Pediatric Endocrine Society (PES) Board Review Course
May 2025

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Below is a copy of ABP content specification outline on topic "Bone and Mineral Metabolism". If the information was reviewed in the presentation, slide number is noted after each specification. Specifications not covered in the talk are expanded on below if necessary.

A. Minerals: physiology and homeostasis

1. Calcium

a. Total versus ionized calcium

1. Know that some extracellular calcium is bound to serum proteins, primarily albumin, while some extracellular calcium is ionized or free **(slide 5)**

2. Know that ionized calcium is biologically active **(slide 5)**

3. Know that in hypoalbuminemia, the total serum calcium concentration is often low despite a normal ionized calcium **(slide 5)**

4. Know that acidosis decreases binding of calcium to serum proteins and thus, in acidosis, the total serum calcium is often low despite a normal ionized calcium **(slide 5)**

5. Recognize the preanalytical factors (eg, prolonged exposure to air, temperature, excess heparin) which may affect accurate laboratory measurement of ionized calcium

b. Maintenance of eucalcemia (slide 17)

1. Intestinal handling of calcium **(slide 14)**
a. Understand the difference between passive and active intestinal calcium absorption and identify the factors (calcium load, hormonal regulation) affecting each

2. Renal handling of calcium (for regulation by PTH, see II.B.1.c.(1)) **(slide 15)**
a. Recognize that in hyperparathyroidism, hypercalciuria is due to the effect of increased extracellular calcium concentration on the kidney and is not due to increased parathyroid hormone concentration **(slide 36)**
b. Know the effects of thiazide diuretics, corticosteroids, and furