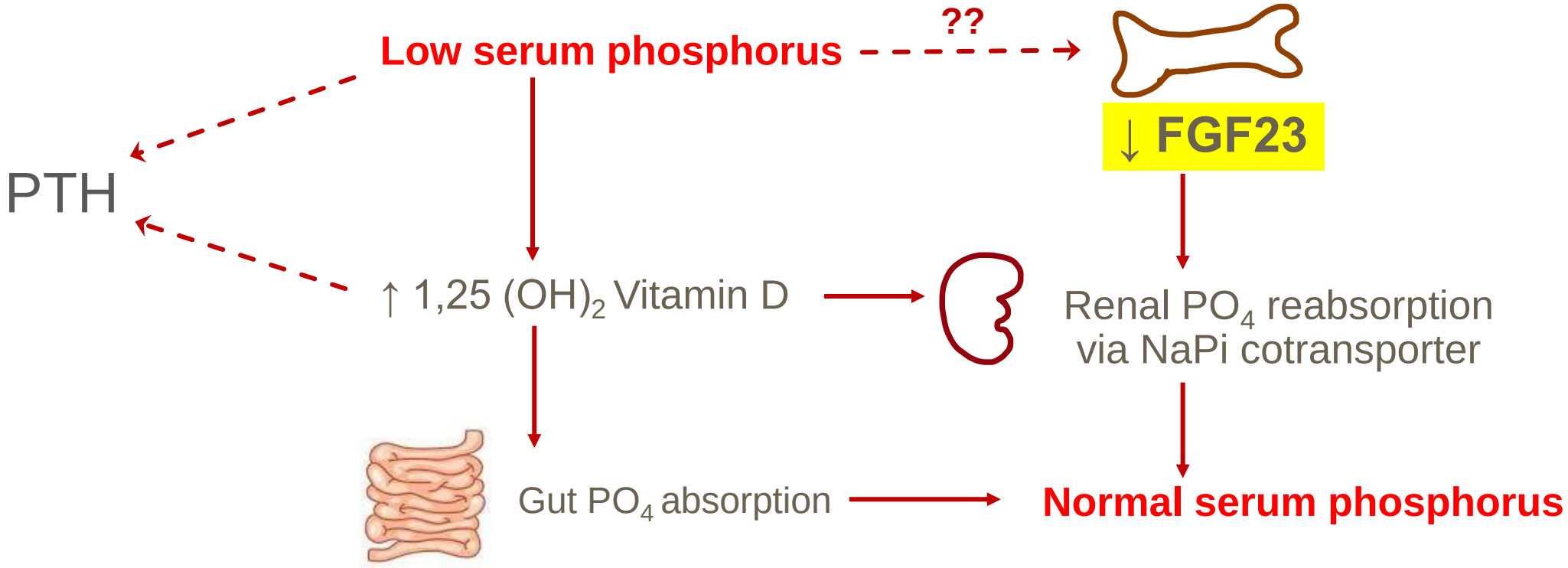
Bone


PTH
Osteoblast
RANK-L
RANK
Release Ca and P in blood
Monocyte
macrophage
lineage
OPG
Recruitment
RANK
Preosteoclast
Osteoclast
Bone
Differentiation
H+
PTH

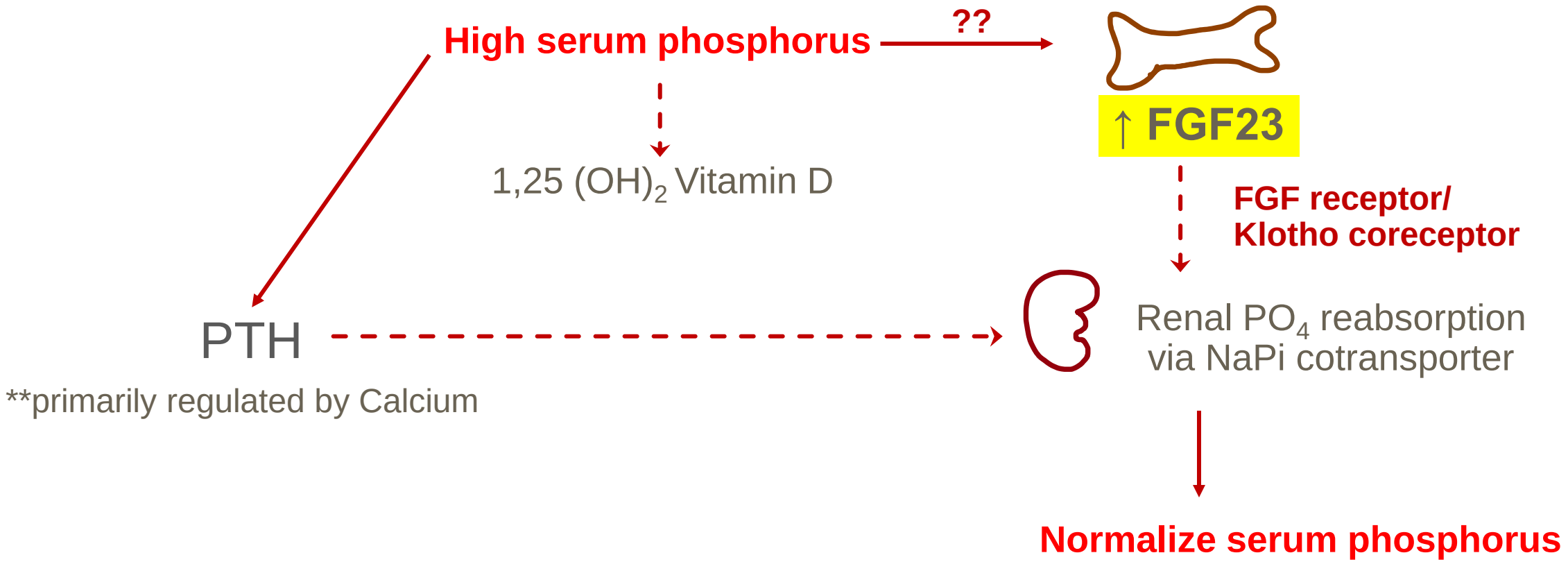
Calcium Regulation



Phosphate Regulation



Phosphate Regulation



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Disorders of Mineral Metabolism

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Hypocalcemia

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Hypocalcemia

- Symptoms:
  - Irritability
  - Muscle twitches
  - Jitteriness
  - Tremors
  - Poor feeding
  - Lethargy
  - Seizures
- Signs:
  - Trousseau's sign
  - Chvostek’s sign

Hypocalcemia - Causes

Neonatal

- **Early-Onset (0-72 hours)**
  - IDM, IUGR, birth asphyxia, prematurity
  - Maternal hypercalcemia
  - Hypoparathyroidism (transient or permanent)
- **Late-Onset (>72 hours)**
  - High phosphorus intake
  - Low magnesium
  - Maternal vitamin D deficiency
  - Hypoparathyroidism

Childhood

- Congenital Hypoparathyroidism
- Acquired hypoparathyroidism
  - surgery, trauma, autoimmune, radiation, infiltration
- Pseudohypoparathyroidism
- Nutritional deficiency
  - calcium or vitamin D
- Hypomagnesemia
  - Chronic diarrhea, malnutrition, Bartter syndrome
- Renal insufficiency
- Acute hyperphosphatemia

Congenital Hypoparathyroidism

- Labs:
  - ↓ Ca, ↑ Phos, ↓ PTH, normal 25(OH)Vitamin D, **low** 1,25 $(OH)_2$ Vitamin D, ↓ urine Ca**
- Causes:
  - Syndromes:
    - DiGeorge syndrome (most common cause in pediatrics)
    - CHARGE , HDR syndrome (Barakat syndrome), Sanjad-Sakati or Kenny-Caffey syndrome
  - Autosomal dominant and Autosomal recessive (production of PTH)
  - X linked recessive (development of parathyroid gland)
  - Activating mutation (AD) or antibody mediated stimulation of CaSR in parathyroid gland
  - Mitochondrial disorders (eg, MELAS syndrome, Kearns-Sayre syndrome)
- Physical findings:
  - Ectopic (intracranial- basal ganglia) calcifications

Pseudohypoparathyroidism (PHP)

- Labs:
  - ↓ Ca, ↑ Phos, ↑ PTH, normal 25(OH)Vitamin D, low-normal $1,25(OH)_2$ Vitamin D

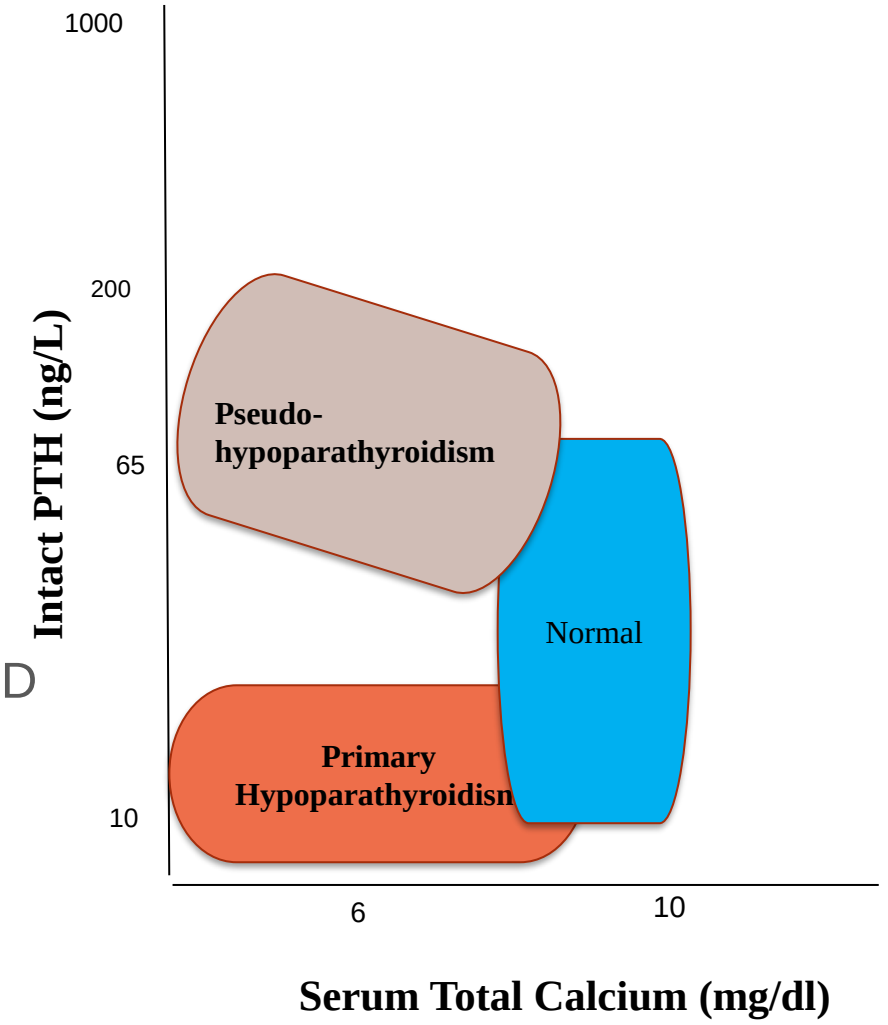
- PTH signaling is impaired; imprinting defect
  - Target tissue resistance in PCT (kidneys) -> hyperphosphatemia and low calcitriol
  - No resistance in DCT (kidneys) -> hence no hypercalciuria (unless over treated)
  - Variable resistance in bone -> ? skeletal fragility, low BMD vs high BMD

- Albright Hereditary Osteodystrophy (AHO):
  - Round facies, obesity, brachydactyly, short stature, developmental delay, dental hypoplasia, subcutaneous calcifications
  - Pseudo-pseudohypoparathyroidism (PPHP): AHO alone, no lab abnormalities

	PHP IA	PHP IB	PHP IC	PHP type II	Pseudo PHP
Gsα mutation	Maternal inheritance	Sporadic or maternally inherited or Methylation defect	None	None	Paternal inheritance
AHO phenotype	**+**	**-**	**+**	**-**	**+**
PTH resistance (↓Ca, ↑Phos, ↑PTH)	**+**	**+**	**+**	**+**	**-**
Other Hormone (TSH, LH/FSH, GHRH) resistance	**+**	**+ (TSH)**	**+**	**-**	**-**
Renal cAMP production to PTH	↓	↓	**normal**	**normal**	**normal**
Phosphaturic response to PTH	↓	↓	↓	↓	**normal**

Hypocalcemia- Evaluation

- Review of maternal, gestational, birth and family Hx
- Laboratory evaluation – the critical labs!
  - Total calcium/albumin, or iCa^{2+}
  - Serum Phosphorus
  - Serum Magnesium
  - Serum Creatinine
  - iPTH (at the time of low calcium)
  - Spot or 24-hour urine Ca/Cr
  - Alkaline phosphatase
  - 25 (OH) vitamin D
  - $1,25\ (OH)_2$ vitamin D
  - Maternal labs – calcium, phosphorus, iPTH, 25 (OH) vitamin D
  - Genetic studies



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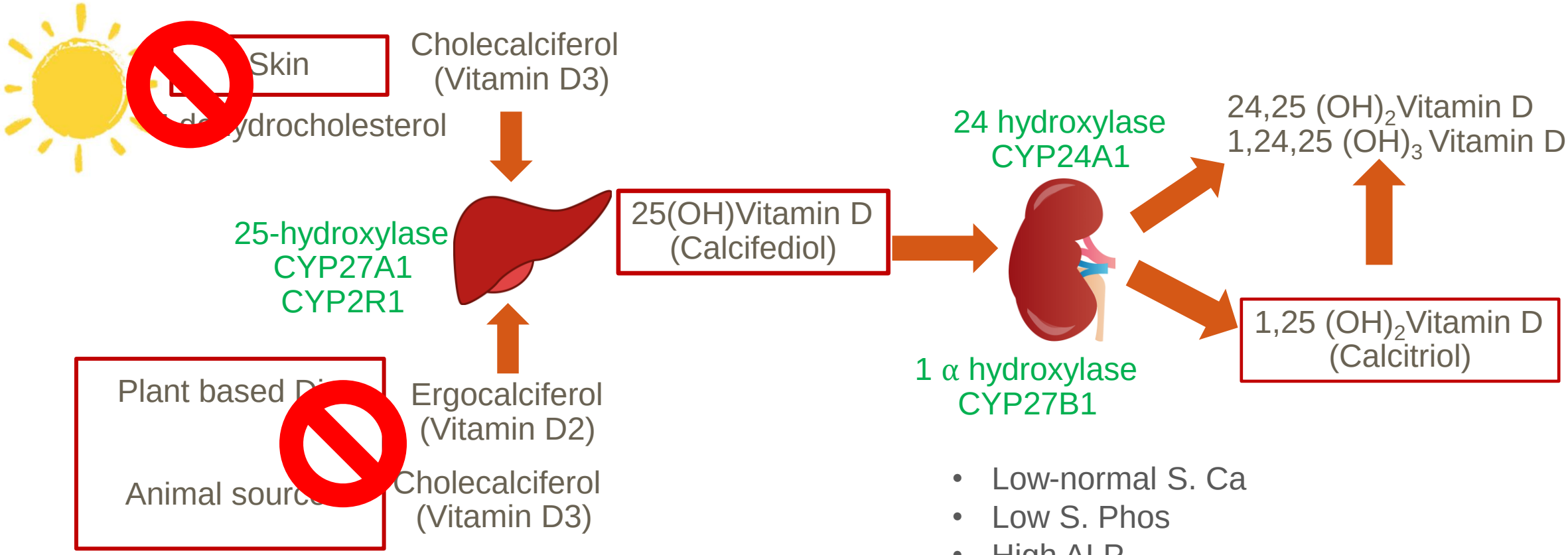
Hypocalcemia - Management

- IV Calcium (Seizures or acute EKG changes)
- Oral calcium (Check elemental calcium)
- Calcitriol (essential for hypoparathyroidism, PHP)
- Don’t forget to treat hypomagnesemia
- Vitamin D supplementation

- Hypoparathyroidism: risk of nephrocalcinosis; goal low normal serum Ca
- Pseudohypoparathyroidism: no hypercalciuria; goal normal Ca and PTH

Vitamin D Deficiency - Nutritional



- Low-normal S. Ca
- Low S. Phos
- High ALP
- High PTH
- Low/normal/high 1,25 D
- Low 25-OHD

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Vitamin D Deficiency - Gastrointestinal

Skin

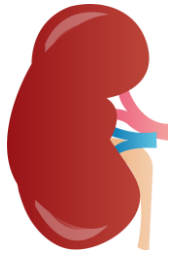
7-dehydrocholesterol

Cholecalciferol
(Vitamin D3)

25-hydroxylase
CYP27A1
CYP2R1

25(OH)Vitamin D
(Calcifediol)

24 hydroxylase
CYP24A1



1 α hydroxylase
CYP27B1

24,25 $(OH)_2$Vitamin D
1,24,25 $(OH)_3$ Vitamin D

1,25 $(OH)_2$Vitamin D
(Calcitriol)

Plant based Diet

Animal sources

Ergocalciferol
(Vitamin D2)

Cholecalciferol
(Vitamin D3)

- Low-normal S. Ca
- Low S. Phos
- High PTH
- High ALP
- Low 25-OHD

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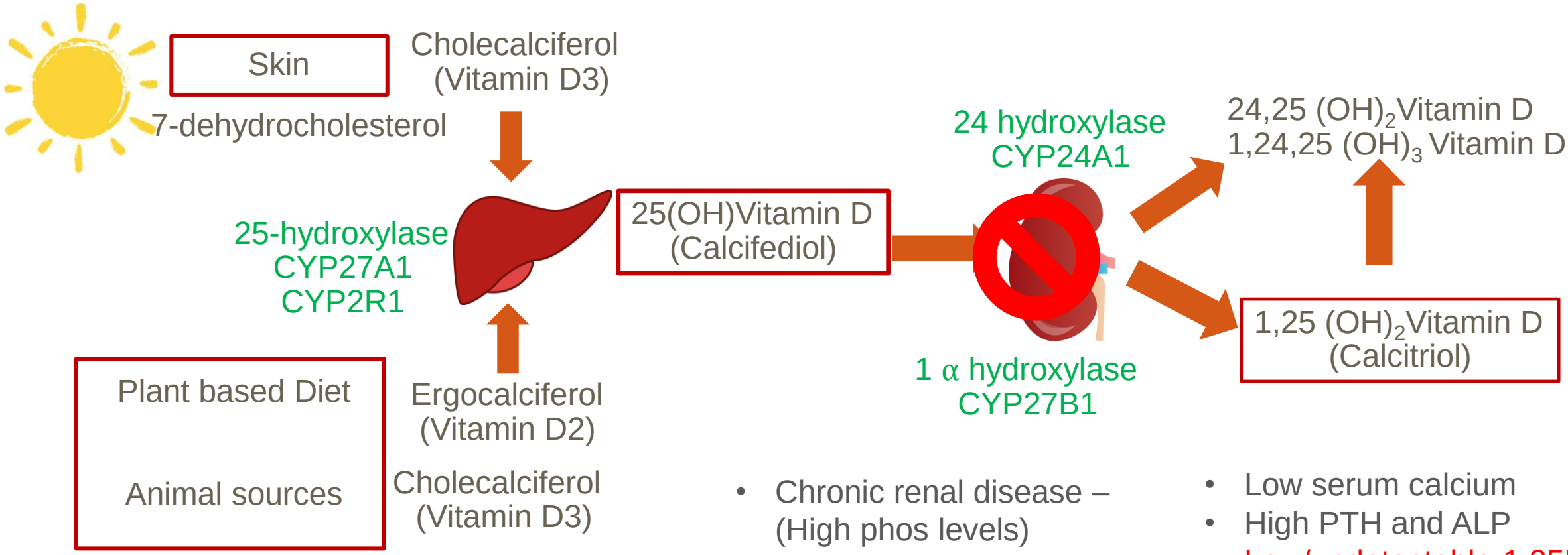
Vitamin D Deficiency - Renal



- Chronic renal disease – (High phos levels)
- Autosomal recessive 1 α hydroxylase deficiency (low phos level)

- Low serum calcium
- High PTH and ALP
- Low/undetectable 1,25D
- Normal 25-OHD

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Vitamin D Receptor Resistance

- Mutations in the gene encoding vitamin D receptor (VDR)
- Labs:
  - Low serum calcium
  - Low serum phos
  - High PTH
  - Very High 1,25 $(OH)_2$ Vitamin D
  - Normal 25 (OH) Vitamin D
- Growth failure, rickets, bone pain, partial or complete **alopecia**

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Hypercalcemia

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Hypercalcemia - Symptoms

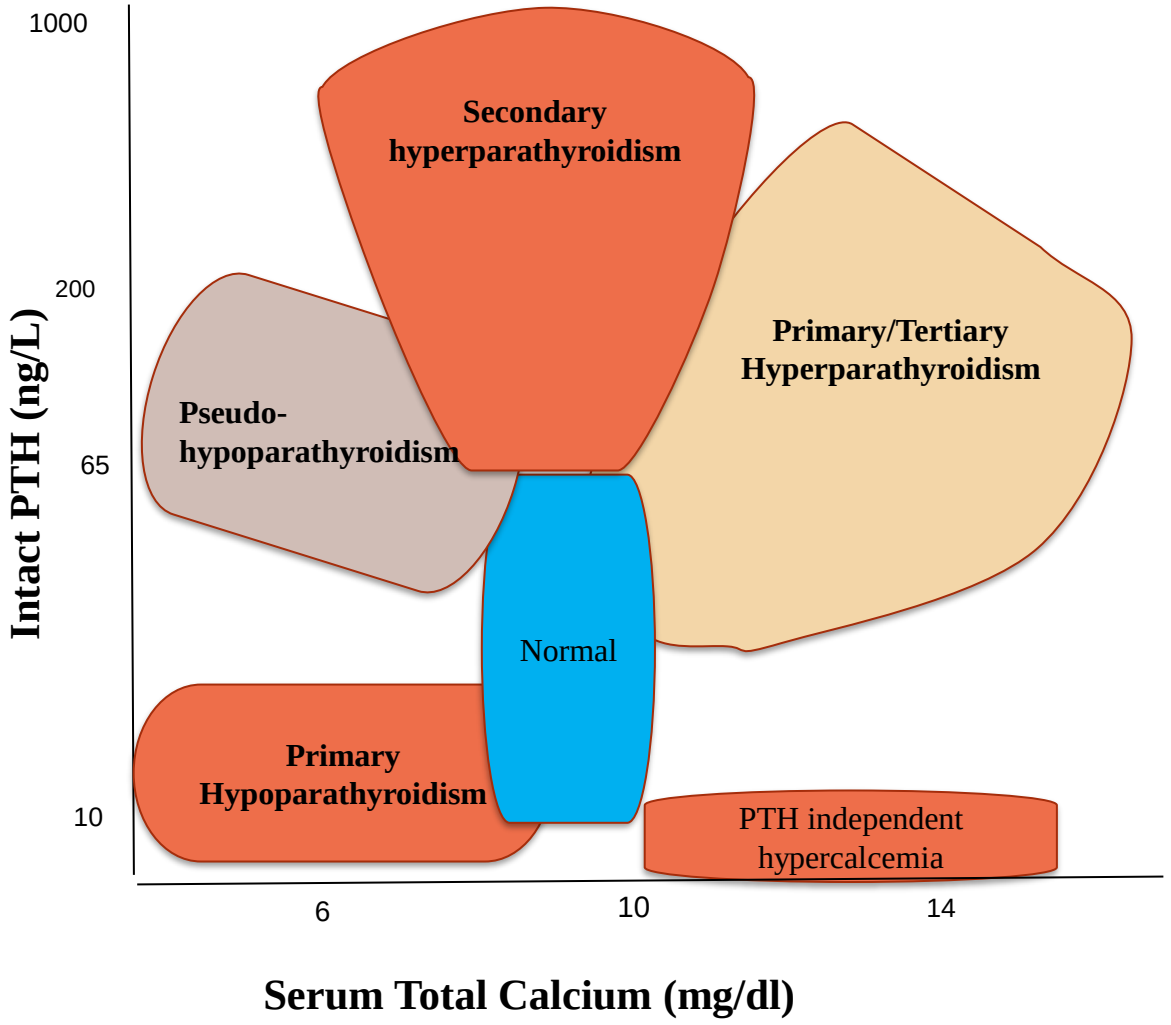
- Polyuria, polydipsia
- Anorexia, nausea and vomiting
- Failure to thrive in infants and toddlers
- Constipation
- Hypotonia
- Irritability/seizure/depression
- Renal calculi
- Bone pain
- Hypertension

Hypercalcemia - Causes

- Excessive Intake
  - Calcium (for phosphorus binding)
  - Vitamin D intoxication
- Bone resorption
  - Hyperparathyroidism
    - Sporadic
    - Inherited (MEN I, IIA)
  - Hyperthyroidism
  - Vitamin A toxicity
  - Immobilization
  - Malignancy
- Renal reabsorption
  - Familial hypocalciuric hypercalcemia
  - Medications (thiazides)
- Others
  - Williams-Beuren Syndrome
    - Cocktail personality, elfin facies, supravalvular aortic stenosis, developmental delay
    - Contiguous gene deletion (7q11.23), *ELN* gene
    - Hypercalcemia spontaneously resolves by age 1
  - Adrenal Insufficiency
  - Hypophosphatasia
  - Granulomatous & inflammatory diseases
    - Activated 1 α hydroxylase

Hypercalcemia - Evaluation

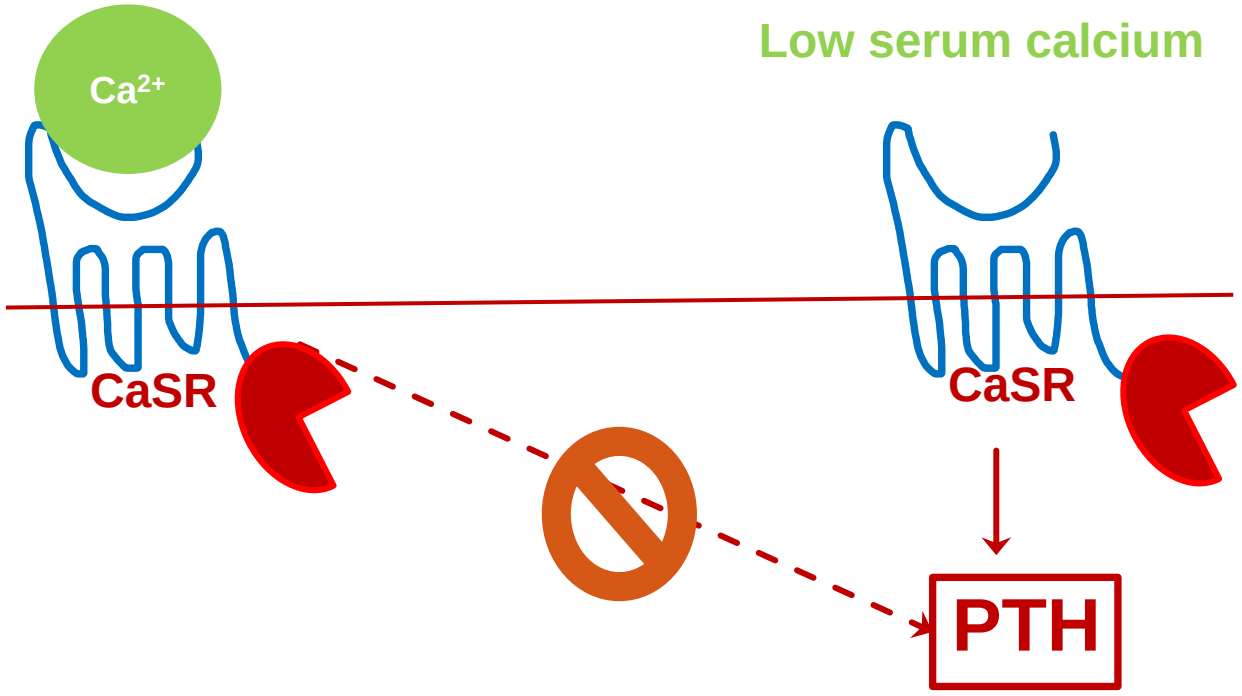
- Critical labs
  - Serum Calcium + albumin; iCa
  - Serum Phosphorus
  - Serum Creatinine
  - iPTH
  - Spot or 24-hour Urine Ca/Cr**
  (can be elevated in hyperparathyroidism)
- 25 (OH) vitamin D
- 1,25 $(OH)_2$ vitamin D
- PTHrP, Vitamin A
- TFTs, Cortisol and ACTH



Malignancy

- Certain neoplasia can secrete high levels of PTHrP
  - binds to PTH/PTHrP receptor -> symptoms of hyperparathyroidism
- Osteolytic metastases with local release of cytokines (including osteoclast activating factors)
- Inflammatory macrophages/monocytes or neoplastic cells may express 1 α hydroxylase activity
  - excess 1,25 $(OH)_2$ Vitamin D

Familial Hypocalciuric Hypercalcemia (FHH) Neonatal Severe Hyperparathyroidism (NSHPT)



- **Inactivating mutation in *CaSR, GNA11, AP2S1 genes***

- **FHH** - Heterozygous
  - "Benign" elevation in S. Ca levels
  - Mildly elevated S. Mg levels
  - S. Phos – low-normal
  - **Low urine Ca/Cr ratio**
  - Inappropriately normal PTH

- **NSHPT** - Homozygous
  - Elevated PTH and S. Ca levels
  - Low S. Phos level

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Hypercalcemia - Management

- **Acute**
  - Hydration (normal saline)
  - Loop diuretics– for fluid overload (not first line) – do not recommend prolonged use
  - Oral phosphate for binding of calcium in intestine
  - Calcitonin
  - Dialysis

- **Long-term**
  - Treat the underlying cause
  - Bisphosphonates, *denosumab
  - Glucocorticoids (inhibits 1 α hydroxylase activity) – decreases GI absorption of calcium
  - Calcimimetic agents (Allosteric activators of CaSR-> reduce PTH secretion)
  - Parathyroidectomy

Hungry Bone Syndrome

- Due to chronic increase in bone resorption

- Bone influx of minerals after acute drop in PTH levels due to continued increased osteoblastic activity
  - Severe hypocalcemia
  - Hypophosphatemia
  - Hypomagnesemia
  - Elevated alkaline phosphatase, osteocalcin, radioactive isotope uptake

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Hypophosphatemia

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Hypophosphatemia

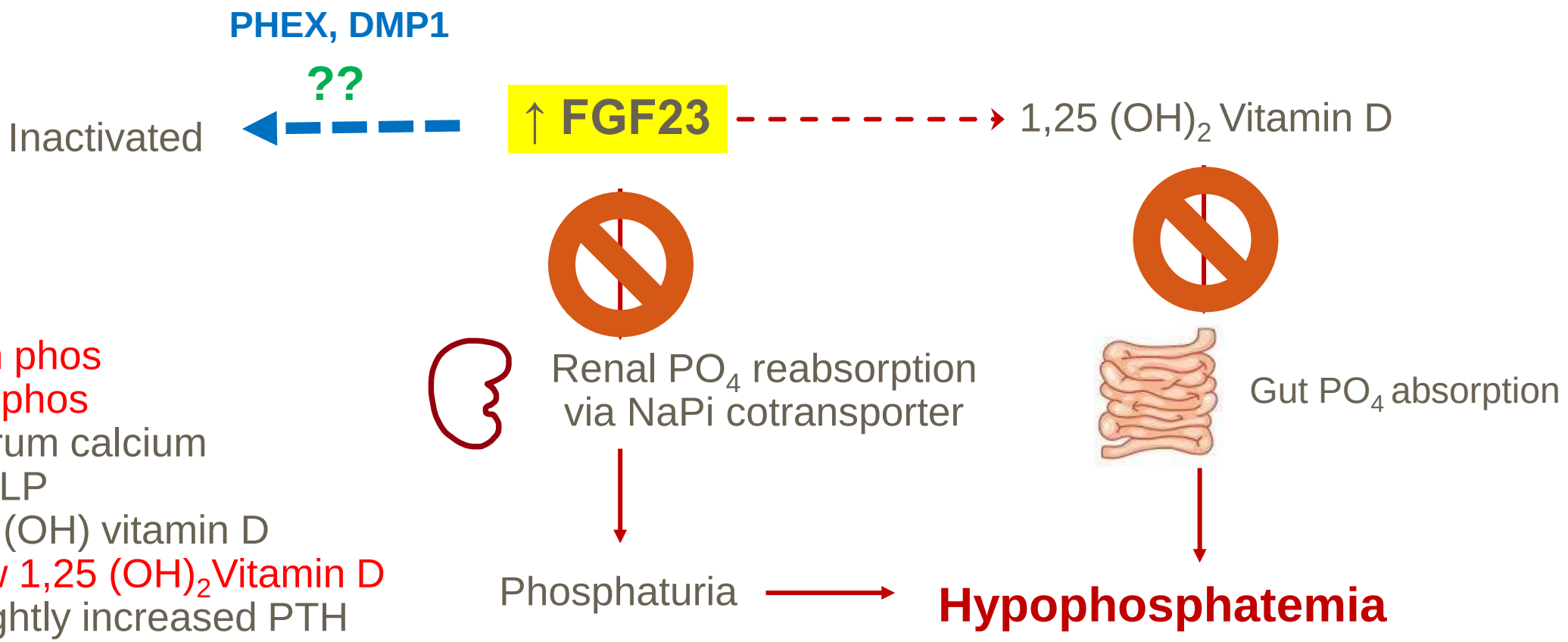
- Symptoms:
  - Muscle weakness
  - Fatigue
  - Acute neurological symptoms – paresthesia, altered mental status, seizures

- Causes:
  - Renal phosphate wasting
  - Hyperparathyroidism (primary, tertiary)
  - Redistribution (refeeding syndrome)

FGF23 Independent Hypophosphatemia

- Fanconi syndrome
  - Renal wasting of phosphorus, glucose, potassium, bicarbonate, uric acid, amino acids
  - Various diseases, medications, toxins
- HHRH (Hereditary Hypophosphatemic Rickets with Hypercalciuria)
  - *SLC34A3* gene mutation – encodes NaPi cotransporter
  - Normal-high serum calcium, low serum phos, normal PTH, normal 25 (OH) vitamin D, high 1,25 $(OH)_2$ Vitamin D, elevated urine Ca excretion
  - Kidney stones, rickets/osteomalacia
- Hyperparathyroidism

FGF23 Mediated Hypophosphatemia



- Low serum phos
- High urine phos
- Normal serum calcium
- Elevated ALP
- Normal 25 (OH) vitamin D
- Normal/low 1,25 $(OH)_2$Vitamin D
- Normal/slightly increased PTH

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FGF23 Mediated Hypophosphatemia

- Disorders of reduced inactivation
  - X-linked hypophosphatemic rickets (XLH)
    - *PHEX*
  - Autosomal dominant hypophosphatemic rickets (ADHR)
    - *FGF23* (at the cleavage site)
  - Autosomal recessive hypophosphatemic rickets (ARHR)
    - *DMP 1, ENPP1, FAM20C*

- Disorders of overproduction
  - Tumor induced rickets/osteomalacia (TIO) (Oncogenic osteomalacia)
    - From underlying mesenchymal tumor
  - McCune Albright syndrome
    - From fibrous dysplasia

Hypophosphatemia - Evaluation

- Fractional excretion of Phosphate (FEP)

$$\left[\frac{\text{Urinary Phosphate} \times \text{Serum creatinine}}{\text{Serum Phosphate} \times \text{Urinary creatinine}}\right] \times 100$$

- TRP (Tubular reabsorption of Phosphorus) % = 1- FEP

- TP/GFR = Serum Phosphate – Urine phosphate x Serum Creatinine / Urine Creatinine

Hypophosphatemia - Treatment

- Phosphorus supplements and calcitriol
  - Renal calcifications
  - Secondary hyperparathyroidism
- Burosumab (FGF23 monoclonal antibody)
  - Binds and blocks FGF23
  - Approved for treatment of XLH (>6 months of age), TIO
- Phosphorus supplements alone for HHRH

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Hyperphosphatemia

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Hyperphosphatemia - Causes

- Acute phosphate load
  - Cell lysis (tumor lysis, rhabdomyolysis, crush injuries, hemolytic anemia)
  - Exogenous phosphate administration (Fleet enema, high phosphate formulas in neonates)
- Renal insufficiency
- Hypoparathyroidism
- Tumoral calcinosis

Tumoral Calcinosis

- Autosomal Recessive disorder due to inactivating mutations in
  - GALNT3 gene
  - FGF23 gene
  - Klotho gene

- Low FGF23 bioactivity leads to hyperphosphatemia
  - ↑calcitriol level -> hypercalcemia-> suppress PTH
  - Vascular and periarticular calcifications
  - Elevated inactive C terminal fragment of FGF23

Hyperphosphatemia - Treatment

- Treat underlying disease
- Manage hypocalcemia
- Low phosphorus diet
- Phosphate binding agents
- Dialysis

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Disorders of Magnesium

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Hypomagnesemia

- Symptoms of hypocalcemia
  - Decreases PTH secretion and action

    - Irritability
    - Muscle twitches
    - Jitteriness
    - Tremors
    - Poor feeding
    - Lethargy
    - Seizures

Hypomagnesemia - Causes

- Primary:
  - Autosomal recessive mutations in TRPM6 (Mg channel in intestine and kidney)
  - Gitelman and Bartter syndrome
  - Autosomal dominant hypocalcemia (activating mutation of CaSR)
  - Several other genetic mutations
- Secondary:
  - Intestinal losses - acute or chronic diarrhea, steatorrhea, or malabsorption, drugs (laxative, PPI)
  - Renal losses- diuretic use, nephrotoxins (such as aminoglycosides, amphotericin B), and renal tubular dysfunction or tubular-interstitial disease
  - Inadequate intake when TPN dependent
  - Shifts from intravascular space: “hungry bone syndrome” or refeeding syndrome

Hypermagnesemia

- Symptoms:
  - Mild: Asymptomatic
  - Rising levels: Flushing, nausea, headaches
  - Severe: hypoventilation, muscle paralysis, arrhythmia, respiratory arrest, asystole

- Causes:
  - Renal insufficiency
  - Excess intake
    - Tocolytic agent (maternal and fetal toxicity)
    - Enema, antacids, adjuvant treatment of moderate - severe asthma

- Also suppresses PTH secretion

Evaluation and Treatment

- FEMg (urine Mg x serum Cr/urine Cr x Serum Mg) x 100
  - If <2%, likely extrarenal losses

- Hypomagnesemia
  - Seizures: IV bolus 2.5-5 mg/kg of 50% magnesium sulfate with EKG monitoring
  - Magnesium supplements (high oral doses can cause diarrhea)
  - Hypocalcemia can be refractory to therapy until Magnesium given

- Hypermagnesemia
  - Remove the source
  - Hydration, loop diuretics, dialysis
  - Hemodynamic, respiratory support
  - Calcium and calcitriol supplementation

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Bone Physiology

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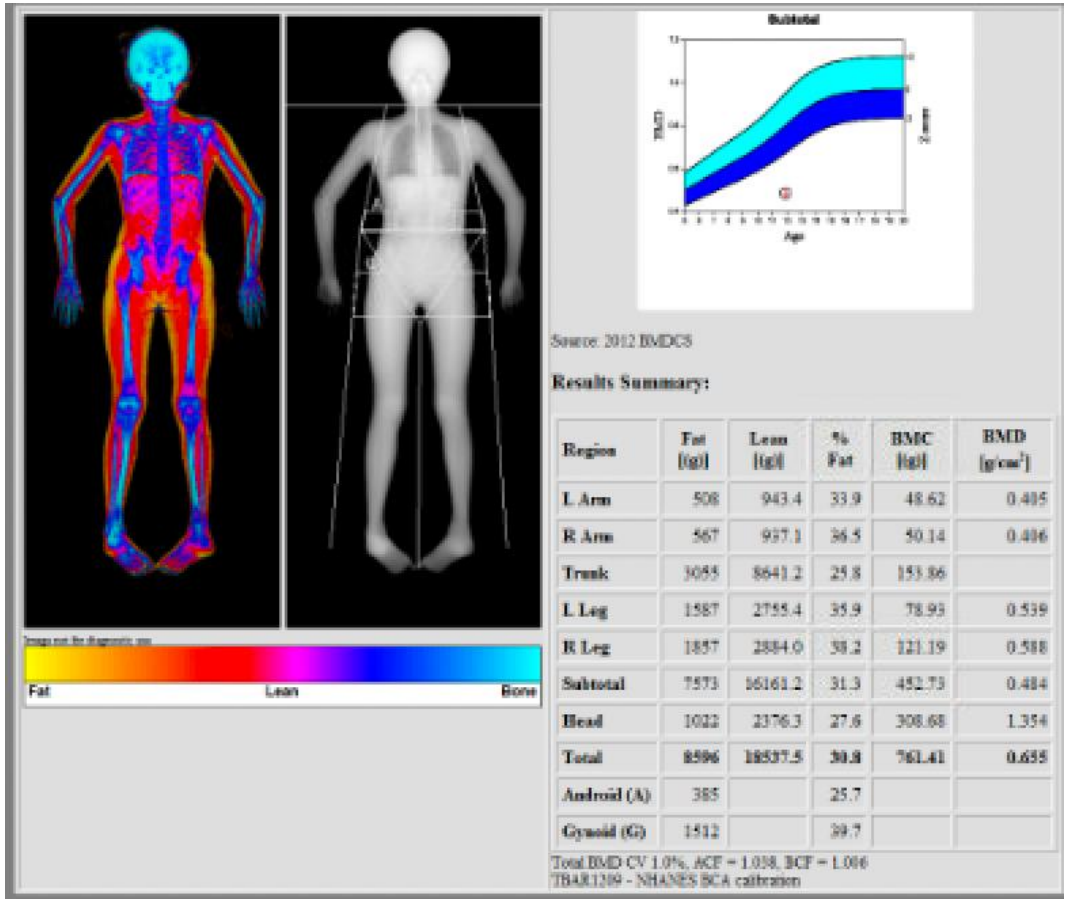
Bone Density Measurement Techniques

- Plain radiograph – very insensitive

- Quantitative CT – vBMD
  - Peripheral vs central
  - Distinguish trabecular vs cortical bone
  - Radiation, inability to reliably measure the same site in a growing child

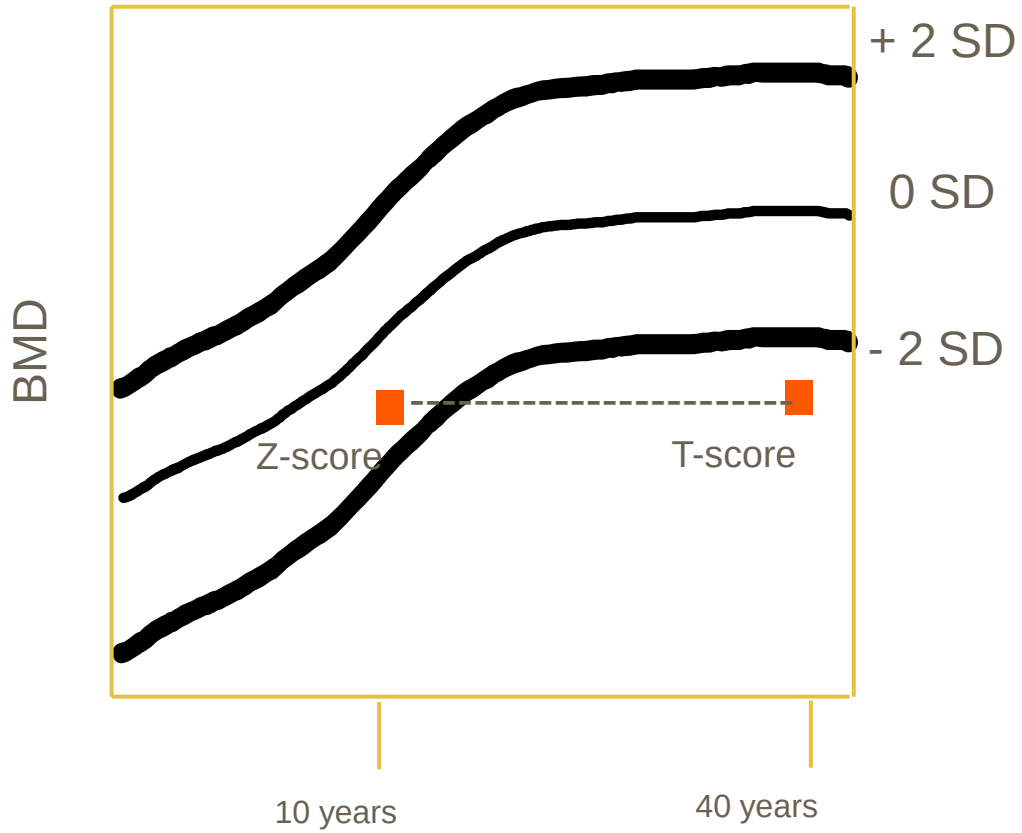
- DXA (Dual energy X ray absorptiometry) - aBMD
  - Low radiation – 2 radiation beams to distinguish bone from soft tissue
  - Short scan time
  - Good reproducibility
  - Appropriate positioning, different body sites
  - Comparison – same scanner; Pediatric software

DXA – Use the Z-score



Region	Fat (g)	Lean (g)	% Fat	BMC (g)	BMD (g/cm²)
L Arm	508	943.4	33.9	48.62	0.405
R Arm	567	937.1	36.5	50.14	0.406
Trunk	3055	8641.2	25.8	153.86	
L Leg	1587	2755.4	35.9	78.93	0.539
R Leg	1857	2884.0	38.2	121.19	0.588
Subtotal	7573	16161.2	31.3	452.73	0.484
Head	1022	2376.3	27.6	308.68	1.354
Total	8596	18537.5	30.8	761.41	0.635
Android (A)	385		25.7		
Gynoid (G)	1512		39.7		

Total BMD CV 1.0%, ACF = 1.038, BCF = 1.016
TBAR1209 - NHANES BCA calibration



Z-score = SD from mean for age, sex, ethnicity
T score = SD score compared to young adults who have attained peak bone mass

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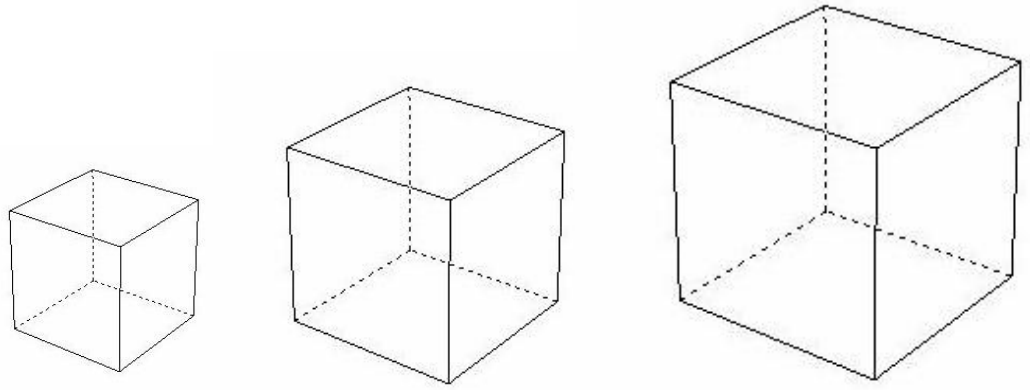
Bone Density affected by Stature and Puberty

Adjust for height and maturity



	1 cm	2 cm	3 cm
BMC (g)	1	8	27
Area (cm^2)	1	4	9
aBMD (g/cm^2)	1	2	3
vBMD (g/cm^3)	1	1	1

Overestimated in Tall Stature
Underestimated in Short Stature

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Bone Disorders

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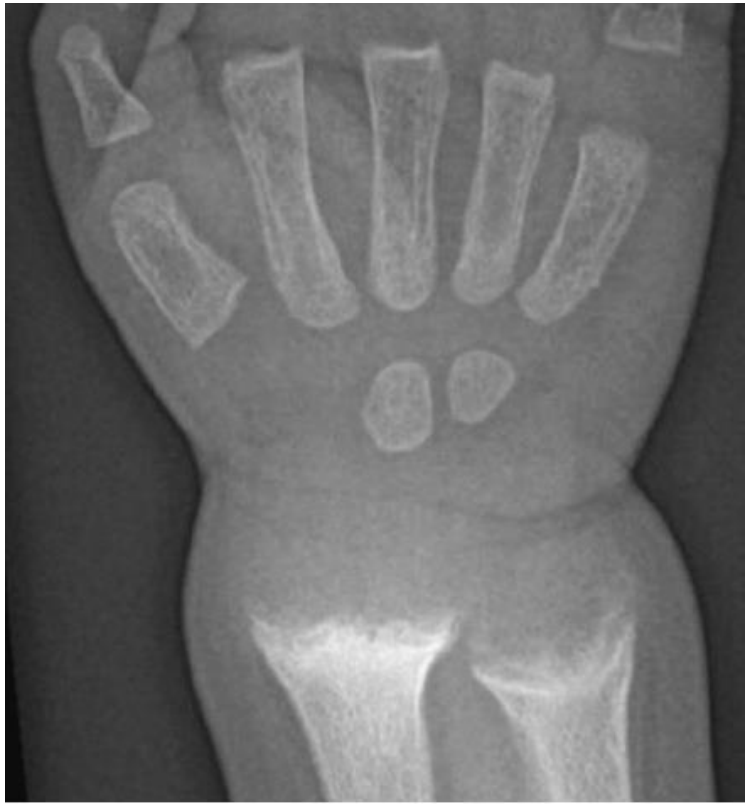
Rickets and Osteomalacia

- Rickets: Defective mineralization of the growth plates
- Osteomalacia: Defective mineralization of cortical and trabecular bone surfaces
- Symptoms
  - Bone pain, anorexia, failure to thrive, gross motor delay
  - Symptoms of hypocalcemia (rarely)

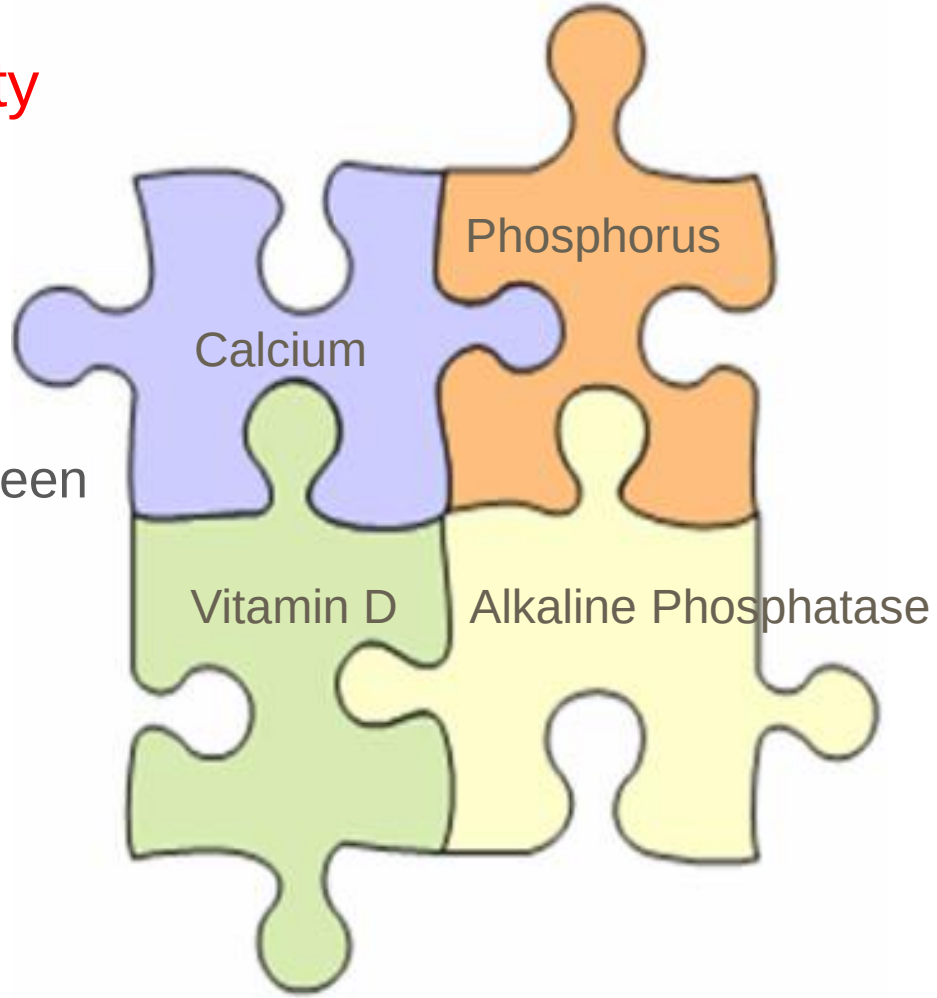
- Signs
  - Flaring, fraying, and cupping of metaphysis and epiphysis
  - Caput quadratum
  - Delayed closure of fontanelles
  - Rachitic rosary
  - Genu varus or genu valgum
  - Poor growth



Rickets and Osteomalacia

- Calcium deficiency**
- Phosphorus deficiency**
- Vitamin D deficiency or resistance
  - Nutritional, maternal deficiency, exclusive breast feeding
  - Inadequate exposure to sun, high melanin content, sunscreen
  - Malabsorption
  - Liver or renal disease
  - VDR mutations
  - Obesity
  - Increase catabolism (like anticonvulsants)
- Hypophosphatasia

** TPN, prematurity



Metabolic Bone Disease of Prematurity

- Rickets or osteopenia of prematurity
  - Can present with bone fragility

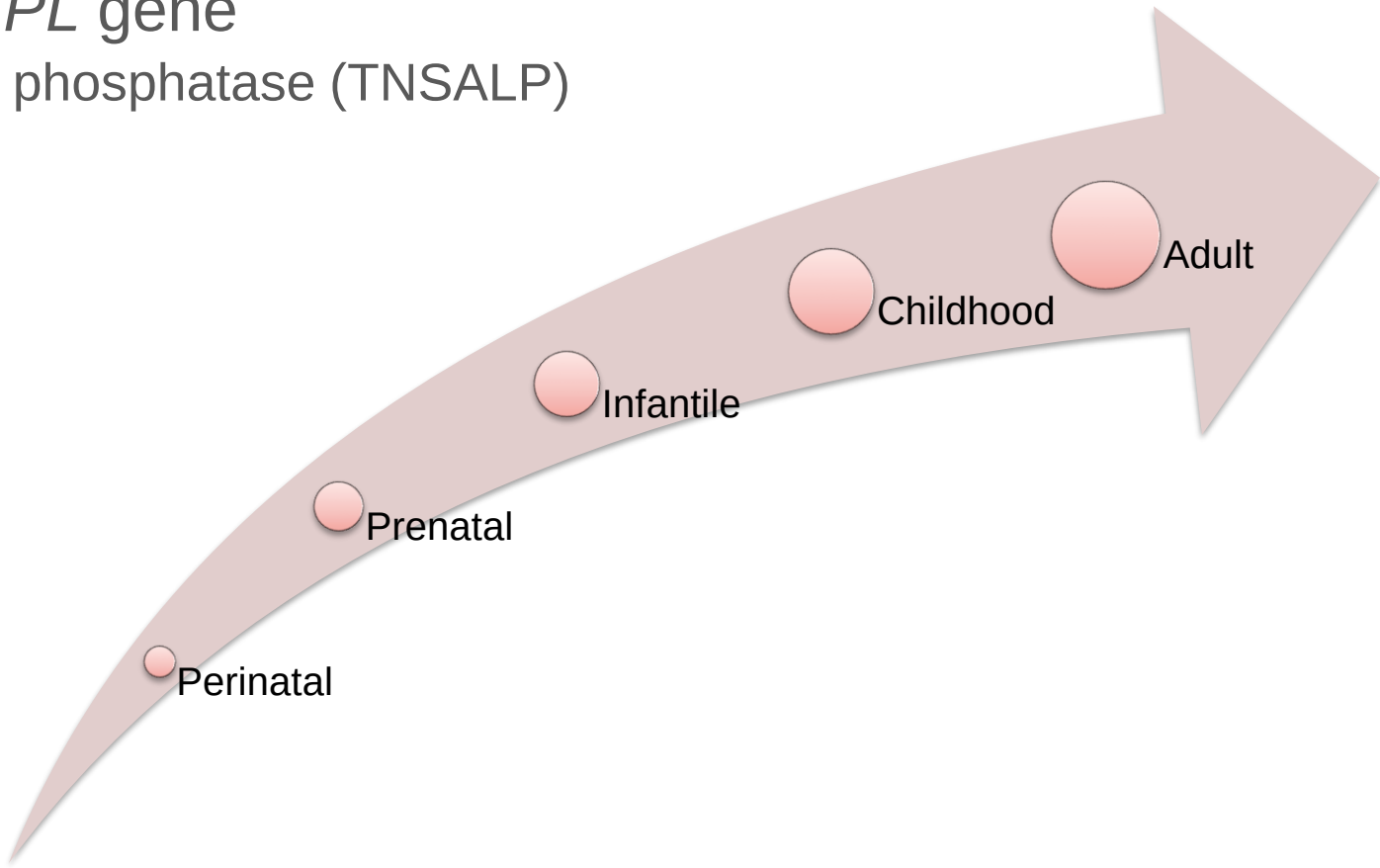
- Multifactorial:
  - Prematurity (Failure to accrue bone mineral in third trimester)
  - Chronic medical problems; Medications used to treat them
  - Inadequate intake of minerals post birth, TPN dependency, aluminum toxicity

- Management:
  - Supplemental minerals +/- calcitriol

Hypophosphatasia

- Loss of function mutations in the *ALPL* gene
  - Deficiency of tissue nonspecific alkaline phosphatase (TNSALP)
  - Autosomal recessive or dominant
  - Undermineralized bone and teeth

- Spectrum of phenotype
  - Mildest – Odontohypophosphatasia
  - Bone and joint pain
  - Stress fractures
  - Craniosynostosis
  - Seizures
  - Early deciduous teeth loss (root intact)



Hypophosphatasia

- Lab Evaluation:
  - Low ALP (age dependent range!)
  - Accumulation of phosphoethanolamine (PEA), pyridoxal 5'-phosphate (PLP), and inorganic pyrophosphate (PPi)
  - Hypercalcemia, hypercalciuria

- Treatment:
  - Enzyme (asfotase alfa) replacement (subcutaneous injections)
  - Supportive management
  - Team approach (dentist, orthopedics, physical therapist, neurosurgery, pain management)
  - Vitamin B6 for seizures
  - Management of hypercalcemia
  - Avoid bisphosphonates

Pediatric Osteoporosis is a Clinical Diagnosis

- Clinically significant fracture history
  - One or more non traumatic vertebral compression fracture

    OR

  - Low BMC/BMD (Z-score < -2*) & long bone fractures
    - 2 or more by age 10**
    - 3 or more by age 19

*BMD as a spectrum

**Integrating fracture characteristics and clinical context into diagnostic approach

Gordon CM. *J Clin Densitometry* 2014 Apr-Jun;17(2):219-24

Osteoporosis

- Primary:
  - Juvenile osteoporosis (IJO or mutations in *WNT, LRP5, PLS3*)
  - Connective tissue disorders: Osteogenesis Imperfecta, Marfan syndrome, EDS, Bruck syndrome, homocystinuria

- Secondary:
  - Immobilization: Cerebral Palsy, muscular dystrophies
  - Chronic disease: Cystic Fibrosis, IBD, malignancy, rheumatologic, transplantation, eating disorders etc.
  - Endocrine disease: Hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, growth hormone deficiency
  - Bone toxic medications: Glucocorticoids, depot provera, antiepileptics etc.

Idiopathic Juvenile Osteoporosis (IJO)

- Rare form of primary osteoporosis
- Symptoms:
  - Presents in prepubertal period in a previously healthy child
  - Bone fragility (VF, sub-metaphyseal fractures of long bones)
  - Proximal muscle weakness and back/hip pain
- Signs:
  - Lack features of Osteogenesis Imperfecta
  - Osteopenia, fractures, radiolucent bands at metaphyses of long bones
- Etiology:
  - Unclear; some have heterozygous mutations of *LRP5*
  - Reduced bone formation based on histomorphometry
- Resolves spontaneously after puberty

Osteogenesis Imperfecta (OI)

- Heterogenous group of connective tissue disorders
- Bone fragility, low bone mass
- Extra-skeletal features:
  - Blue-grey sclera
  - Skin laxity
  - Hearing loss
  - Joint hyperextensibility
  - Short stature
  - Dentinogenesis imperfecta
  - Cardiovascular, respiratory, neurological manifestations

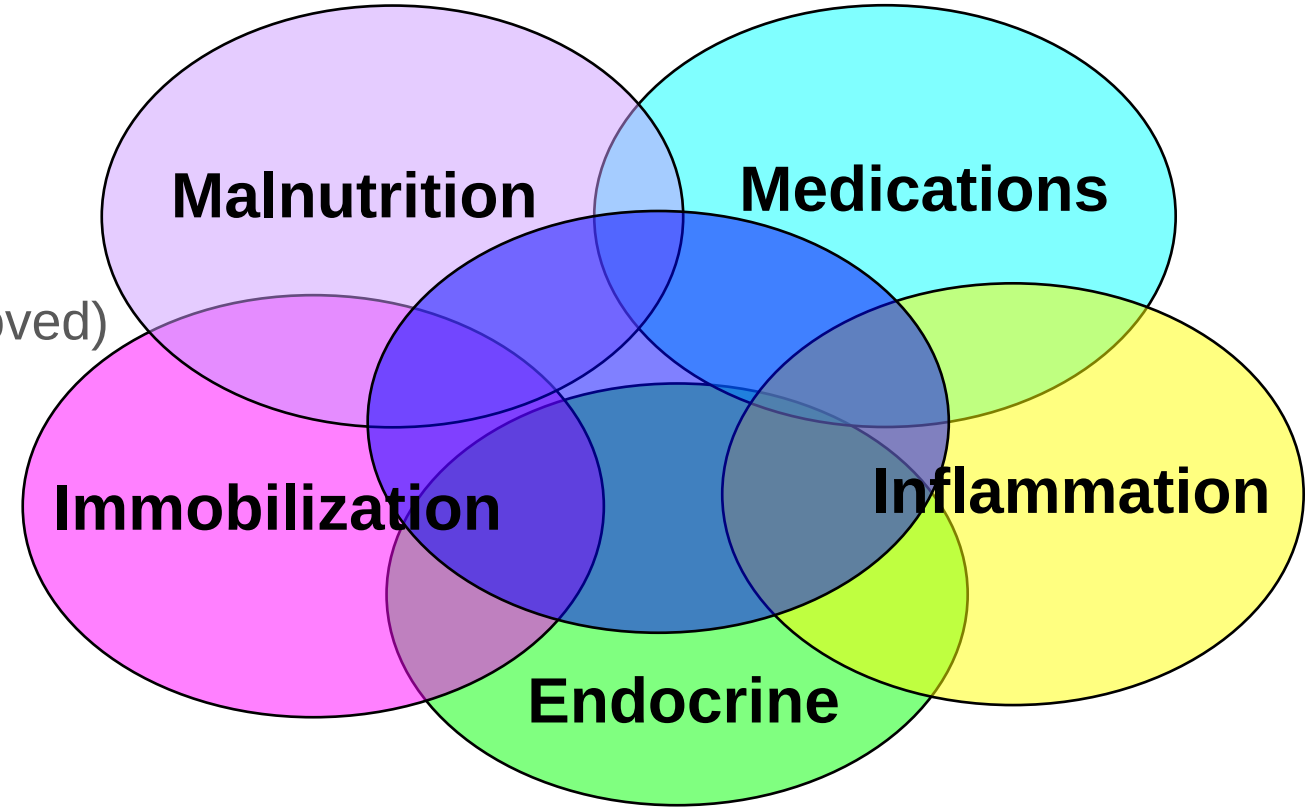
Osteogenesis Imperfecta (OI)

- Etiology
  - Majority – autosomal dominant mutations in *Col1A1, Col1A2* (encode collagen I)
  - Autosomal recessive
  - X Linked recessive

- Broad spectrum of clinical presentation; Sillence classification
  - Type 1 (mild)
  - Type 2 (perinatal lethal)
  - Type 3 (severe)
  - Type 4 (moderate)

Management of Pediatric Osteoporosis

- Pharmacologic therapy:
  - Anabolic
    - Growth Hormone
    - PTH (black box warning – recently removed)
    - Anti Sclerostin antibody*
  - Antiresorptive
    - Sex steroids
    - Bisphosphonates
    - RANK-L blocking antibody*



Bisphosphonates

- Synthetic pyrophosphate analogues
  - Binds to hydroxyapatite crystals
  - Inhibits osteoclast mediated bone resorption

- Increase BMC/BMD, reshape vertebral bodies, increase cortical thickness

- Pediatric uses:
  - Primary Osteoporosis (IJO and OI)
  - Secondary Osteoporosis except eating disorders
  - Hypercalcemia
  - Fibrous Dysplasia

Osteopetrosis

- Rare disorder of defective bone resorption (osteoclasts)
- Symptoms:
  - Increased bone density, altered architecture, bone fragility
  - Narrow bone marrow space – pancytopenia, extramedullary hematopoiesis (HSM)
  - Compression of cranial nerves
  - Hypocalcemia - seizures
- Genetics:
  - Autosomal Dominant (mild), Autosomal recessive (malignant infantile), intermediate, X linked recessive (extremely rare)
- Management:
  - Only treatment for malignant infantile form is hematopoietic stem cell transplantation
  - Supportive management including calcium, vitamin D supplements

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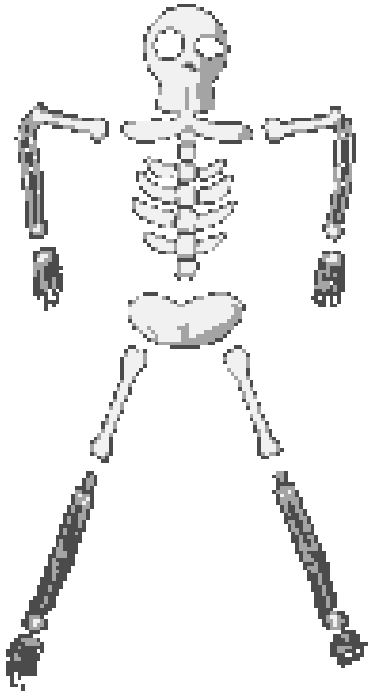
Supplemental material in handout



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Audience Response Question 1

A 2.5-year-old female presents to your clinic with progressive bowing of legs. She was born full term and has no significant past medical or family history. She is taking vitamin D 600 IU daily supplements as recommended by her pediatrician. Radiographs demonstrate rickets. Her lab evaluation showed:

Serum calcium 9.5 mg/dl, Serum phosphorus 2.5 mg/dl, Serum magnesium 2 mg/dl

iPTH 37 pg/ml, ALP 700 U/L

25 (OH) Vitamin D 35 ng/ml, 1,25 $(OH)_2$ Vitamin D 145 pg/ml

Options

Of the following, she most likely has a mutation in which gene:

A. *PHEX*
B. *DMP1*
C. *SLC34A3*
D. *FGF23*

Answer

C. *SLC34A3*

Hypophosphatemic rickets with hypercalciuria

Serum calcium 9.5 mg/dl, iPTH 37 pg/ml, ALP 700 U/L

Serum phosphorus 2.5 mg/dl, Serum magnesium 2 mg/dl

25 (OH) Vitamin D 35 ng/ml

$1,25\ (OH)_2$ Vitamin D 145 pg/ml

Audience Response Question 2

A 4-year-old male presents to emergency room with seizures. He also had seizures last week at an outside hospital which were thought to be febrile seizures. Vitals stable and exam was unremarkable. Height 55%tile, weight 75%tile. Lab evaluation showed:

Serum calcium 4.1 mg/dl, albumin 4.3 mg/dl

Serum phosphorus 9 mg/dl, Serum magnesium 2 mg/dl

iPTH 250 pg/ml, ALP 200 U/L

25(OH)Vitamin D 30 ng/ml

Options

What is the most likely defect associated with this condition?

A. Autosomal dominant mutation
B. Autosomal recessive mutation
C. X linked recessive mutation
D. Imprinting defect

Answer

D. Imprinting defect

Based on lab findings of hypocalcemia, hyperphosphatemia, elevated PTH the most likely diagnosis is pseudohypoparathyroidism. No features of Albright hereditary osteodystrophy on examination.

PHP Ib (epigenetic GNAS1 imprinting defect)

or

PHP II (some have PRKAR1A mutations)

Audience Response Question 3

A 15-year-old boy with Duchenne muscular dystrophy presents to clinic with acute onset back pain. He has been on glucocorticoids since age 8. He has never had any long bone fractures. He is slightly obese, sitting in wheelchair, has calf muscle hypertrophy, and is prepubertal. He has lower thoracic spine tenderness. Radiograph shows vertebral compression fractures from T10-L1. Lab evaluation showed:

Serum Calcium 9.1 mg/dl, albumin 4 mg/dl

Serum Phosphorus 4.5 mg/dl, Serum Magnesium 2 mg/dl

iPTH 30 pg/ml, ALP 80 U/L

25 (OH) vitamin D of 45 ng/ml

Options

What are the factors contributing to secondary osteoporosis?

A. Muscle dystrophy (inflammation)

B. Chronic glucocorticoid therapy

C. Immobilization

D. Hypogonadism

E. All of the above

Answer

E. All of the above

Key points:

Low bone turnover state with low bone formation rate
Secondary osteoporosis can be multifactorial
Treatment should address all the factors affecting bone health

Audience Response Question 4

A 2.5-year-old female presents to your clinic with progressive bowing of legs. She was born full term and has no significant past medical or family history.

On physical examination, her height is at the 2nd percentile and her weight is at the 45th percentile for age. She has thin eyelashes and patchy hair on her scalp. Rachitic rosary is noted at the chest wall and both wrists and ankles are widened. There is bilateral genu varum.

Radiographs demonstrate rickets.

Options

Of the following the lab findings most likely to be found in this patient:

	S. Calcium (mg/dl)	S. Phosphorus (mg/dl)	Alkaline Phosphatase (IU/L)	25 OH D (ng/ml)	1,25 $(OH)_2D$ (pg/ml)
A.	8	3.5	450	22	321
B.	7.5	4.5	388	32	60
C.	9.8	4.5	100	25	25
D.	9.5	2.5	420	30	108

Answer

A. Very elevated 1,25 $(OH)_2$ D level

Key points:

Growth failure, rickets, bone pain, partial or complete **alopecia**

End organ resistance -> VDR mutation

Audience Response Question 5

- A 2-year-old boy presents to PCP's office for a viral illness. Subsequent lab evaluation is within normal limits except an elevated alkaline phosphatase level of 1400 IU/L.

- PCP asks for patient to return for a more thorough examination and does not find any signs/symptoms of liver disease or rickets.

- 4 weeks after this visit, repeat labs are done which show serum alkaline phosphatase level of 650 IU/L.

Options

What is the next best step in management of this patient?

A. Treat with calcium and vitamin D
B. Order a GGT level
C. Order a skeletal survey to look for occult fracture
D. Repeat alkaline phosphatase level in 2-3 months

Answer

D. Repeat alkaline phosphatase level in 2-3 months

Key points:

Transient benign hyperphosphatasemia of infancy and childhood is not completely understood but could result in elevation of alkaline phosphatase after a viral illness or so. It usually self resolves within a few weeks to months.

Disorders of Growth

Susie Cabrera MD

Associate Professor of Pediatrics

Medical College of Wisconsin

knowledge changing life

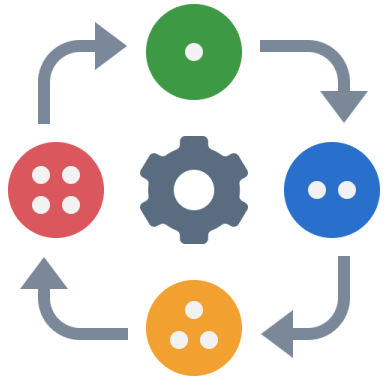
ABP Content Domains

- GH/IGF-1 axis
- Regulation of growth in the fetus, neonate, child, and adolescent
- Short stature
- Congenital and acquired GH deficiency
- Disorders of GH action and GH sensitivity (primary IGF-1 deficiency)
- Idiopathic short stature
- Syndromes associated with short stature
- Growth disorders not related to the GH-IGF axis
- Skeletal dysplasia
- Effects of chronic illness on growth including cancer therapy
- Tall stature
- Overgrowth syndromes

We will also cover previous content specs

Let’s start with normal physiology

Phases of Typical Linear Growth



1. Intrauterine growth

- Most rapid growth during lifetime (100 cm/yr)
- **Nutrition** and **maternal/fetal health** are key drivers
- Paternally expressed **IGF-2** in fetus and placenta is important in fetal growth

2. Infancy (birth to age 2)

- Growth remains rapid (25-50 cm/year)
- **Nutrition** remains key driver 6-9 months of life, then **GH** gains importance
- **Physiological rechanneling** (crossing height percentiles) during transition from prenatal to postnatal growth

3. Childhood

- Slowest and longest period of growth (5 cm/yr)
- **Growth hormone** is primary driver
- Shifting percentiles is *abnormal* in this phase

4. Adolescence

- Final 15% of growth (8-10 cm/year)
- **Girls**: accelerate at 10 years, peak 9 cm/yr at 11.5 years, with average 7.5 cm growth post-menarche
- **Boys**: accelerate at 12 years, peak 10 cm/yr at 13.5 years, with 97% height attained at bone age of 15 years
- **Growth hormone** secretion increased by **sex steroids**

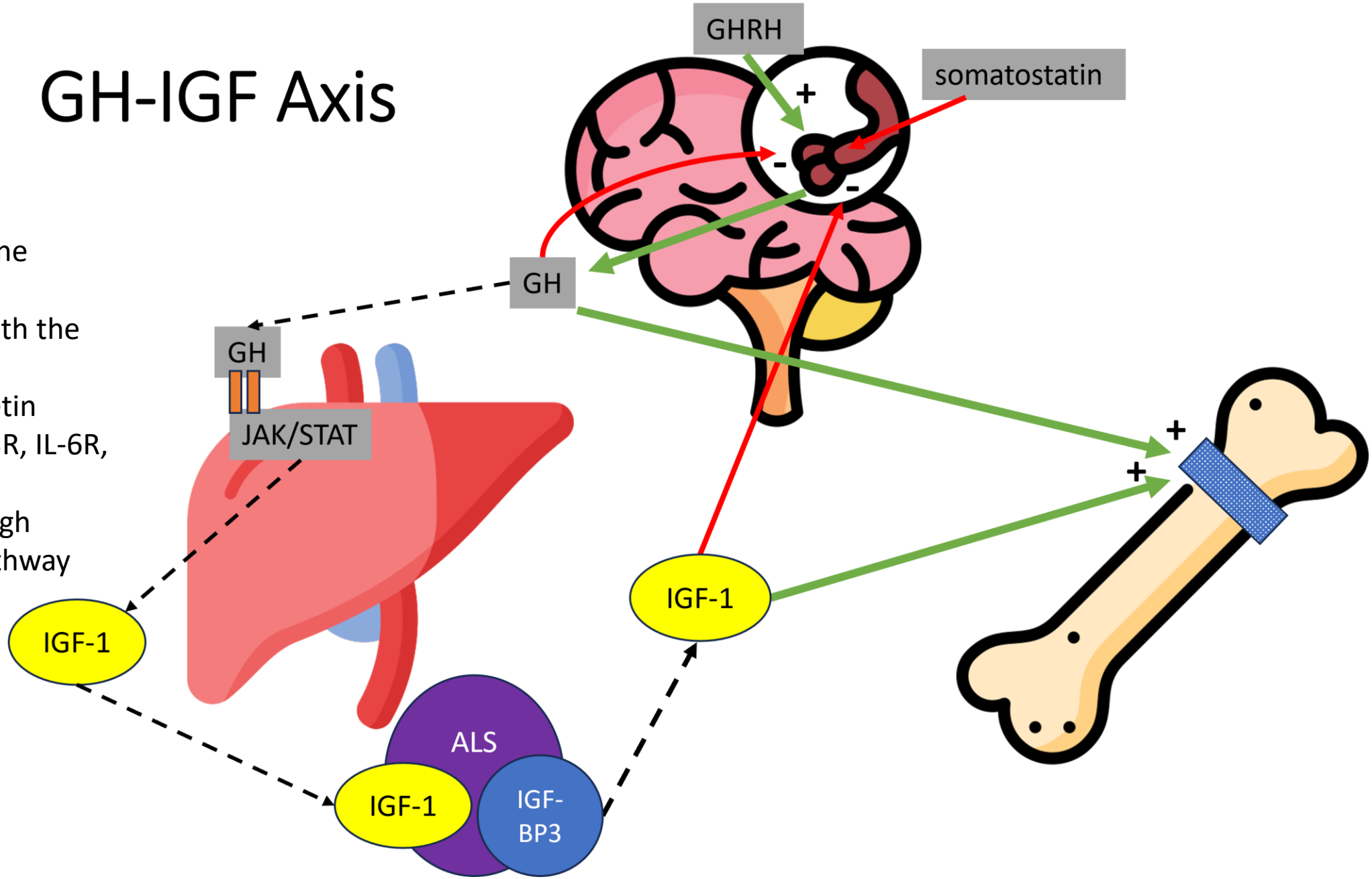
Regulators of Linear Growth

	Variables
Endocrine System	Growth Hormone, IGF-1, Thyroid Hormone, Glucocorticoids, Estrogens, Androgens, Insulin
Nutrition	Undernutrition, Overnutrition
Autocrine/Paracrine at Growth Plate Chondrocytes	Fibroblast Growth Factors (FGF), C-Type Natriuretic Peptide, PTHrP and Indian Hedgehog (IHH), IGF-1 and IGF-2
Pro-inflammatory Cytokines	TNF-α, IL-1β, IL-6
Cartilage Matrix	Collagen type I, Collagen type II, Collagen type III, Aggrecan
Intracellular Signaling	*SHOX* encoded transcription factor, RAS-mitogen-activated protein kinase (MAPK) pathway
Growth Plate Senescence 	Intrinsic developmental program of growth plate. Decrease of chondrocyte proliferation → involution of growth plate → inert cartilage remodeled into bone → epiphyseal fusion

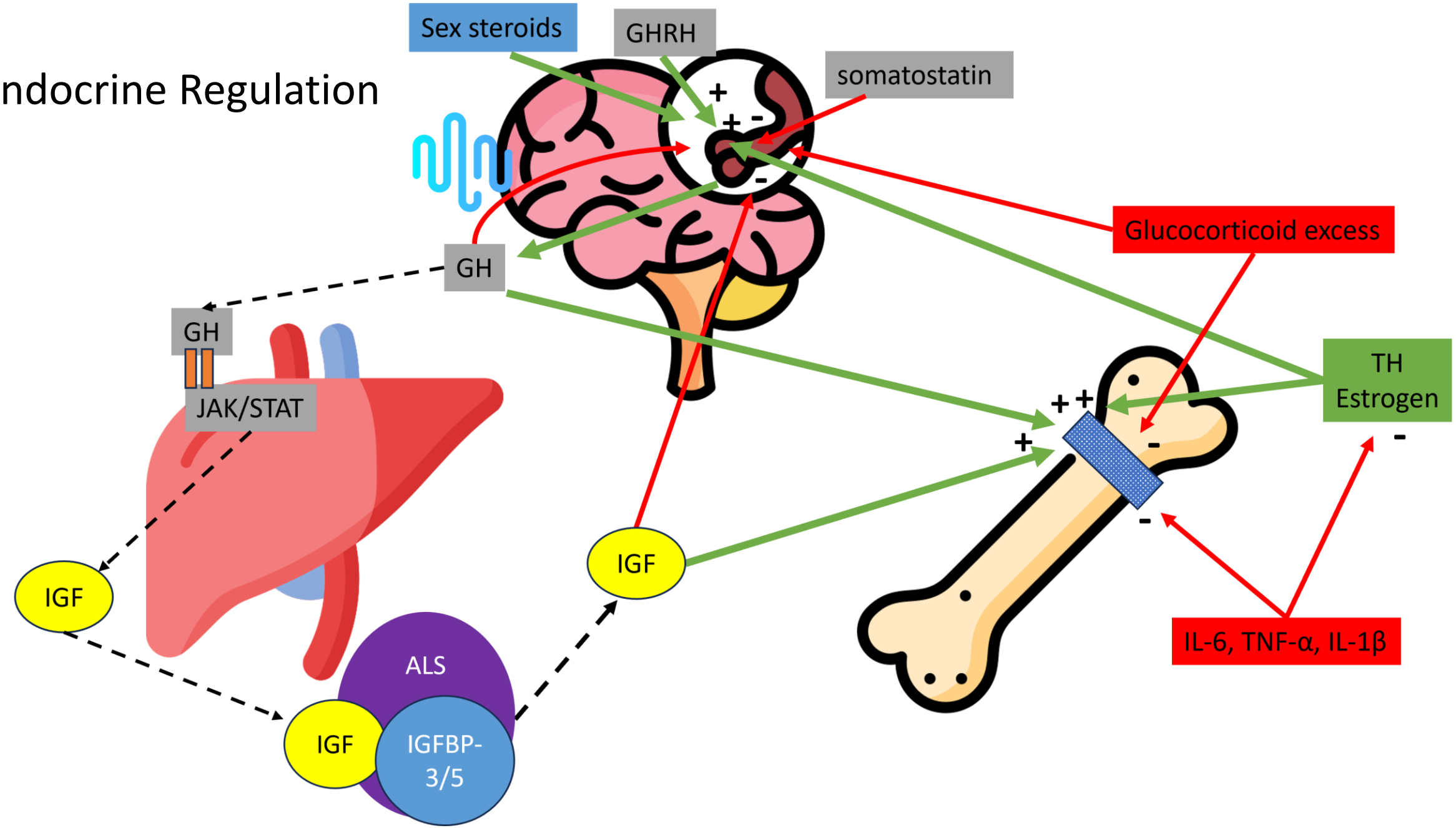
GH-IGF Axis

GHR

- Class I cytokine receptor
- Homology with the PRLR, EPOR, thrombopoietin receptor, IL-3R, IL-6R, IL-7R
- Signals through **JAK/STAT** pathway

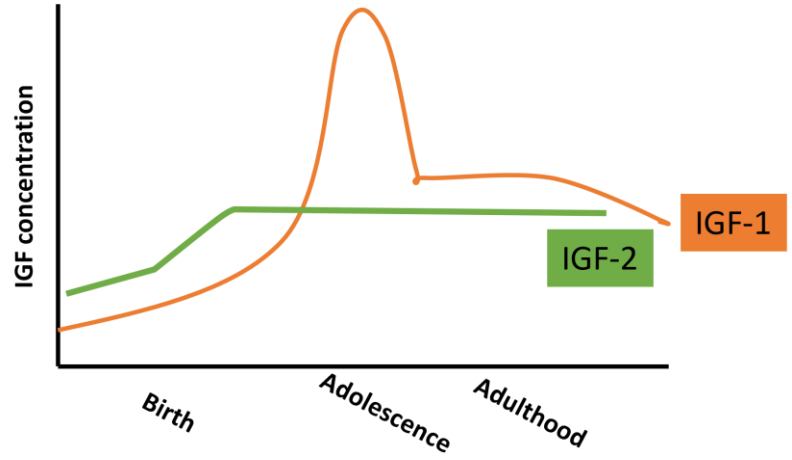


Endocrine Regulation



Insulin-like growth factors

- Polypeptides with homology to insulin
- **IGF-1**: Primarily produced in liver and acts in an *endocrine* manner as the major mediator of GH-stimulated somatic growth.
  - Produced in growth plates and acts as *paracrine* factor. Acts in an *autocrine* manner in muscle and adipocytes
- **IGF-2**: Primarily a *paracrine* factor, expressed at high levels in fetal tissues; IGF-2 is maternally imprinted

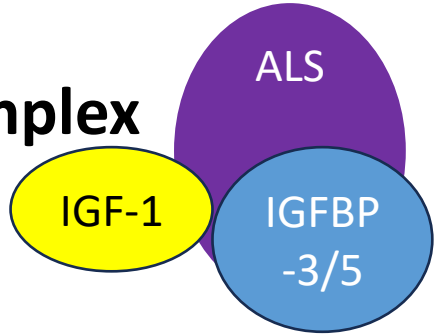


Note: IGF-2 and IGF-1 levels not to scale

- Bind and activate the **IGF1 receptor**, a class II tyrosine kinase receptor
  - Heterotetrameric glycoprotein with 2 alpha and 2 beta subunits
  - Similar structure to insulin receptor
  - High affinity for IGF-1 and IGF-2
  - 100-fold lower affinity for insulin
  - Stimulate cell growth and proliferation
  - Inhibit apoptosis via activation of **PI3K/AKT** pathway
- **IGF2/mannose-6-phosphate receptor** inhibits IGF-1 and IGF-2 activities by sequestering and degrading these hormones

IGF Binding Protein Superfamily

- Family of bioactive binding proteins that bind IGFs with higher affinity than IGF1R
  - Extend half life of IGFs
  - Transport IGFs to target cells
  - Modulate interaction of IGFs with surface membrane receptors
  - Six IGFBPs have been identified
- IGFBPs mostly act to *inhibit IGF action* by competing with IGFRs
- IGFBP-1: stimulated by prolonged fasting; suppressed by insulin
- **IGFBP-3**: major IGFBP in human serum; primarily stimulated by GH
  - Testosterone, estrogen, and thyroxine also promote IGFBP-3 synthesis
- IGFBP-3 and IGFBP-5 unique in that they circulate as a **ternary complex**

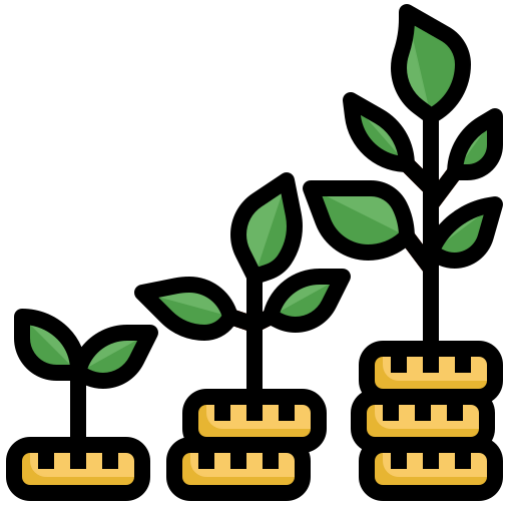


Evaluation of Growth

Clinical Evaluation of Growth

- **Measurement**
  - Wall-mounted stadiometer for standing height
  - Recumbent length board for recumbent length
- **Growth Charts**
  - CDC and WHO curves for height, weight, BMI
  - Velocity charts
  - Growth charts for certain genetic syndromes (Turner Syndrome, Down Syndrome)

Growth Charts



CDC (2000)

- 2-19 years
- Standing height (> 2 years)
- Cross-sectional data across U.S.
- Reference population from national surveys from 1963-1980
- ~50% ever breastfed and only 1/3 breastfed at 3 months
- Observationally describe how children in the population grow

WHO (2006)

- Birth to 2 years
- Recumbent length (≤ 2 years)
- Longitudinal data across 6 diverse countries
- Children predominantly breastfed for at least 4 months and still at 12 months
- Identify how children **should** grow when provided optimal conditions (ideal growth)
- Better description of physiological growth in infancy

Clinical Evaluation: Body Proportions

Body Proportion Measure	Technique	Diagnostic clues
Upper to lower segment ratio	LS: pubis symphysis to floor (legs) US: standing height – LS (head + trunk)	Normal: U/L 1.7 at birth; 1.0 by age 10 yrs Early growth cessation: ↑ U/L Late growth cessation: ↓ U/L
Arm span to height	Arm span (AS) – distance from end of middle fingers with outstretched arms versus standing height	AS < height until age 8 yrs AS = height at 8-12 years AS > height once > 12 years
Sitting height index	Sitting height / standing height (Reference data by age and sex from NHANES III)	Elevated sitting height index: SHOX deficiency, hypochondroplasia
Limb segment proportions	Proximal limbs: humerus & femur Middle limbs: radius/ulna & tibia/fibula Distal limbs: hands & feet	Rhizomelia – proximal shortening Mezomelia – middle shortening Acromelia – distal shortening

Clinical Evaluation of Growth

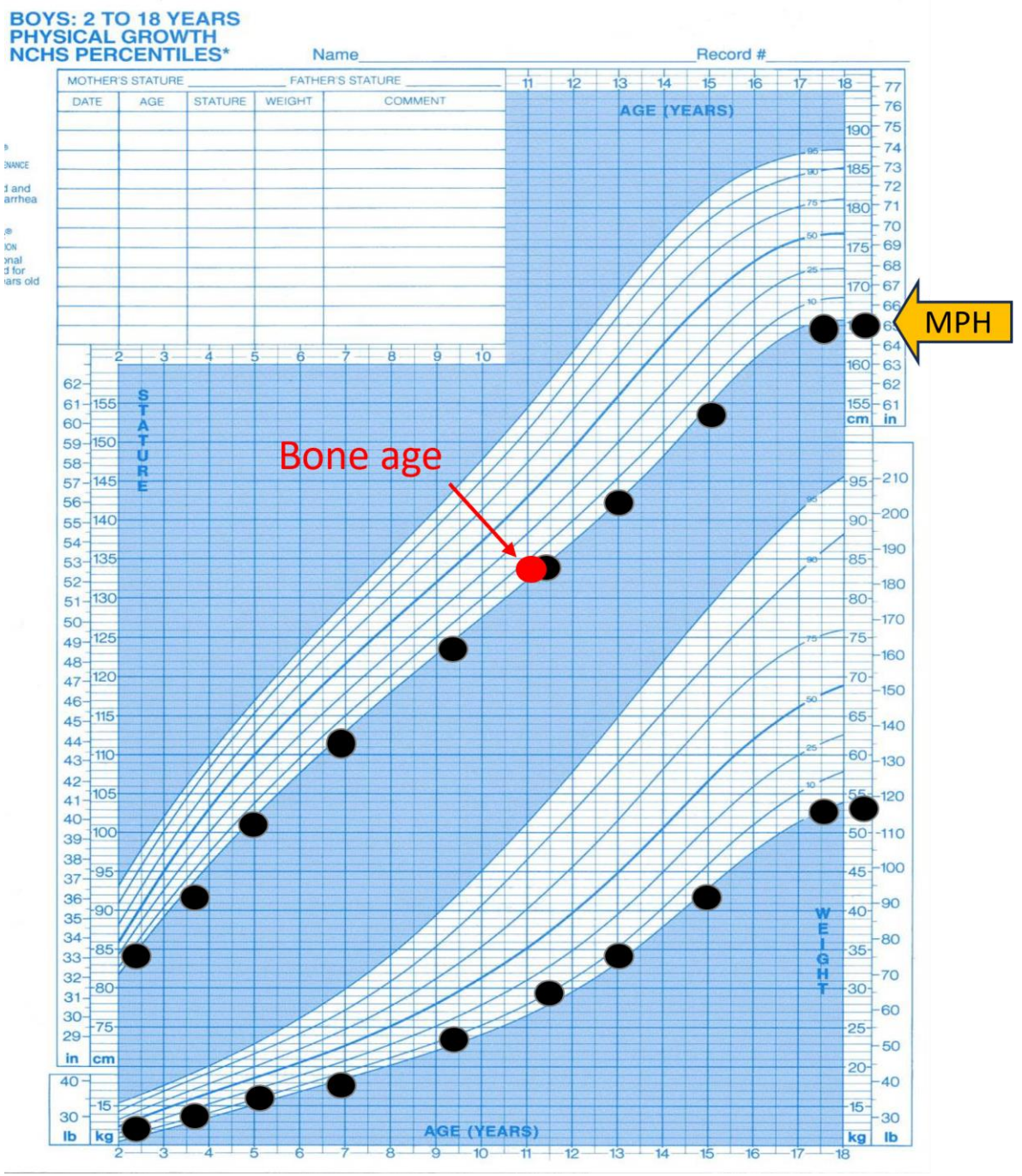
- **Skeletal Maturation**
  - Bone age radiograph, compared to published standards (Greulich and Pyle or Tanner-Whitehouse), to assess degree of skeletal ossification
  - Mirrors physical development tempo, indicates remaining growth potential
  - Factors that drive growth (TH, GH, E2, nutrition) positively regulate skeletal maturation
  - Dental maturation correlates with skeletal maturation
- **Prediction of Adult Height (humility needed!)**
  - Simplest/least accurate: child follows constant height centile until adulthood
  - Mid-parental height (MPH): [Note - assumes height inherited in polygenic fashion!]
    - For boys: [mother's height + 5 inches] + father's height / 2
    - For girls: [father's height – 5 inches] + mother's height / 2

    } **~70% of kids within ± 2-2.5 inches**
  - **Bayley-Pinneau** prediction: adult height predicted by combining child's bone age with height measured at time of the radiograph (Greulich and Pyle Atlas)

Physiologic Short Stature

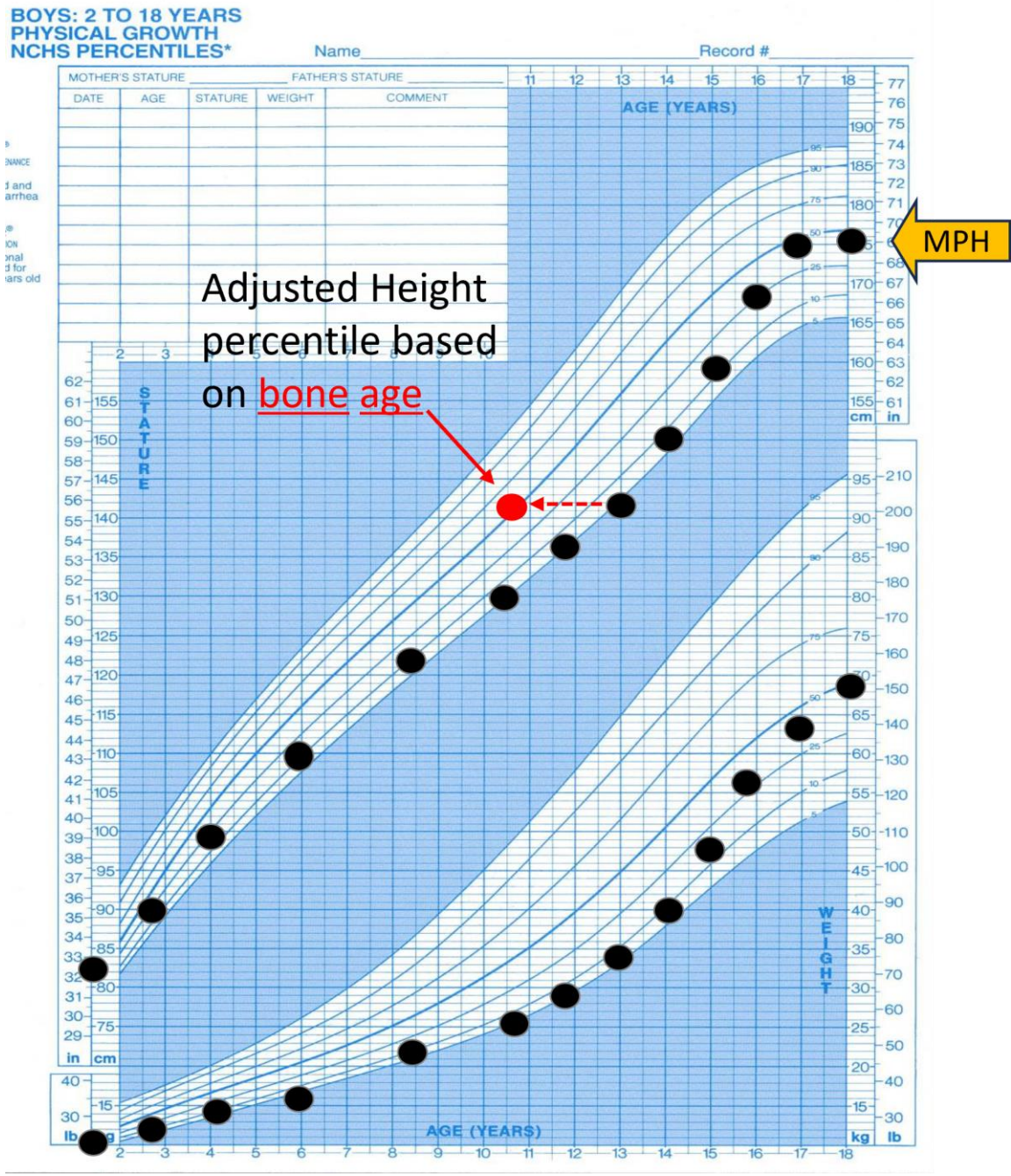
Normal variant: Familial Short Stature

- Height velocity (HV) and bone age are within normal range for familial potential (MPH)
- One or both parents are short
- Rx: reassurance



Normal variant: CDGP

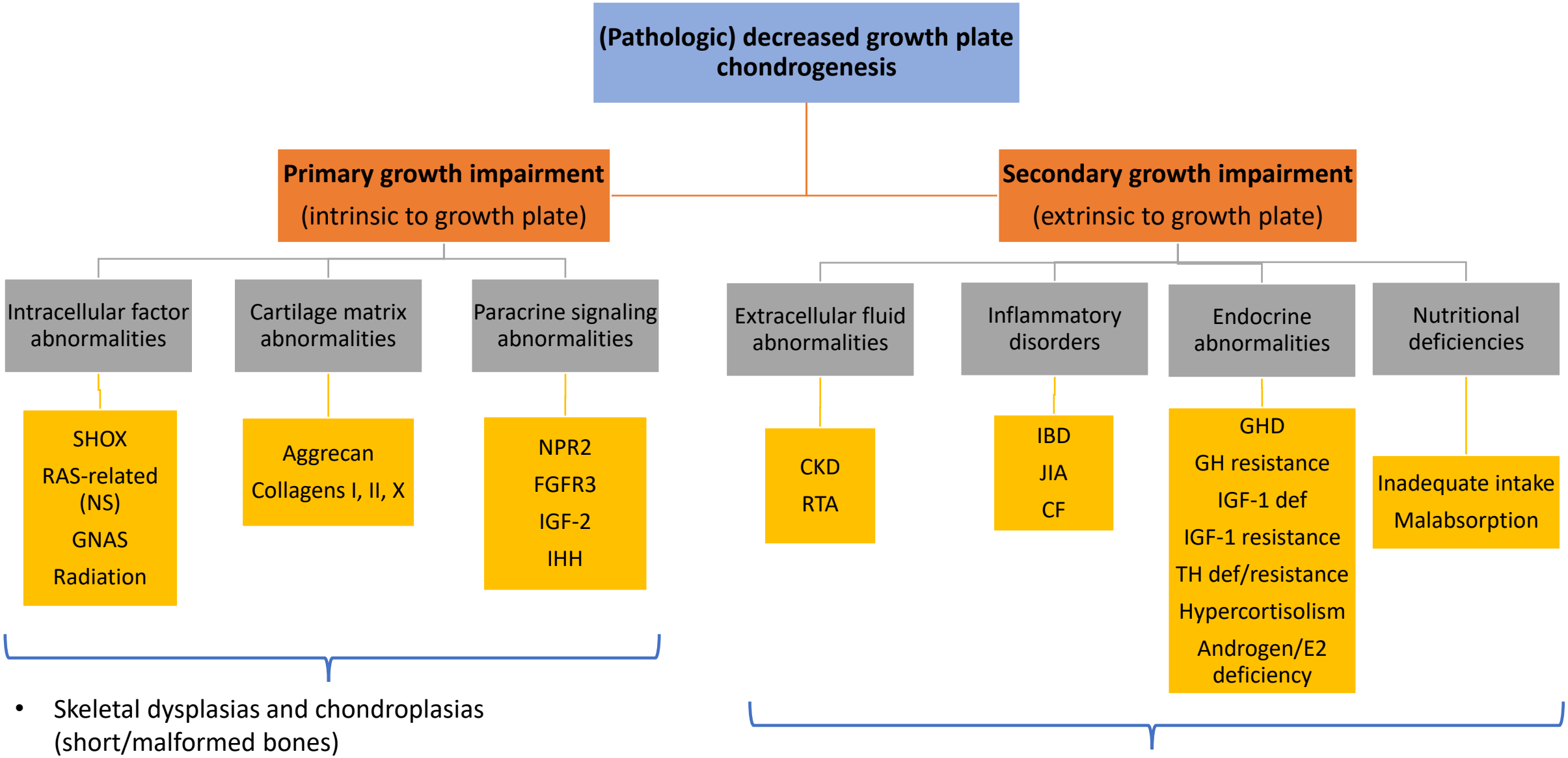
- Constitutional Delay of Growth and Puberty (CDGP)
- Growth is appropriate for bone age, which is delayed relative to chronological age
- Predicted height by bone age aligns with MPH and is within normal range for population
- Often a positive family history for CDGP
- Rx: reassurance and observation
- Consider course of testosterone or estrogen if puberty is delayed and there is increased psychosocial stress



When to suspect pathologic short stature

1. Disproportionate growth (suggests skeletal dysplasia)
2. Downward crossing of height percentile after 2 years of age
3. Growth velocity below the 3rd percentile (-2 SDS) for at least 1 year
4. Height percentile less than the 3rd percentile (-2 SDS)
   - Especially if height centile is less than mid-parental height calculation

- Differential diagnosis very broad, driven by medical history and physical examination



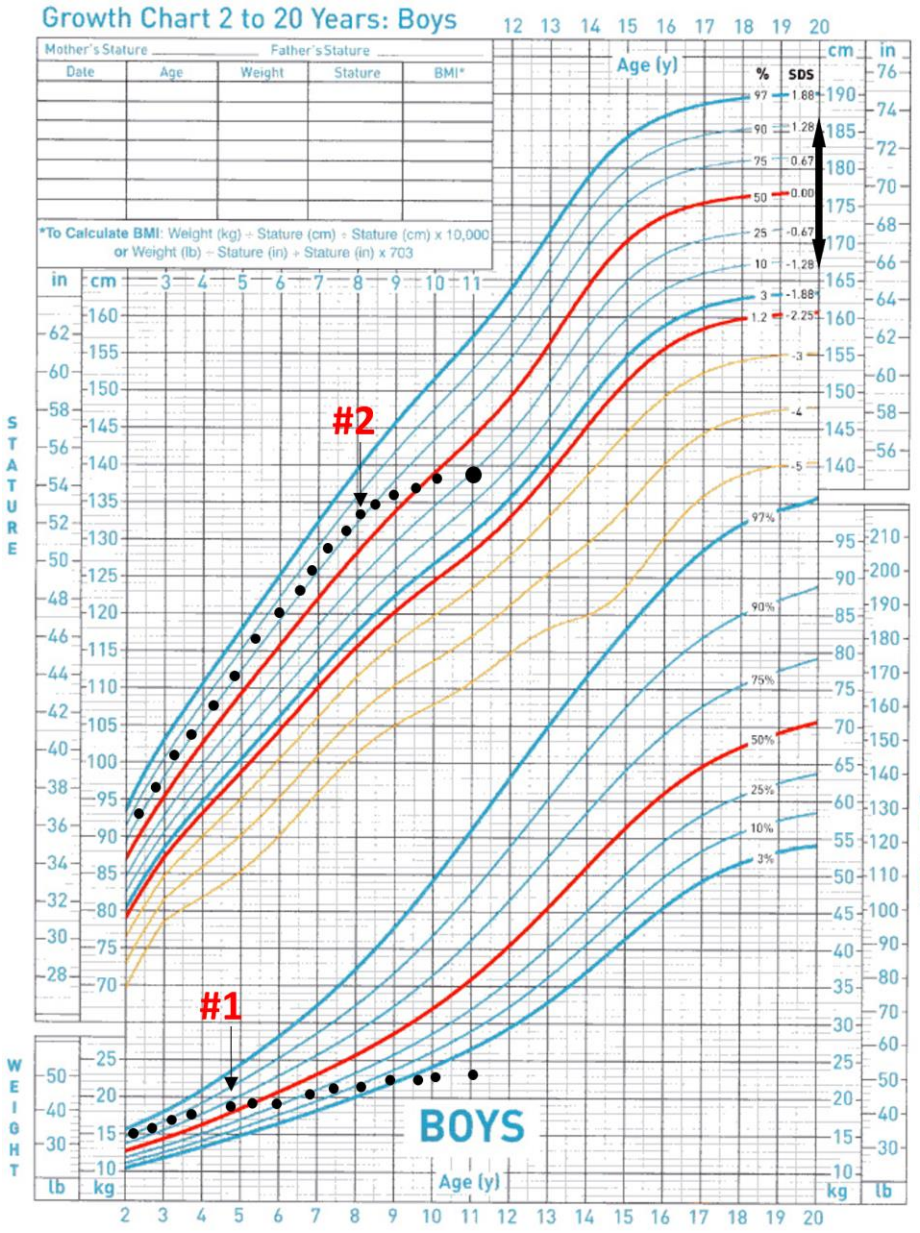
- Skeletal dysplasias and chondroplasias (short/malformed bones)
- Genetic defect affects growth plate and other tissues → syndromes with short stature and other congenital abnormalities

- Primary issue is in extra-skeleton organ system (kidneys, thyroid, immune system), causing abnormal concentration of molecules needed for growth (steroids, inflammatory cytokines, phosphate)

Short Stature: Secondary Growth Impairment

Short Stature: Nutritional Deficiencies

- Most common cause of poor growth globally
- Energy needs exceed intake (EDOs, picky eating) or due to malabsorption (celiac, IBD, CF)
- Malnutrition decreases GH sensitivity and downregulates GHR → decreased IGF-1
- Weight failure precedes height failure
- Bone age and puberty are delayed
- Assess dietary intake and for S/Sx of malabsorption (celiac disease can present as isolated growth failure +/- weight loss)
- **Remember**: short stature genetic conditions can include low BMI in their phenotype (RSS, Noonan)



Compliments of P. Wolfgram

GH Deficiency

- 1:4000 prevalence during childhood
- Isolated or multiple pituitary hormone deficiency (MPHD)
- Congenital or acquired
- Must exclude other causes

GH Research Society recommendations for diagnosis of GHD in childhood and adolescence (2000):

1. Severe short stature (height less than -3 SDS)
2. Height less than 1.5 SD below MPH
3. Height less than 2 SDS and GV less than 1 SDS for CA or a decrease in height SD of less than -1.5 SD sustained over 2 years
4. S/Sx worrisome for intracranial lesion
5. S/Sx suggestive of MPHD
6. Neonatal S/Sx of GHD

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GHD: Congenital

- Neonatal presentation:
  - Hypoglycemia
  - Congenital hyperbilirubinemia (associated with ACTH def)
  - Micropenis
- Typically, AGA with decreased GV in first year of life, falling to a height SDS below -2 SD
- Phenotype affected by ± MPHD
- "Cherub-like" phenotype: midface hypoplasia, frontal bossing, hypotonia, truncal adiposity, delayed dentition, high-pitched voice

Causes of Congenital GHD
Genetic • Isolated: GH1, GHRHR • Bio-inactive GH (d/t defect in GH1) • MPHD: LHX3, LHX4, PROP1, POU1F1
Congenital malformations of brain, hypothalamus, or pituitary gland (structural brain abnormality) • Small anterior pituitary, ectopic posterior pituitary Holoprosencephaly or anencephaly • Optic nerve hypoplasia/septo-optic dysplasia
Midline Facial Defects • Cleft lip/cleft palate • Single central incisor
Idiopathic

GHD: Acquired

- Presents with growth failure, delayed bone age, and increased weight to height ratio
- Somatotrophs vulnerable to disruptions in blood supply (trauma, infarction) as they only receive blood from portal vessels, not the anterior pituitary artery

Causes of Acquired GHD
Pituitary/Midline Tumors • Midline brain tumors: germinomas, meningiomas • Optic gliomas (*50% associated with NF1*)
Cystic Lesions • Rathke's cleft cysts, arachnoidal cysts • Craniopharnygiomas (*GHD is most common hormone deficiency, in 75-100% cases before Rx*)
Radiotherapy
Chemotherapy
Trauma (TBI)
Infiltration (Langerhan cell histiocytosis with pituitary involvement – DI nearly 100%; *GHD in 40%)*
Inflammation or Infection (neurosarcoidosis, meningitis, hypophysitis)
Pituitary Infarction
Psychosocial (emotional) deprivation (growth arrest lines with recovery when circumstances improve)

GH Insensitivity/Resistance

- Group of inherited disorders with reduction or absence of biologic effects of GH, many related to loss-of-function *GHR* mutations
- **Laron Syndrome**
  - Homozygous or compound heterozygous mutations in *GHR*
  - Severe **post**natal short stature
  - Dysmorphic features: small face, hypoplastic "saddle" nasal bridge, high-pitched voice, truncal adiposity, micropenis
  - Hypoglycemic episodes in infancy; hyperlipidemia
- ***STAT5B*** missense mutation
  - Severe postnatal growth failure and immune dysregulation
- Milder phenotypes exist (partial GHI) d/t heterozygosity for dominant-negative GHR mutations

Lab evaluation

- ↓↓ IGF-1, IGFBP-3, and ALS
- ↑ basal and stimulated GH levels
- With classic GHI: **↓↓ GHBP levels**
- With less common GHI: nl/↑GHBP

Treatment

- Trial of rhGH (preferred; better safety profile and more convenient)
- If no response, recombinant human IGF-1 (mecasermin) in those aged > 2 yrs. Dosed BID, after meals. May cause hypoglycemia.

IGF-1 Deficiency/Resistance

Primary IGF-1 Deficiency/Resistance

- *IGF-1* defects
  - Prenatal growth failure, microcephaly, severe neurocognitive deficits, sensorineural hearing loss
- *IGF-1R* defects
  - Partial loss-of-function
  - **SGA** without catch-up growth
  - Variable degree of growth restriction and delays in psychomotor/mental development
  - Delayed bone age
  - Dx: Nl/↑IGF-1, IGFBP-3, GH
  - May be misdiagnosed as ISS; requires molecular genetic diagnosis

Acid-Labile Subunit Deficiency

- ALS is essential for stabilization of the IGF-1/IGFBP-3 complex as part of the ternary complex
- Defects in *IGFALS*
  - Delayed pubertal onset, slow pubertal progression, but only mild to moderate growth failure
  - ↓↓ ALS, IGF-1, IGFBP-3 (IGFBP-3 lower than IGF-1)

Treatment:

- Trial of rhGH
- If no response, rhIGF-1 therapy
- No effective Rx for IGF-1R defects.

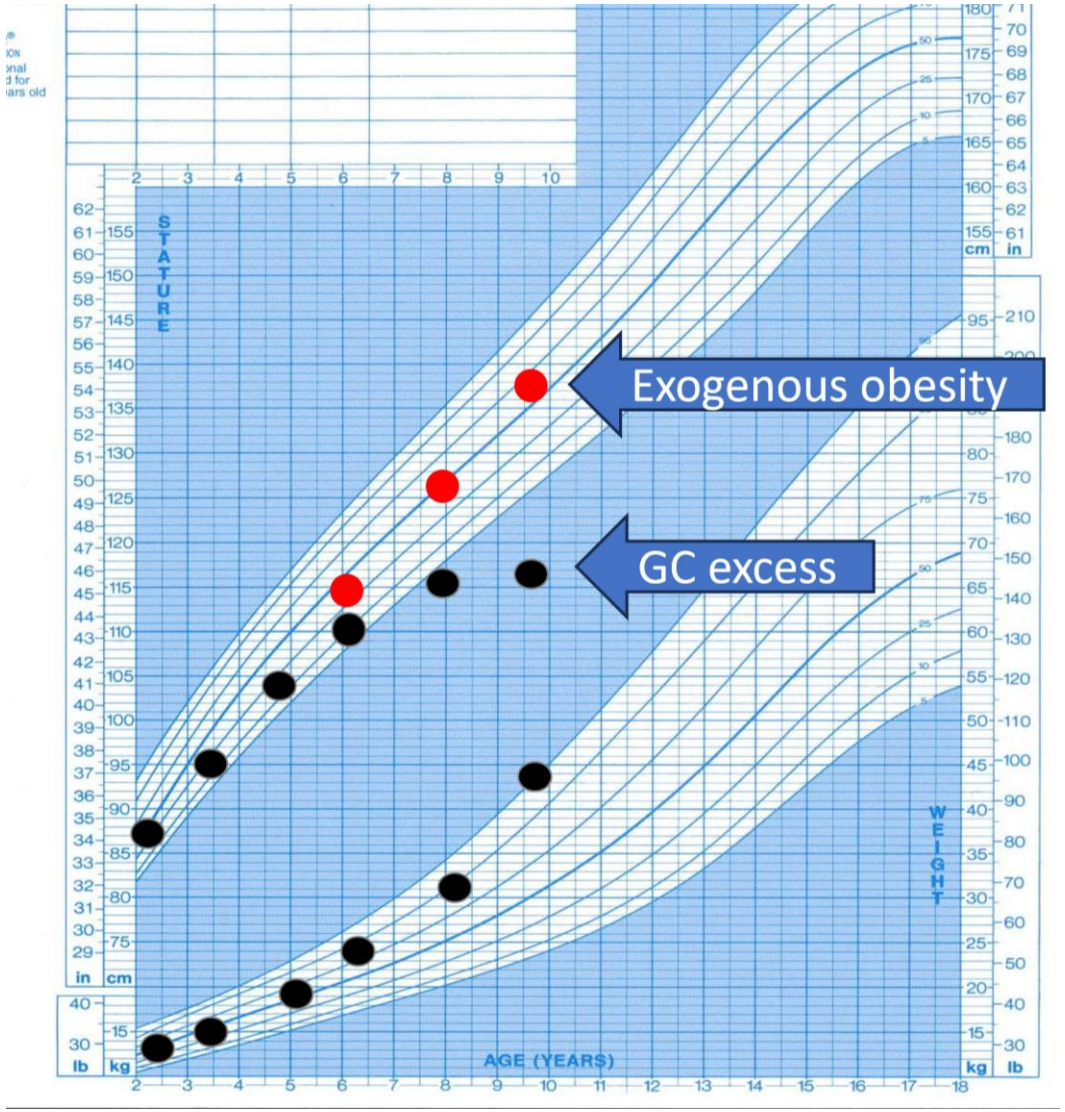
Thyroid Hormone Deficiency or Resistance

- Thyroid hormone (TH) promotes skeletal maturation
  - Directly and indirectly increases IGF-1, IGBP-3, and GH
  - Stimulates key growth factor signaling pathways (IGF1, FGF, PTHrP, Wnt)
  - Stimulates osteoblast activity
- **Hypothyroidism**
  - Most common manifestation in children is declining height velocity, resulting in short stature
  - Initiation with L-T4 associated with period of rapid catch-up growth, frequently without restoration of full growth potential

- **Thyroid Hormone Resistance**
  - **TRβ resistance** (85% cases)
    - Labs: ↑ FT4 and FT3 with unsuppressed TSH level
    - Growth failure, tachycardia, ADHD/hyperactivity, **goiter**
  - **TRα resistance**
    - Labs: low T4, borderline high T3, normal/slightly increased TSH
    - **Prominent growth failure**, delayed dentition, neurocognitive deficits
    - Radiographs: Wormian bones, epiphyseal dysgenesis

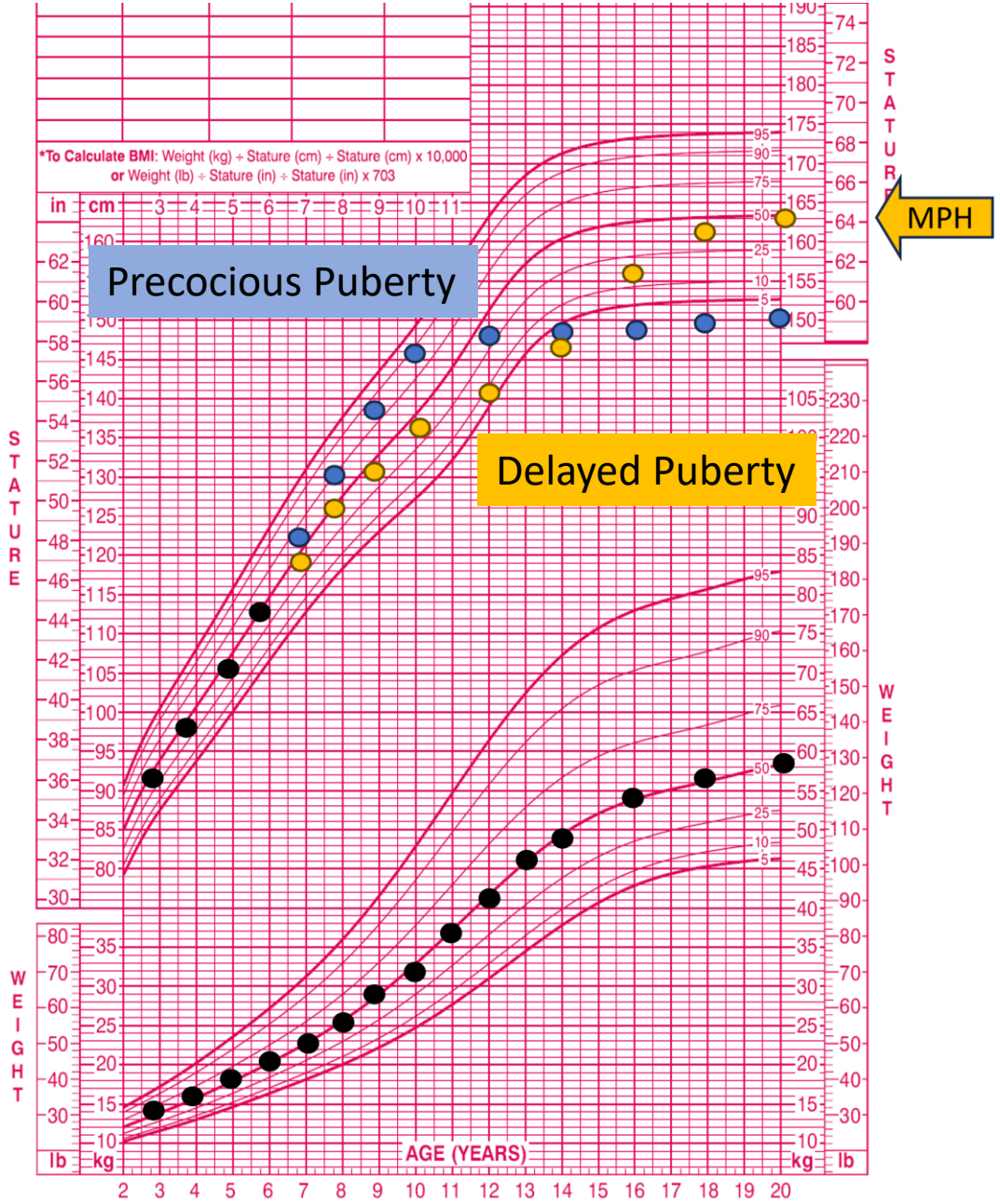
Glucocorticoid Excess

- GCs (exogenous or endogenous) primarily slow growth by *direct action* at the growth plate; also interfere with bone and collagen formation
- Growth impact of GC therapy worse with longer duration of action, duration of use
- GH secretion is normal; IGF1 and IGFBP concentrations are normal
  - rhGH Rx not very effective
- Children with GC excess may present primarily with linear growth deceleration with weight acceleration and lack the “classic” Cushingoid features



Premature Sex Steroid Exposure

- Estrogen accelerates linear growth by stimulating GH secretion and acting directly on chondrocytes
- Estrogen acts on growth plate to accelerate growth plate senescence, decreasing remaining growth potential
- Androgens, aromatized to E2, act on growth plate



Effects of Chronic Illness on Growth

- Chronic inflammatory disorders negatively impact growth by multiple mechanisms
  1. TNF α, IL-1β, IL-6 act inhibit chondrocytes
  2. Malnutrition → reduced IGF-1 levels
  3. Required glucocorticoid therapy
  4. **Relative GH resistance**, possibly due to downregulation of STAT5/JAK2 signaling
- **IBD (Crohn disease)**
  - Poor growth and/or delayed puberty may be the presenting manifestation
  - **50% kids with Crohn Disease have decreased height velocity prior to GI symptoms**
  - Nutritional deficiencies, inflammation, and glucocorticoid therapy.
  - IGF-1 and GH may be decreased
- Conditions that affect content of the extracellular fluid slow linear growth directly at chondrocytes and indirectly through endocrine and nutritional factors
- **CKD:**
  - 1/3 have growth failure, more common with younger age of onset and greater severity
  - Disturbances of GH metabolism and IGF-1 (GH insensitivity, decreased IGF bioavailability due to increased IGFBP concentrations (decreased renal clearance))
  - Metabolic acidosis, uremia, malnutrition, calcium and phosphate imbalance
- **Hypophosphatemia:**
  - low phosphate in extracellular fluid directly impairs growth plate chondrocyte differentiation

Effects of Cancer Therapy on Growth: Radiation

- **Childhood cancer survivors are at increased risk of growth failure**
- Radiation arrests growth plate chondrogenesis, disrupts metaphyseal bone and cartilage absorption, and alters diaphyseal periosteal activity
- Cranial Radiation Therapy (CRT)
  - Greatest growth risk with highest RT doses, younger age, female gender, and prepubertal status
  - GHD most common endocrine late effect of those with h/o CRT with risk highest if the tumor, surgery, or RT > 18 Gy occurs in the hypothalamus-pit region
- Spinal Radiation directly injuries vertebral bodies → disproportionate short stature (↓ U/L ratio, arm span > height)
- *Craniospinal Radiation* has most significant impact on growth of all pediatric cancer radiation treatments
- Total Body Irradiation → ↑ risk GHD and disproportionate short stature
- Cumulative impact of multiple RT courses/types on growth

Effects of Cancer Therapy on Growth: Chemo

- Tyrosine kinase inhibitors
  - Imatinib, sorafenib, sunitinib, used in CML
  - Decreased signal transduction through IGF-1 receptor (a tyrosine kinase receptor) or disrupted growth plate chondrocyte recruitment
- Anti-CTLA-4 monoclonal antibodies (ipilimumab)
  - Risk of immune hypophysitis with resultant GHD and other anterior pituitary deficiencies
- Retinoic acid (neuroblastoma)
  - Irreversible growth plate damage, causing growth failure
- Prolonged systemic glucocorticoid treatment

Short Stature: Primary Growth Impairment

Condition intrinsic to the growth plate

Russell Silver Syndrome

- DNA hypomethylation in *IGF2,* resulting in reduced paternal IGF2 expression
- Pre- (IUGR) and post-natal growth restriction (AH -4 SDS)
- Phenotype: SGA with relative macrocephaly, triangular face, micrognathia, asymmetry
- Labs: ↓ IGF-2, nl/↑ IGF-1, IGFBP-3, GH

Netchine-Harbison Clinical Scoring System (≥4/6)

- ❑ **SGA**: birth weight &/or length ≤ -2 SDS
- ❑ **Postnatal growth failure**: Height at 24 mos ≤ -2 SDS ***OR*** height ≤ -2 SDS from mid-parental target height
- ❑ **Relative macrocephaly at birth**: Head circumference at birth ≥ 1.5 SDS above birth weight &/or length SDS
- ❑ **Protruding forehead**: forehead projecting beyond the facial plane on side view as a toddler
- ❑ **Body asymmetry**: leg length discrepancy (LLD) of ≥ 0.5cm or arm asymmetry ***OR*** LLD < 0.5cm with at least 2 other asymmetrical non-facial body parts
- ❑ **Feeding difficulties &/or low BMI**: BMI ≤ -2 SDS at 24 mos ***OR*** use of a feeding tube or cyproheptadine for appetite stimulation

Molecular Testing:

11p15 LOM (30-60%) and mUPD7 (5-10%)

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Albright Hereditary Osteodystrophy (AHO)

- Pseudohypoparathyroidism type 1a
- Autosomal dominant inheritance of loss-of-function mutation of the maternal allele of *GNAS1*, the gene encoding Gs-alpha
- Short stature, subcutaneous calcifications, brachydactyly (3rd, 4th and 5th metacarpals and metatarsals)
- Round facies, obesity, developmental delay
- Resistance to PTH, gonadotropins, TSH, and GHRH
- If paternally transmission of mutated *GNAS1*: AHO phenotype ONLY with no hormonal resistance

When to Suspect an Osteochondrodysplasia

Prenatal Onset	Postnatal Onset
IUGR Bowing/shortening of long bones, vertebral defects Shortening of ribs; abnormal calvaria ossification Fractures/decreased bone density	Short stature/growth failure; bone deformities Recurrent/pathologic fractures Abnormal radiographs

Diagnostic Evaluation

Clinical Assessment	Radiologic Evaluation
Head circumference, length, height Body segment proportions (↓ arm span; ↑ sitting ht index) Scoliosis or spinal/chest deformities Brachydactyly; Madelung deformity	Skeletal radiographs for appearance of epiphyses, metaphyses, vertebral bodies (enchondromas, vertebral segmentation defects, scoliosis)

Disorders of FGF3 Signaling (gain-of-function mutations)

- Impaired endochondral bone formation

Achondroplasia: most common	AD but most cases are sporadic; rhizomelic dwarfism, large head, midface hypoplasia, lumbar lordosis Motor delays common; IQ normal
Hypochondroplasia: milder phenotype	Short stature typically recognized in early-mid childhood, brachydactyly, large head, ↓ elbow extension

SHOX Deficiency Syndromes

- Skeletal manifestations associated with areas with intrauterine expression of SHOX, affecting chondrocyte proliferation and apoptosis

Leri-Weil dyschondrosteosis (LWD)	SHOX haploinsufficiency; mesomelic dwarfism; Madelung deformity
Turner Syndrome	SHOX haploinsufficiency
Langer's mesomelic dwarfism	homozygous defect (complete SHOX deficiency)

Turner Syndrome

- Dx: 1 X chromosome with complete or partial absence of the 2nd X chromosome, associated with ≥ 1 typical clinical TS manifestations
- Significant phenotypic variability by karyotype
- Short stature is MOST common feature
- Intrinsic growth failure due to absence of *SHOX* in the pseudo-autosomal region of the 2nd X chromosome
- *Prenatal growth restriction*: mild IUGR, average BW 1-2 cm below mean values
- Skeletal anomalies: scoliosis, kyphosis, cubitus valgus, genu valgum, Madelung deformity, short 4th and 5th metacarpals and metatarsals

When to consider TS genetic testing

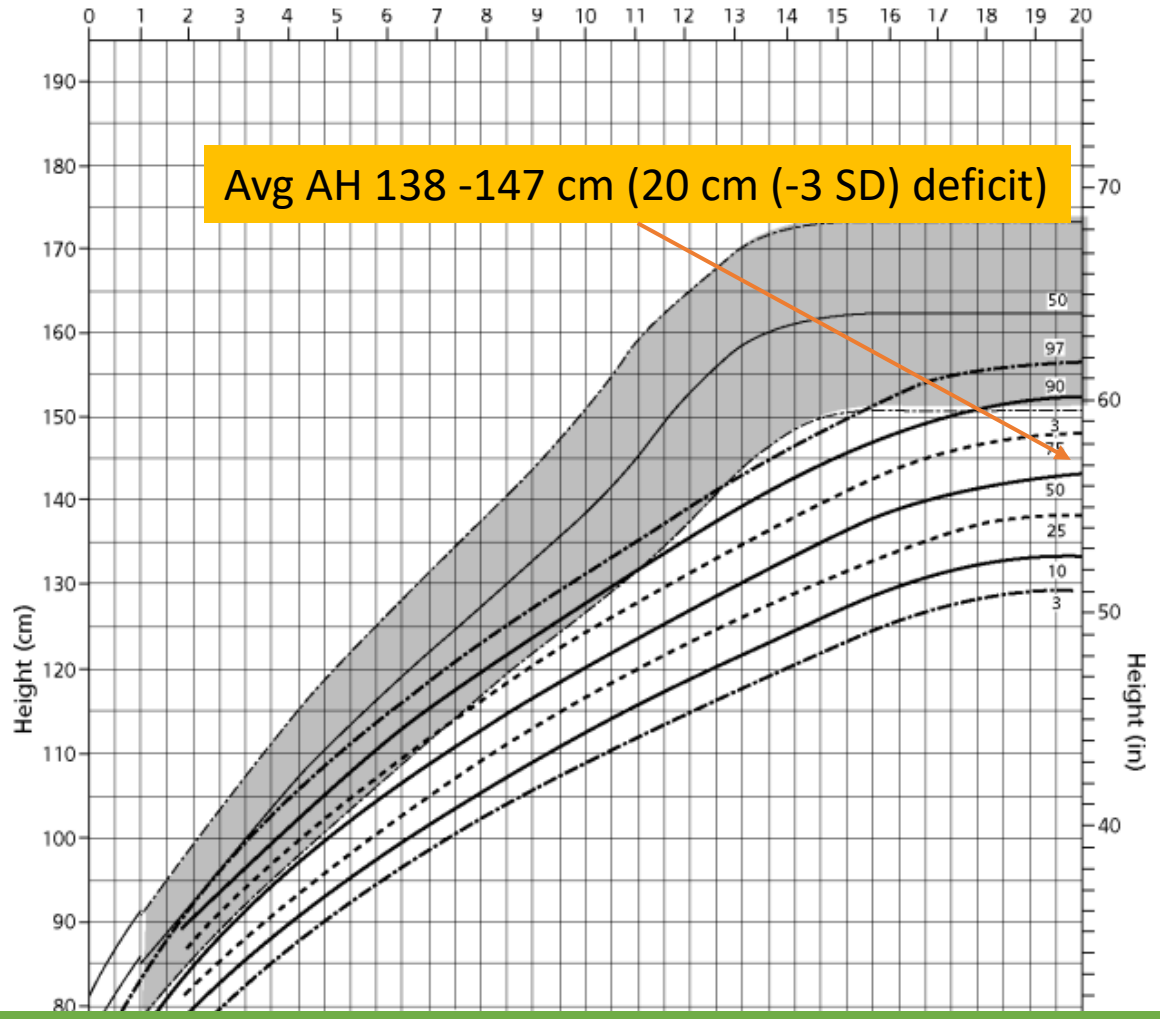
ONE of the following:

- Fetal cystic hygroma or hydrops
- **Unexplained short stature**
- Left-sided outflow CHD (exclude: bicuspid AoV)
- Unexplained delayed or stalled puberty/menarche, or secondary amenorrhea
- Infertility
- Characteristic physical features (epicanthal folds, down-slated palpebral fissures, low-set ears, narrow palate, webbed neck, short broad neck

At least 2 of the following:

- Renal anomaly (horseshoe, hypoplasia/aplasia)
- Madelung deformity
- Neuropsychologic or psychiatric problems
- Multiple typical or melanocytic nevi
- CHD (include: BAC)
- Impaired hearing before 40 years old + short stature

Gravholt et al, Clinical Practice guidelines for the care of girls and women with Turner Syndrome; Eur J Endocrinol 2024



Postnatal Growth Pattern:

- Rapid downward trend in height centiles 0-2 yrs
- Height deficit established by 3 years
- Suboptimal linear growth through childhood
- Estrogen-mediated growth spurt is absent or minimal
- Limbs more affected than trunk: ↑U/L and sitting height

TS: Growth

- GH Rx offered at ≥ 2 yrs if evidence of growth failure, short stature, or likelihood of short stature
  - GH continued until bone age ≥ 14 yrs , GV < 2cm/year or patient satisfied
  - Start 1.3-1.5 mg/m^2/d (45-50 µg/kg/d) → 2 mg/m^2/d (68 µg/kg/d)
  - Maintain IGF-1 in nl range for age & puberty
- Success most likely if catch-up growth to normal range within 2 years of Rx and if Rx starts at least 4 years before puberty
- Adjunctive Rx with oxandrolone and/or very low-dose E2 supplementation not recommended

Noonan Syndrome & RASopathies

- AD inheritance; 2/3 have *de novo* mutation
- Due to **RAS/MAPK pathway hyperactivation**
- Clinically heterogeneous
- Mild hypertelorism, downslanting palpebral fissures, low-set/posteriorly rotated ears; pectus excavatum; kyphoscoliosis
- **Right** sided CHD (pulmonic stenosis, hypertropic cardiomyopathy)
- Mild/moderate intellectual disability
- Unilateral or bilateral cryptorchidism

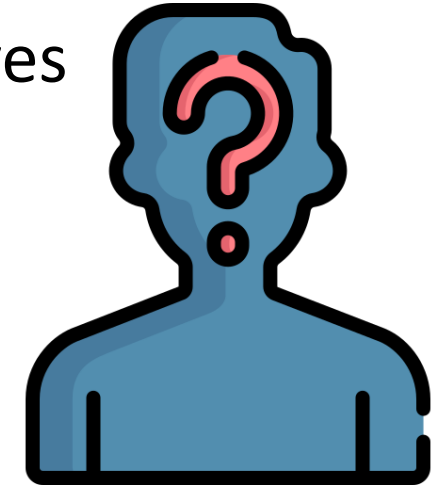
- Growth Pattern:
  - Normal birth weight and height
  - Postnatal growth failure
  - Delayed puberty with prolonged or absent adolescent growth phase
  - Mean AH -2 SDS
- Lean body/low BMI
- Dx: classical facial features or typical cardiac malformations
- 40% have ***PTPN11*** pathogenic variants
- May have GHD or GHR
- Rx: rhGH; variable efficacy

Prader Willi Syndrome

- Paternal imprinting of 15q11.2-q13 (70%)
  - 25% have maternal uniparental disomy (UDP(15q)m)
- Neonatal hypotonia, FTT in early infancy, followed by obesity
- Intellectual disability, behavioral disorders, small hands and feet
- Short stature
- Endocrinopathies: hypogonadotropic hypogonadism, GHD, central adrenal insufficiency
- Increased risk of premature death: sleep apnea, sudden death
- GH Rx increases linear growth, lean body mass, decreased fat mass
- GH Rx may also increase sudden death d/t worsening sleep apnea
  - Consider serial sleep studies before and after rhGH initiation

Idiopathic Short Stature

- Presumed inheritance of multiple sequence variants with cumulative mild, negative impact on growth
- Short stature, slowed linear GV, ± delayed skeletal maturation, ± attenuated pubertal growth spurt *without* familial short stature, chronic illnesses or apparent endocrinopathies
- Normal GH secretory dynamics
- Mixed response to rhGH and no clear data that GH Rx improves psychological, social, or educational function or that benefit exceeds risk in context of high cost and medicalization



Intrauterine Growth Restriction (IUGR)

- Birth weight or height < 3rd percentile
- 10-15% SGA infants will have short stature (90% exhibit catch-up), comprising ~20% all short children
- Etiology: abnormal GH production and secretory pattern; insensitivity to GH and IGF-1 activity
- SGA infants with rapid early childhood weight gain have increased risk of premature adrenarche, insulin resistance, functional ovarian hyperandrogenism, attenuated pubertal growth spurt
- Increased lifetime risk of CV disease, hypertension, and T2D

Causes of IUGR	
Intrinsic Fetal Abnormalities	Chromosomal disorders Syndromes (SRS, Noonan, PWS) Congenital infections Congenital anomalies
Placental Abnormalities	Abnormal implantation of the placenta Placental vascular insufficiency or infarction Vascular malformations
Maternal Disorders	**Malnutrition (#1 global cause)** Vascular disorders (HTN, toxemia, uncontrolled DM) Uterine malformations or constrained growth Drug ingestions (tobacco, **EtOH**, narcotics)

Diagnostic Approach to Short Stature

- Time course (prenatal, postnatal, or both)
- Inheritance pattern by family history (mono-, poly-, or oligogenic)
- Medical history and physical exam (intrinsic or extrinsic cause). Evaluate dental age.
- Anthropometrics (body proportions; compare weight and height gains)
- Skeletal maturation (bone age)
- Consider screening labs: CMP, CBC, ESR, TFTs, tTg IgA, IgA IGF-1, IGF-BP3 ± karyotype
  - IGF-1 must be interpreted relative to normative values by age and puberty

Consideration for GHD

- IGF-1 has incomplete sensitivity and specificity for GHD
  - Low IGF-1 can occur in **malnutrition**, GHI, *IGF-1* mutations, ALS deficiency
  - High IGF-1 can occur in *IGF-1R* and *PAPPA2* mutations
  - IGF-1 levels are stable, not pulsatile like GH concentrations
- GH stimulation testing
  - Serial GH measurements after administration of 2 different GH secretagogues
    - Clonidine, arginine, glucagon, insulin-induced hypoglycemia
  - GHD is *generally* defined as a peak GH < 10 mcg/L
  - Fraught with issues about false positives, threshold value, etc, etc
- Obtain head imaging (MRI) of pituitary if GHD is confirmed to exclude anatomical abnormalities or tumor

rhGH Therapy

- Increases GV and AH
  - Greatest impact with younger age at start and greater bone age delay
- Adverse Effects (<3%; usually acute): idiopathic intracranial hypertension, SCFE, progression of pre-existing scoliosis, fluid retention/edema
- Continue until GV < 2-2.5 cm/yr
- In those with previous malignancy: increase risk of meningioma. No increase risk of secondary malignancies.

FDA-Approved Pediatric Indications for GH Therapy
GHD
CKD
Turner Syndrome
SHOX haploinsufficiency
Noonan Syndrome
Prader-Willi Syndrome
SGA without catch-up growth
ISS

Note: FDA approval ≠ insurance coverage

Overgrowth/Tall Stature

Tall Stature

- Defined as length or height greater than the + 2 SDS (>97th percentile)
- Evaluation must consider age of onset, mid-parental height and pubertal status
- Is the growth velocity abnormally rapid?
  - Up-crossing of 2 major height percentiles between age 2 and onset of puberty
  - GV above the 90th percentile for age
    - > 9 cm/year between age 2-4 years
    - > 8.5 cm/year between 4-6 years
    - >6 cm/year or > 6.5 cm/year between 6 years to puberty in boys and girls, respectively

Overgrowth Syndromes

Fetal Overgrowth	Postnatal Overgrowth → Childhood Tall Stature	Postnatal Overgrowth → Adult Tall Stature
Maternal DM	Familial tall stature	
Sotos Syndrome		Androgen or E2 deficiency/resistance in males
Weaver Syndrome		Testicular feminization
Beckwith-Wiedemann		**Excess GH secretion**
Other IGF-II excess syndromes	Exogenous obesity	
Congenital hyperinsulinism	Excess GH secretion (McCune Alright, MEN1, NF1)	
	Precocious puberty	
	Marfan Syndrome	
	Klinefelter syndrome	
	Homocystinuria	
	XYY	
	Fragile X	
	Hyperthyroidism	

Fetal Overgrowth Syndromes (LGA)

- Maternal diabetes is #1 cause!
- **Sotos Syndrome** (“cerebral gigantism”)
  - 80% have a loss-of-function *NSD1* mutation
  - >90th percentile for height and weight at birth
  - Prominent forehead, dolichocephaly, macrocephaly, high arched palate, hypertelorism, prominent ears; large hands and feet with thickened subcutaneous tissue; intellectual disability
  - Rapid childhood growth with early epiphyseal fusion, yielding a normal AH
  - GH secretion and IGF levels are *normal*

Fetal Overgrowth Syndromes Cont'd

- **Beckwith-Wiedemann Syndrome**
  - Most common overgrowth syndrome, due to somatic growth and organomegaly
  - Excessive IGF-2, encoded by *IGF2*
  - Macrosomia with omphalocele or umbilical hernia
  - Macroglossia, renal medullary hyperplasia, neonatal hypoglycemia d/t islet cell hyperplasia
  - Embryonal tumor risk: Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma
  - Rapid childhood growth with early epiphyseal fusion, yielding a normal AH

Postnatal Statural Overgrowth

- **Obesity**
  - Increases estrogen by aromatization
  - Increased free IGF-1, leptin, prolactin, adrenal androgens
  - ➢ Rapid skeletal growth and early onset of puberty
  - Labs: Normal/high GH and IGF-1, hyperinsulinemia
  - Remember: obesity with *short stature/growth failure* is unusual and should prompt consideration for hypercortisolism, hypothyroidism, PWS, GHD
- **Precocious puberty**
  - Rapid childhood growth with decreased AH from predicted
- **Dosage effects of the SHOX gene**
  - Women with 47,XXX: mean AH is 5-10 cm taller than population mean
  - Men with 47,XXY: mean AH is 3.5 cm taller than population mean

Klinefelter Syndrome

- 47,XXY karyotype (3 active copies of SHOX)
- Clinical features:
  - Male with disproportionate tall stature with relatively long legs (arm span > height; ↓U/L ratio)
  - Small/firm testes with azoospermia (hypergonadotropic hypogonadism)
  - Gynecomastia
  - Learning disability

Excess GH Secretion

- **Pituitary gigantism**
- **GH secreting tumors**:
  - McCune Albright Syndrome (constitutive GNAS activation → somatotropic tumors & GH excess)
  - MEN1
  - Neurofibromatosis
  - Tuberous sclerosis
  - Carney Complex
- Dx: ↑IGF-1 and IGF-BP3, serum GH nl/↑, GH not suppressed during OGTT. If GH excess confirmed, must image the hypothalamus/pituitary gland
- Metabolic impact with severe/long-standing GH excess: insulin resistance/T2D, hyperTG, cardiovascular disease (HTN, LVH, cardiomyopathy), sleep apnea
- Rx: transsphenoidal resection (1st line), bromocriptine, octreotide, GH antagonist (Pegvisomant), radiotherapy (for refractory cases, high complication rate)

Marfan Syndrome vs Homocystinuria

Marfan Syndrome	Homocystinuria
Autosomal dominant	Autosomal recessive
Fibrillin-1 mutation, resulting in abnormal aggregation of fibrillin-1 which impairs microfibril formation	**Cystathionine synthase deficiency**
Shared Clinical Features: • Tall stature • Marfanoid appearance • Arachnodactyly • Ectopia lentis	
<u>Unique (non-overlapping features):</u> • Superior lens dislocation • Scoliosis • Joint laxity • **Aortic aneurysm**	<u>Unique (non-overlapping features):</u> • Inferior lens dislocation • **Intellectual impairment** (50% of those affected) • Fine, sparse hair • **Thromboembolic phenomena**


Q & A

Q1:

A 4-year-old girl is referred for evaluation of short stature. She was born at 39 weeks gestation with a birth weight of 2200 grams and length of 42 cm. She receives physical therapy for gross motor delays and was recently started on cyproheptadine for appetite stimulation. On examination, her height is -3.2 SDS and her weight is -3.9 SDS. Her annualized growth velocity over the past 2 years is 4.3 cm/year. She has a prominent forehead and micrognathia.

Which of the following is the most likely cause of her clinical presentation?

A. *FGF3* gain-of-function

B. *GHR* loss-of-function

C. *IGF-2* hypomethlyation

D. *SHOX* haploinsufficiency

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Q2:

An 11-year-old girl is seen in clinic for short stature. She has a distant history of cancer, diagnosed at 3 years of age, and in remission since age 5. Review of her growth data reveals a height percentile at the 50th percentile at 6 years of age, with subsequent decline in percentiles until 6 months ago. She has recently had a slight increase in height percentile, from the 1st to the 3rd percentile. Today, her height is 51" (3rd percentile) and weight is 70 lbs (25th percentile). Her mid-parental height is 65". Her arm span is 54". The distance from her pubis symphysis to the floor is 27.5 inches. She has Tanner 2 breasts and pubic hair.

Which of the following previous cancer treatments best explains her short stature?

A. Cranial radiation

B. Cyclophosphamide therapy

C. Spinal radiation

D. Tyrosine kinase inhibitor therapy

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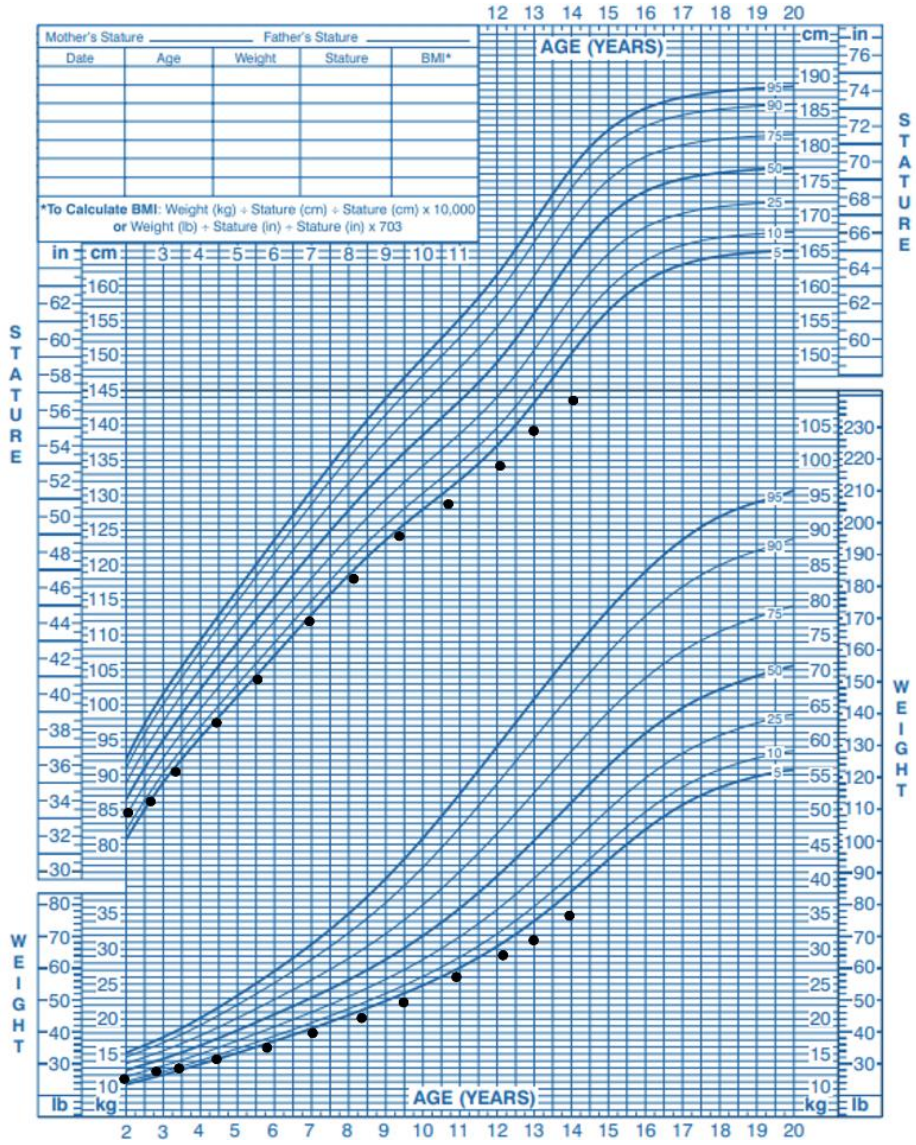
<u>Disproportionate Growth Failure</u>:
Arm Span (54") greater than Height (51")
Lower segment: 27.5"
Upper segment: 51 – 27.5 = 23.5
U/L = 23.5/27.5 = 0.85 (should be 1)

Q3:

A 14-year-old boy is seen for evaluation of poor growth. His growth curves are reviewed (Figure). His father is 70 inches tall and his mother is 61 inches tall. He denies any apocrine body odor, acne, or voice deepening. He takes cetirizine 10 mg daily and intranasal fluticasone 50 mcg once daily for environmental allergies. On examination, he is anxious but otherwise well-appearing. He has sparse axillary hair, Tanner 2 pubic hair and his testes are 3 mL bilaterally.

Which of the following would be most likely found during his growth evaluation?

	IGF-1 (ng/mL; reference range 168-576 ng/mL)	Peak GH level (ng/mL) after stimulation with arginine and clonidine	Skeletal (bone) age
A	25	3.2	11 years
B	195	9.9	12 year 6 months
C	357	11.4	14 years
D	85	10.5	11 years 6 months



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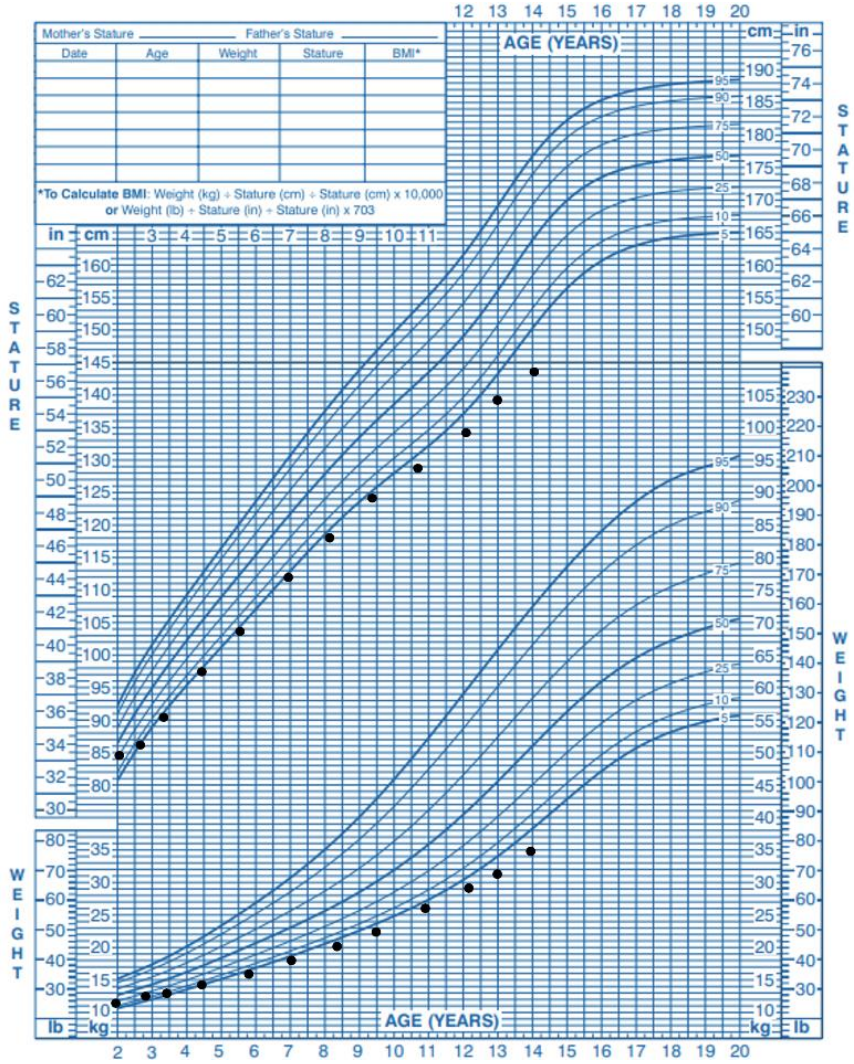

Q4:

A 9-year-old girl presents with accelerated linear growth. Her annualized growth velocity has been 15 cm/year over the past 18 months. On examination, her height is 158 cm (> 99th percentile) and her weight is 38 kg (90th percentile). Her mid-parental height is 163 cm (50th percentile). She is pre-pubertal with Tanner 1 breasts. IGF-1 level is 560 ng/mL and GH level is 10 ng/mL. Pituitary MRI reveals a 2.5 cm macroadenoma.

Which of the following is the recommend initial therapy for this child?

A. Cranial radiation

B. Octreotide

C. Pegvisomant

D. Transsphenoidal pituitary surgery

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Q5:

An 8-year-old pre-pubertal boy with intellectual disability and myopia is referred for evaluation of tall stature. Review of his growth curves reveals steady increases in height percentiles since early childhood. On examination, his height is +3.7 SDS and his weight is +1.8 SDS. His mid-parental height calculation is +2 SDS. He has a thin body habitus with long, thin fingers. The hair on his scalp is thin and lightly colored. He has reduced joint mobility at his elbows and knees.

Which of the following is he most at risk of developing?

A. Thromboembolism

B. Gynecomastia

C. Aortic aneurysm

D. Wilms tumor

Q5:

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Epidemiology and Basic Statistics for the Boards

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Domain 19: Core Knowledge in Scholarly Activities – 4%

Topics Outline:

A. Principles of biostatistics in research
B. Principles of epidemiology and clinical research design
C. Ethics in research
D. Quality improvement and patient safety

Types of Variables

Nominal:

- Qualitative not quantitative
- Nominal/Categorical
  - Categories that have no particular order or rank
    - Eye color; ethnicity
  - Dichotomous
    - Yes/No; Dead/Alive

Ordinal:

- Inherent order among categories but differences may not be the same throughout the scale
  - Pain scale; Anxiety scale; Apgar score; GCS score
  - May approach an interval scale if there are enough categories – 100 point visual analog score (VAS) for pain

Types of Variables

Interval Variables:

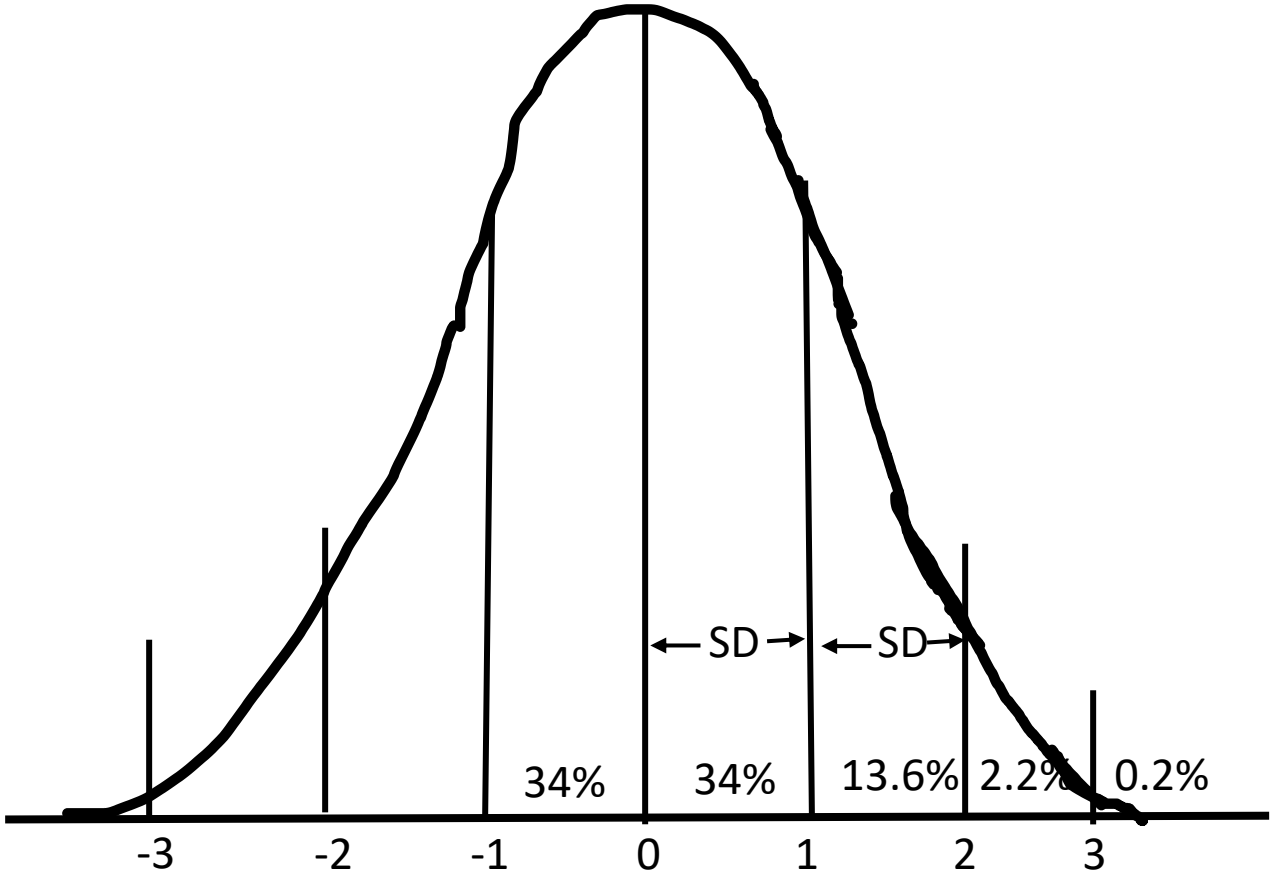
- Quantitative not qualitative
- Continuous: value can take any number in a range
  - Height, weight, length of stay, age, blood glucose
  - Some overlap with ordinal variables if that ordinal variable has enough categories (i.e. 100 pt pain scale)
  - Distribution can vary: symmetrical or skewed
  - More powerful

Types of Variables

Interval versus Ordinal:

- Interval Data
  - Number of Children in a Family
    - Values 0 1 2 3 4 5 . . .
    - 3 children are 3 times as many children as 1 child.
    - Does a difference of 1 child means the same throughout the range of possible values?
- Ordinal Data
  - Heart Murmur
    - Values I II III IV V VI
    - Is a IV/VI murmur twice as loud as a II/VI murmur?
    - Is the difference between I and II the same as the difference between III and IV?

Distribution of Data –
Normal Distribution

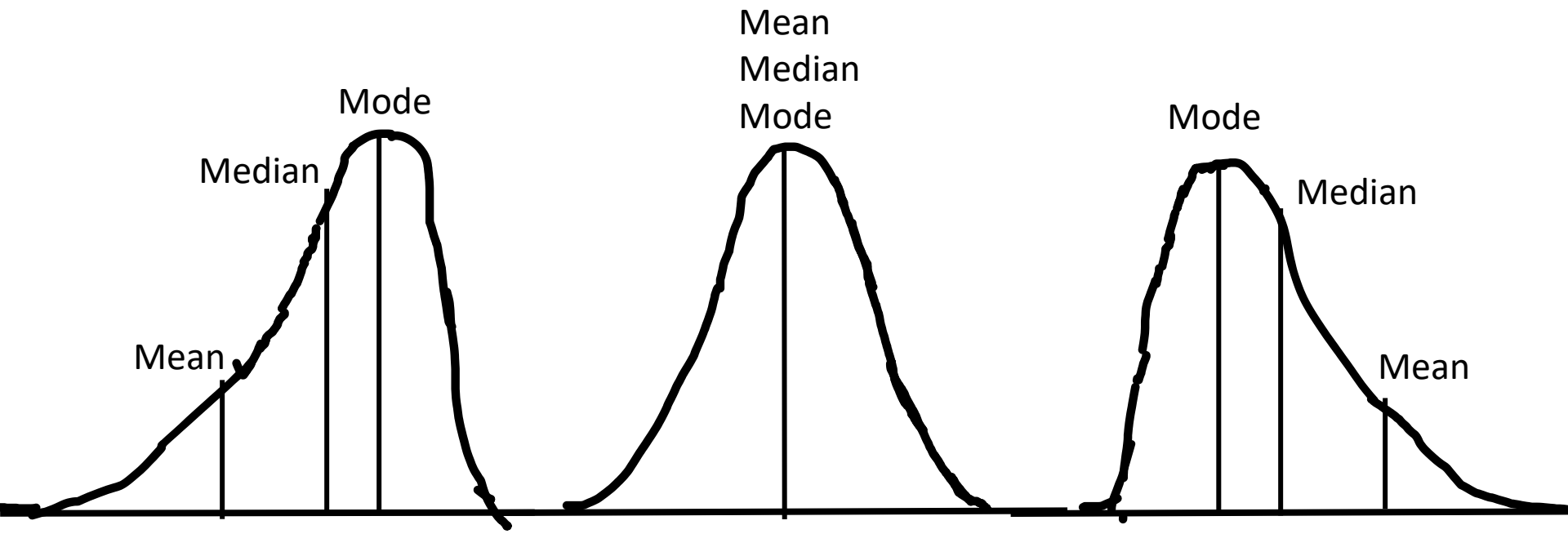


- What % fall within ± 1 standard deviation of mean? 68%
- What % fall within ± 2 standard deviations of mean? 95%
- What % fall within ± 3 standard deviations of mean? 99%

Distribution of Data
Measures of Central Tendency

- Mean = average
  - Reported and analyzed when distribution is normal/symmetrical/parametric
  - If there are outliers, the mean tends toward the outlier values
- Median = value of middle observation
  - Reported and analyzed when distribution is skewed or non-normal/nonparametric or ordinal data
- Mode = most common value

Distribution of Data

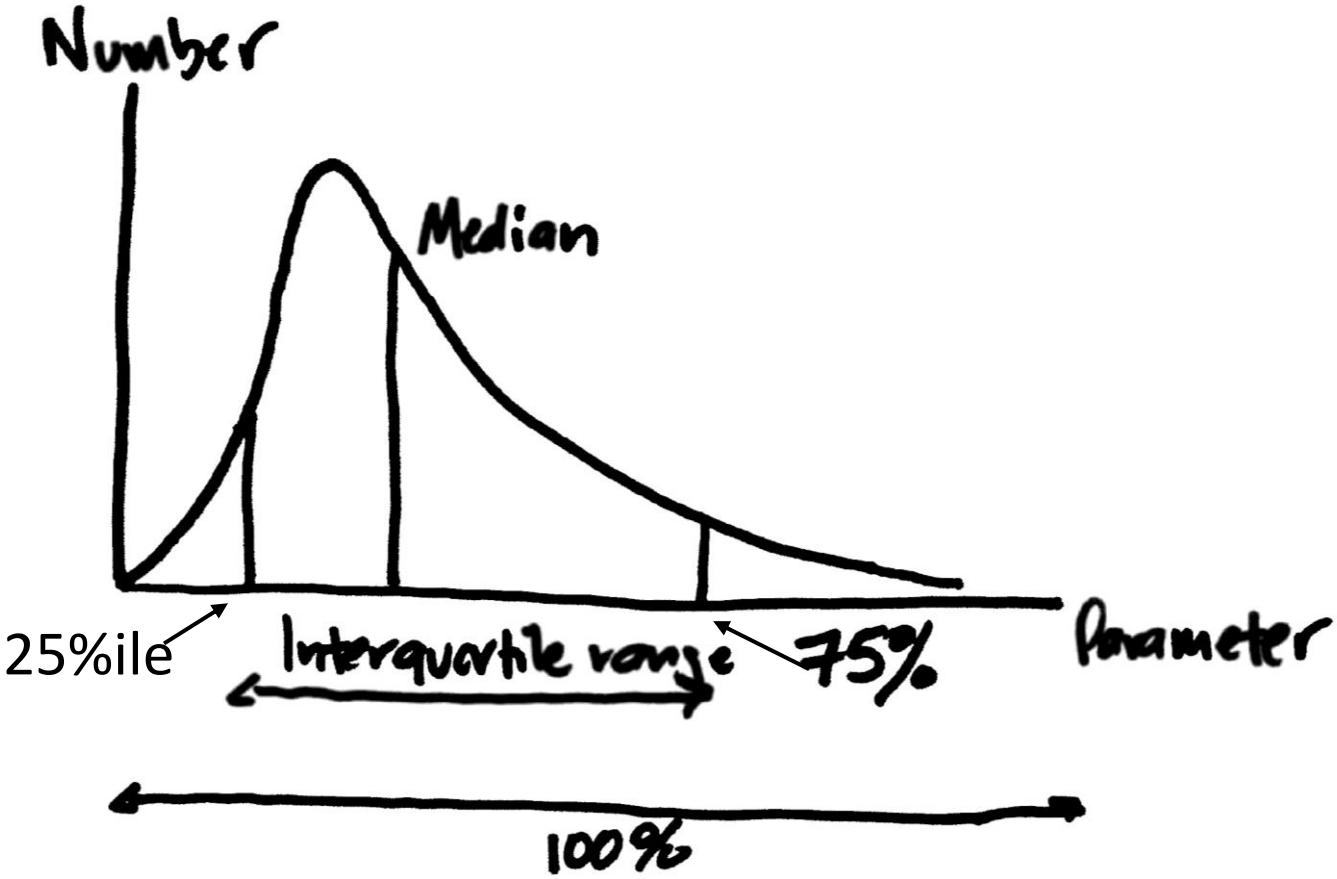


Negatively Skewed
= Left skewed

Normal Distribution

Positively Skewed
= Right skewed

Distribution of Data
Skewed (Non-Normal) Distribution



Descriptive Statistics

- Standard Deviation:
  - Quantifies the spread of individual observations of a value of a variable around the mean value of the sample
  - Add up the square of each difference from the mean, divide by number of data points, then take square root
  - Variance – measures the spread; SD= square root of variance

Descriptive Statistics

- Standard Error:
  - Measures the variability of the sample mean as an estimate of the true value of the population mean (from which the sample was drawn)
  - Indicates the degree to which the sample mean reflects the true population mean
  - SE= SD/square root of n

Distribution of Data

Synonyms:

- Normal distribution
  - Parametric
  - Bell-shaped
  - Symmetric
- Non-normal distribution
  - Non-parametric
  - Skewed
  - Not symmetric
  - How analyze? Can transform data

Hypothesis Testing

- Hypothesis Testing- test of statistical significance

- Null Hypothesis = H_0
  - The assertion that there is no relationship between the exposure and the disease

Hypothesis Testing

- One-tailed test: hypothesis is that one is greater than the other

- Two-tailed test: hypothesis is that the groups are different

Hypothesis Testing

- Type I error
  - Null hypothesis is rejected when it is actually true
  - False positive, α
- Type II error
  - Mistaken failure to reject the null hypothesis when the alternative hypothesis is true
  - False Negative, β

Hypothesis Testing

- Sample Size – What do you need to calculate?
  - Specify desired α and β
  - Proportion of baseline population that has the exposure or disease being studied
  - Magnitude of expected effect or detectable difference
  - If don't find a significant difference, need to see if study was adequately powered to find the difference
  - Larger sample size increases the power

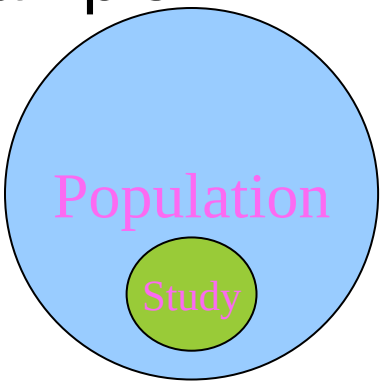
Hypothesis Testing
p-value

- Probability that the observed result (or results even more extreme) could have occurred simply by chance under the null hypothesis

- What if p>0.05? What does it mean - does it always mean that there is no difference?
  - No –study could be underpowered

Hypothesis Testing
Confidence Interval

- 95% confidence interval (CI): range of values which we can be 95% confident includes the population statistic from which the study sample was drawn
  - Mean
  - Proportion
  - RR or OR



- Relates to how precise the measurement is

- Things that affect the width of the confidence interval
  - Level of confidence
  - Sample size
  - Variability of the data (e.g. standard deviation)

Interpreting Confidence Intervals

- Means
  - Typically expressed as the 95% CI around the difference between means
  - Null value is 0
  - If 95% CI includes 0, not statistically significant

- OR/RR/Hazard Ratio
  - Null value is 1
  - If 95% CI includes 1, not statistically significant

P-value vs CI

- Confidence intervals versus p values
  - “Is the difference large enough to recommend a change in treatment”? (confidence intervals)
  - “Is there a difference?” (p values)

- Statistical significance can be associated with a clinically insignificant difference (large sample size).

- Clinical significance can be associated with a non-significant p-value (sample size too small).

Common Statistical Tests

- What test should you use to analyze your data?
  - Look at the type of variables you have – continuous vs categorical
  - Look at the distribution of the data you have – normally distributed (parametric) vs non-normally distributed (non-parametric)

Common Statistical Tests

- If you are comparing continuous outcome variables between 2 groups use….
  - Parametric distribution: t-test
    - **Unpaired or Student's T-test –** two independent samples
    - **Paired t-test –** not independent, ex: pre- and post- in same individual
  - Nonparametric distribution: Wilcoxon Rank Sum = Mann Whitney U test

Common Statistical Tests

- If you are comparing continuous outcome variables between >2 groups use….
  - Parametric distribution: **ANOVA**
    - Like a t-test for more than one group
    - If significant, only means that at least one of the groups is different than at least one other group
  - Nonparametric distribution: **ANCOVA**
    - Merger of ANOVA and regression for continuous variables

Common Statistical Tests

- If you are comparing a categorical outcome variable between 2 groups use….
  - Parametric: **Chi-Square Test**
  - Nonparametric: **Fisher exact test** (use if any cell has <5 participants)

Common Statistical Tests

- If you are comparing 2 continuous outcome variables, use….

- Correlation
  - Parametric: **Pearson** correlation
  - Nonparametric **Spearman** correlation
  - Obtain **correlation coefficient**, r (-1 to 1), indicates the strength of the relationship; p-value

- Linear Regression- can control for other variables
  - Fit to a line
  - R^2 = goodness of fit -> 1 is the best or maximum fit

Regression

- Statistical technique which focuses on the relationship between dependent variable (outcome) and ≥ 1 independent variables
- Allows to control for other variables
- Linear regression – dependent variable is continuous/interval variable
  - Fit to a line
  - R^2 = goodness of fit -> 1 is the best or maximum fit
- Logistic regression – dependent variable is dichotomous (yes/no, dead/alive)

Relative vs Absolute Risk

- **Relative Risk:** Assessing the risk for outcome in one group compared to another (ex. with or without a particular risk factor). Divide one risk by the other.

- **Absolute Risk:** Actual risk for an outcome in a group compared to actual risk for outcome in another. Difference in risk between groups.

Measures of Disease Risk

- Studies often focus on assessing the risk for disease with or without a particular trait
- Such measures of risk can be derived from the 2x2 contingency table with same Chi square statistic
- Two Measures
  - Relative Risk (RR)
  - Odds Ratio (OR)

Measures of Disease Risk - Difference Between Probability and Odds

- Probability can be expressed as a percentage
  - Relative Risk (RR) is a ratio of two proportions
- Odds ALWAYS implies a ratio of two probabilities
  - Probability of event happening over probability of event not happening
  - Odds Ratio (OR) is a ratio of two ratios.

Measures of Disease Risk
Probability and Odds

	Probability	Odds
You will fall asleep at your desk at least one night while studying for the boards	95%	95:5 =19:1 19
Passing your endocrinology board exam on the first try	80%	80:20 = 4:1 4
Learning statistics in this board review lecture	60%	60:40 = 3:2
Heads when tossing a coin	50%	50:50 = 1:1 1
Rolling 6 with a fair die	17%	1:5 (0.20)
Drawing an ace from a deck of cards	7.6%	1:12 (0.083)

As the probability decreases (< 10%), the probability and the odds converge.

Measures of Disease Risk: Relative Risk

		Disease		
		Yes (Disease +)	No (Disease -)	
Risk Factor	Present (RF +)	a	b	a + b
	Present (RF -)	c	d	c + d
		a + c	b + d	a + b + c + d = n

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

Risk of disease in exposed divided by risk of disease in unexposed

Measures of Disease Risk: Relative Risk

- Relative risk = risk ratio =

$$\frac{\text{\% of those with a risk factor who have the disease}}{\text{\% of those without the risk factor who have the disease}}$$

  Comparing probabilities of disease in each group:
  - RR = 1 (no difference or the null value)
  - RR > 1 (risk factor increases risk of disease)
  - RR < 1 (risk factor decreases risk of disease)

- Used in prospective cohort studies, randomized controlled clinical trials.
- Start with risk factor (exposure), not disease
- P-value obtained from the Chi-square test
- RR gives magnitude of the difference

Measures of Disease Risk: Odds Ratio

		Disease		
		Yes (Disease +)	No (Disease -)	
Risk Factor	Present (RF +)	a	b	a + b
	Present (RF -)	c	d	c + d
		a + c	b + d	a + b + c + d = n

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

Odds of risk factor in those with disease over the odds of risk factor in those without disease

Measures of Disease Risk: Odds Ratio

- Odds ratio= OR = odds of having a risk factor in those with a disease compared to the odds of risk factor without disease. Comparing the odds of the risk factor in each group.
  - OR = 1 (no difference or the null value)
  - OR > 1 (odds of disease increased with risk factor)
  - OR < 1 (odds of disease decreased with risk factor)

- Used in case-control studies, outcome is chosen, so prevalence is artificial.
- Start with disease, look at risk factors.
- P-value is obtained from Chi-square test.
- OR gives magnitude of the difference

Relationship between RR and OR when Disease is Rare

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{a/b}{c/d} = \frac{ad}{bc}$$

$$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

		Disease		
		Yes (Disease +)	No (Disease -)	
Risk Factor	Present (RF +)	a	b	a + b
	Present (RF -)	c	d	c + d
		a + c	b + d	a + b + c + d = n

Titanic

	Dead	Alive	
Male	709	142	851
Female	154	308	462
	863	450	1313

- Males look like they more likely to die.
- RR for death if male (709/851) divided by (154/462) = 2.5
  - 2.5 greater probability of dying
- Odds ratio= (709/154) divided by (142/308) = (709)*(308)/(142)*(154)=10
  - 10 fold greater odds of dying if male

Which one is better?

- Relative Risk - is the most interpretable and consistent with the way people think
  - We like to think about the risk of disease associated with a particular exposure
  - Useful in large prospective cohort studies

- Odds Ratio - is calculated from case control studies, where the prevalence of disease is artificially created
  - Approaches the relative risk when outcome is uncommon (<10%)
  - Retrospective studies
  - Logistic regression software will give OR

Number Needed to Treat (NNT)

- NNT is the number of patients who need to be treated in order to prevent one additional "outcome"

- NNT = 1/ARR
  - Attributable (Absolute) Risk Reduction
  - ARR = risk of outcome in non-intervention group – risk of outcome in intervention group
  - Relative Risk Reduction = ARR/placebo or non-intervention group rate

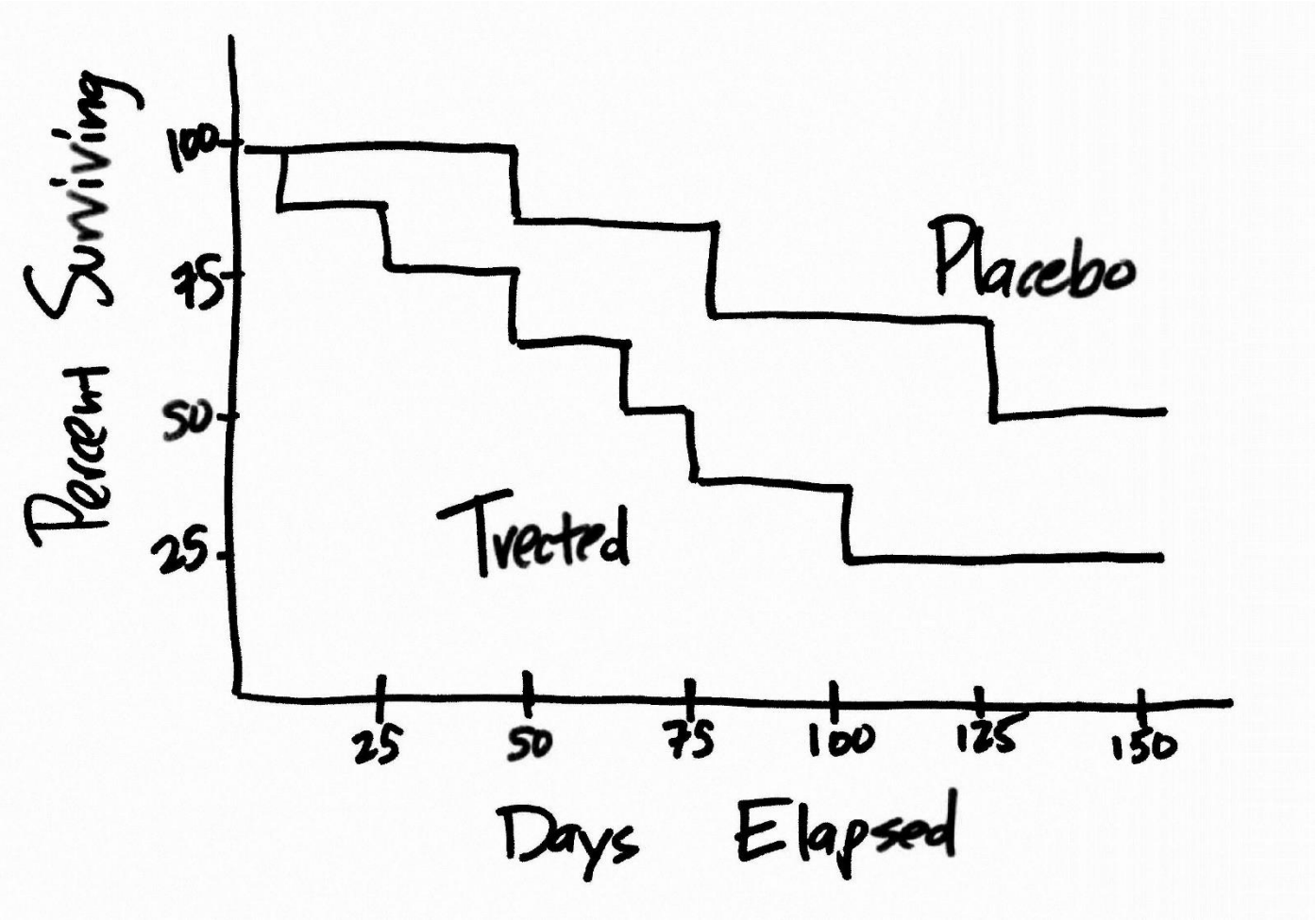
Survival Analysis

- Testing “whether” or “when” an event occurs
- Survival analysis – time to an event
  - Studying the occurrence and timing of events

- Related to logistic regression as the dependent variable is dichotomous (dead/alive)
  - Duration of follow-up not necessarily equal for all patients
  - Not all patients have to experience the event

- **Hazard Ratio-** probability of event in a treatment group relative to control group probability over unit of time – - measure of effect size for time to event data, estimates treatment effect

Survival Analysis
Kaplan-Meier Survival Curve



Statistics

- Problem of multiple comparisons- if you do many comparisons, the chance of finding a rare event increases, and the likelihood of incorrectly rejecting a null hypothesis (false positive, type 1 error) increases
  - Bonferroni adjustment: # tests/α (0.05) – use a more stringent p-value
  - ANOVA with posthoc pairwise testing

Diagnostic Tests

- When evaluating a diagnostic test, it is important to have an independent "gold standard"

- This is the current test felt to be the best currently available to diagnose a particular disease or condition under reasonable conditions

Diagnostic Tests

Test \ Disease	+	-
+	a	b
-	c	d

Sensitivity: Proportion of people with the disease, that have a positive test.

a/(a+c)

-useful for a rare disease that has high morbidity/mortality – want to detect all cases

– high sensitivity -> few false negatives

Specificity: Proportion of people without the disease who have a negative test.

d/(b+d)

-few false positives

Diagnostic Tests

Test \ Disease	+	-
+	a	b
-	c	d

Positive Predictive Value:

-Probability that if the test is positive, the person has the disease

a/(a+b)

Negative Predictive Value:

-Probability that if the test is negative, the person does not have the disease

d/(c+d)

Diagnostic Tests

HbA1c \ T2DM	+	-
+	100	20
-	25	125

Sensitivity:
80%

Specificity:
86%

Positive Predictive Value:
83%

Negative Predictive Value:
83%

Diagnostic Tests

Likelihood ratio =

$$\frac{\text{Probability of test result in the presence of disease}}{\text{Probability of test result in people without disease}}$$

Quantifies change from pre-test probability
to post-test probability

$$\text{Likelihood Ratio} = \frac{\text{Sensitivity}}{\text{1-Specificity}}$$

Diagnostic Tests

Test \ Disease	+	-
+	a	b
-	c	d

False Positive=
1 - specificity

False Negative=
1 – sensitivity

Likelihood Ratio=
sensitivity/ 1-specificity

Diagnostic Tests

HbA1c \ T2DM	+	-
+	100	20
-	25	125

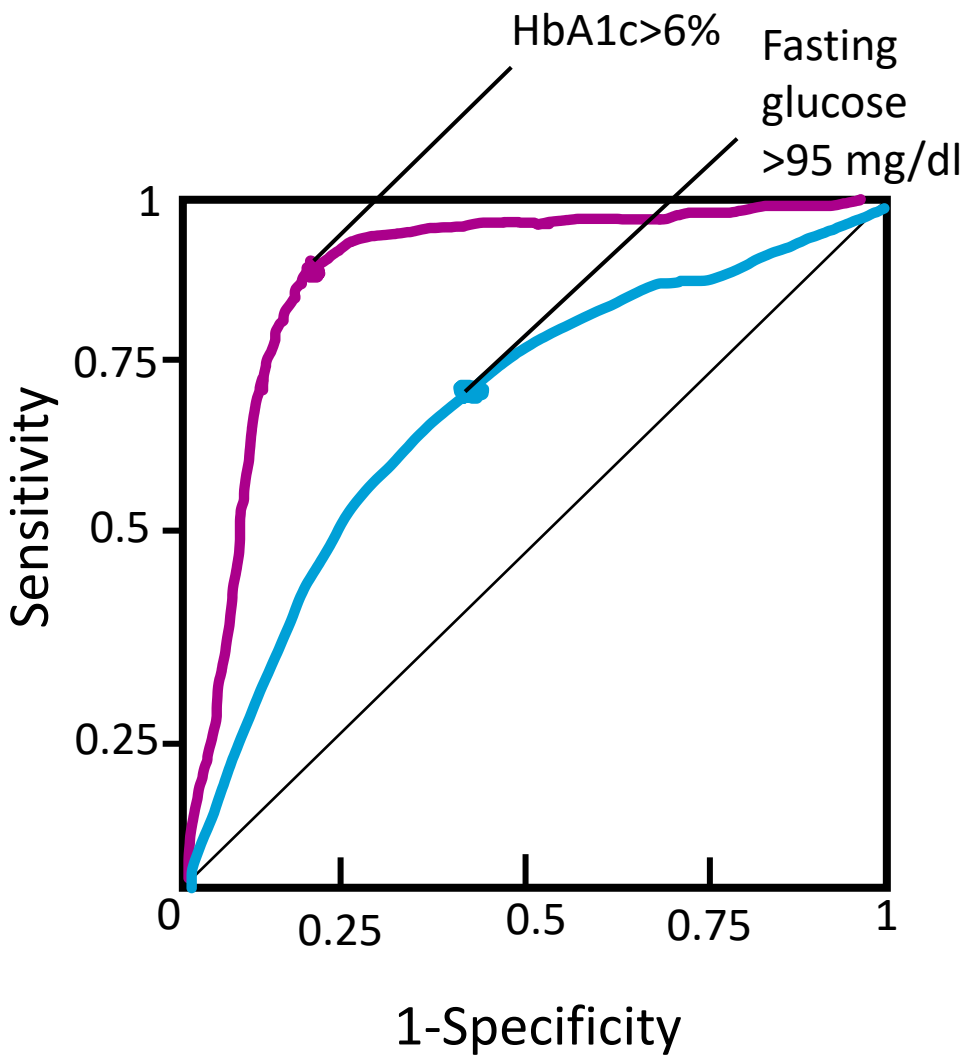
False Positive=
1 - specificity =14%

False Negative=
1 – sensitivity = 20%

Likelihood Ratio=
sensitivity/1-specificity = 5.7

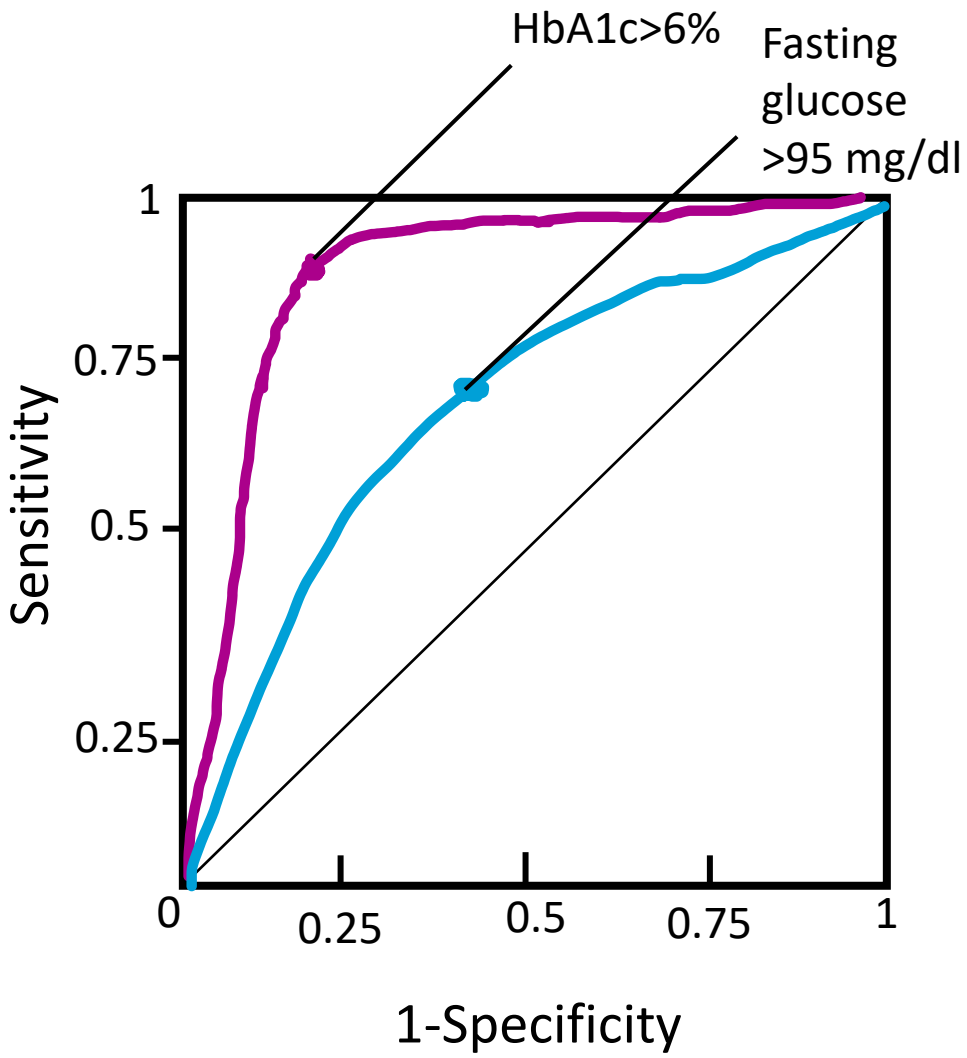
Diagnostic Tests – Receiver Operator Characteristic (ROC) Curves

- Ideal test would have a sensitivity and specificity of 1 (100%)
- Overall accuracy of test described by the area under the curve (the larger the area the better the test)
- Shows trade-off between sensitivity and specificity



Diagnostic Tests – Receiver Operator Characteristic (ROC) Curves

- Helpful for determining cut-offs for lab screening
- Test with curve that is straight line going through points (0,0) and (1,1) is no better than pure chance to detect the presence of the disease
- The top curve represents the best screening test



Systemic Review vs Meta-Analysis

- Systemic review answers a defined research question by collecting and summarizing all empirical evidence that fits pre-specified eligibility criteria.

- Meta-analysis is the use of statistical methods to summarize the results of these studies.

Domain 19: Core Knowledge in Scholarly Activities

Topics Outline:

A. Principles of biostatistics in research

B. Principles of epidemiology and clinical research design

C. Ethics in research

D. Quality improvement and patient safety

Study Design

- Types of Research Designs
  - Case Report
    - Use: hypothesis generating
  - Case Series
    - Use: Characterize disease and hypothesis generating
  - Analysis of Secular Trends / Cross-Sectional
    - Uses aggregate population data
    - Compare geographic or time trends of an illness to trend in risk factors

Study Designs

- Types of Research Designs
  - Case Control Study
    - Start with Disease status and then look back at whether had Exposure
    - Ex: study comparing two groups of infants – with and without HI; look to see who exposed to toxin in utero
  - Cohort Study
    - Start with Exposure status and then see who develops Disease
    - Ex: Compare two groups of children – one exposed to cigarette smoke, and one not; See who develops asthma.

Study Designs

- Case Control Study
  - Adv: Good for study of rare diseases, also can look at many different risk factors for a disease
  - Disadv: Can be prone to bias – ex. Recall bias
- Cohort Study
  - Adv: Can study many outcomes from a single exposure; Can use for more common diseases
  - Disadv: Long and expensive

Study Designs

- Clinical Trial
  - Risk factor or exposure is controlled by investigator
  - Experimental as opposed to observational
  - Intervention study
  - Adv: most convincing demonstration of causality
  - Disadv: Logistic and ethical problems dealing with human subjects

Bias

- Flaw in study design, or method of collecting or interpreting data, that can cause incorrect conclusions about what the study showed.

- Many types – some examples:
  - Selection bias
  - Misclassification bias
  - Recall bias
  - Reporting bias
  - Performance bias
  - Attrition bias

Study Designs

- Clinical Trial
  - **Randomization**:
    - Purpose: decrease bias by evenly distributing known and unknown confounders between the groups
    - Avoid selection bias
  - **Blinding:**
    - Single – study participant
    - Double – study participant and investigator
    - Triple – study participant, investigator, and DSMB/statistician/data collector, etc.
    - Purpose: Avoid ascertainment/information bias
    - Alternative: Open label study

Study Designs – Clinical Trial

- **Surrogate marker** is a biomarker that is intended to substitute for a clinical outcome.
  - Useful when the clinical outcome is undesired (ex. death) or in distant future (ex. diabetic complication in a child with diabetes)
  - Changes induced on the surrogate endpoint are meant to reflect changes on clinical outcome
  - May correlate with the treatment's effect on real clinical outcome but does not have guaranteed relationship, so may not predict an actual effect (=disadvantage)

Study Designs – Clinical Trial

- **Intention to Treat Analysis:** method to analyze prospective randomized study where all participants are included and analyzed in the groups they were originally assigned to, no matter what treatment they actually received – considered gold standard
  - Preserved benefits of randomization
  - Avoids bias
  - Opposite is **Per protocol** or **As treated analysis** – ex. May be randomized to tx but stop taking tx because it didn't work. If you do not include them in the tx group, the tx could look more effective than it was.

Study Design

- **Association vs Causality** - association between two variables implies that knowing the value of one variable provides information about the value of the other

- Does not imply causation (exposure produces the effect or outcome).

- How confirm causality?
  - Randomized controlled study

Study Designs

Prospective

Retrospective

Has the outcome of interest occurred at the time the investigator initiates the study???

Study Designs

Most case-control studies are retrospective and most cohort studies are prospective, BUT not always!

Study Designs

Longitudinal – over time

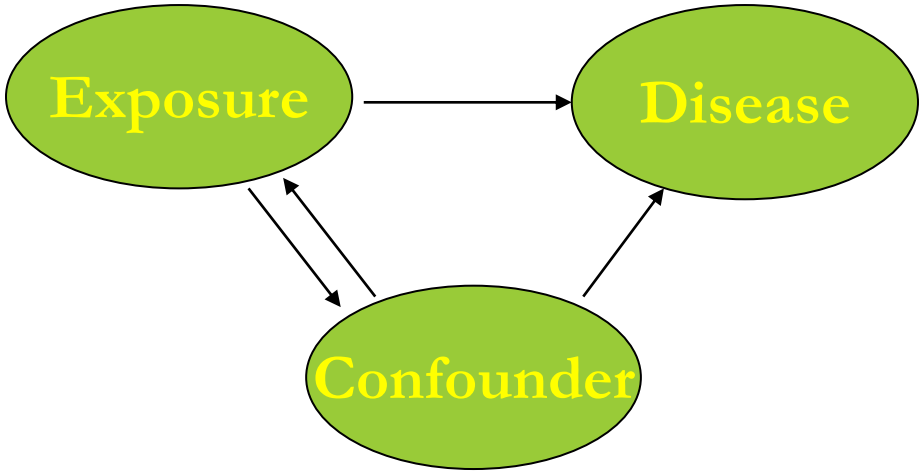
Cross-sectional – one slice of time; at that point

Study Design

- Control group
  - comparison group
  - both groups should be as similar as possible except for the variable being studied
  - “placebo-control” group
  - Randomized controls vs non-randomized controls
  - Historical vs concurrent controls

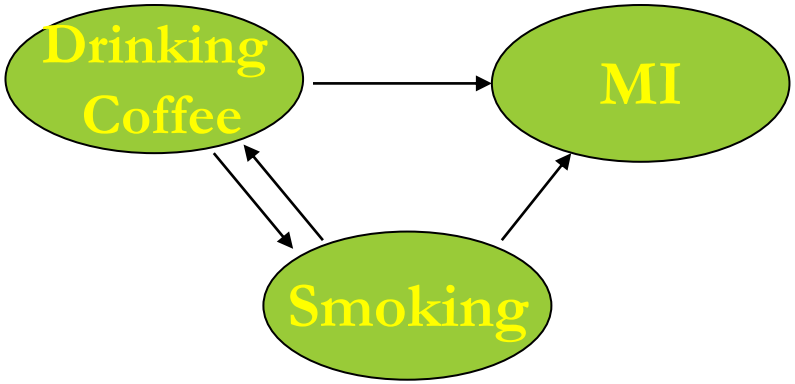
Study Design

- Confounding variables
  - Variable independently associated with both the exposure and the outcome of interest
  - Race/ethnicity, gender, SES can be confounders



Study Design

- Confounding variables
  - Ex. smoking in the relationship between drinking coffee and MI



  - As long as you measure it, you can adjust for a confounding variable, statistically

  - How to avoid confounding: Randomization, Restriction, Matching

Study Design

- Effect Modification (or Interaction)
  - Association between the exposure and disease under study varies by the level of a third factor
  - Different strata
  - Ex. Effect of physical activity on MI risk; EM by gender
  - Described and reported, but cannot control for EM

Study Design

- Generalizability = External validity
  - How applicable is it to the general population?
  - To other races, ethnicities
  - Non-representative samples can bias results
  - Source of data can affect results – ex. measuring the prevalence of dyslipidemia recruiting from Lipid Clinic vs recruiting from primary care. Need to know what question you are asking.

Diagnostic Tests – Prevalence vs Incidence

- Disease prevalence:
  - Number of existing cases at a specific time/number of people in the total population at that time
  - Cross-sectional measure

- Disease incidence:
  - Number of new cases over a period of time/ number of people at risk of developing the disease during that time
  - Time is in the denominator, ex. /Person-years

Qualitative Research Methods and Analysis - Measurement

- Validity
  - Face- does the content of the test appear appropriate for its aims
  - Construct- does it measure the concept it is supposed to
  - Criterion- do the results accurately measure the concrete outcome they are supposed to
  - Predictive- does the measure accurately predict outcomes
  - Content –whether the measure used covers all of the content in the underlying construct
- Reliability

Measurement

- Reliability
  - Consistency across
    - Raters: Intra-Rater and Inter-Rater
    - Time: Test-retest
    - Respondents
    - Items: internal consistency – looks at consistency within a set

- Absence of error, or extent to which random error is minimized

Measurement

- Inter-observer Reliability
  - Kappa
    - correlation-like measure that controls for the problem of inflated percent agreement due to chance
    - Ranges from +1 to -1
    - Needs to be >0.4, prefer between 0.4-0.7

Measurement

- Internal Consistency – how well is a sample of items representative of a domain
  - Cronbach's Alpha
    - Ranges 0-1
    - Tells proportion of a scale's true variance that is due to the true score on the measure (as opposed to error)
    - 0.7 is adequate, 0.8-0.85 is good, 0.9 indicates redundancy

Validity vs Reliability

- Reliability as consistency
- Can be consistent but not accurate
- Accuracy gets to validity

Cost-Effectiveness

- Cost versus charges
  - Cost – cost of services (equipment, personnel, etc.)
  - Charges – what the hospital bills the insurance and patient
- Cost-effectiveness ratio
  - Ratio of dollars expended to health care outcome obtained
- Quality-adjusted life years (QALY)
  - Fundamental component of cost-effectiveness research
  - Measures how well a tx lengthens and/or improves patients' lives – quality and quantity of life
  - To calculate: utility value or weight associated with a state of health x time lived in a state of health
  - One QALY represents 1 year in perfect health (0 death, 1 perfect health)
- Cost Benefit analysis – compare the costs and benefits of an intervention in monetary units

Domain 19: Core Knowledge in Scholarly Activities

Topics Outline:

A. Principles of biostatistics in research

B. Principles of epidemiology and clinical research design

C. Ethics in research

D. Quality improvement and patient safety

Professionalism and Misconduct in Research

- Identify and manage potential conflicts of interest in the funding, design, and/or execution of a research study

- Forms of Research Misconduct
  1. Plagiarism
  2. Falsification
  3. Fabrication

Professionalism and Misconduct in Research

- Misconduct is not making an honest mistake.

- Requires that there is a departure from accepted practice in the research community, that the misconduct was intentional, knowing, or reckless, and that it was proven by preponderance of evidence.

- Know how, and to whom, to report concerns of research misconduct - Office on Research Integrity and Committee on Publication Ethics

Ethics in Research

Research involving human subjects

- Nuremberg Code – 1947
  - 10 principles to satisfy ethical conduct for human experimentation
  - Includes voluntary consent
- Helsinki Declaration- 1964
  - Formal code of ethics for physicians involved in clinical research

Ethics - Research Involving Human Subjects

- Federal guidelines and Ethical safeguards
  - 1974 National Research Act – required Institutional Review Boards for all research funded in part by the government
  - 1978 Belmont Report- ethical principles and guidelines for protection of human subjects
    1. Respect for persons (individual autonomy)
    2. Beneficence
    3. Justice
  - Informed consent
  - Data safety monitoring boards – no vested interest in outcome

Ethics - Research Involving Human Subjects

- Unconventional patient care vs. research
- Ethical Considerations of Study Design
  - Placebo
  - Harm of intervention
  - Deception
  - Flawed design

IRB vs DSMB

- IRB – appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects in accordance with FDA regulations. Has the authority to approve, require modification or disapprove research.

- DSMB – independent group of experts that prospectively identifies and documents activities to protect the safety of the subjects, the validity of the data and integrity of the research study.

Minimal Risk

- Risk where the probability and magnitude of harm or discomfort anticipate in the research are not greater in and of themselves than those normally encountered in daily life or during the performance of routine physical or psychological examinations or tests.

- Protections for vulnerable populations such as children

Informed Consent - Components

1. Description of the investigation – that it involves research, purpose of study, duration of participant's involvement, description of procedures and any that are experimental
2. Description of any foreseeable risks or discomforts
3. Description of potential benefits expected
4. Disclosure of alternative procedures or treatments that might be beneficial to person
5. Description of the extent that confidentiality will be maintained
6. If more than minimal risk, description of compensation and medical treatment in case of injury
7. Identification of contact people
8. That participation in voluntary, and that failure to participate will not involve any penalty or loss of benefits to which they are otherwise entitled

Consent vs Assent

- Consent may only be given by individuals who have reached the legal age of consent (typically 18 years of age).

- Assent is the agreement of someone not able to give legal consent to participate in the activity.

Domain 19: Core Knowledge in Scholarly Activities

Topics Outline:

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Quality Improvement Models and Tools

- Models provide systematic formal framework for creating QI processes in practice.
- Common QI models:
  - Model for improvement (Plan-Do- Study-Act (PDSA) cycles – combines Total Quality Management and Rapid Cycle Improvement models
  - Six Sigma – Method of improvement that tries to decrease variation and defects
  - Lean – Approach to drive out waste and improves efficiency in work so that all work adds value

Quality Improvement and Patient Safety
–
Project Design - PDSA

- Plan
  - Objectives, questions and predictions (why?)
  - Plan to carry out the cycle (who, what, where, when)
  - Plan for data collection
- Do
  - Carry out the plan, begin analysis of the data
  - Document problems & unexpected observations
- Study
  - Complete the analysis, compare data to predictions
  - Summarize what was learned
- Act
  - What changes need to be made?
  - Next Cycle?

Quality Improvement and Patient Safety

- Aim of quality improvement project should be specific, measurable, achievable, realistic, and time-limited

- Quality Improvement Tools

Quality Measures

Measure		Examples
Outcome Measure	What is your primary result?	Percentage of infants discharged from NICU who received HBV
Process Measure	Are the parts or steps in the system performing as planned? Early indicators of whether or not changes are improvement.	Pharmacy documentation in EHR regarding infant's HBV status? Percentage of nurses receiving education Percentage of parents receiving VIS to ensure consent
Balancing Measure	What happened to the system as we improved the outcome and process measure? Unintended consequences.	Anaphylaxis, fever/apnea after immunization, premies given too early

Common Cause vs Special Cause Variation

- Common cause variation – expected variation within a given system
  - Typical temperature range during a specific season 55-75F
- Special cause variation – changes that are unexpected or outside the norm
  - Temperatures outside of the normal range, ex. 90F, as a result of special cause variation such as heat wave

Run Chart

- Used to plot data over time, noting interval of time
- X-axis is time and Y-axis is the metric being studied (could be count or rate)

Statistical Process Control (SPC) Charts

- More useful way to show changes over time
- Central line is mean
- Study how a process changes over time – x axis always time
- Display the mean (center line) and upper and lower control limits, which are ~ 3 SD above and below mean

SPC Charts

- Spikes in control limits usually correspond to time periods with small sample sizes
- Values close to 0 or 100 will likely not have control limits calculated

- Compare current data to historical data

- Is process variation consistent or unpredictable?

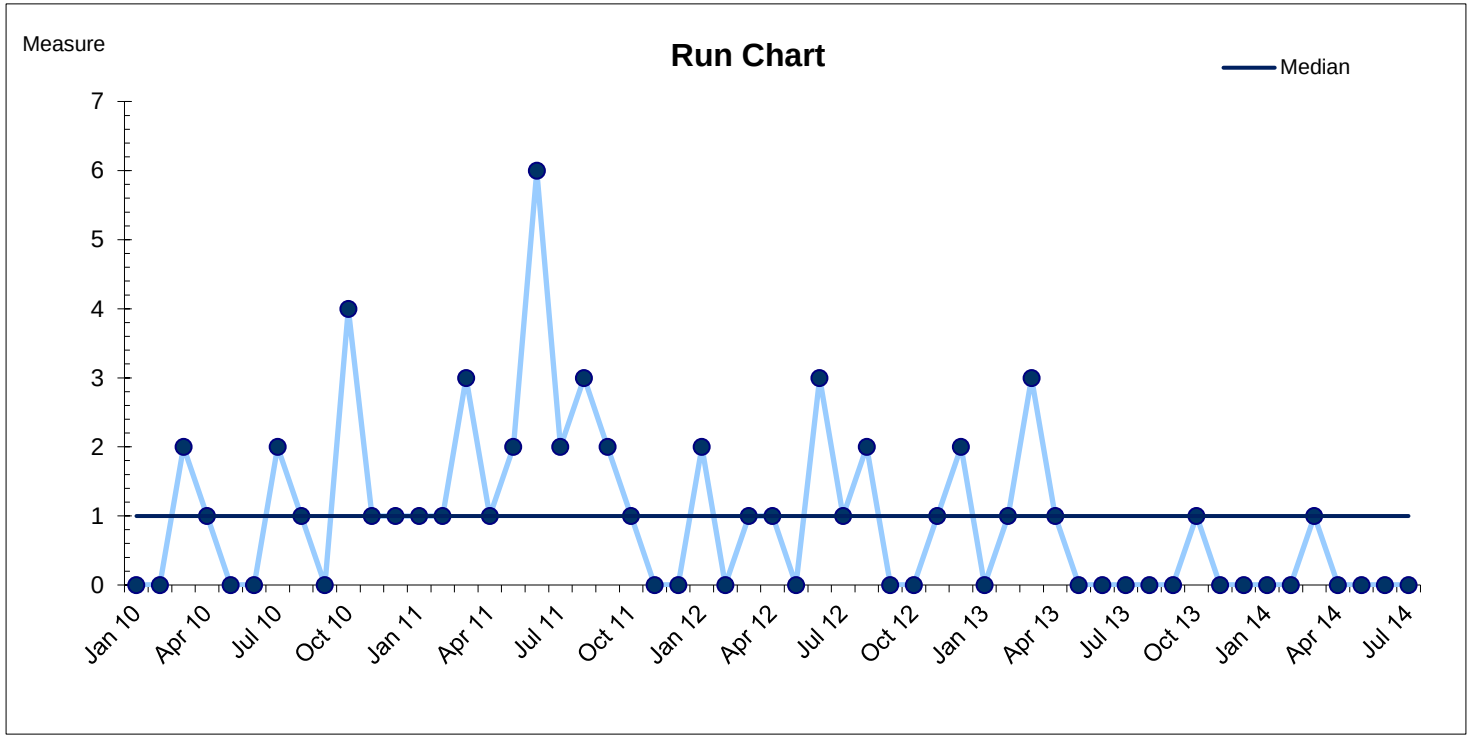
Difference Between a Run Chart and a SPC Chart

Run Chart

- Simple
- Measure of central tendency is median
- No measurement of variation
- First blush look at the data
- Investigative tool
- Different rules for special cause

SPC Chart

- More complex
- Measure of central tendency is mean
- Upper and lower control limits
- Provides more insight
- Use real time to compare to historical data
- Compare process before and after intervention


Measure
Run Chart
Median
7
6
5
4
3
2
1
0
Jan 10
Apr 10
Jul 10
Oct 10
Jan 11
Apr 11
Jul 11
Oct 11
Jan 12
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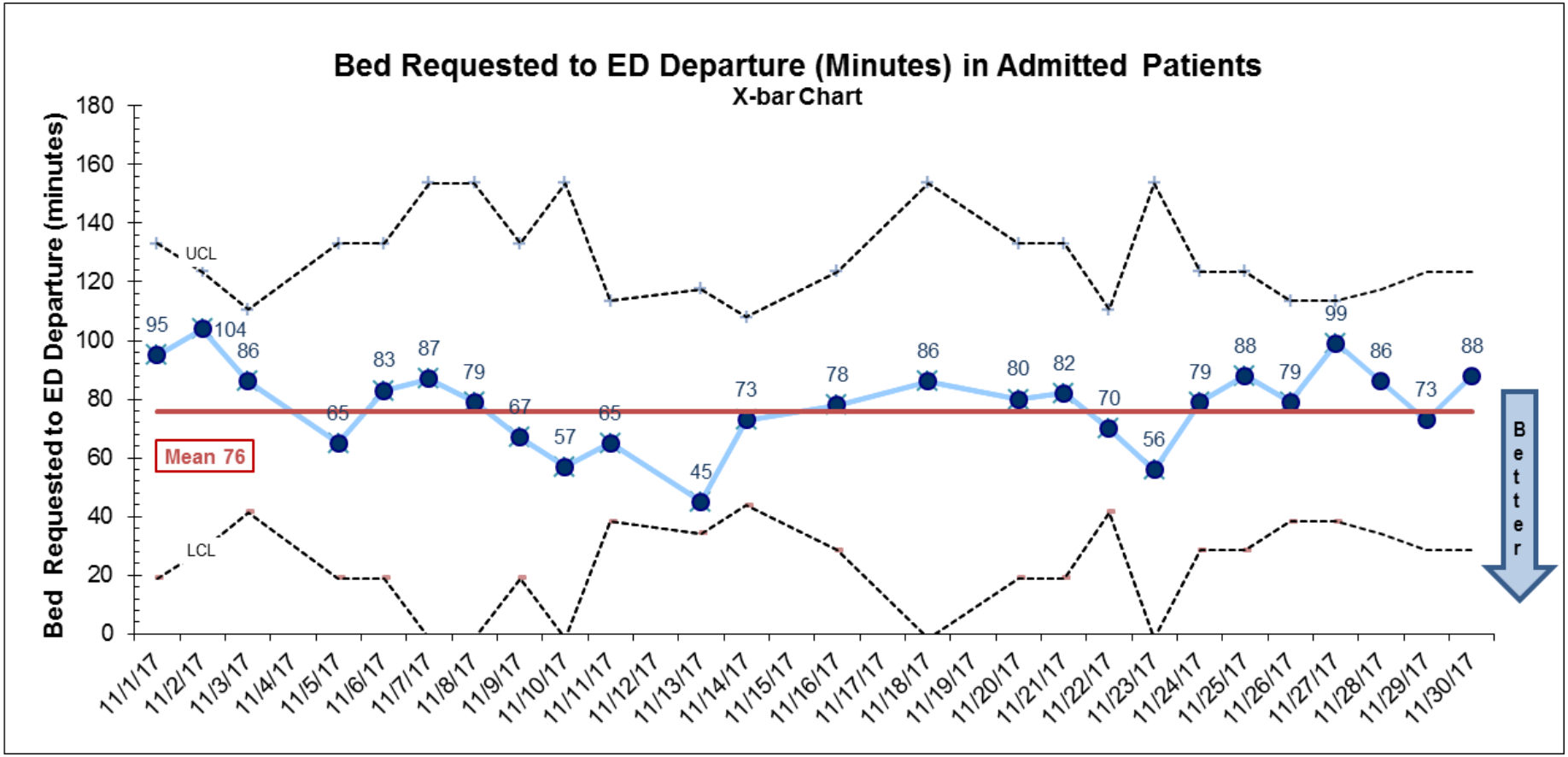
Jul 14


Bed Requested to ED Departure (Minutes) in Admitted Patients
X-bar Chart
Bed Requested to ED Departure (minutes)
180
160
140
120
100
80
60
40
20
0
UCL
LCL
Mean 76
95
104
86
65
83
87
79
67
57
65
45
73
78
86
80
82
70
56
79
88
79
99
86
73
88
Better
11/1/17
11/2/17
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11/4/17
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11/29/17
11/30/17

How to Measure the Impact of an Intervention

- Should have 10-20 data points suggesting your process is in control
- Looking for special cause
  - Unusual, not previously observed, non-quantifiable variation
  - If special cause is present, you may reset the mean central line
- Upper and lower control limits play a role in determining special cause

Rules for Determining Special Cause

- Single point outside of the control limit
- Eight of more consecutive point above or below the centerline
- Six consecutive points increasing (trend up) or decreasing (trend down)
- Two out of three consecutive points near a control limit (outer on-third)
- Fifteen consecutive points close to the centerline (inner one-third)

GOOD LUCK!

Board Review Course Stats Questions

Question 1:

You are studying prolactin levels before and after weight loss in children with optic nerve dysplasia. Differences in prolactin levels in your study follow a normal distribution. Your primary outcome should be analyzed with which statistical test?

A. Independent or Student's t-test

B. Wilcoxon Signed Rank Test for Paired Samples

C. Mann Whitney U test

D. Chi Square test

E. Paired t test

ANSWER:

1. You are studying prolactin levels before and after weight loss in children with optic nerve dysplasia. Differences in prolactin levels follow a normal distribution. Your primary outcome should be analyzed with which statistical test?

A. Independent or Student's t-test (continuous or interval variable, independent, parametric, 2 different groups)

B. Wilcoxon Signed Rank Test for Paired Samples (paired data, continuous or interval variable, non-parametric, 2 groups)

C. Mann Whitney U test (continuous or interval variable, independent, non-parametric, 2 groups)

D. Chi Square test (nominal variable, cell size > 5)

E. Paired t test (paired data, continuous or interval variable, parametric, 2 groups).

Correct answer E

In this example you are comparing a normally-distributed, continuous variable (prolactin), so you need a parametric test that is used to compare a continuous variable between 2 groups. The variable is being compared in the same individuals, before and after an intervention, so you need a paired test. Thus, the paired t-test is the correct answer.

Question 2:

Which of the following is true of a power calculation?

A. As power decreases, the chances of a Type II error decreases.
B. The power of a study is usually set at 95%.
C. The power of a study is directly linked to the probability of making a Type I error.
D. Power analysis may be done a priori or post-hoc
E. The size of the difference to be detected can usually be determined by the statistician.

ANSWER:

2. Which of the following is true of a power calculation?

A. As power decreases, the chance of a Type II error decreases. (As power decreases, the chance of Type II error increases)

B. The power of a study is usually set at 95%. (Power is usually set at 80%.)

C. The power of a study is directly linked to the probability of making a Type I error. (Power of a study is directly linked to the probability of making a type II error)

D. Power analysis may be done a priori or post-hoc (this is true)

E. The size of the difference to be detected can usually be determined by the statistician. (The size of the difference to be detected by the investigator – it is a clinical decision based on prior literature or pilot studies)

Correct answer D. The power analysis can be done a priori (ahead of time) or post-hoc (after the study is done). However, if it is done post-hoc, and power is inadequate, you may have increased type II error.

Question 3:

You are reading the results of a recent clinical trial of growth hormone therapy in children between 1 and 3 years of age who are below the 5th percentile for height at enrollment. At the end of the 5 year treatment period, the treatment group mean change in height is 10.1 cm (sd 6 cm) and the mean change in the height in the placebo group is 9.7 cm (sd 5.9 cm), $p < 0.0001$. Which of the following most accurately describes the results?

A. Results are statistically significant and clinically relevant.
B. Results are statistically significant but not clinically relevant.
C. Results are not statistically significant but are clinically relevant.
D. Results are not statistically significant or clinically relevant.

ANSWER:

3. You are reading the results of a recent clinical trial of growth hormone therapy in children between 1 and 3 years of age who are below the 5th percentile for height at enrollment. At the end of the 5 year treatment period, the treatment group mean change in height is 10.1 cm (sd 6 cm) and the mean change in the height in the placebo group is 9.7 cm (sd 5.9 cm), $p < 0.0001$. Which of the following most accurately describes the results?

A. Results are statistically significant and clinically relevant.

B. Results are statistically significant but not clinically relevant. (this is true)

C. Results are not statistically significant but are clinically relevant.

D. Results are not statistically significant or clinically relevant.

Correct answer B

The p-value is <0.05, so it is statistically significant, but most clinicians would agree that 0.4 cm difference in the means is not clinically significant.

Question 4:

You conduct a 2-year, prospective, randomized, double-blinded, placebo-controlled clinical trial of a new medication X for youth-onset type 2 diabetes. By the end of the 2 year trial, out of the 300 randomized participants (150 per arm), 14 in the medication X arm say they didn't take the medication and 10 are lost to follow up, and 12 in the placebo arm say they didn't take their treatment and 15 were lost to follow-up. You now want to analyze the data in the most scientifically rigorous way. What should you do?

A. Compare the 126 remaining in the medication X arm to the 123 in the placebo arm that took their treatment and stayed in the trial, because then you will be comparing those that actually took the treatment they were supposed to take for the length of the trial.
B. Compare 140 in the medication X arm to 135 in the placebo arm, since these are the participants who remained in the study until the end.
C. Compare all of the 150 assigned to the medication X arm to all of the 150 assigned to the placebo arm.
D. Compare 136 in the medication X arm to the 138 in the placebo arm, who actually took the assigned treatments.

Question 5:

In Question 4, what is the most scientifically-sound analysis method called, and why is it considered the gold standard?

A. “As Treated” analysis because it represents what actually happened.
B. “Intention to Treat” analysis because it minimizes bias.
C. “As Treated” analysis because it minimizes bias.
D. “Intention to Treat” analysis because it preserves blinding.

ANSWERS to 4 and 5:

Question 4:

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B. Compare 140 in the medication X arm to 135 in the placebo arm, since these are the participants who remained in the study until the end.

C. Compare all of the 150 assigned to the medication X arm to all of the 150 assigned to the placebo arm. (This is correct)

D. Compare 136 in the medication X arm to the 138 in the placebo arm, who actually took the assigned treatments.

Question 5:

In Question 4, what is the most scientifically-sound analysis method called, and why is it considered the gold standard?

A. "As Treated" analysis because it represents what actually happened.

B. "Intention to Treat" analysis because it minimizes bias. (This is true.)

C. "As Treated" analysis because it minimizes bias.

D. "Intention to Treat" analysis because it preserves blinding.

Correct answers 4. C, 5. B.

Intention to Treat Analysis is considered the gold standard for analyzing prospective randomized treatment trials. In an intention to treat analysis, all participants are included and analyzed in the groups that they were originally assigned to, no matter what treatment they actually received or for how long. The idea is that using an intention to treat analysis preserves the benefits of randomization and avoids bias. For example, if someone is randomized to take the true medication but stops taking the medication because it didn't work, and you do not include them in the medication group in the analysis, the medication could look more effective than it actually was (because the denominator will be smaller). The opposite is a "per protocol" or "as treated" analysis. Sometimes a paper will report the results of an "intention to treat" analysis AND an "as treated" analysis, but the "intention to treat" is the gold standard.

Thyroid Physiology and Congenital Hypothyroidism

PES Board Review Course in Pediatric Endocrinology – 2025

Todd D. Nebesio, MD

Division of Pediatric Endocrinology/Diabetology

Indianapolis, IN

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Riley Hospital for Children
Indiana University Health

Embryology of the formation and migration of the thyroid

- **The thyroid is the largest endocrine gland in humans**
  - **1 to 2 grams at birth**
  - **Increases by about 1 gram per year until 15 y.o.**

- **The thyroid is the first endocrine structure formed in the fetus (occurs during 1st trimester)**

- **Most critical events in thyroid morphogenesis occur within the first 60 days of gestation**

Embryology of the formation and migration of the thyroid

- **Thyroid follicular cells (thyrocytes) arise from embryonic endoderm**
- **Development starts at the base of the tongue (foramen cecum)**
- **Thyroid is pulled downward by the heart during its descent into chest**
- **Various genes implicated: *FOXE1* (a.k.a. TTF2, TITF2, and FKHL15), *NKX2-1* (a.k.a. TTF1 and TITF1), *PAX8*, *NKX2-5***
- **Other genes involved: *CDCA8*, *GLIS3*, *JAG1*, *TBX1*, and *TSHR***
  - **TSH is the predominant regulator of thyroid growth and expansion**
  - **TSH not involved in thyroid gland formation and organogenesis in humans**

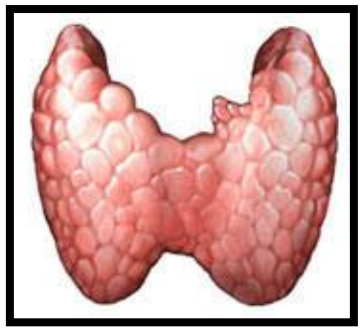
Genes expressed in thyroid development

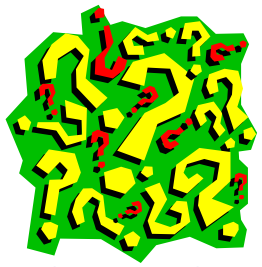
TTF-2 (or TITF2)
FOXE1* or *FKHL15
Chromosome 9q22.33
- Tongue
- Palate
- Epiglottis
- Esophagus
- Hair follicle
- Thyroid

(Bamforth-Lazarus syndrome)

TTF-1 (or TITF1)
NKX2-1
Chromosome 14q13.3
- Lungs
- Hypothalamus
- Basal ganglia
- Thyroid

(Brain-Lung-Thyroid syndrome)





Other genes (> 98%)

NKX2-5
Chromosome 5q35.1
- Heart
- Thyroid

PAX8
Chromosome 2q14.1
- Kidney
- Mid and Hindbrain
- Thyroid

Genes expressed in thyroid development

Gene (location)	Inheritance	Thyroid description	Associated findings
FOXE1 (9q22.33)	Recessive	Absent or hypoplastic	Bamforth-Lazarus syndrome
NKX-2.1 (14q13.3)	Dominant	Absent, hypoplastic, or normal	Brain-Lung-Thyroid syndrome
PAX8 (2q14.1)	Dominant	Absent, ectopic, hypoplastic, or normal	Unilateral renal agenesis
NKX2-5 (5q35.1)	Dominant	Absent or ectopic	Congenital heart defects
GLIS (9p24.2)	Recessive	Absent or normal	NDM, polycystic kidneys, glaucoma, hepatic fibrosis, exocrine pancreas deficiency
JAG1 (20p12.2)	Dominant	Absent, ectopic, or normal	Alagille syndrome
TBX1 (22q11.21)	Dominant	Hypoplastic	DiGeorge syndrome
CDCA8 (1p34.3)	Dominant	Absent, ectopic, or hemiagenesis	None
TSHR (14q31.1)	Recessive or dominant	Hypoplastic (mild, moderate, or severe) or normal	None

TSH unresponsiveness syndromes → TSH receptor (*TSHR*) defect

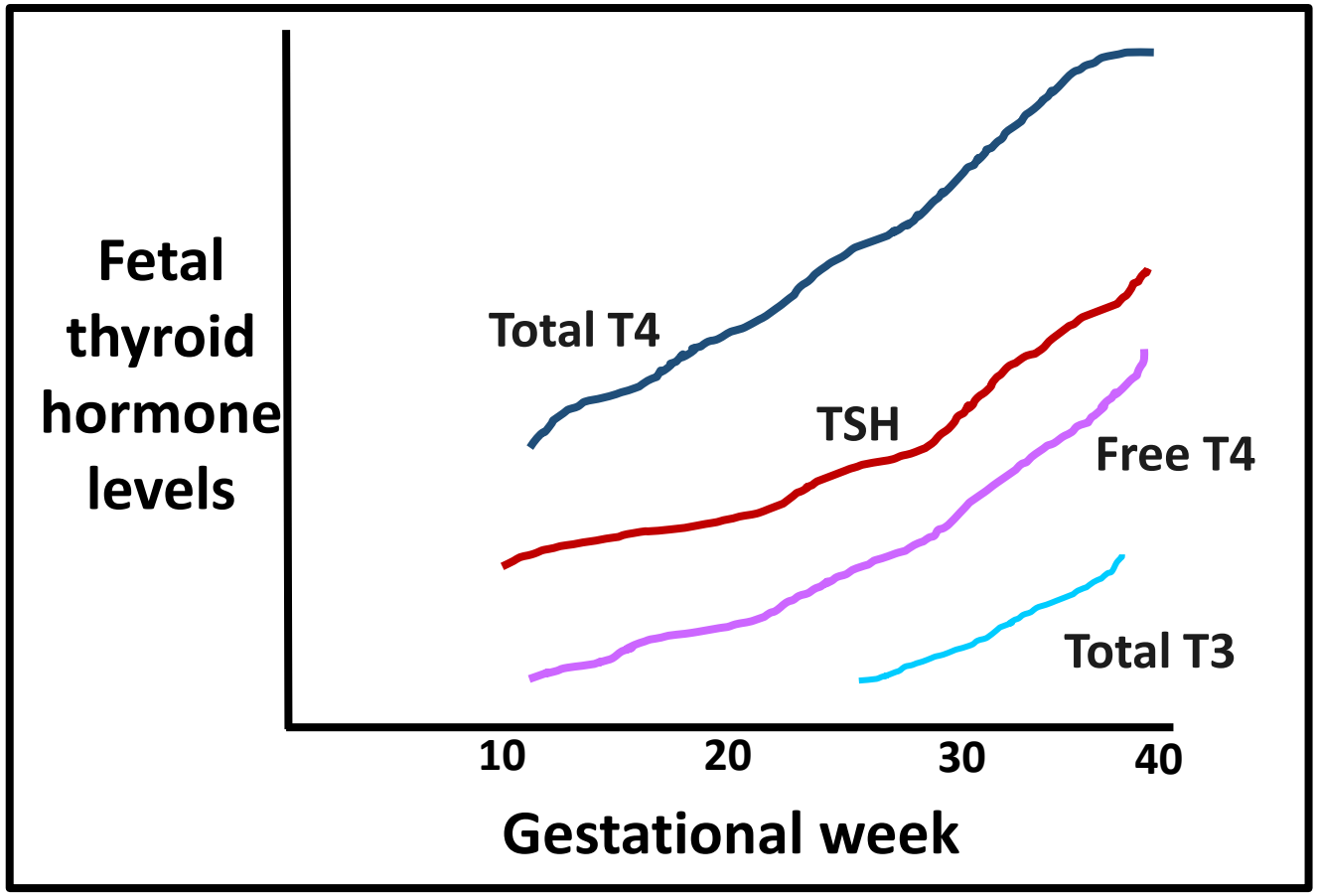
- **Complete resistance**
  - Autosomal recessive
  - Severe thyroid gland hypoplasia
  - Positive newborn screen – uncompensated
- **Moderate resistance**
  - Autosomal recessive
  - Hypoplasia or normal size
  - Variable newborn screen (+/-) – partially compensated
- **Mild resistance**
  - Autosomal dominant
  - Normal size or slight hypoplasia
  - Normal newborn screen – near to fully compensated

TSH receptor (TSHR) mutations are not associated with true athyreosis or ectopic thyroid tissue

TSH unresponsiveness syndromes → Pseudohypoparathyroidism

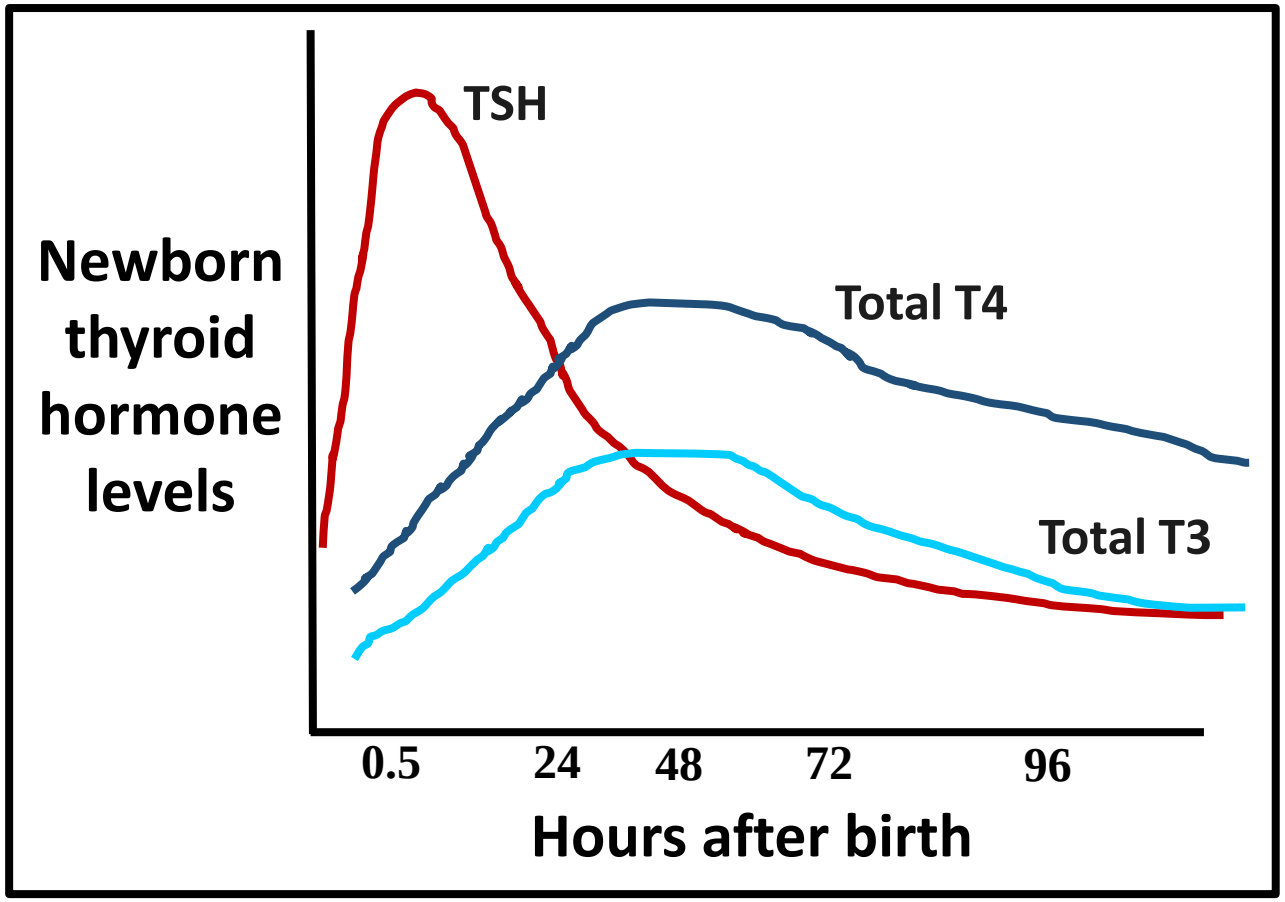
- **Inactivating mutations in the gene (GNAS) encoding the alpha subunit for the stimulatory G-protein ($G_s\alpha$)**
- **Autosomal dominant**
- **Most common form is pseudohypoparathyroidism type 1a (PHP1a)**
  - **Albright hereditary osteodystrophy (AHO) phenotype**
  - **Resistance to multiple hormones: PTH, TSH, GHRH, LH, and FSH**

Pattern and timing of HPT function in the developing fetus



- 4 weeks: TG synthesis
- 8-10 weeks: iodine trapping
- 10-12 weeks: TSH is detected (when hCG ↓)
- 12 weeks: T4 production
- 30 weeks: T3 production rises

TSH surge after birth

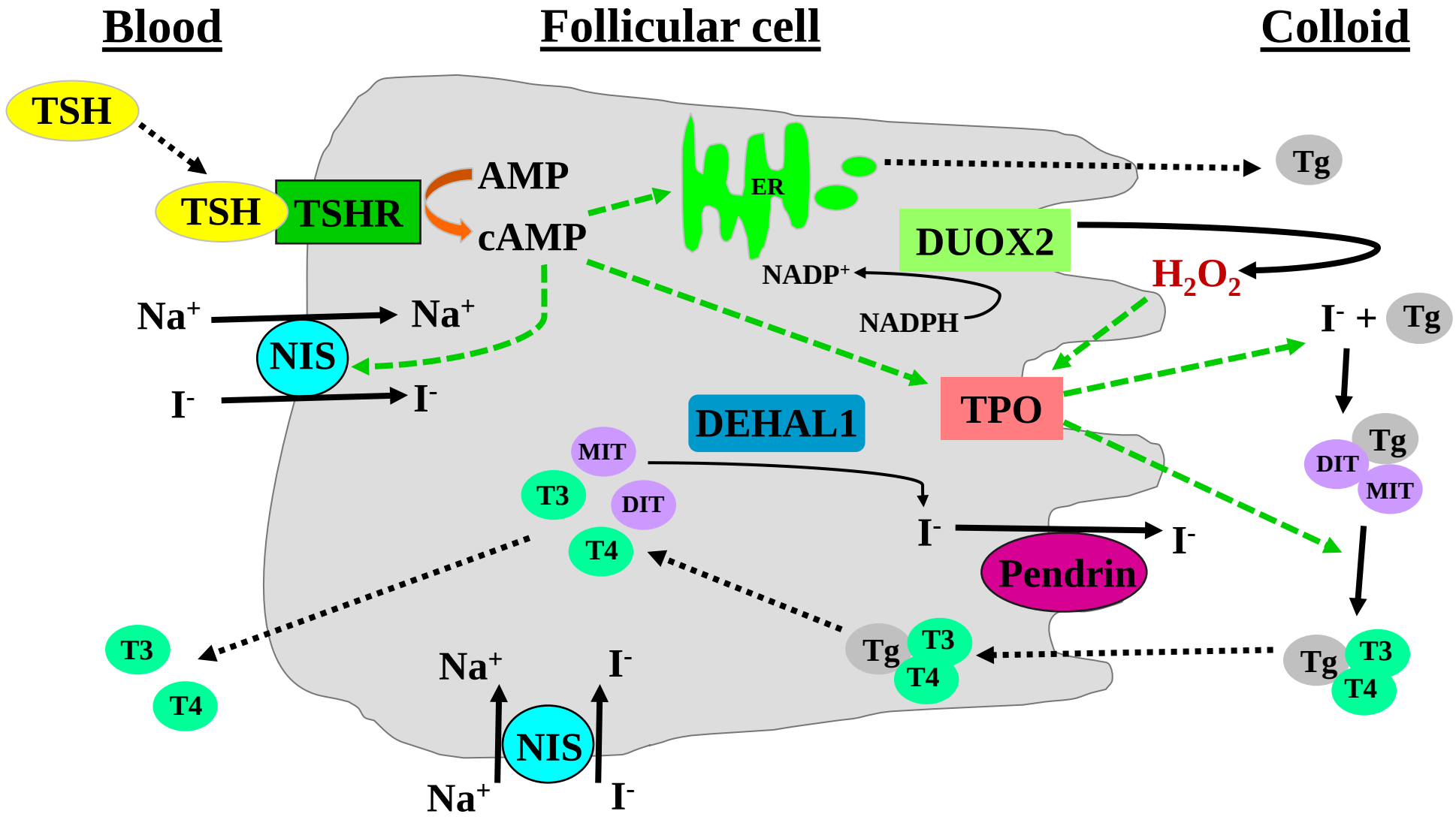


- Due to cold stress, TSH peaks to 60-70 at 30 minutes of life, and then returns to normal neonatal levels by 5 days
- T4 and T3 peak at 48-72 hours of life, and then gradually decline over several weeks

Approximate thyroid function values

Age	Total T4 (mcg/dL)	Free T4 (ng/dL)	Total T3 (ng/dL)	TSH (mU/L)
Cord blood	7.4 – 13.0	1.7 – 4.0	15 – 75	1 – 17
1 to 5 days	11.8 – 22.6	2.2 – 5.3	32 – 216	1 – 39
1 to 4 weeks	7.0 – 16.6	0.8 – 2.0	160 – 340	1.7 – 9.1
1 to 12 months	7.2 – 16.5	0.8 – 2.0	110 – 280	0.8 – 6.4
1 to 5 years	7.3 – 15.0	0.8 – 2.0	105 – 269	0.8 – 6.4
5 to 10 years	6.4 – 13.3	0.8 – 2.0	83 – 213	0.4 – 4.0
10 to 15 year	5.6 – 11.7	0.8 – 2.0	83 – 213	0.4 – 4.0
Adult	4.3 – 12.5	0.8 – 2.0	70 – 204	0.4 – 4.0

Thyroid hormone synthesis/processing



Thyroid hormone synthesis/processing

1) TSH binds to the TSH receptor → cAMP activation
2) Sodium-Iodide symporter (NIS) → iodide trapping
3) Iodide diffuses to the apex and enters the colloid via Chloride-Iodide transporter (Pendrin)
4) Oxidation of iodide to iodine by H_2O_2
5) Organification – iodine is bound to tyrosine residues in TG to form iodothyronines (MIT and DIT)
6) Coupling: MIT + DIT = T3 and DIT + DIT = T4
7) Endocytosis – TG enters follicular cell from colloid
8) Hydrolysis – release DIT and MIT; secretion of T3 and T4
9) Deiodination – recycling of iodide

Thyroid hormone transport

- **Placenta acts as a protective barrier to the fetus**
  - **↑ Type III monodeiodinase activity (inactivation)**
  - **About a 1/3 of maternal T4 crosses the fetus at term**

- **Majority (>99%) of thyroid hormone is bound to proteins**
  - **Bound to TBG, transthyretin, or albumin**
  - **Amount in serum: albumin > transthyretin >> TBG**
  - **Binding to T4: TBG >> transthyretin >>> albumin**
  - **T3 is less tightly bound to proteins than T4**

Thyroid hormone transport

- **Thyroid hormone acts mostly intracellularly and is transported across the plasma membrane**
  - **MCT8**
  - **MCT10**
  - **OATP1C1**

- **MCT8 is the most important plasma membrane transporter**

MCT8 deficiency

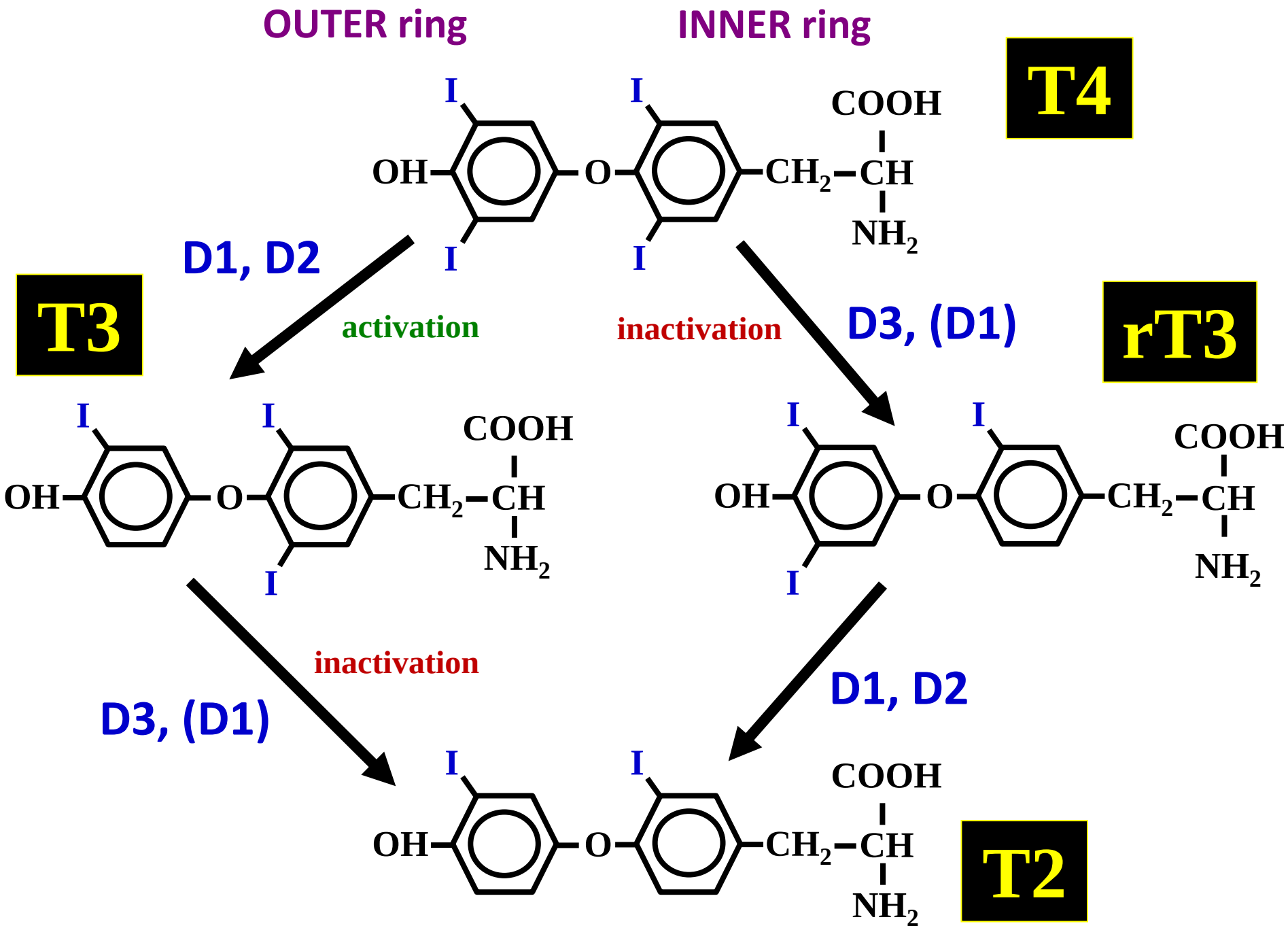
- **Genetic mutations in *SLC16A2***
- **Allen-Herndon-Dudley syndrome**
- **X-linked**

- **Impaired T4 and T3 transport into cells**
  - **Defects in brain and other tissues**
- **Severe intellectual disability, developmental delays, hypotonia, dysarthria, ataxia**
  - **Neurological abnormalities <u>not</u> reversed with T4**

- **TFTs (by 1 m.o.): ↓ T4, ↑↑ T3, ↓↓rT3, normal or slightly ↑TSH**

Metabolism of thyroid hormone

- **Type 1 deoidinase (D1): inner and outer ring**
  - **Activation**
  - **Liver, kidney, muscle**
  - **Activity decreased in sick euthyroid**
- **Type 2 deiodinase (D2): outer ring**
  - **Activation**
  - **Brain, pituitary, adipose**
- **Type 3 deiodinase (D3): inner ring**
  - **Inactivation**
  - **Placenta, brain, and most other tissues**


OUTER ring
INNER ring
T4
D1, D2
activation
T3
inactivation
D3, (D1)
rT3
inactivation
D3, (D1)
D1, D2
T2
I
OH
O
CH2
CH
COOH
NH2

Receptors and Action

- **TSH acts through a 7-transmembrane receptor that signals through Gs alpha to increase cAMP production leading to downstream effects**
- **Thyroid hormone receptors belong to the nuclear (steroid) hormone receptor superfamily**
- **Various isoforms:**
  - **TRα1 – CNS, heart, skeletal muscle**
  - **TRα2 – widely distributed in tissues**
  - **TRβ1 – liver, kidney**
  - **TRβ2 – pituitary, brain**

Transplacental passage affecting fetal thyroid production

- **Radioactive iodine**
  - **Given after 8-10 weeks gestation is trapped by and destroys the fetal thyroid gland**
- **IV contrast**
- **Topical iodine-containing antiseptics**
- **Amiodarone**
- **Iodine-containing nutritional supplements**
  - **Excess iodine resulting in fetal hypothyroidism**
- **Maternal Graves (blocking antibodies, MMI > PTU)**

Fetal thyroid enlargement

- **Fetal thyroid enlargement can be detected by prenatal ultrasound**
- **Goiter is non-specific for hypothyroidism or hyperthyroidism**
- **Goiter can be large enough at birth to cause airway compression**

Fetal hypothyroidism

- **Fetal brain type 2 deiodinase is preferentially increased with hypothyroidism (T4 → T3)**

- **Maternal hypothyroidism is associated with increased fetal loss**
  - **Pre-eclampsia**
  - **Placental abruption**
  - **Miscarriage**
  - **Preterm birth**

Maternal hypothyroidism and the fetus

- **Fetus does not make a significant amount of T4 until the 2nd trimester; entirely dependent on the maternal thyroid supply in the 1st trimester**
- **Some studies (controversial) have shown that offspring have lower IQ with maternal hypothyroidism**
- **#1 cause of combined maternal and fetal hypothyroidism is iodine deficiency**

Congenital hypothyroidism and iodine deficiency

- **Recognize that worldwide iodide deficiency is the most common cause of primary hypothyroidism and of preventable intellectual disability**
- **Iodine RDA: approximately 150 mcg/day (increased in pregnancy)**
- **Only 75% of the world's population uses iodinated salt (almost 2 billion are iodine deficient)**
- **Endemic goiter**

Breast feeding and anti-thyroid drugs

- **Very small amount of anti-thyroid drugs are secreted in breast milk (methimazole > PTU)**

- **Breast feeding is safe at low to moderate doses of anti-thyroid drugs**
  - **PTU: ≤ 300 mg/day (ATA says ≤ 450 mg/day)**
  - **Methimazole: ≤ 20 mg/day**
  - **Mothers should take the medication immediately following a feed and in divided doses**

- **Infants of affected mothers should be screened with thyroid function tests – reassuring data but limited number of patients**

Incidence of congenital hypothyroidism

- **Overall incidence of CH: 1 in 2000 to 1 in 4000**
- **Increased incidence in Down syndrome (28x)**

- **Dysgenesis: 1 in 3,500**
  - **75-85% of cases of CH**
- **Dyshormonogenesis: 1 in 20,000**
  - **about 15% of cases of CH**
- **Transient**
  - **10-15% of cases of CH**
- **Central**
  - **less than 5% of cases of CH**

Congenital hypothyroidism is the most common disease screened for in newborns

Effect of prematurity on thyroid function in the neonate

- **Cord T4 and free T4: lower in preterm infants; proportional to weight and gestational age**
- **Lower TSH surge (vs term infant)**
  - **Accompanied by lower T4 and T3 rise after birth**
- **Hypothyroxinemia of prematurity**
  - **Immaturity of the HPT axis**
  - **Sick euthyroid syndrome or a reflection of the stress and illness of the infant**
  - **Unclear benefit to treat with LT4**

Thyroid dysgenesis

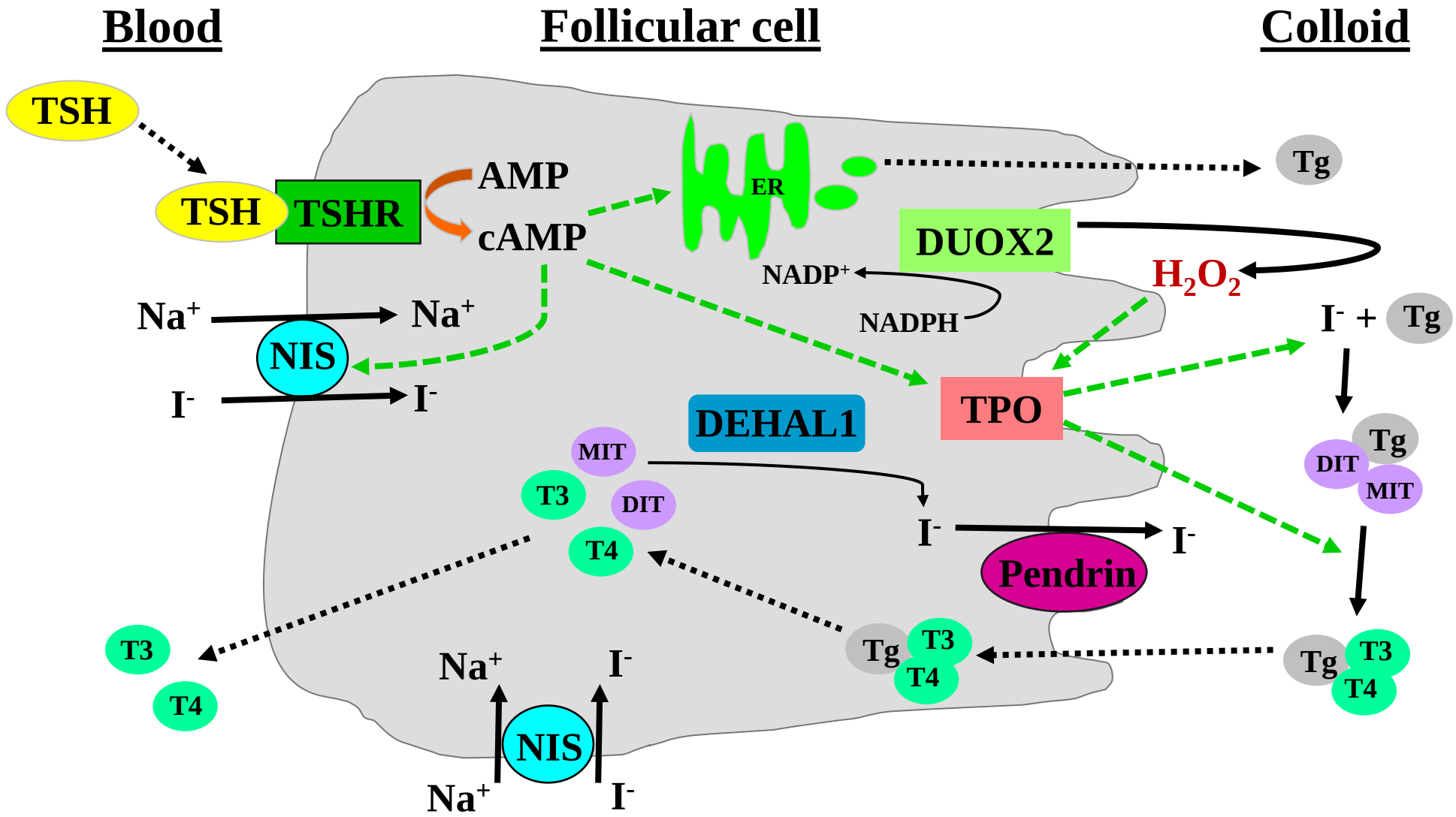
- **2% of cases are familial; 98% are sporadic**
- **Few genes have been implicated (*see slides #4 and #5*)**

- **Agenesis – failure to develop**
- **Hemiagenesis**
- **Ectopic – failure to migrate; most commonly sublingual (can also be lingual)**
- **Hypoplastic – small but in the normal location**

Thyroid dyshormonogenesis

- **Several different steps can be affected**
- **The most common cause of dyshormonogenesis is due to an organification defect**
- **Inheritance pattern: autosomal recessive**

Thyroid hormone synthesis/processing



Genetic defects in synthesis/processing

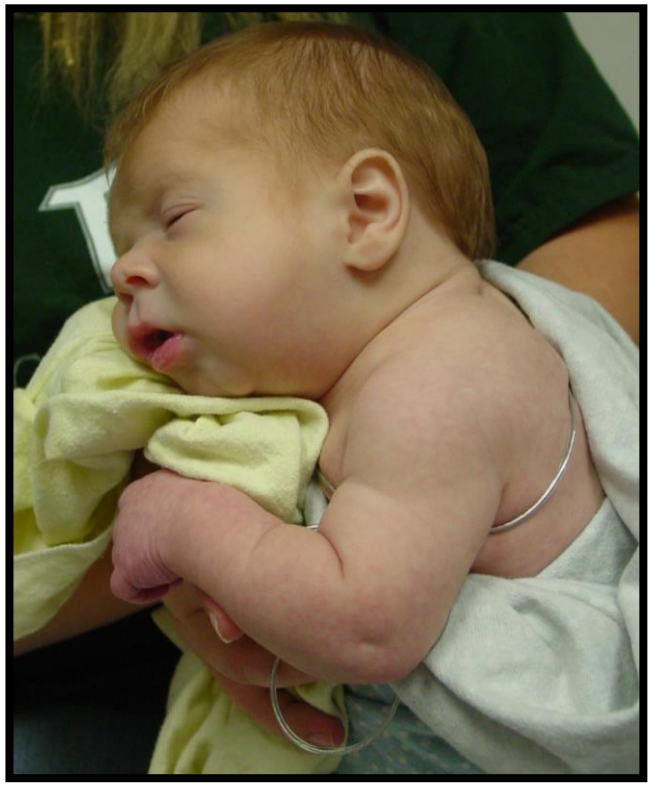
Process	Affected substance	Gene (location)	Features
Iodide trapping	Sodium iodide symporter (NIS)	SLC5A5 or NIS (19p13)	Decreased radionuclide uptake
Iodide transport into follicular lumen	Pendrin	SLC26A4 or PDS (7q31)	Sensorineural deafness (Pendrin syndrome)
Matrix for hormone synthesis	Thyroglobulin	TG (8q24)	Very low Tg levels
Iodine organification and coupling reaction	Thyroid peroxidase	TPO (2p25)	#1 cause of dyshormonogenesis
H_2O_2 generation	Thyroid oxidase (THOX)	DUOX2 (15q13.3	Transient (AD) or permanent (AR)
Intrathyroidal iodide recycling	Iodotyrosine deiodinase	IYD or DEHAL1 (6q25.1)	Newborn screen is usually normal

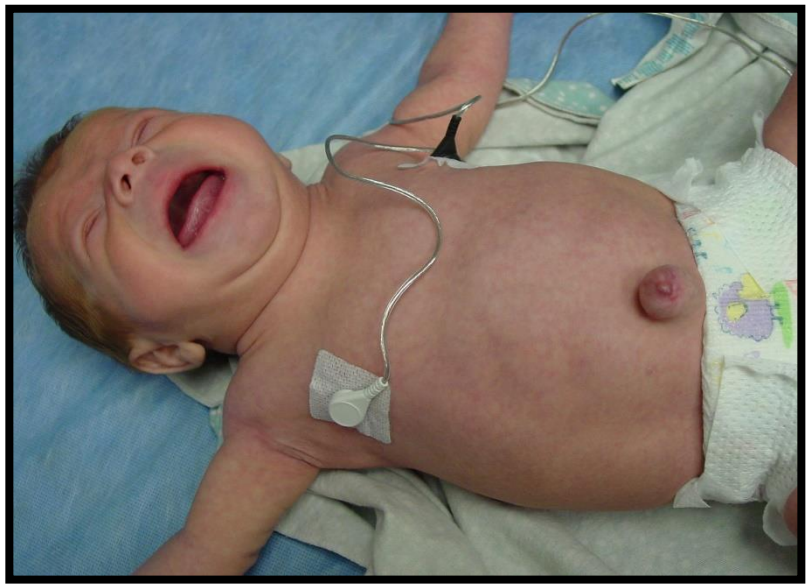
Pendred syndrome

- ***SLC26A4*** **or** ***PDS*** **gene is expressed in the thyroid and cochlea**
  - **Encodes for the protein pendrin**
- **Defect in the transport of iodine from the follicular cell to the colloid**
- **Usually presents with goiter in late childhood or adolescence – most are euthyroid**
- **Variable thyroid disease within the same family with the same mutation**
- **About 10% of cases of childhood sensorineural deafness**

Clinical findings of congenital hypothyroidism

- **Nonspecific, subtle signs and symptoms of CH are sometimes present in the newborn period**
- **Symptoms: lethargy, decreased activity, cold to touch, constipation, feeding problems**
- **Signs: mottled skin, jaundice, macroglossia, umbilical hernia, distended abdomen, hoarse cry, dry skin, large fontanelle with wide sutures, hypotonia, delayed/slow reflexes, goiter**
- **Obvious features are not noted until 3 m.o.**





3 m.o. full-term male

- “Sleeps all of the time”
- “Never smiles or looks at me”
- “Very floppy”

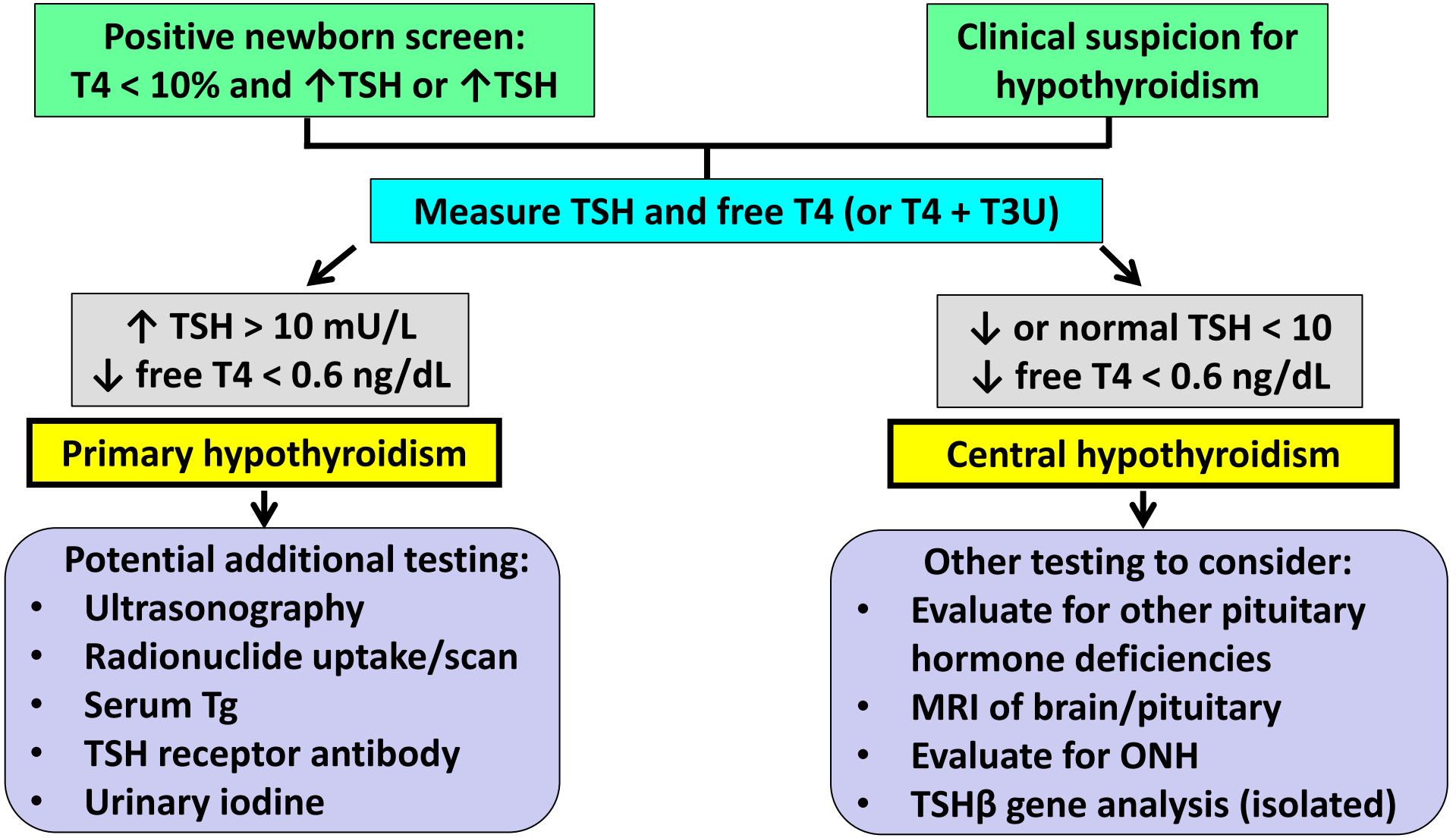
- 1 stool per week
- Hoarse cry
- Gags and chokes on feeds
- Low heart rate alarms

- Never had a newborn screen
- TSH > 400 → athyreosis

Patterns of osseous maturation in neonate

- **Commonly ossified bones at birth:**
  - **Knee – distal femoral epiphysis → ossification center appears at about 36 weeks gestation**
  - **Knee – proximal tibial epiphysis**
  - **Foot – cuboid bone**
- **Thyroid hormone deficiency delays this process**
- **Also see delayed closure of the fontanelles (especially the posterior)**

Diagnostic algorithm of congenital hypothyroidism



Advantages/disadvantages of neonatal thyroid screening systems

Thyroid disorder	Primary T4 with follow-up TSH	Primary TSH
Primary congenital hypothyroidism	Very good	Very good
Central congenital hypothyroidism	Some	Not good
Mild congenital hypothyroidism	Not good	Good
Delayed rise in TSH (e.g. preterm, acutely ill term infant)	Good (but should get a follow-up test in cases with a low T4 and normal TSH)	Good (but only if get a routine 2nd test)
MCT8 mutation	Not very good	Not good

Delineating errors in thyroid hormone synthesis

- **Genetic testing can confirm specific mutations**

- **Iodine trapping defect (NIS)**
  - **Decreased or absent I-123 uptake**
- **Oxidation/organification defect**
  - **Increased I-123 uptake**
  - **Positive perchlorate discharge (>10%) test**
- **Thyroglobulin defect**
  - **Low serum Tg levels**
- **Iodotyrosine deiodinase (DEHAL)**
  - **Low serum/urinary iodine levels**

Techniques for defining thyroid anatomy

- **Radionuclide scans (scintigraphy)**
  - **Tc99m**
  - **I-123**
- **Ultrasonography**
  - **with or without Color Doppler**
- **Serum thyroglobulin levels**
  - **Lowest in agenesis**
  - **Intermediate in ectopic**
  - **Highest in infants with normally positioned glands**

Thyroid scintigraphy

Tc99m

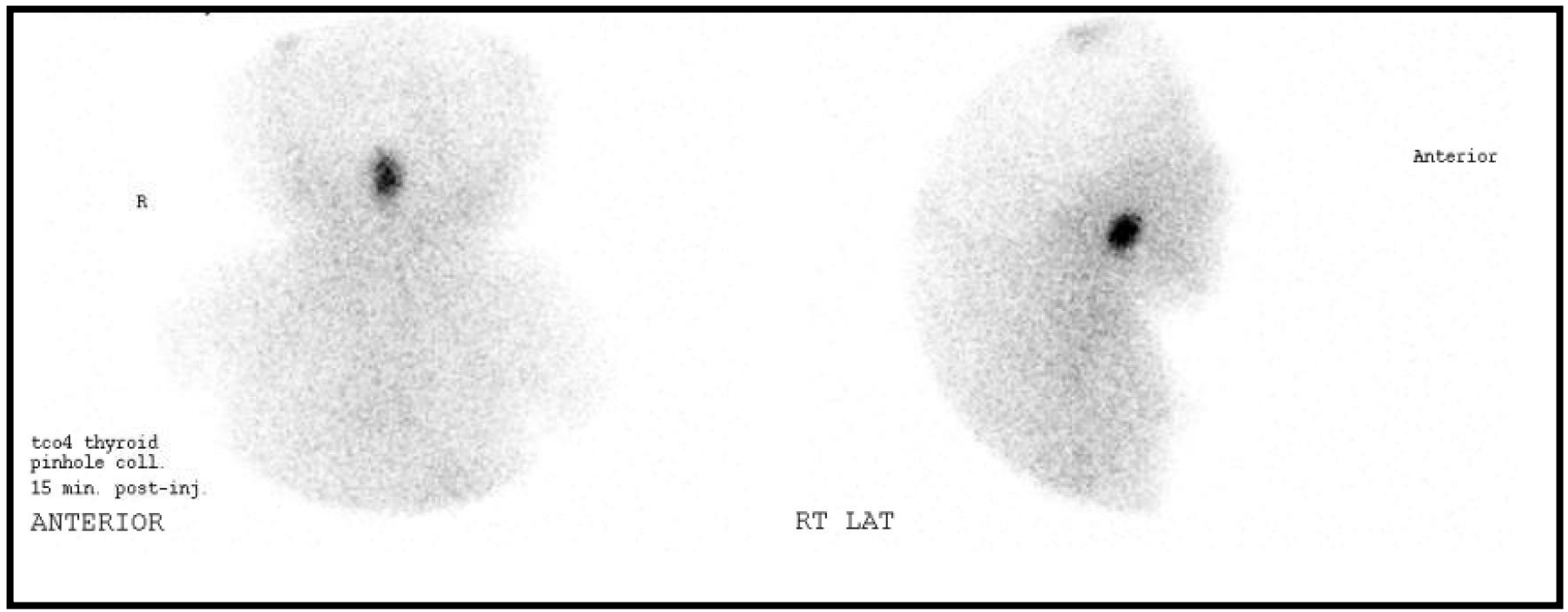
- Less expensive
- IV administration
- ½ life = 6 hours
- Only reflects thyroid trapping ability – enters the cell via NIS but cannot be organified
- Detects dysgenesis

I-123

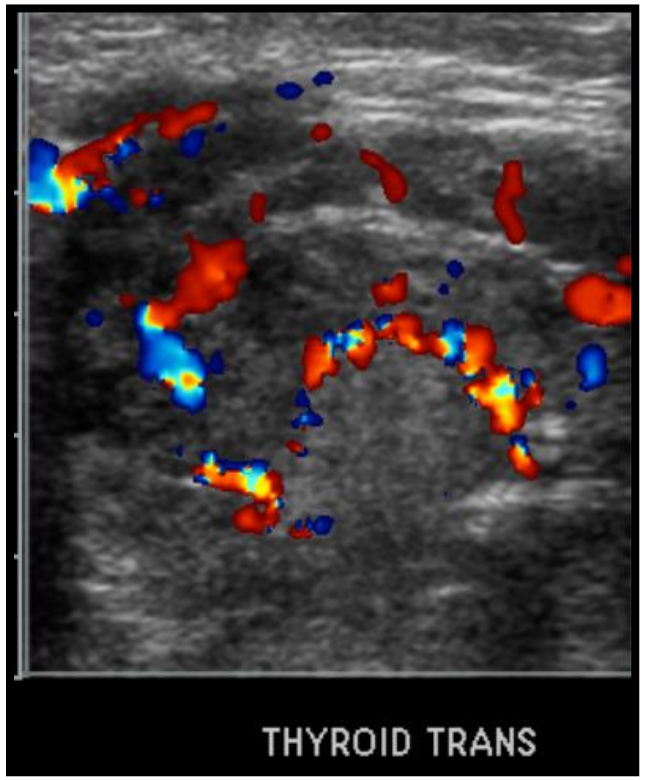
- More expensive
- Oral administration
- ½ life = 13 hours
- Also enters via NIS but then is organified
- Detects dysgenesis and also organification defects

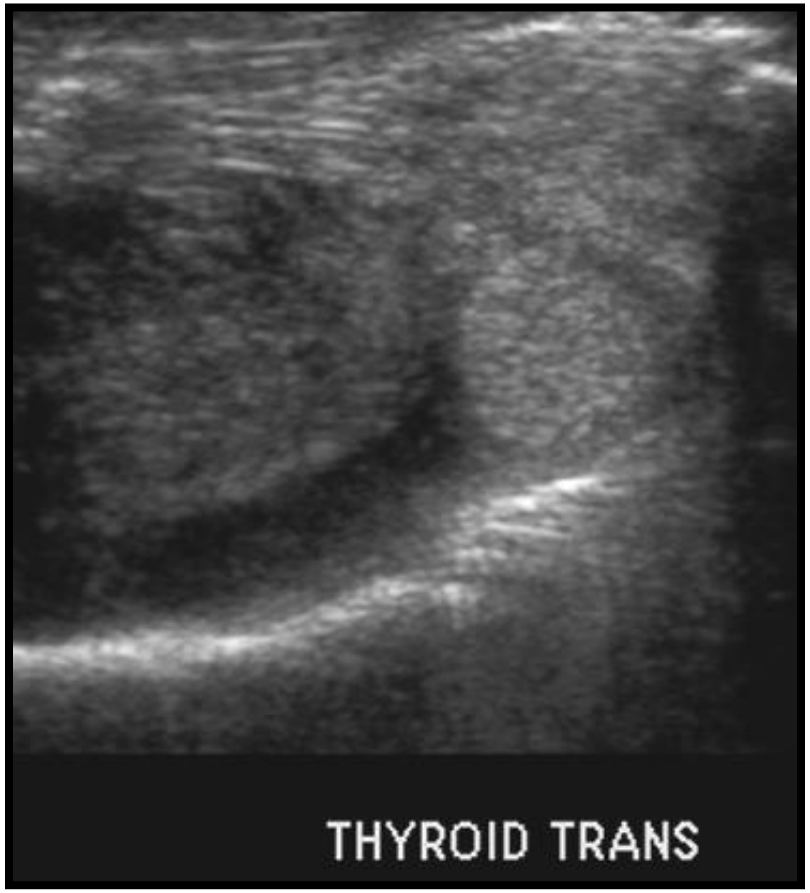
Absent radionuclide uptake may occur in conditions with a normally positioned thyroid gland, such as TSHβ gene mutations, TSH receptor inactivating mutations, iodine trapping defects (e.g. NIS), and TSH receptor blocking antibodies.

Sublingual thyroid gland

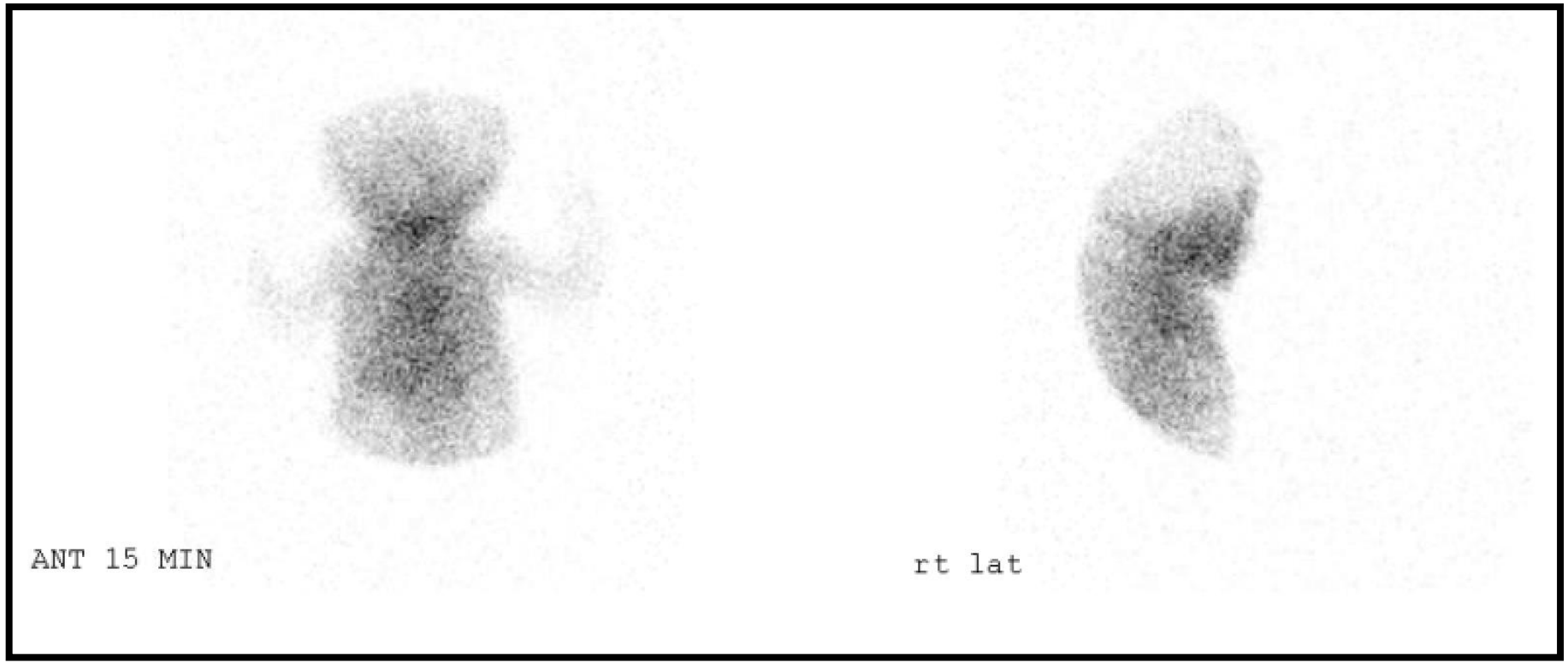


Sublingual thyroid gland





Absent thyroid gland



Maternal TSH receptor antibody (TRAb)

- **TRAb (a.k.a. TBII)**
  - **Graves disease – both blocking and stimulating**
  - **Hashimoto – blocking antibodies in about 10% of women**

- **IgG antibody that readily crosses the placenta**
  - **Transient hypothyroidism**
  - **Incidence: 1 in 180,000**
  - **Half-life: 3 to 4 weeks**
  - **Usually disappear from infant by 3 to 6 months but dependent on the antibody amount and potency**
    - **Trial off when TRAb is negative but safest to treat until 2-3 y.o.**

Maternal TSH receptor antibody (TRAb)

- **Maternal TRAb can inhibit TSH-induced iodine uptake and result in apparent absence of the thyroid gland (on Tc99m and I-123 scans)**
- **Similar findings are seen in cases of permanent CH such as agenesis, iodine trapping defects (i.e. NIS), TSH β gene mutations, and inactivating mutations of the TSH receptor**
- **Thyroid ultrasound will reveal a normal thyroid gland in the normal location**

Congenital central hypothyroidism

- **Often associated with other pituitary hormone deficiencies**
  - **GH deficiency: hypoglycemia in newborn period**
  - **ACTH deficiency: hypoglycemia**
  - **LH/FSH deficiency: micropenis and cryptorchidism in males**
  - **ADH deficiency: least common**
- **Rare to have isolated TSH deficiency**
  - **TSH β subunit gene mutation**
  - **TRH gene mutation/deficiency**
  - **TRH receptor inactivating mutation**

Congenital central hypothyroidism

- **Be aware of intracranial anatomical defects which may accompany TRH or TSH deficiencies**
- **Midline brain abnormalities**
  - **Absent septum pellucidum**
  - **Absent corpus callosum**
  - **Holoprosencephaly and hydranencephaly**
  - **Septo-optic dysplasia**
- **Cleft lip/palate**
- **Single central maxillary incisor → hypopituitarism (and GHD)**

Treatment of congenital hypothyroidism

- **Initial dosage of LT4 is 10-15 mcg/kg/day**
- **Goal is normalize the T4 level within 2 weeks and TSH within a month (i.e. < 10)**
- **Serum T4 or free T4 should ideally be in the upper half of the reference range during the first 3 years of treatment**
  - **TSH may inappropriately be elevated because of relative pituitary resistance→ need to use T4 or free T4 levels to titrate dose in this situation**

Treatment of congenital hypothyroidism

- **Infants with low serum T4 (< 10 mcg/dL) and a TSH > 15 mU/L during the first year of life have lower IQ values than patients with T4 concentrations that are held constant at higher concentrations**

- **Avoid concomitant administration of LT4 with**
  - **Soy**
  - **Fiber**
  - **Iron**
  - **Calcium carbonate**
  - **Simethicone**

Treatment of congenital hypothyroidism

- **Know the potential side effects and consequences of overtreatment with LT4**
  - **Premature suture closure; craniosynostosis**
  - **Advanced bone age**
  - **Lower cognitive outcome**

Mild congenital hypothyroidism frequently normalizes and treatment may not be necessary

- **More commonly seen in screening programs with lower TSH cutoffs**
- **Clues to suggest that it may resolve:**
  - **TSH trending toward normal (screen → serum)**
  - **Free T4 is normal to upper part of normal range**
- **Reasonable to follow trend of TFTs at weekly intervals – need to start LT4 at 4 weeks of life if TSH > 10**

ABP outline – handout

- **Additional ABP specifications and information are contained in the handout**

Thyroid Disease

PES Board Review Course in Pediatric Endocrinology – 2025

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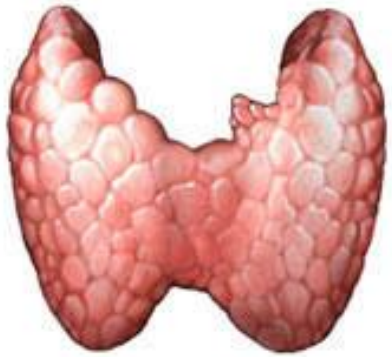
Topics to be covered from ABP outline

- **Diffuse thyroid enlargement**
- **Thyroiditis**
- **Acquired hypothyroidism**
- **Thyroid hormone resistance**
- **Thyroid hormone excess**
- **Thyroxine-binding globulin (TBG) deficiency and excess**

Diffuse thyroid enlargement (goiter)



Normal thyroid growth

- **Thyroid gland increased by about 1 gram per year until the age of about 15 y.o.**
- **Adult thyroid gland is approximately 15 to 20 grams**
- **Rapid increase in thyroid volume occurs normally during puberty with maximum growth rate at 12.5 y.o.**

Diffuse thyroid enlargement

- Chronic lymphocytic thyroiditis (Hashimoto)
- Colloid goiter
- Thyroid hormone resistance
- Subacute or acute thyroiditis
- Graves disease
- Congenital hypothyroidism (dyshormonogenesis)
- Iodine deficiency (endemic goiter)
- Excessive iodine ingestion (Wolff-Chaikoff effect)
- Infiltrative disorders
  - Histiocytosis
  - Cystinosis
  - Neoplasms: lymphoma or teratoma
  - Adults: sarcoidosis and amyloidosis (rare in children)

Evaluation of diffuse thyroid enlargement

- **Lab tests: TSH (a.k.a thyrotropin), T4, thyroid antibodies**
- **Imaging**
  - **Ultrasound**
  - **Thyroid scintigraphy/uptake**
- **Concerning signs/symptoms would lead to additional imaging and evaluation**
  - **Tracheal compression: dyspnea, stridor, cough, choking sensation**
  - **Vocal cord paralysis: dyspnea, hoarseness**

Treatment of euthyroid diffuse thyroid enlargement

- **Conservative management – observation**
- **Surgery**
  - **Pros: rapid resolution, able to examine pathology**
  - **Cons: hypothyroid, hypoparathyroidism, scar, nerve/blood vessel injury (and it's surgery!)**
- **Radioactive iodine**
  - **Pros: decrease in size, no scar**
  - **Cons: not a rapid decrease, radiation-induced dysfunction**
- **Levothyroxine**
  - **Best result if TSH is elevated and positive antibodies, but usually only a small (and often variable) reduction in size**
  - **Controversial: long-term efficacy unknown, cardiac/bone risk**

Thyroiditis

Thyroiditis (= inflammation)

- **Acute suppurative – very, very, very rare**
- **Subacute (de Quervain) – very, very rare**
- **Subacute (lymphocytic) – relatively uncommon**
  - **a.k.a. silent or sporadic**
  - **??? Hashitoxicosis**
- **Chronic – common**
  - **a.k.a. Hashimoto thyroiditis**

Acute (suppurative) thyroiditis

- **Infectious: bacterial (68%) or fungal (15%) etiology (not viral)**
- **Most common route of infection is from a left pyriform sinus fistula**

- **Signs/symptoms: pain (radiating to ear), tenderness, warmth, fever, dysphagia, and dysphonia; antecedent URI; ↑ CRP and ESR; ↑↑ WBC**

- **2/3 with normal TSH – can also see ↑ TSH and ↓ TSH**
- **Ultrasound → abscess, swelling**
- **Treatment: antibiotics and possible surgery (I&D)**

Subacute (de Quervain) thyroiditis

- Viral (e.g. mumps, adeno, EBV, coxsackie, influenza)
- Most common cause of a painful thyroid gland
- Signs/symptoms: viral prodrome (fever, malaise, myalgia), constant tenderness over entire thyroid; ↑ CRP and ESR; normal to mild ↑ WBC
- Biochemical hyperthyroidism (↓ TSH) in about 50%
- Spontaneous and variable remitting inflammation that lasts for weeks to months → hyperthyroid → euthyroid → hypothyroid → euthyroid or hypothyroid (5-30%)
- Treatment: NSAIDs or glucocorticoids

Subacute (lympocytic) thyroiditis

- **Also known as “silent” or “sporadic” thyroiditis in the adult literature and textbooks**
- **Hashitoxicosis???**

- **Transient hyperthyroidism due to lymphocytic invasion and destruction of thyroid tissue**
- **Variable symptoms but generally mild and intermittent**
- **50-60% will have some thyroid enlargement**
- **Hyperthyroidism → euthyroid and/or hypothyroidism**
- **Propensity for transient thyroid abnormalities to recur in affected individuals**

Chronic thyroiditis

- **Chronic lymphocytic thyroiditis = Hashimoto thyroiditis**
- **The most common cause of diffuse thyroid gland enlargement outside of the newborn period**
- **Variable clinical course**
- **Postpartum thyroiditis**
  - **Destructive thyrotoxicosis (presents by 14 weeks postpartum)**
  - **Usually a transient hypothyroidism → development of persistent hypothyroidism in up to 30% of cases**

Acquired hypothyroidism

Etiologies of hypothyroidism

Primary

- Hashimoto
- Iodine deficiency/excess
- Neck irradiation
  - e.g. Wilms, craniospinal
- Drugs
- Syndromes
- Infiltrative processes
- Cystinosis
- Congenital

Secondary (central)

- Hypopituitarism
- Cranial radiation
- CNS process
  - Tumor, infection, injury
- Isolated TSH β gene mutation

Other

- Hepatic hemangioma
  - ↑ type 3 deiodinase

Agents and drugs that may interfere with thyroid function

- **Increased clearance:**
  - Phenobarbital
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Rifampin
- **Impaired or disrupted peripheral metabolism:**
  - Glucocorticoids
  - Amiodarone
  - PTU
  - Propranolol
- **Effects on thyroid hormone production and secretion:**
  - Iodine-containing products (anti-septics, betadine, IV contrast, etc)
  - Lithium
  - Amiodarone

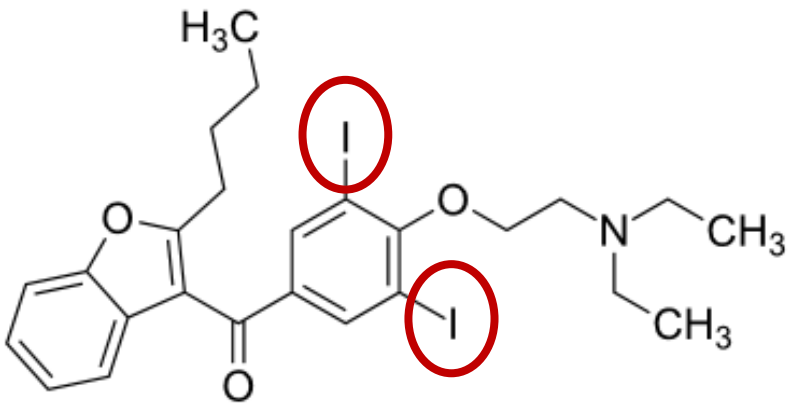
Agents and drugs that may interfere with thyroid function

- **Effects on the hypothalamic-pituitary-thyroid (HPT) axis:**
  - **Decrease TSH**
    - **Dopamine**
    - **Dopamine agonists (bromocriptine, cabergoline)**
    - **Glucocorticoids**
    - **Opiates**
    - **Octreotide**
  - **Increase TSH**
    - **Hypocortisolism (Addison)**
    - **Dopamine receptor blockers (metoclopramide)**

Iodine effects on thyroid function

- **Iodine is the rate-limiting step in thyroid hormone synthesis**
- **#1 cause of hypothyroidism in the world is due to iodine deficiency**
  - **Salt has been iodized in the USA since 1924**
- **Wolff-Chaikoff effect**
  - **Protective mechanism when the body is exposed to excess amounts of iodine**
  - **Inhibits organification of iodine: ↓ T4 and T3 synthesis**
  - **Dose dependent effect that may last weeks or longer → escape**

Amiodarone



- Incidence of thyroid dysfunction: up to 24%
- <u>Hypothyroidism</u>
  - Inhibits the conversion of T4 to T3
  - Inhibits thyroid hormone synthesis and secretion (Wolff-Chaikoff effect)
- Occurs most often during the first year of treatment
- Lipophilic → long half-life (about 100 days)
  - Total body iodine stores do not return to normal for 6 to 9 months after stopping the medication

Amiodarone

- **Hyperthyroidism can also occur but it is less common than hypothyroidism**
- **Occurs on average after about 3 years of treatment**

- **Type 1**
  - **↑ iodine leads to ↑ T4 production**
  - **Underlying autoimmune thyroid disease (+Abs); enlarged nodular thyroid**

- **Type 2**
  - **Inflammatory process causing thyroid damage (↑ IL-6)**
  - **Normal thyroid size; normal ultrasound**

Lithium

- **Hypothyroidism and goiter are the most common thyroid problems in individuals treated with lithium**
  - **Inhibits thyroid hormone synthesis and secretion**
  - **Increased autoimmune thyroid disease**

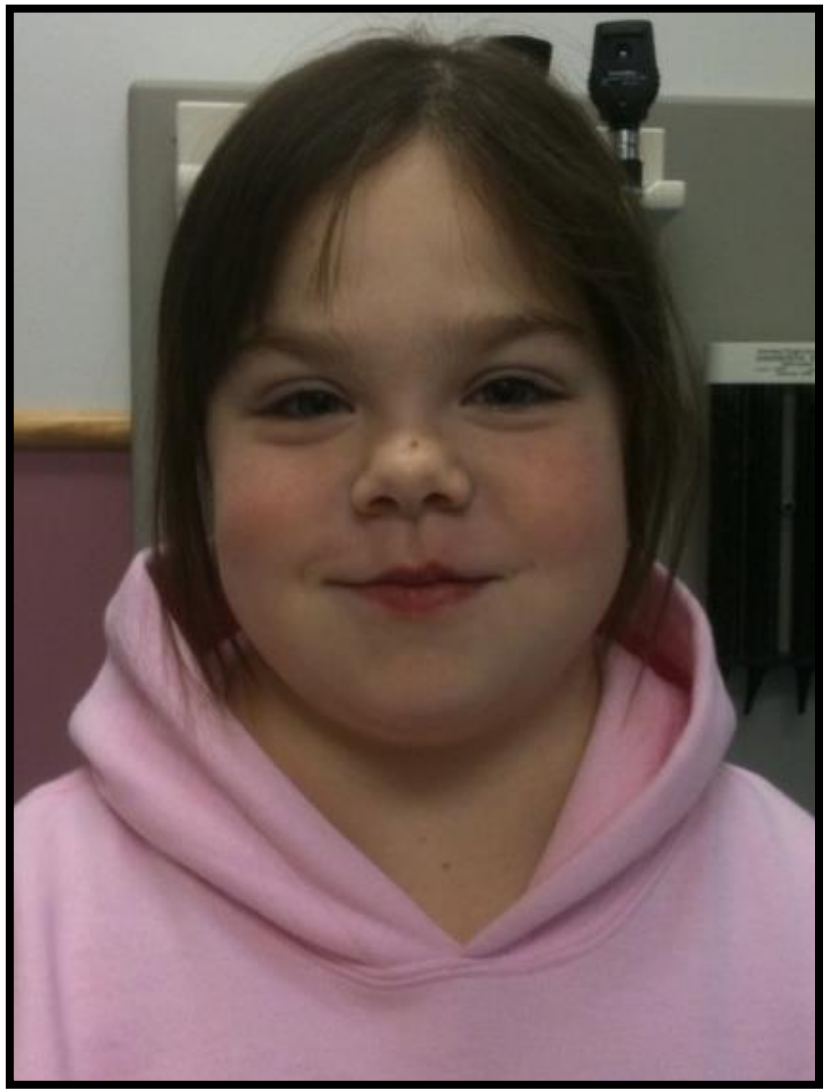
- **Very infrequent occurrence of hyperthyroidism**
  - **Most commonly a transient and painless thyroiditis**
  - **Also reports of induced thyroid autoimmunity**

Cystinosis

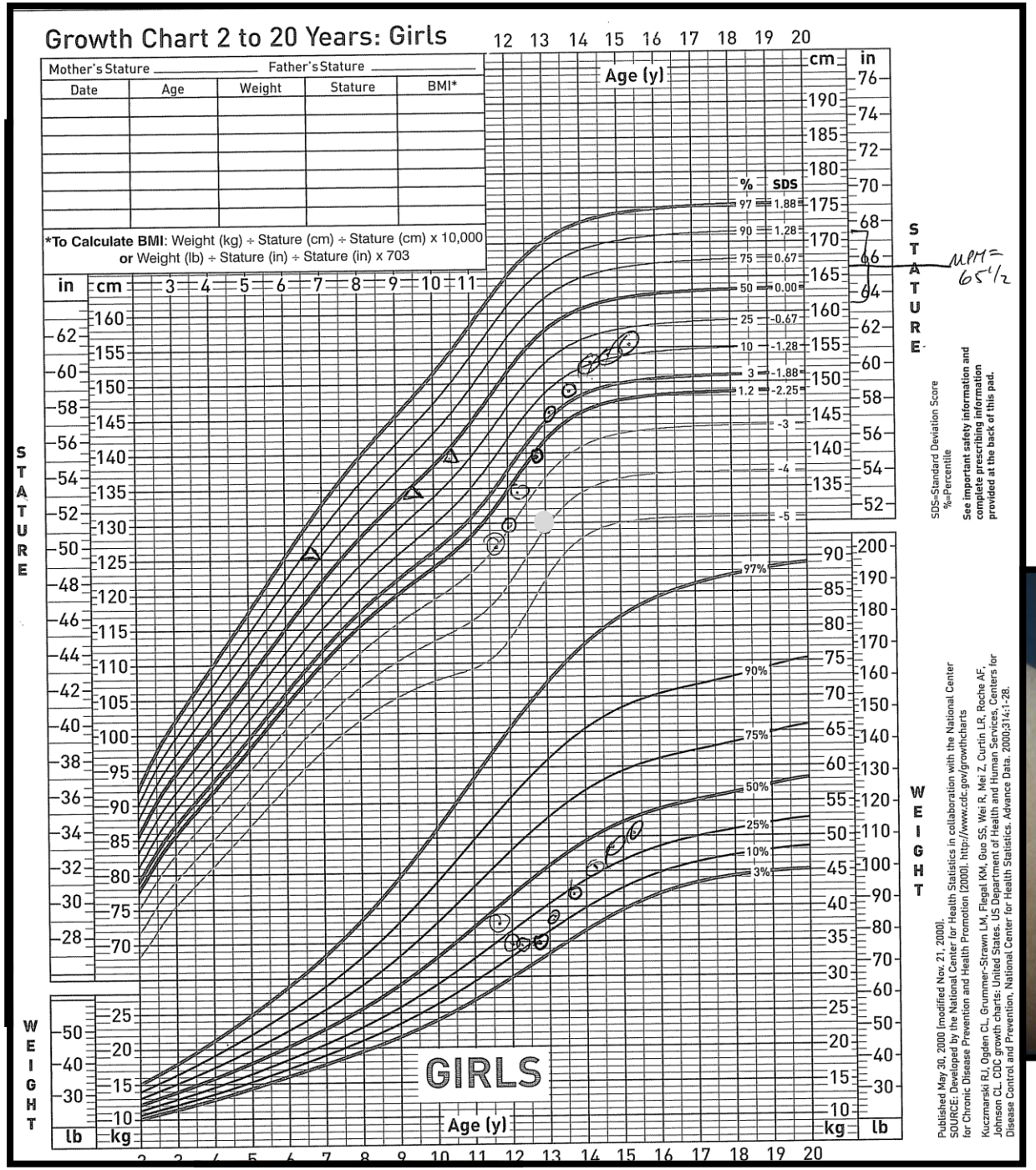
- **Rare autosomal recessive lysosomal storage disease**
- **Most common hereditary cause of renal Fanconi syndrome in children**

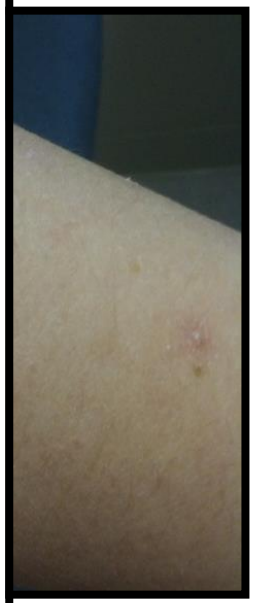
- **Cystine and crystal formation builds up in various tissues**
  - **Thyroid follicular cells → fibrosis and atrophy**

- **Common to see subclinical hypothyroidism in children**
- **Hypothyroidism occurs in >50% of patients by the 2nd decade of life**



11-year-old girl





Clinical and lab findings in acquired hypothyroidism*

- Reduced heart rate and decreased cardiac contractility
- Delayed relaxation phase of DTRs
- Dry skin (↓ sweat and sebaceous gland activity)
- Periorbital puffiness, non-pitting edema (hyaluronic acid)
- Hypercholesterolemia (↑ LDL)
- Hyponatremia (increased total body water)
- Anemia (↓ erythropoietin, ↓ oxygen requirement)
- Elevated creatinine kinase and LDH (from skeletal muscle)
- Reduced GFR
- Elevated liver transaminases

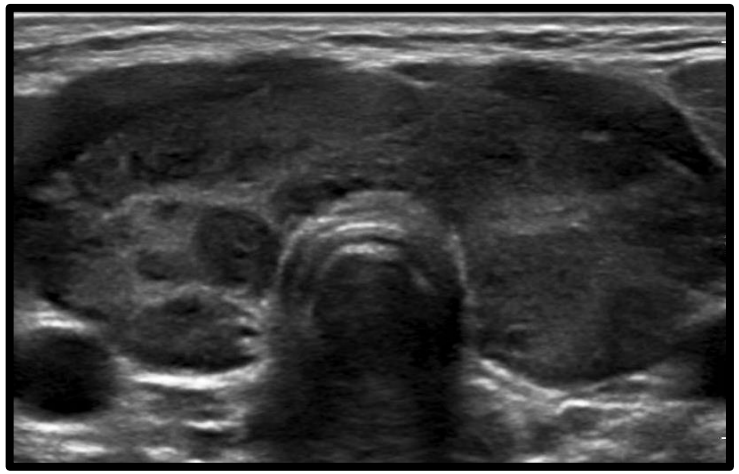
* Clinical features of central hypothyroidism are milder than primary hypothyroidism

Endocrine abnormalities in acquired primary hypothyroidism

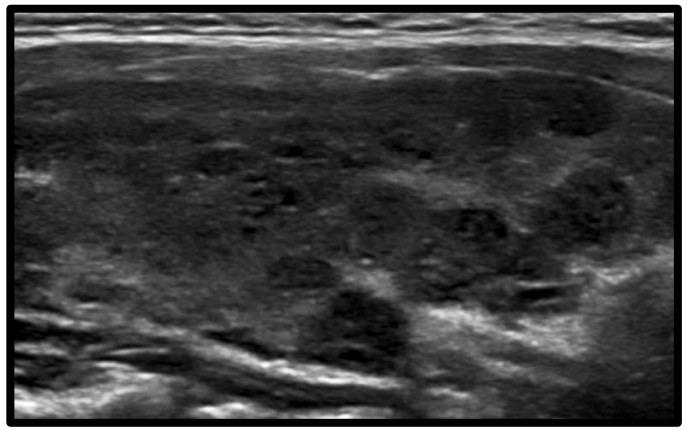
- **Elevated prolactin**
  - **Due to TRH stimulation from the hypothalamus**
- **Delayed puberty / irregular periods**
  - **Altered and blunted LH pulsatility**
  - **Elevated prolactin**
- **Pseudoprecocious puberty (van Wyk-Grumbach syndrome)**
- **Decreased and impaired spontaneous GH secretion**

Exam and imaging in Hashimoto thyroiditis

- **Physical exam**
  - Diffuse enlargement
  - Irregular cobblestone texture
  - Asymmetry (may mimic a nodule)



- **Imaging characteristics**
  - Ultrasound:
    - Diffusely enlarged with heterogeneous echotexture
    - Hypoechoic micronodules (1-6 mm)
  - Nuclear imaging:
    - Early disease can have increased uptake
    - Most common to see decreased, patchy uptake



Patient populations at increased risk for autoimmune thyroid disease

- **Down syndrome (about 40% with + antibodies)**
  - **Prevalence of antibodies increase with age, especially after 6 y.o.**
- **Turner syndrome (about 30% with + antibodies)**
- **Type 1 diabetes mellitus (about 25% with + antibodies)**

Association of Hashimoto with other autoimmune diseases

- **Autoimmune polyglandular (polyendocrine) syndrome, type 1 – *AIRE***
  - **Mucocutaneous candidiasis (1st sign – typically before 5 y.o.; >80%)**
  - **Hypoparathyroidism (usually before puberty or by 10 y.o.; 75-85%)**
  - **Addison disease (usually in adolescence or by 15 y.o.; 60-70%)**
  - **Other features: oophoritis, alopecia, vitiligo, hepatitis, thyroiditis, keratitis**
- **Autoimmune polyglandular (polyendocrine) syndrome, type 2 – polygenic**
  - **Addison disease**
  - **Autoimmune thyroid disease**
  - **Type 1 diabetes**
- **Other: type 1 diabetes, celiac disease, IPEX**

Diagnosis of primary hypothyroidism

- ↑ TSH – treatment indicated when TSH > 10
- Positive antibodies in Hashimoto thyroiditis
  - Thyroid peroxidase (TPO)
  - Anti-thyroglobulin
  - TPO (90%) is more commonly positive than anti-thyroglobulin antibody (50%)
  - About 5-10% may have negative thyroid antibodies
  - Antibodies are not functional – just a marker of inflammation
- Ultrasound
  - Not routinely done in the United States unless there is a palpable nodule, asymmetry, or other clinical concerns

Frequency of positive thyroid antibodies

- **Incidence of thyroid antibodies in the pediatric population is not well characterized**
- **10-12% of the adult population (and >30% of elderly adults) have positive thyroid antibodies**
- **If TSH, T4, and thyroid exam are normal, levothyroxine treatment is not indicated for antibody titer alone**
- **Waxing and waning course**
- **About 25% of those children with a positive thyroid antibody will develop hypothyroidism (TSH > 10) requiring levothyroxine**

Dosage in primary hypothyroidism

- **Levothyroxine (LT4) tablet monotherapy**
  - **Evidence does not support using T3 alone or combination therapy with T4 and T3**
- **Neonates: 10-15 mcg/kg/day**
- **3-6 m.o.: 8-10 mcg/kg/day**
- **6-12 m.o.: 6-8 mcg/kg/day**
- **1-3 y.o.: 4-6 mcg/kg/day**
- **3-10 y.o.: 3-4 mcg/kg/day**
- **10-15 y.o.: 2-4 mcg/kg/day**
- **> 15 y.o.: 2-3 mcg/kg/day**

Evidence to support the above statements is lacking – the more important aspect is consistency and regularity in taking the LT4

Levothyroxine treatment

- **Half-life of LT4 is about 7 days**
- **Wait at least 4 to 6 weeks after a dose adjustment to get to a steady state before rechecking TSH**

- **Goal in primary hypothyroidism is to get the TSH into the normal reference range**
- **Goal in central hypothyroidism is to get the free T4 into the upper half of the reference range (about 1.6 mcg/kg/day)**

- **Absorption can be affected by: soy, fiber, iron, and calcium**

Levothyroxine treatment – prognosis

- **Be aware of ultimate outcome of acquired hypothyroidism, including impact of the disorder on the patient's growth and mental development**

- **Recognize the occurrence of pseudotumor cerebri in some hypothyroid children treated with thyroxine**
- **Be aware that delay in the treatment of acquired hypothyroidism and overzealous replacement therapy may have an adverse effect on ultimate height**
  - **Low dose LT4 and slow normalization of TFTs**
  - **Other interventions have had variable and mixed results**

Thyroid hormone deficiency may develop during treatment of GHD

- **TSH deficiency (central hypothyroidism) may occur after initiation of GH therapy**
- **More likely to occur if brain MRI is abnormal and/or baseline T4 or free T4 are on the lower side**
- **Thought to be due to increased somatostatin secretion in response to pulsed doses of GH**
- **Check TFTs within 3-4 months after starting GH injections and then annually, or sooner if poor growth velocity and patient is compliant with the GH injections**

Thyroid hormone resistance

Thyroid hormone resistance (a.k.a. RTH)

- **Mutations in the thyroid hormone receptor β gene**

- **Precise incidence is unknown**
- **Estimated prevalence of 1 in 40,000**

- **Autosomal dominant inheritance**
- **Rare report of an autosomal recessive inheritance**
- **De novo mutation occurs about 22% of the time**
- **15% of individuals with RTH do not have a detectable mutation in the TRβ gene**

Thyroid hormone resistance (a.k.a. RTH)

- TRα1 – CNS, heart, skeletal muscle
- TRα2 – widely distributed in tissues
- TRβ1 – liver, kidney
- TRβ2 – pituitary, hypothalamus

- Pituitary resistance to thyroid hormone (PRTH) vs. Generalized resistance to thyroid hormone (GRTH)
- Old terms – same condition with same mutations
  - Due to the subjective nature of thyroid symptoms and the poor specificity of thyroid signs
  - Hyperthyroidism and hypothyroidism can coexist depending on tissue TR

Clinical findings – RTH

- **Goiter (66-95%)**
- **Tachycardia (33-75%)**
- **ADHD (40-60%)**
- **Hyperkinetic behavior (33-68%)**
- **Emotional disturbances (60%)**
- **Less common: learning disability, developmental delay, short stature, low BMI**
- **Positive family history**
- **Labs: ↑ free T4, ↑ T3, and non-suppressed TSH**

Diagnostic approach – RTH

- **Confirm elevated free T4 by equilibrium dialysis with a non-suppressed TSH**
  - **Eliminate lab assay interference: heterophile antibodies, protein binding abnormality**
- **Check TFTs in first-degree family members**
- **Sequence TRβ gene**
- **If negative gene testing and normal TFTs in first-degree family members, then**
  - **Check pituitary glycoprotein α-subunit (r/o TSH adenoma)**
  - **T3 suppression 3-day test → blunted and incomplete TSH suppression with supraphysiologic doses of T3 with negative genetic testing points to nonTR-RTH**

Treatment – RTH

- Compensated “euthyroid” state – may not need any treatment
- Recognize the correct diagnosis and avoid unnecessary treatment (e.g. anti-thyroid drugs)
- Atenolol (not propranolol) – for tachycardia, palpitations
- Single large dose of T3 every other day – may be used to reduce thyroid size (surgery is not effective)
- LT4 treatment of infants is controversial and done when
  - Marked elevation of TSH
  - History of adverse events in other affected family members
  - Failure to thrive and/or growth retardation
  - Developmental delays

Thyroid hormone excess

TSH receptor antibodies

- **2 types of antibodies:**
  1) **Stimulating → bind to TSH receptor on thyroid follicular cells and lead to autonomous thyroid hormone production**
  2) **Inhibitory → bind to TSH receptor and block intracellular signaling**
- **Radioreceptor assays**
  - **TSH receptor antibody (TRAb) or TSH-binding inhibitory immunoglobulin (TBII)**
  - **Measures both stimulating and blocking antibodies**
- **Bioassays**
  - **Stimulation of adenyl cyclase in a cell line transfected with the TSH receptor → thyroid stimulating immunoglobulin (TSI)**
  - **Measures only stimulating antibodies**

Neonatal Graves disease

- **Prevalence of neonatal hyperthyroidism in infants of mothers with Graves disease occurs between 1.5-2.5% (one study reported up to 20%)**

- **TRAb are IgG antibodies that readily cross the placenta**
- **The higher the maternal TRAb, the more likely neonatal Graves disease will occur**
  - **Greater than 3.3x the upper limit: 100% sensitive, 43% specific**

- **TRAb should be checked between 20-24 weeks gestation to determine if the fetus is at risk**

Neonatal Graves disease – fetus

- **Fetal hyperthyroidism is most commonly detected in the 3rd trimester but can be apparent at the 20 week ultrasound:**
  - **Goiter (could be from hypothyroidism or hyperthyroidism)**
  - **Increase thyroid vascularity**
  - **Tachycardia**
  - **Heart failure with non-immune hydrops**
  - **Preterm birth**
  - **Advanced skeletal maturation**
  - **Craniosynostosis**

Neonatal Graves disease – presentation

- Goiter +/- tracheal compression
- Low birth weight / IUGR, poor weight gain, feeding difficulties, diarrhea
- Stare, periorbital edema, small fontanelle
- Hyperthermia, warm/moist skin, irritability
- Tachycardia, heart failure, hypertension, tachypnea
- Hepatomegaly, splenomegaly, cholestasis
- Thrombocytopenia, hyperviscosity

  → can be confused with sepsis or congenital viral infection
- Mortality rate: up to 20%

Neonatal Graves disease – screening and course

- **Overt hyperthyroidism may be present at birth**
- **Delayed presentation occurs due to TSH-receptor blocking antibodies or maternal anti-thyroid drugs**
- **>95% of affected infants present between 1 and 29 days of life, and most present within the first 2 weeks**

- **Check TFTs at 3 to 5 days of life or sooner if clinical concerns**
- **If normal, repeat TFTs at 10 to 14 days of life**
- **Clinical assessment at 1 month, 2 months, and 3 months to identify the small population of delayed presentation**

Neonatal Graves disease – treatment

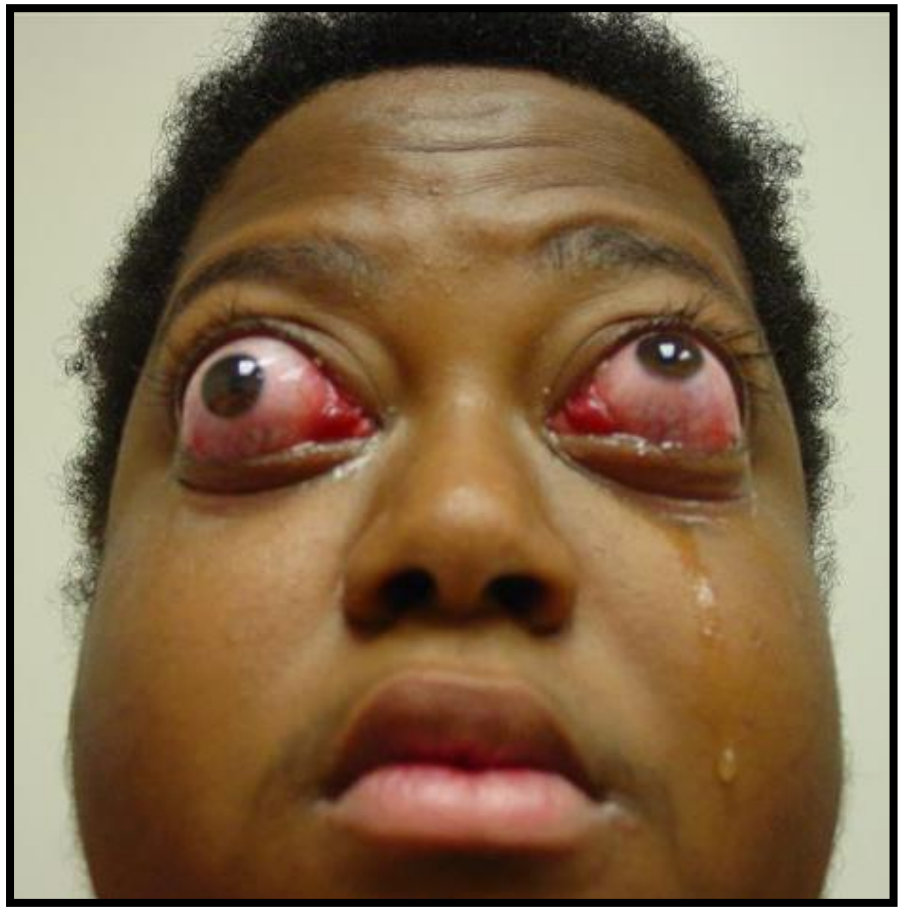
- Treatment of asymptomatic neonates is controversial
- Options for treatment if symptomatic are
  - Methimazole
  - Propranolol
  - Potassium iodide oral solution
  - Prednisolone
- Check labs weekly until stable then every 2 weeks
- Wean methimazole dose when free T4 is in normal range
- Treatment duration is typically 1 to 2 months (but may last longer depending on TRAb level)

Signs/symptoms of Graves disease in children

- **Goiter (>95%)**
- **Increased linear growth**
- **Weight loss, hyperphagia, loose stools**
- **Tachycardia, palpitations, hypertension, wide pulse pressure**
- **Diaphoresis**
- **Tremors, tongue fasciculations, milk maid's grip**
- **Jittery, anxious, "ants in their pants"**
- **Fatigue, exercise intolerance**
- **Irregular menses**

Signs/symptoms of Graves disease in children

- **Eye disease is less common in children and adolescents compared to adults**
  - **Lid lag**
  - **Corneal dryness**
  - **Erythema**
  - **Tearing**
  - **Strabismus**
  - **Vision loss**



Initial treatment

- β blockers are used to treat the hyperthyroid symptoms

- Propranolol
  - Blocks T4 → T3 conversion
  - Non-selective – blocks β1 and β2
- Atenolol
  - Once-a-day
  - Cardio-selective (β1)
- Metoprolol XR
  - CNS penetration – useful if having psychosis, anxiety
  - Cardio-selective (β1)

Medical treatment

- PTU is contraindicated due to hepatotoxicity
- Methimazole (MMI)
  - Dose is 0.1-1.0 mg/kg/day (typical dose: 0.2-0.5 mg/kg/day)
  - Rash is most common adverse event (20%)
  - Bone marrow suppression and liver toxicity are most severe adverse events (<1%)
  - Check CBC and LFTs before starting treatment
- After MMI for 12-24 months, remission rate is 20-30%
- Low chance of remission if large thyroid, young age, more severe presentation (high free T4 and TRAb)

Definitive treatment

- **Indicated if adverse effects from methimazole, unable to achieve remission, or patient preference**
- **Goal is to achieve permanent hypothyroidism**
- **Options:**
  - **Radioactive iodine (I-131)**
  - **Surgery**

Radioactive iodine (I-131) ablation

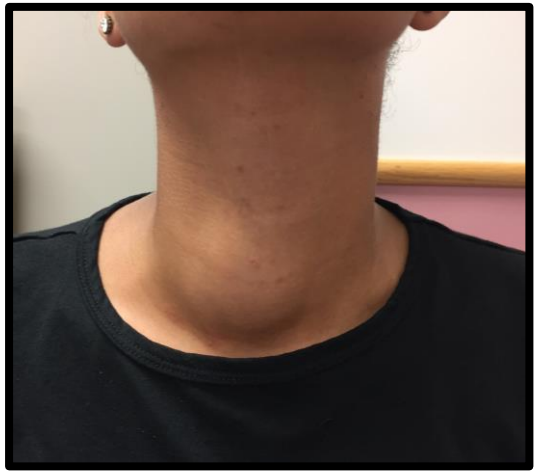
- **Not recommended in children < 5 y.o.**
- **Considered safe in children 5-10 y.o. if dose is < 10 mCi of I-131**
- **Safe in children > 10 y.o.: >150 µCi of I-131 per gram of thyroid tissue for ablation**
- **Theoretical risks of cancer; long-term data appears reassuring if complete ablation occurs**
- **Reasons to do RAI: family choice (no scar), minimal to no eye disease, no thyroid nodule, goiter < 80 grams**
- **Important to remember that TRAb can persist for years in a subset of women → risk of neonatal Graves**

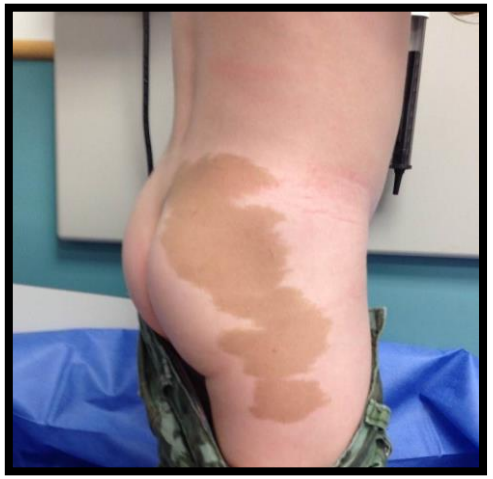
Surgery – thyroidectomy

- Important to achieve a euthyroid state before surgery
  - MMI given for 1-2 months before operation
- Potassium iodide (KI) given in the preoperative period to reduce gland vascularity and diminish blood loss
  - 1-2 drops TID for 10 days before surgery
- Reasons to do surgery: family choice, age < 5-10 y.o., access to high volume and experienced surgeon, significant eye disease, goiter > 80 grams (>3-4x enlarged)
- Risks: transient or permanent hypoparathyroidism (hypocalcemia), recurrent laryngeal nerve injury, hematoma, permanent scar

Other (rarer) causes of hyperthyroidism

- Autonomously functioning (hot) nodule
- Hashitoxicosis
- Familial non-autoimmune hyperthyroidism
- McCune-Albright syndrome
- Thyroid hormone resistance (RTH)
- Acute (suppurative) thyroiditis
- Subacute (viral) thyroiditis
- TSH adenoma → ↑ pituitary glycoprotein α-subunit
- Ingestion of ground beef (inclusion of strap muscles)
- Factitious → ↓ thyroglobulin level





Familial non-autoimmune hyperthyroidism

- a.k.a. Hereditary toxic thyroid hyperplasia
- Due to an activating mutation of the TSH receptor
- Autosomal dominant
- Hyperthyroidism with variable age at onset (infancy to adulthood, even within same family)
- Hyperplastic goiter of variable size but with steady growth
- Negative thyroid autoantibodies

Differential diagnosis of hyperthyroidism

	Graves disease	Hashitoxicosis	(Sub)acute thyroiditis	LT4 ingestion
Thyroid exam	Non-tender goiter	Non-tender goiter	Tender goiter	No goiter, no tenderness
TSH	↓	↓	↓	↓
Free T4, T3	↑↑	Normal or ↑	Normal or ↑	↑
Thyroglobulin	↑	Variable	Variable	↓
Antibodies	+ TRAb + TPO +/- anti-TG	+ TRAb (10%) + TPO + anti-TG	Negative antibodies	Negative antibodies
Uptake scan	↑	↓ (usually)	↓	↓

Thyroxine-binding globulin

Thyroxine-binding globulin (TBG)

- **Very little thyroid hormone is free and unbound**
  - **99.97% of T4 is bound**
  - **99.7% of T3 is bound**
  - **Therefore, <0.3% of thyroid hormone is “free”**

- **Most thyroid hormone is bound to proteins**
  - **70-80% to TBG**
  - **15-25% to transthyretin (thyroxine-binding prealbumin)**
  - **<10% to albumin**
  - **Potency of binding to T4: TBG >> transthyretin >>> albumin**

Factors affecting TBG levels

Decreased TBG

- Inherited
- Androgens
- Glucocorticoids
- Severe illness
- Hepatic failure
- Nephrotic syndrome
- Nicotinic acid
- L-asparaginase

Increased TBG

- Inherited
- Pregnancy
- Estrogens
- Hepatitis
- Porphyria
- Opioids (e.g. heroin, methadone)
- Mitotane
- SERMs (e.g. tamoxifen)

Euthyroid sick syndrome

- Significant decrease in TBG
- ↓ in type 1 deiodinase (T4 → T3)
- ↑ in type 3 deiodinase (T4 → rT3)
- Labs in severe illness can look similar to central hypothyroidism:

	Mild illness	Moderate illness	Severe illness
Total T3	↓	↓↓	↓↓↓
Free T4	Normal	Normal to ↓	↓
rT3	↑	↑↑	↑↑↑
TSH	Normal	Normal to ↓	↓

- TSH will rise during the recovery phase

TBG deficiency – inherited

- X-linked condition
- Partial (1 in 4000) or complete (1 in 15,000)
- Heterozygous males are more frequently detected
- Depending on X inactivation, females may have normal, partial, or complete deficiency

- T4 and T3 levels low, TSH is normal, free T4 and free T3 are normal, high T3 uptake (T3U)
- Benign condition → no treatment needed

T3U = 1 / TBG

TBG excess – inherited

- **X-linked condition**
- **Estimated to occur in 1 in 25,000**

- **T4 and T3 levels elevated, TSH is normal, free T4 and free T3 are normal, low T3 uptake (T3U)**

T3U = 1 / TBG

- **Like TBG deficiency, it is a benign condition → no treatment needed**

Familial dysalbuminemic hyperthyroxinemia

- **Genetic variant of albumin resulting in a marked increased affinity for T4 (but not T3)**
- **Mutation in *ALB* (albumin) gene**
- **Autosomal dominant**
- **Prevalence: 1 in 10,000**

- **Normal TSH, normal T3, elevated T4**
- **Normal T3U**
- **Normal free T4 by equilibrium dialysis – may have high direct free T4 due to lab artifact**

ABP outline – handout

- **Additional ABP specifications and information are contained in the handout**

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Type 2 diabetes in Children and Adolescents

2025 PES Board Review Course in Pediatric Endocrinology

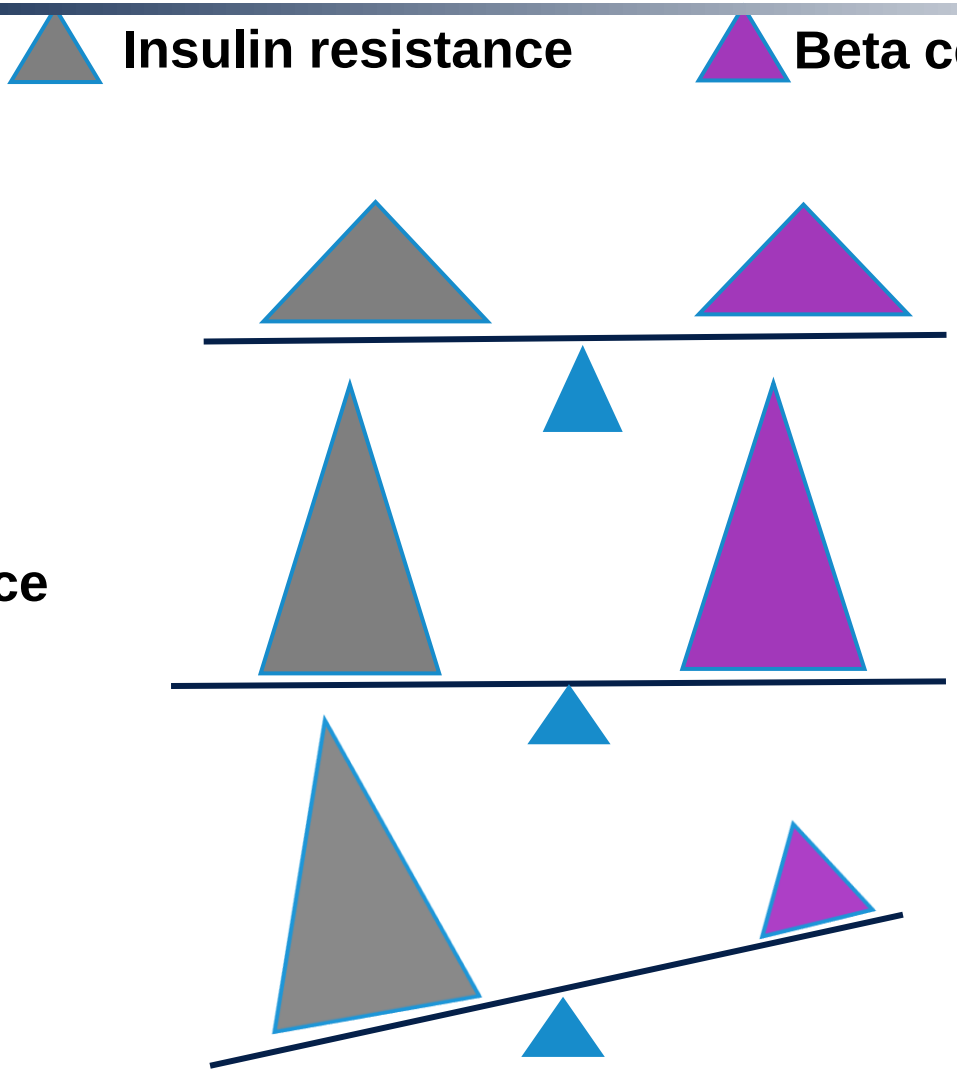
Shylaja Srinivasan, MD, MAS
Assistant Professor of Pediatrics
University of California, San Francisco

- Lecture content updated and modified from Dr. Philip Zeitler's 2021 slides

Content Domain	Exam Weights
1. Normal Physiology and Structural Development of Endocrine Systems	6%
2. Pharmacology	2%
3. Diabetes Mellitus	11%
4. Disorders of Growth	10%
5. Disorders of the Thyroid Gland	9%
6. Disorders of Puberty	8%
7. Disorders of the Adrenal Gland	7%
8. Disorders of the Hypothalamic-Pituitary Axis	6%
9. Hypoglycemia	5%
10. Disorders of Sex Development	5%
11. The Posterior Pituitary Gland and Disorders of Vasopressin and Water Metabolism	5%
12. Disorders of Weight Homeostasis	5%
13. Disorders of Mineral and Bone Metabolism	5%
14. Combined Endocrine Disorders and Enteric Neuroendocrine Tumors	3%
15. Lipid Disorders	3%
16. Gender Medicine	2%
17. Population Health and Screening	2%
18. Systems-Based Practice	2%
19. Core Knowledge in Scholarly Activities	4%
	100%

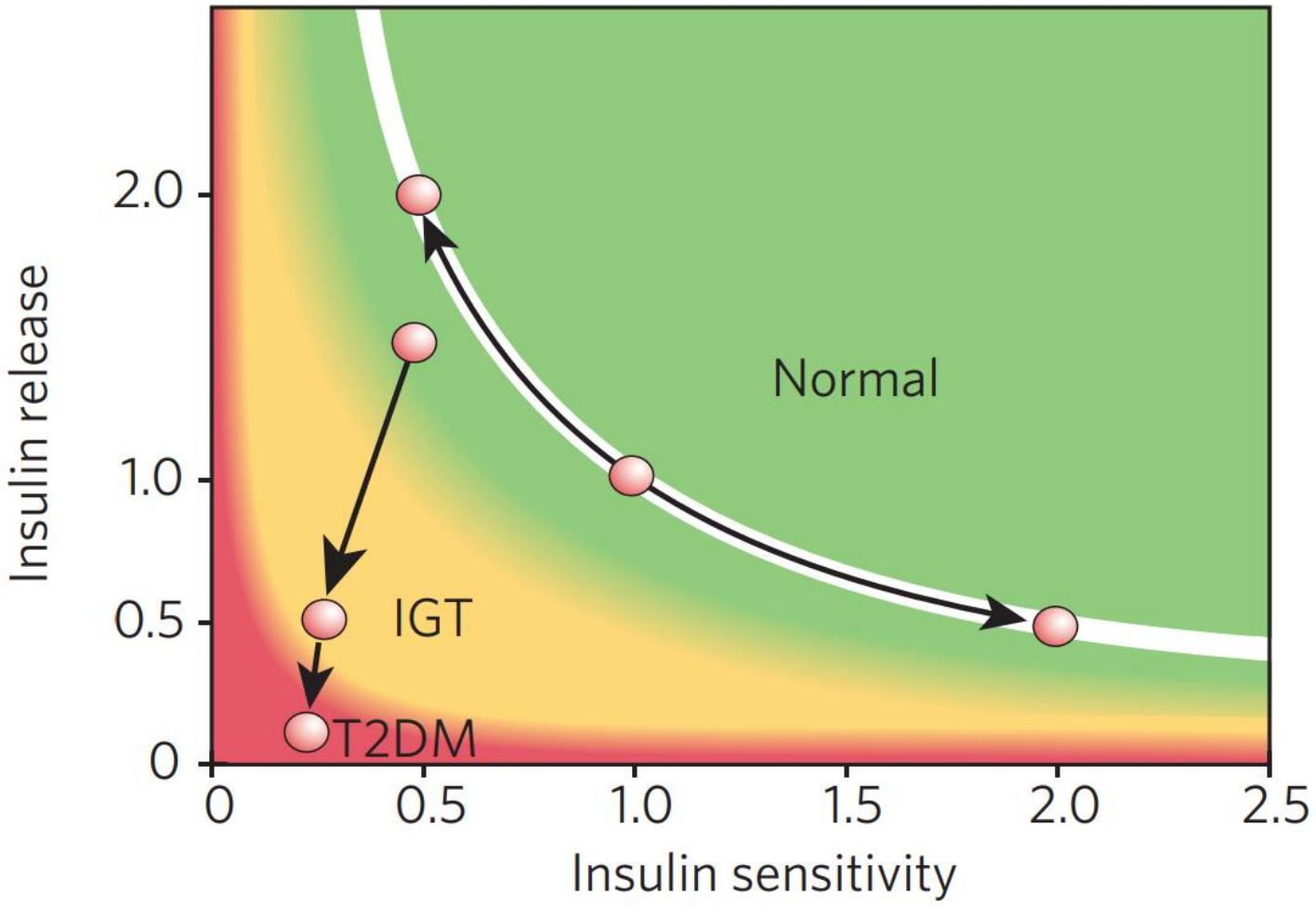
Know the roles of insulin resistance, obesity, and insulin deficiency in the pathophysiology of type 2 diabetes

Glucose homeostasis is a balance between insulin action and secretion



Diabetes occurs when this balance is lost

The relationship between insulin secretion and insulin action is a hyperbolic function



Kahn SE et al: *Nature* 2006

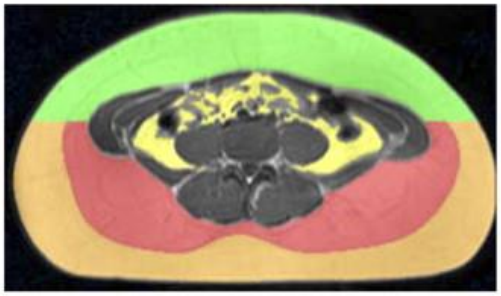
Causes of insulin resistance

- **Inherited**
  - Rare mutations: insulin receptor, glucose transporter, signaling proteins
  - Insulin receptor antibodies
- **Acquired**
  - Obesity
  - Inactivity
  - Inflammation
  - Fatty acids
  - Medications

Central obesity is “central” to the development of insulin resistance in T2D

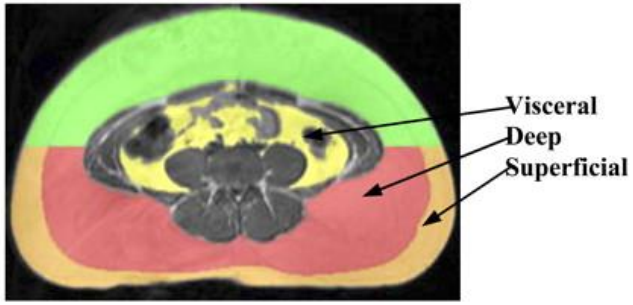
Males

Tertile 1
Age: 14
BMI: 35.3
Percent Fat: 41.7%



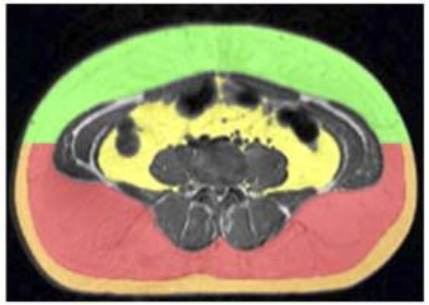
Proportion of Visceral Fat: 0.08
Visceral Fat: 56 cm^2
Subcutaneous Fat: 628 cm^2
Deep-to-Superficial Ratio: 0.84
Matsuda Index: 2.60
Fasting Insulin: 23 µU/ml
2-hr Glucose: 80 mg/dl
TG: 100 mg/dl
HDL: 39 mg/dl

Tertile 2
Age: 14
BMI: 34.0
Percent Fat: 39.3%



Proportion of Visceral Fat: 0.10
Visceral Fat: 68 cm^2
Subcutaneous Fat: 616 cm^2
Deep-to-Superficial Ratio: 2.08
Matsuda Index: 1.17
Fasting Insulin: 33 µU/ml
2-hr Glucose: 118 mg/dl
TG: 109 mg/dl
HDL: 34 mg/dl

Tertile 3
Age: 14
BMI: 33.1
Percent Fat: 38.4%



Proportion of Visceral Fat: 0.15
Visceral Fat: 89 cm^2
Subcutaneous Fat: 519 cm^2
Deep-to-Superficial Ratio: 2.84
Matsuda Index: 0.82
Fasting Insulin: 43 µU/ml
2-hr Glucose: 124 mg/dl
TG: 140 mg/dl
HDL: 40 mg/dl

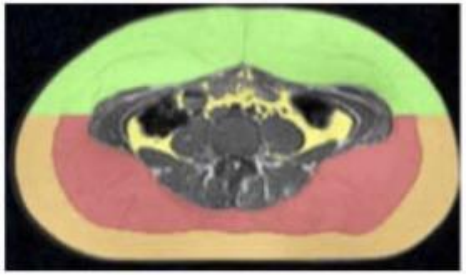
Insulin sensitivity ↓ as visceral fat ↑

Taksali et al., Diabetes., 2008

Increase in visceral fat and decrease in subcutaneous fat leads to decreased in insulin sensitivity

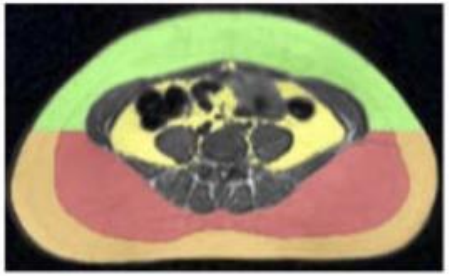
Females

Tertile 1
Age: 12
BMI: 33.3
Percent Fat: 40.4%



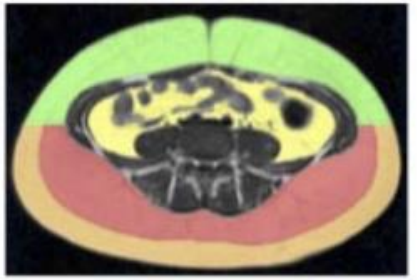
Proportion of Visceral Fat: 0.05
Visceral Fat: 28 cm^2
Subcutaneous Fat: 518 cm^2
Deep-to-Superficial Ratio: 1.15
Matsuda Index: 1.90
Fasting Insulin: 33 µU/ml
2-hr Glucose: 95 mg/dl
TG: 15 mg/dl
HDL: 44 mg/dl

Tertile 2
Age: 13
BMI: 27.7
Percent Fat: 38.2%



Proportion of Visceral Fat: 0.11
Visceral Fat: 50 cm^2
Subcutaneous Fat: 409 cm^2
Deep-to-Superficial Ratio: 1.26
Matsuda Index: 1.15
Fasting Insulin: 32 µU/ml
2-hr Glucose: 165 mg/dl
TG: 82 mg/dl
HDL: 61 mg/dl

Tertile 3
Age: 11
BMI: 27.6
Percent Fat: 37.7%

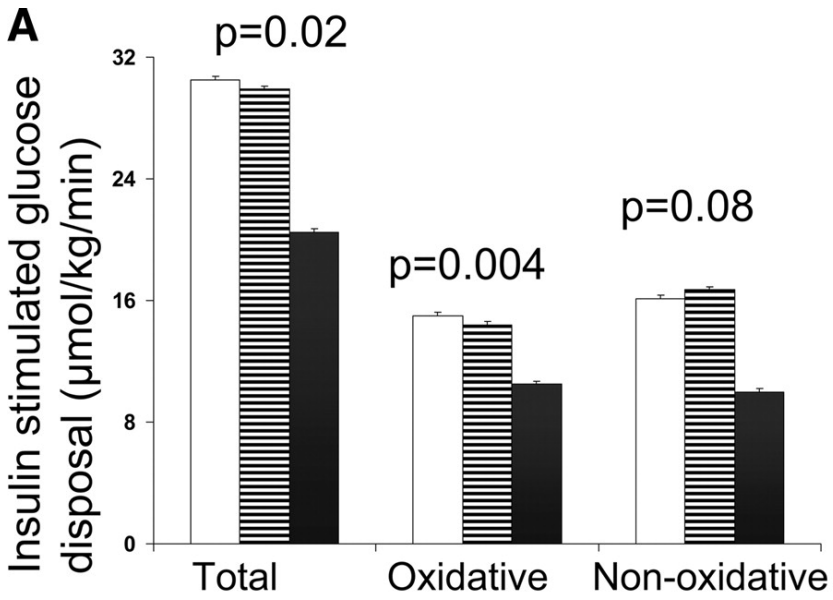


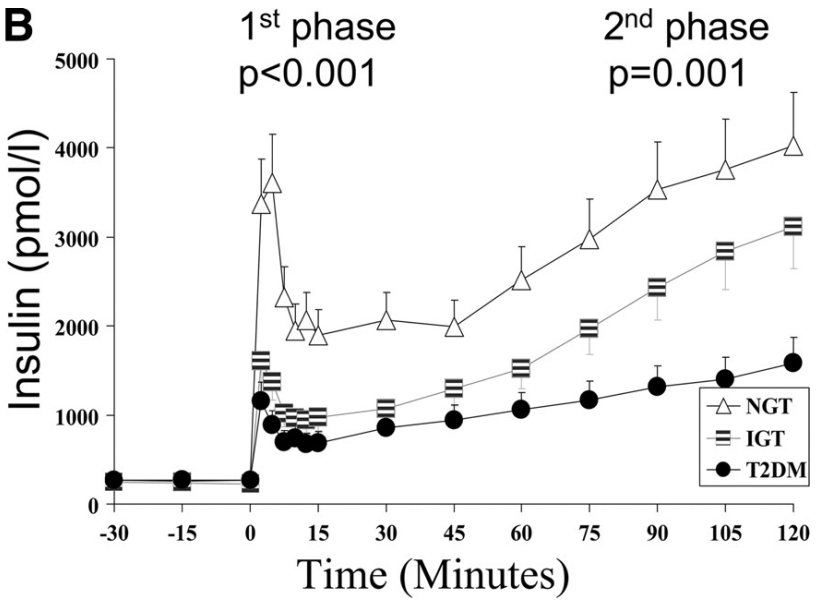
Proportion of Visceral Fat: 0.15
Visceral Fat: 58 cm^2
Subcutaneous Fat: 338 cm^2
Deep-to-Superficial Ratio: 1.39
Matsuda Index: 0.27
Fasting Insulin: 77 µU/ml
2-hr Glucose: 185 mg/dl
TG: 143 mg/dl
HDL: 33 mg/dl

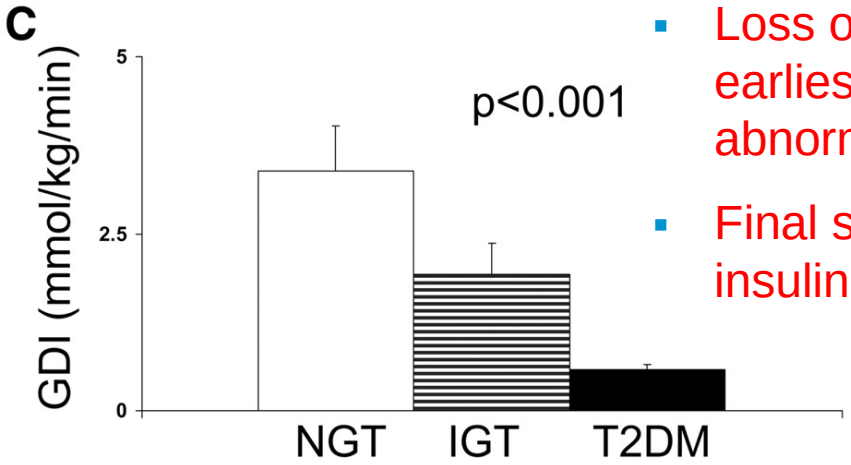
Insulin sensitivity ↓ as visceral fat ↑

Taksali et al., Diabetes., 2008

Insulin sensitivity and insulin secretion in the development of T2D



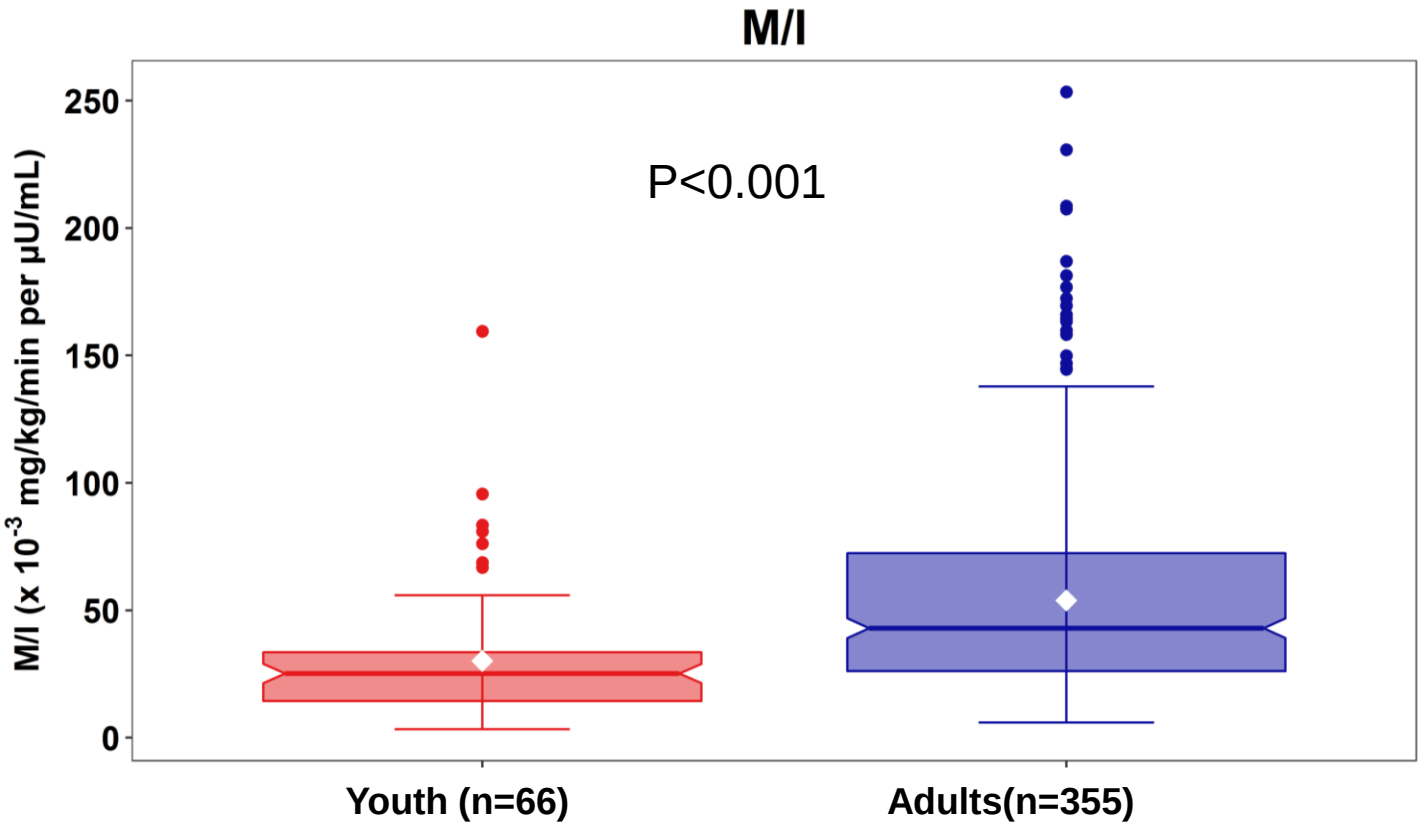




- Loss of 1st phase response is the earliest identifiable β-cell abnormality
- Final step is loss of 2nd phase insulin response

Bacha et al., *Diabetes*., 2009

Youth have greater insulin resistance for any degree of adiposity compared to adults



RISE consortium., *Diabetes Care*., 2018

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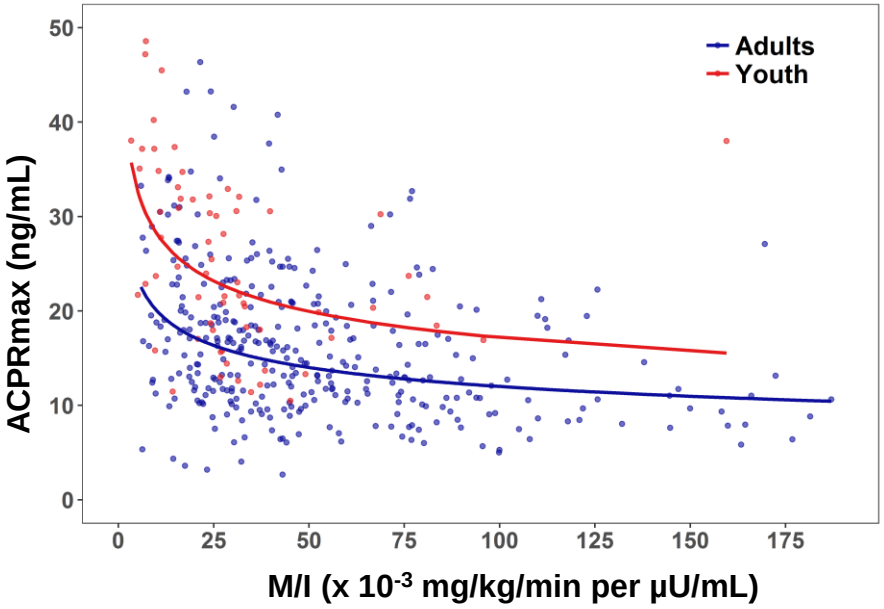
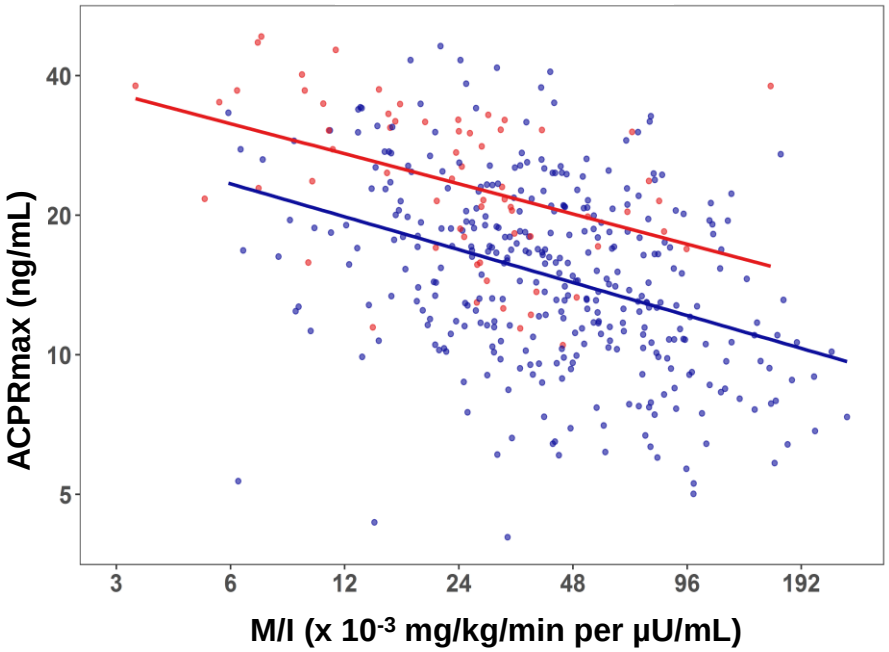
Youth have greater insulin secretion for any degree of insulin resistance compared with adults

ACPRmax



Log ACPRmax



Slope p<0.001 Group*Slope p=ns

RISE consortium., *Diabetes Care*., 2018

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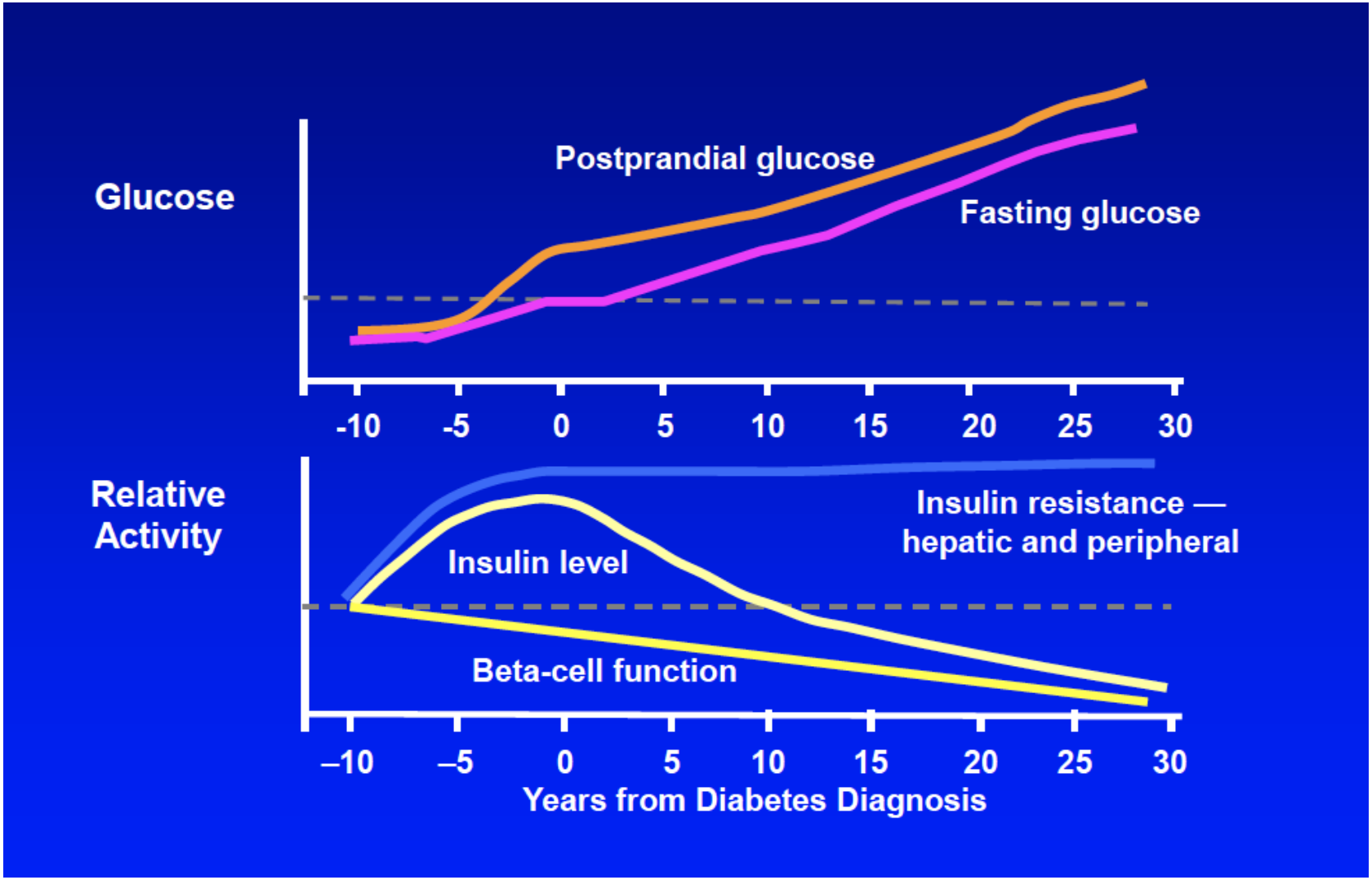
Development and Progression of T2D



Adapted from Ramlo-Halsted et al., *Primary Care: Clinics in Office Practice*., 1999

Summary of pathophysiology of youth T2D

- T2D occurs when β-cells cannot secrete sufficient insulin to compensate for insulin resistance
- Overweight and obesity are major contributors to the development of insulin resistance
- Youth with T2D have
  - Severe peripheral and hepatic insulin resistance
  - Increased fasting hepatic glucose production
  - Inadequate first- and second-phase insulin secretion
  - Greater insulin resistance for any degree of adiposity compared to adults
  - Greater insulin secretion for any degree of insulin resistance compared with adults.
- Upregulation of α-cell function with hyperglucagonemia has been implicated in the adult T2D but data are mixed in youth

Know the effect of adiponectin, leptin, IL-6, and TNF-alpha on insulin sensitivity and markers of insulin resistance

Know the cellular origin of adiponectin, ghrelin, amylin, glucagon- like peptide-1 (GLP-1) and leptin

Understand the actions of glucagon-like peptide-1 (GLP-1) on the GI system, pancreas, and brain

Adiponectin

- Synthesized by adipose tissue and serum concentration inversely correlated to body fat percentage
- Lower in diabetes
- Function
  - Increased insulin sensitivity
    - Improved markers of insulin resistance
  - Decreased gluconeogenesis
  - Increased glucose uptake
  - Increased beta oxidation of fatty acids

Leptin

- Synthesized in white adipose tissue
- Serum concentration is directly correlated with total body fat
- It signals the hypothalamus about the quantity of stored fat
- Inhibits appetite
- Obesity is associated with ↑ leptin levels
- Leptic signaling dysfunction in T2D

IL 6

- Synthesized and secreted by the adipose tissue
  - Adipose contributes up to 35 % of circulating IL6
- Stimulates recruitment and activation of macrophages in adipose tissue
- In the liver, IL-6 promotes STAT3-SOCS-3 pathway mediated impairment of insulin action
- In muscle, IL-6 promotes insulin-regulated glucose metabolism

TNF- α

- Secretion increased in adipose tissue from obese humans
- Induces insulin resistance by downregulating the tyrosine kinase activity of the insulin receptor and decreasing the expression of GLUT-4- reduces lipoprotein lipase activity in white adipocytes
- Stimulates hepatic lipolysis

Ghrelin

- Synthesized from cells lining the fundus of the stomach and in epsilon cells of the pancreas
- Rises before meals and falls after
- Stimulates appetite

Amylin

- Co-secreted from beta cells with insulin
- Contributes to glucose regulation
  - Decreased appetite
  - Slowed gastric emptying
  - Reduction in gastric enzymes
  - Suppression of glucagon
- ↑ in obesity (downregulation of receptor)
- Deficient in T2D

GLP-1

- Secreted by the L cells of the intestine in response to nutrients
- Rapidly metabolized by DPP-4
- Decreases serum glucose
  - Pancreas
    - Stimulates insulin secretion
    - Inhibits glucagon secretion
    - Increases beta cell mass
  - GI tract
    - Slows gastric emptying, leading to lower post-prandial glucose excursion
  - CNS
    - Decreased appetite through central actions on the hypothalamus
- GLP-1r (and GIPr) agonists available as Rx options for T2D and obesity
- DPP-4 inhibitors decrease metabolism of endogenous GLP-1

Know the effects of exogenous obesity on adiponectin and leptin levels

Obesity is associated with …..

- ↓ adiponectin levels
- ↑ leptin levels (development of resistance)

Know the association between insulin resistance and amylin levels

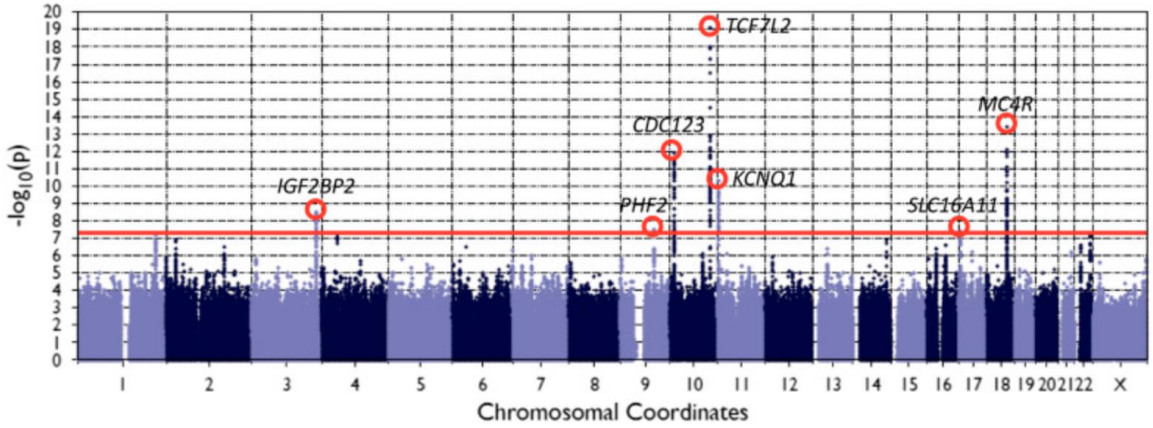
Amylin

- Amylin levels are ↑ in obesity with normal glucose tolerance (downregulation of receptor)
- But ↓ in insulin resistance and T2D

Understand the inheritance of type 2 diabetes and its implications for testing and counseling of family members

T2D is a complex disease

- Caused by complex interplay of environmental and numerous genetic variants of small and moderate effect sizes
- Monogenic diabetes- MODY- caused by single gene mutations
- Adults ~ 1000 genetic variants identified
- Youth- Similar genetic architecture but effect sizes are larger
- Strong family history of type 2 diabetes in first- or second-degree relatives
- High risk for T2D in offspring of a pregnancy complicated by gestational diabetes mellitus



GWAS of T2D in youth

Srinivasan et al., *Diabetes*., 2021

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Know screening criteria for type 2 diabetes in youth

ADA recommendations for screening for T2D in youth

- After the onset of puberty or Age ≥ 10 years (whichever is earlier)
- Overweight (BMI >85th) or Obese(BMI >95th percentile)
- **AND** who have one or more risk factors:
- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs or conditions associated with insulin resistance
  - acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

More on Screening for T2D in youth

- If tests are normal, repeat testing at a minimum of 2-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating)
- Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents
- Children and adolescents with overweight or obesity in whom the diagnosis of T2D is being considered should have pancreatic autoantibodies tested to exclude autoimmune T1D

Recognize the clinical and laboratory findings in type 2 diabetes and differentiate from other types of diabetes

Clinical features of T2D

- Overweight or obese
- Mid-to late puberty
- Overrepresentation of youth of color and females
- Family history of T2D
- Maternal diabetes or gestational diabetes or T2D
- Signs or conditions associated with insulin resistance
  - acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight

Laboratory diagnosis of T2D

FPG ≥126 mg/dL . Fasting is defined as no caloric intake for at least 8 h
OR
2-h PG ≥200 mg/dL during 75 g OGTT
OR
A1C ≥6.5%.
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

- In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
- Pancreatic autoantibodies should be measured to exclude the possibility of autoimmune type 1 diabetes
- Genetic testing for MODY should be considered based on clinical characteristics and presentation

ADA, Standards of Care., 2025

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Prediabetes

- Impaired fasting glucose (100-125 mg/ dL) and impaired glucose tolerance (IGT) (2-hour glucose of 140-199 mg/dL on an OGTT)
- HbA1c 5.7%-6.4%.
  - HbA1c 6.0%-6.4% are at particularly high risk for developing diabetes
- Impaired fasting glucose and IGT are considered risk factors for both the development of diabetes and for cardiovascular disease
- Can occur with pubertal decrease in insulin sensitivity
- High rate of spontaneous remission of prediabetes in youth with obesity when puberty ends

- Magge et al., *J Pediatrics*., 2019

T1D vs T2D

Distinguishing between T1D and T2D can be difficult in adolescents

- Age
  - T2D exceedingly rare before puberty
- Weight and BMI
  - All cases of T2D > 85%ile
  - ~ 30%+ of T1D cases > 85%ile
- Pancreatic auto-antibodies
  - 15%+ of clinically defined adolescents with T2D may have antibodies
- Presentation
  - Casual diagnosis uncommon, but not impossible in T1D
- Ketosis
  - 25% of T2D may present with ketosis
- Family history
  - Family history of T2D common

Characteristic	Type 1 Diabetes	Type 2 Diabetes	Classic MODY
Age at onset	Peaks at 5 and 15 years of age	Teenage years, young adults	<25 years of age
Predominant ethnic groups affected	White	Hispanic, African American, Native American	Occurs in all ethnic groups
Male-to-female ratio	1.1:1	1:1.5	1:1
Severity at onset	Acute, severe, insulin required	Subtle, insulin not required	Subtle, insulin not required
Islet autoimmunity	Present	Absent	Absent
HLA-DR3, -DR4	Very common	No increased frequency	No increased frequency
Ketosis, DKA	Common	Uncommon	Rare
Long-term course	Insulin-dependent	Noninsulin-dependent	Noninsulin-dependent
Prevalence of obesity	Uncommon	≥90%	Uncommon
Proportion of cases of 100% youth-onset diabetes	Most common form of youth-onset diabetes	Rising in frequency; ± as common as type 1 diabetes in specific populations	≤5% of youth-onset diabetes in whites
Percentage of probands with an affected first-degree relative	≤15%	Variable but common	100%
Mode of inheritance	Nonmendelian, generally sporadic	Nonmendelian but strongly familial	Autosomal dominant
Number of genes controlling inheritance	Polygenic	Polygenic	Monogenic
Pathogenesis	Autoimmune beta cell destruction: insulinopenia	Insulin resistance plus relative insulinopenia	Insulinopenia

Recognize the various presentations of type 2 diabetes

Clinical presentations of T2D

- Varies widely
  - Asymptomatic or minimally symptomatic, diagnosed incidentally during routine laboratory testing
  - Severe presentation with symptomatic hyperglycemia, weight loss, metabolic decompensation, DKA, or HHNK syndrome
- Pediatric Diabetes Consortium study
  - The majority of participants (n = 282, 67%) presented with symptoms of diabetes and confirming laboratory data
  - A third of the participants (n= 139) were identified by high-risk screening
  - Diabetic ketoacidosis (DKA) was present in 11% during diagnosis
  - 2% had hyperglycemic, hyperosmolar state

Kligensmith et al., *Pediatric Diabetes*., 2016

DKA and HHS in T2D

- **Diabetic ketoacidosis**
  - Hyperglycemia, ketosis and acidosis
- **Hyperglycemic hyperosmolar state**
  - Severe hyperglycemia, marked increase in serum osmolality and severe dehydration *without* significant ketoacidosis
  - Enough circulating insulin to prevent excessive lipolysis and subsequent ketogenesis

Differences in treatment strategy between HHS and DKA include the volume of fluid administered, the timing of administration of insulin, and monitoring of the corrected sodium decline

Glaser et al., ISPAD 2022 guidelines

Know the implications of large, pivotal diabetes trials

Lessons learned from adult trials

UKPDS

- Tight control matters in T2D
- Sulfonylureas associated with increased CV risk and earlier β-cell failure

DPP

- In adults at risk for T2D, lifestyle intervention and metformin can reduce incidence of type 2 diabetes

ACCORD

- Tight control associated with mortality in those with elevated CV risk

GRADE

- Comparison of 4 medications when added to metformin
- Rates of HbA1C lowering > for glargine and liraglutide compared to glimepiride and sitagliptin

SEARCH for Diabetes in Youth

- Population based observational study to characterize the descriptive epidemiology of diabetes in youth < 20 years in the US
- 5 centers across US
- T2D rare in children < 10 years regardless of race and ethnicity
- Incidence
  - Unadjusted incidence rates of T2D ↑ by 7.1% annually (9.0 vs 12.5 cases per 100,000 youths per year in 2002-2003 and 2011-2012)
  - Increases in all subgroups except Non-Hispanic White
- Prevalence of T2D ↑ by 0.34 per 1000 youths to 0.67 per 1000 youths
- Future projections- By 2050, at current incidence rates, numbers may double, and may increase by more than fourfold if incidence rates increase as data suggest

The TODAY Cohort- Medication trial of T2D

Age	14.0 (12,16)
Duration of T2D (months)	5 (4,9)
BMI Z score	2.21 (1.89, 2.47)
Tanner 4/5	83.9%
Female	64.9%
Ethnicity	
White	19.9%
Hispanic	42.2%
Black	31.6%
American Indian	6.2%
Family Hx diabetes	
Nuclear	59.6%
Nuclear + GP	89.4%
GDM	33.3%
Acanthosis	97.0%

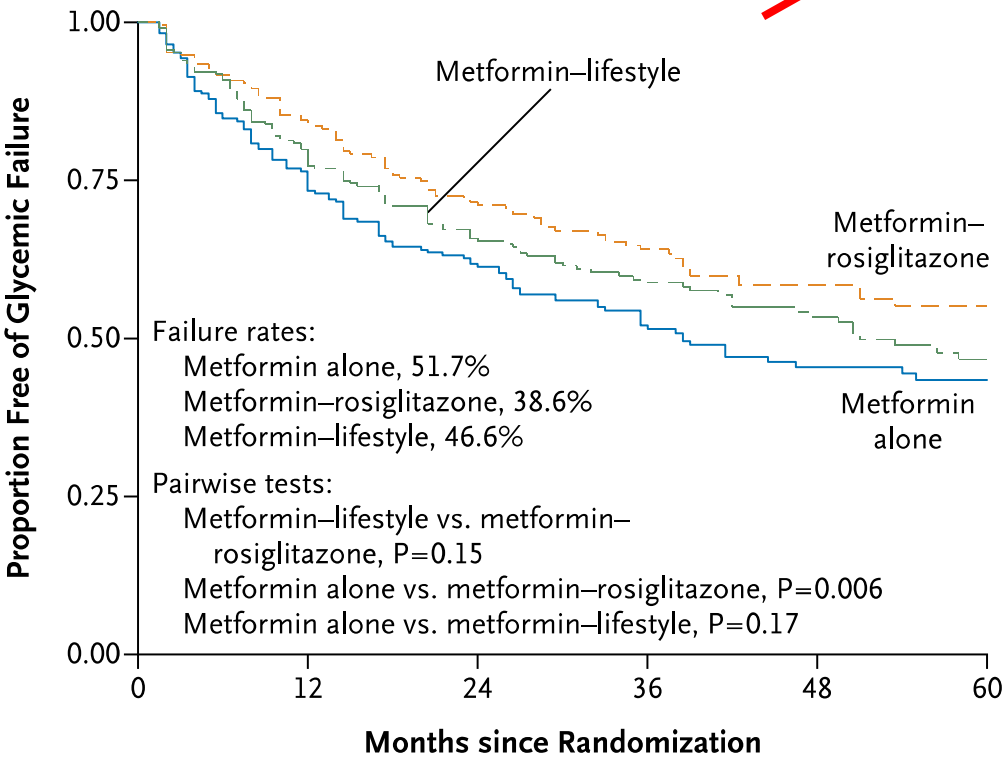
Lives with	
Both parents	38.7%
Mother only	47.0%
Father only	5.1%
Neither	9.2%
Parental Education	
Less than 12th grade	26.5%
High school	25.1%
Some college	31.8%
Bachelor's degree and above	16.6%
Income	
<$25K	21.5%
$25K-$50K	33.7%
$50K-$75K	24.8%
>$75K	20%

Median (25th, 75th %tiles)

Adapted from Copeland et al, *J Clin Endocrinol Metab*., 2010

TODAY Study: Results

n= 699



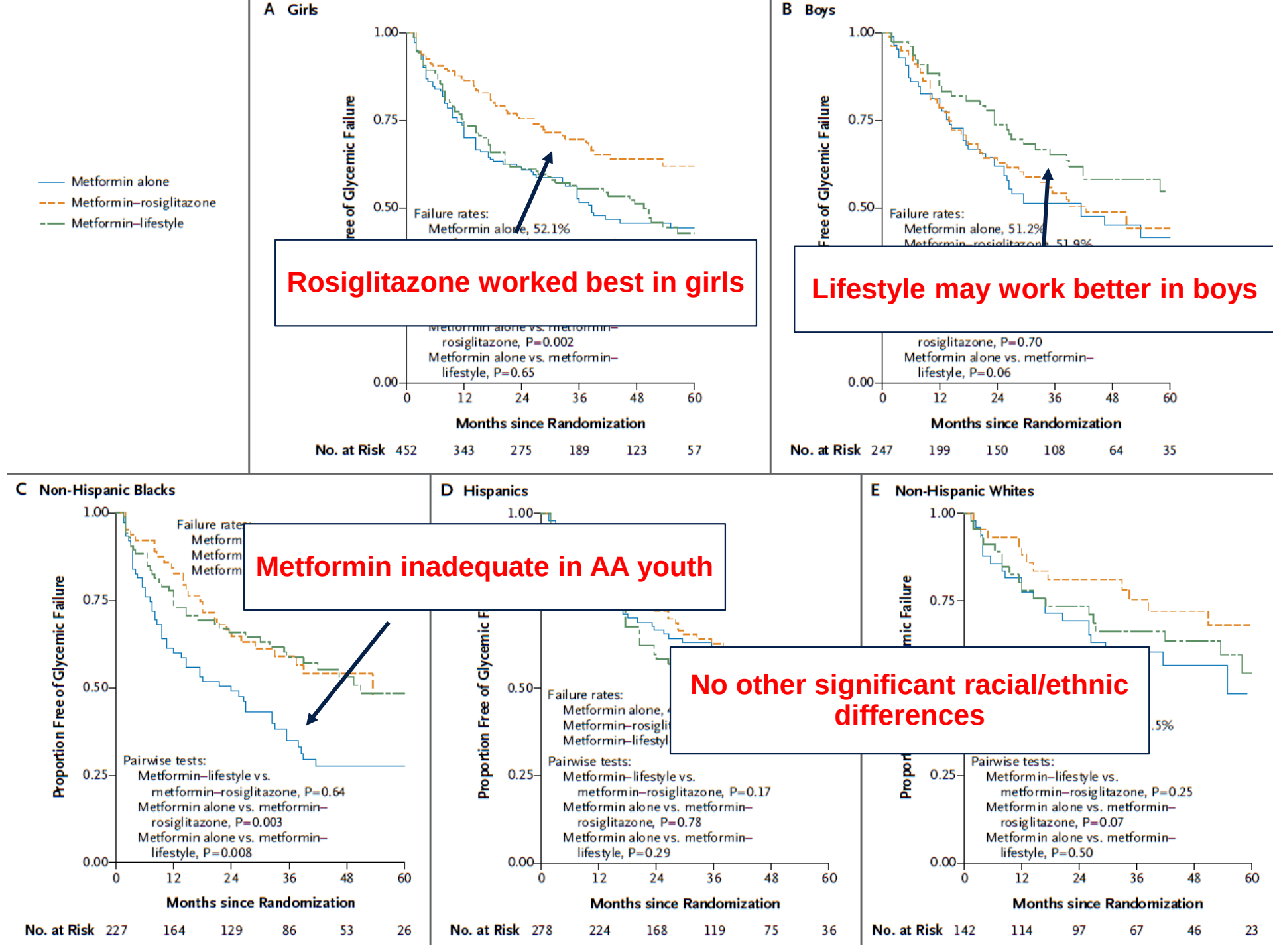
No significant difference with addition of lifestyle intervention

Small but significant improvement with rosiglitazone

High failure rate overall for metformin treatment

45.6% reached the primary outcome of loss of glycemic control despite combination therapy

Zeitler et al: A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes
TODAY Study Group: N Engl J Med 2012; 366:2247-2256


Metformin alone
Metformin–rosiglitazone
Metformin–lifestyle
A Girls
Proportion Free of Glycemic Failure
1.00
0.75
0.50
0.00
Failure rates:
Metformin alone, 52.1%
Metformin alone vs. metformin–rosiglitazone, P=0.002
Metformin alone vs. metformin–lifestyle, P=0.65
0
12
24
36
48
60
Months since Randomization
No. at Risk 452 343 275 189 123 57
Rosiglitazone worked best in girls
B Boys
Failure rates:
Metformin alone, 51.2%
rosiglitazone, P=0.70
Metformin alone vs. metformin–lifestyle, P=0.06
No. at Risk 247 199 150 108 64 35
Lifestyle may work better in boys
C Non-Hispanic Blacks
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.64
Metformin alone vs. metformin–rosiglitazone, P=0.003
Metformin alone vs. metformin–lifestyle, P=0.008
No. at Risk 227 164 129 86 53 26
Metformin inadequate in AA youth
D Hispanics
Failure rates:
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.17
Metformin alone vs. metformin–rosiglitazone, P=0.78
Metformin alone vs. metformin–lifestyle, P=0.29
No. at Risk 278 224 168 119 75 36
E Non-Hispanic Whites
Pairwise tests:
Metformin–lifestyle vs. metformin–rosiglitazone, P=0.25
Metformin alone vs. metformin–rosiglitazone, P=0.07
Metformin alone vs. metformin–lifestyle, P=0.50
No. at Risk 142 114 97 67 46 23
No other significant racial/ethnic differences

TODAY study summary

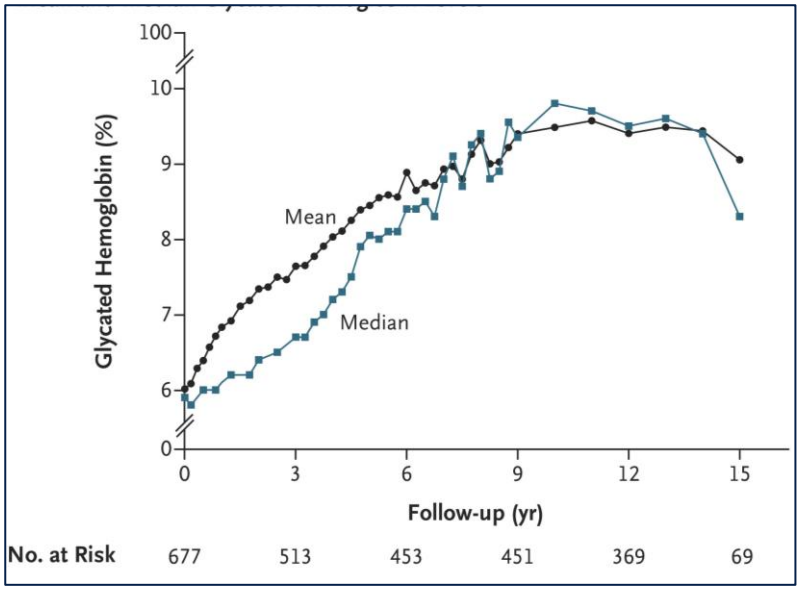
- Metformin monotherapy is inadequate for half of youth with T2D
- The role of intensive lifestyle interventions in youth T2D is uncertain
- There are important sex and race/ethnicity differences among youth with type 2 diabetes in the US
- Youth with type 2 diabetes have progressive loss of β-cell function that is rapid relative to adults and is irrespective of treatment

TODAY study summary contd…..

- Initial treatment with metformin is usually successful - even for participants on insulin
- Youth who cannot achieve HbA1c in the non-diabetes range on metformin are less likely to maintain glycemic control on oral meds and will require insulin
- Weight loss is associated with improved glycemic and non-glycemic measures
- Pregnancy outcomes in youth-onset T2D are troubling

TODAY long-term follow up- Increase in HbA1C trend over time

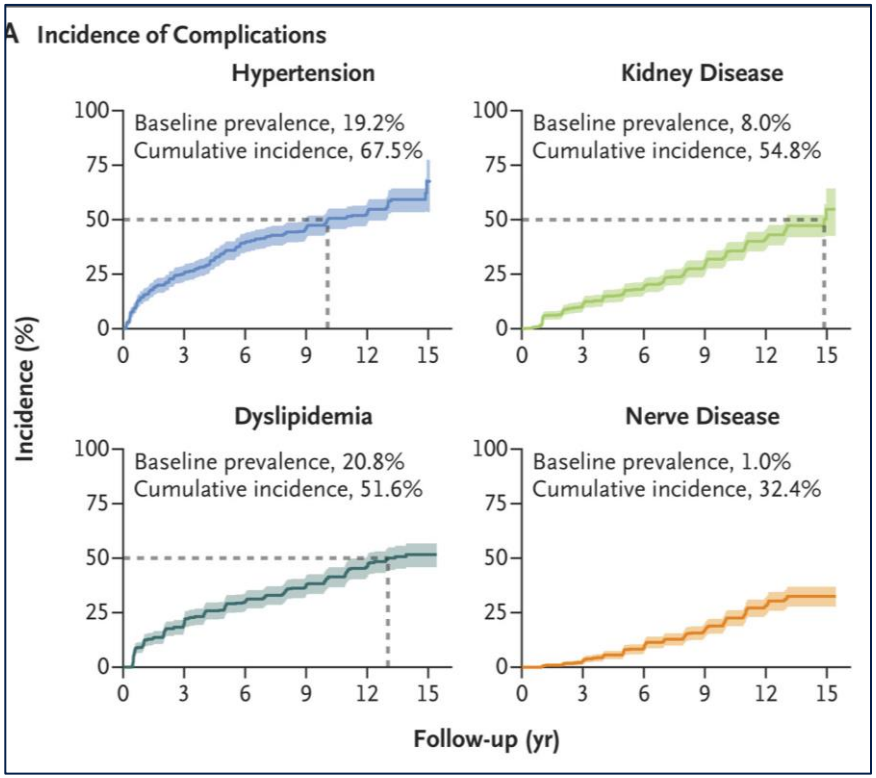
- Study end, mean age = 26.4 ± 2.8 y
- Mean time from diabetes Dx = 13.3± 1.8 y
- Median HbA1C ↑ over time
  - % of participants with HbA1C <6% ↓ from 75% at baseline to 19% at 15 years
  - % with HbA1C of at least 10% was 0% at baseline and 34% at 15 years

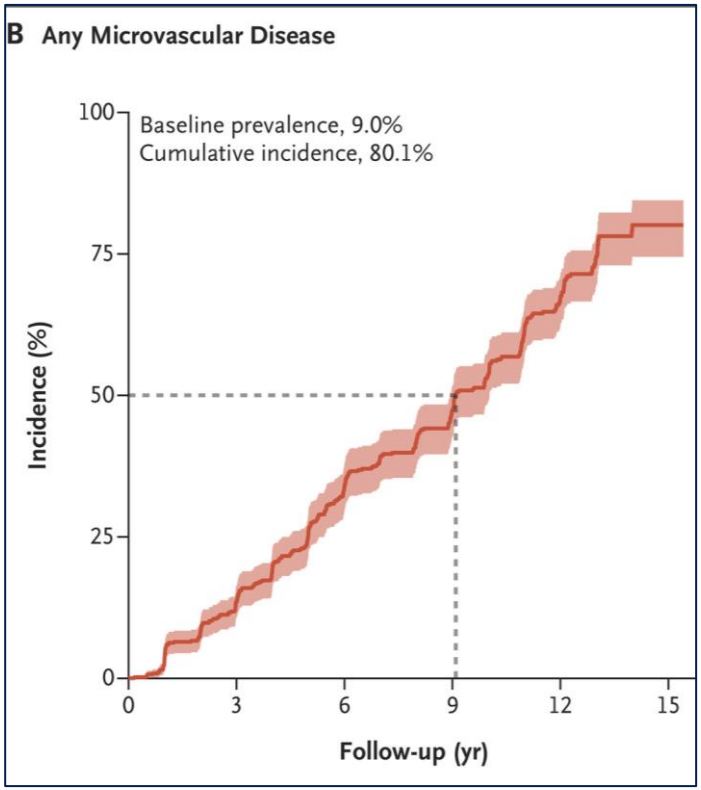


TODAY study group., *NEJM*., 2021

UCSF Benioff Children's Hospitals

Results: Complications appear early and accumulate rapidly





- Prevalence of retinal disease was 13.7% from 2010 to 2011 and 51.0% from 2017 to 2018
- **The cumulative incidence of any microvascular complication was 50.0% by 9 years and 80.1% by 15 years**

TODAY study group., *NEJM*., 2021

UCSF Benioff Children's Hospitals

Results: Predictors of complications

- Factors associated with an increased risk of the development of any microvascular complication:
  - youth of color
  - high baseline HbA1C
  - low insulin sensitivity
  - hypertension
  - dyslipidemia
- There were no differences according to the original treatment assignment.

TODAY study group., *NEJM*., 2021

RISE study

- 91 obese pubertal youth with pre-diabetes or early T2D
- Randomized to
  - 3 months insulin glargine + 9 months metformin
  - 12 months metformin
- β- cell function measured at 12 and 15 months
- Metformin alone/basal insulin followed by metformin did not halt the deterioration in β cell function
- Youth have greater insulin secretion for any degree of insulin resistance compared with adults
- Youth have greater insulin secretion for any degree of insulin resistance compared with adults

The Rise Consortium., *Diabetes Care*., 2018

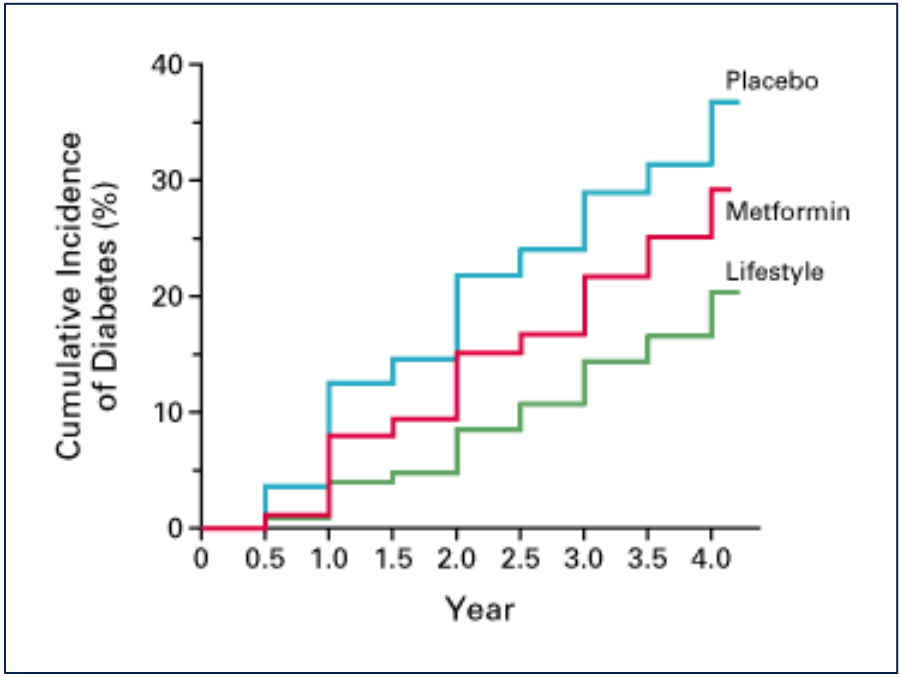
DISCOVERY study

- NIH funded multicenter observational study of youth at risk for diabetes
- Goal is to identify unique drivers of youth-onset type 2 diabetes
  - Biological, social and environmental factors
- Proposed n= 3600, ages 9-14 years

Understand that a reduced calorie diet and exercise are more effective than metformin in slowing the progression of type 2 diabetes

The Diabetes Prevention Program demonstrated that type 2 diabetes can be prevented in adults

- 3234 subjects with elevated fasting glucose levels and IGT
- Randomized to placebo, lifestyle or metformin
- Average age: 55 years
- Followed for 4 years



Risk reduction: 58% lifestyle
31% metformin

DPP Research Group *NEJM* 346:393-403, 2002

UCSF Benioff Children's Hospitals

Lifestyle education in T2D

- All youth with T2D and their families should receive comprehensive diabetes self-management education/support that is specific to youth and is culturally competent
- Lifestyle change must be part of any intervention
- Little evidence that this is effective on its own in children

Arslanian et al., *Diabetes Care*., 2018

Understand the treatment of type 2 diabetes, including the mechanisms of action of the medications used (See handout)

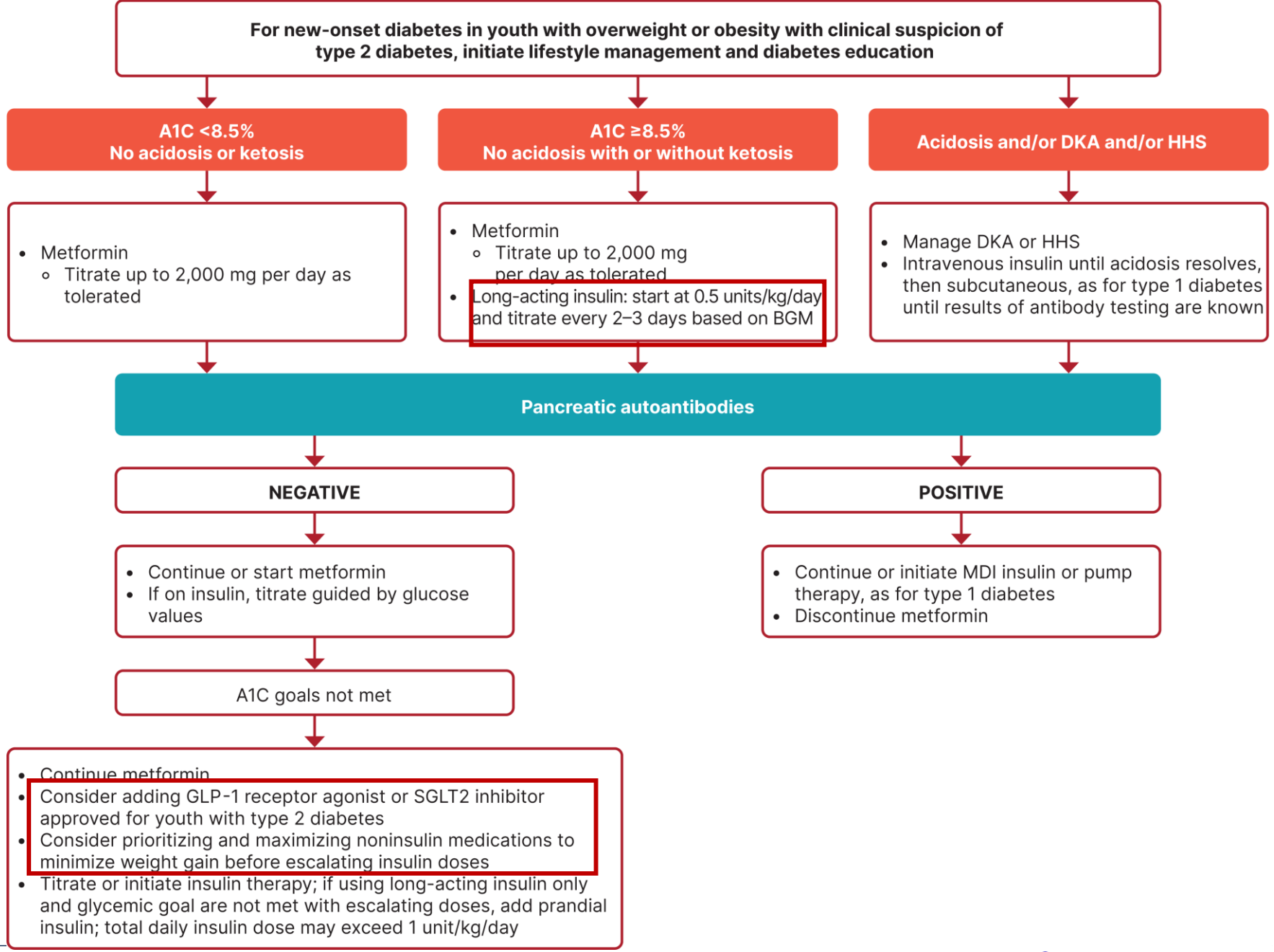
Treatment goals

- Diabetes defined by increased risk of complications
- UKPDS
  - Tight control leads to reduction in
    - Retinopathy
    - Nephropathy
    - Neuropathy
    - Cardiac events
  - There is a "legacy" effect of tight control leading to reduction in events even after intensive intervention is discontinued

Treatment goals: Aggressive management recommended

- Primary: Hemoglobin A1C <6.5 -7%
  - Revised in 2025 ADA and 2022 ISPAD guidelines
  - Taking into account low rate of hypoglycemia
- Home glucose monitoring should be individualized taking into account pharmacologic treatment
- Insufficient evidence regarding the frequency of fingerstick glucose measurements
- Monitoring (if not taking insulin)
  - Fingerstick blood glucose
  - Twice a day
  - 3 to 5 days a week
  - When ill
- Limited data on CGM use

Arslanian et al., *Diabetes Care*., 2018



American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Recognize the public health implications of type 2 diabetes in youth and possible public health interventions aimed at the prevention of type 2 diabetes

T2D prevention in youth

- Limited data in youth
- Some evidence that intensive lifestyle education based approaches are helpful for T2D prevention

Recognize that the co-morbid conditions associated with type 2 diabetes are the same as those associated with metabolic syndrome (eg, hypertension, hyperlipidemia, polycystic ovary syndrome, non- alcoholic fatty liver disease), and their treatment

Know when to monitor for lipids, blood pressure, and urine micro- albumin in patients with type 2 diabetes at diagnosis

Screening for co-morbidities

- Comorbidities more common at diagnosis than in T1D
- Co-morbidities increase more rapidly than in T1D
- Screening
  - Timing
    - At diagnosis
    - Yearly
  - Lipids
  - Urine albumin/creatinine ratio
  - Retinal screen
  - Evaluation for MASLD (AST and ALT)
  - Depression screening
  - BP at every visit
  - Screening for symptoms of obstructive sleep apnea at each visit

Arslanian et al., *Diabetes Care*., 2018

Know the treatment of co-morbid conditions associated with type 2 diabetes and metabolic syndrome

Dyslipidemia

- Testing when initial glycemic control has been achieved and annually thereafter
- Optimal cholesterol goals
  - LDL <100 mg/dL
  - HDL >35 mg/dL
  - Triglycerides <150 mg/dL
- If LDL cholesterol is >130 mg/dL, optimize glycemia and dietary counseling (7% sat fat, < 200 mg chol)
- If LDL cholesterol > goal after 6 months of dietary intervention, start statin, with goal of LDL <100 mg/dL
- If triglycerides are >400 mg/dL fasting or >1,000 mg/dL non-fasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL fasting (to reduce risk for pancreatitis).
- Adolescent girls on statins or fibrates should receive pregnancy counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Hypertension

- Blood pressure should be measured at every visit
- For BP (BP≥ 90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on 3 separate measurements, ambulatory blood pressure monitoring should be strongly considered
- After excluding secondary causes, if > 95%ile for age, sex, and height, intensify lifestyle intervention
- If BP remains > 95%ile for age after 6 months, initiate antihypertensive therapy
  - ACE inhibitors or angiotensin receptor blockers
  - Titrate to BP < 90th %ile or <130/80 if ≥13 years
  - Individuals of childbearing age should receive reproductive counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Nephropathy

- Calculate eGFR at diagnosis and annually
- Random urine albumin/creatinine ratio at diagnosis and annually
- If ACR > 30 mg/g, repeat on first-morning urine
  - Should be confirmed on two of three samples
- Either an ACE inhibitor or an ARB recommended for modestly elevated UACR (30–299 mg/g creatinine)
- Strongly recommended for those with UACR >300 mg/g creatinine and/or eGFR <60 mL/min/1.73 m2
- Referral to nephrology recommended in case of uncertainty of etiology, worsening UACR, or decrease in eGFR

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Neuropathy

- At diagnosis and annually
- The examination should include
  - Inspection
  - Assessment of foot pulses
  - Pinprick and 10-g monofilament sensation tests
  - Testing of vibration sensation using a 128-Hz tuning fork
  - Ankle reflexes

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Retinopathy

- Dilated fundoscopy or retinal photography at diagnosis and annually
- Less frequent examination (every 2 years) may be considered if there is adequate glycemic control and a normal eye exam
- Retinal photography (with remote reading or use of a validated assessment tool) can be used for screening
- Such programs should provide pathways for timely referral for a comprehensive eye examination when indicated

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

MASLD

- Metabolic Dysfunction–Associated Steatotic Liver Disease–ALT and AST at diagnosis and annually
  - Biopsy only gold-standard diagnostic procedure
  - Treatment unclear
    - Reduction in weight and carbohydrate intake
    - Vitamin E 800 IU/day
    - Metformin
    - Incretin based therapies
- Referral to gastroenterology should be considered for persistently elevated or worsening transaminases

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Other screening

- Polycystic ovary syndrome - evaluate for symptoms and treat as indicated
- Sleep Apnea - screen for symptoms at every visit and refer as needed
- Depression and eating disorders - assess for depression, anxiety, and eating disorders at all visits
- Smoking assessment and cessation
- Preconception counseling

American Diabetes Association. Standards of Medical Care in Diabetes., *Diabetes Care*., 2025

Audience response questions

Question 1

Of the following, which is the last to occur in the sequence of events leading to clinically apparent T2D?

A) decrease in serum adiponectin

B) increased DPP-1 inhibition of GLP-1

C) loss of first-phase insulin secretion

D) loss of second-phase insulin secretion

E) worsening of pubertal insulin resistance

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E) worsening of pubertal insulin resistance

Question 1

- The final step in the development of T2D is loss of 2nd phase insulin response following IV glucose challenge
- Loss of 1st phase response is the earliest identifiable β-cell abnormality and is present before clinically apparent diabetes
- A decrease in adiponectin is a marker of insulin resistance and occurs before any β-cell abnormalities are present
- DPP-4 is not an inhibitor of GLP-1
- Pubertal insulin resistance plays an important role in increasing risk for diabetes, but leads to hyperinsulinemia unless β-cell dysfunction is present

Question 2

A 14 year-old M is referred for evaluation of new-onset diabetes. He presented to his PCP for routine physical and was noted to be obese with BMI of 32 kg/m^2, acanthosis nigricans at his neck and in his axillae, and otherwise normal Tanner IV exam. Laboratory testing revealed a hemoglobin A1c of 6.8%, fasting glucose of 112 mg/dL, fasting insulin of 65 µU/ml

Of the following, the next best step in establishing the diagnosis of type 2 diabetes is:

A) Fasting C-peptide measurement

B) Fasting and 2-hour insulin measurement following 75 grams oral glucose

C) Fasting lipid panel

D) Pancreatic autoantibody determination

E) Repeat Hemoglobin A1c determination

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E) **Repeat Hemoglobin A1c determination**

Question 2

- The most important first step in this patient is establishing the diagnosis of diabetes
- The ADA criteria require repeat determination in the asymptomatic patient
- HbA1c must be performed in a certified chemistry laboratory; POC A1c are not acceptable for diagnosis
- Insulin and C-peptide measurements play no role in the diagnosis of diabetes. Elevated levels suggests T2D but are not diagnostic of diabetes or diabetes type
- Pancreatic autoantibodies distinguish T1D from T2D, but are not diagnostic of diabetes
- A fasting lipid panel is important to identify associated comorbidities but does not contribute to diagnosis of diabetes

Question 3

A 15 y/o F of Mexican descent presents with concerns of polyuria and polydipsia. Initial BG is 315 mg/dl. Her height and weight are at the 45th and 99th percentiles respectively. Her HbA1C is 9.1%. Serum electrolytes are normal. Urine analysis shows small ketones and 4+ glucose

Which one of the following statements reflects the best initial treatment choice?

A) Initial treatment should be with metformin, as long as liver and kidney function are normal

B) Insulin therapy should be initiated at diagnosis

C) Metformin plus a GLP-1 receptor agonist is likely more effective than metformin alone

D) The choice or insulin or metformin will depend on pancreatic autoantibody status

E) A combination of insulin plus metformin should be initiated regardless of whether the patient has type 1 or type 2 diabetes

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Question 3

- Insulin therapy should be initiated at diagnosis if HbA1C > 8.5%
- Insulin therapy is started before autoantibody results
- GLP-1 receptor agonists are currently not first line therapy
- Metformin can also be started at diagnosis but would not be initiated for suspected T1D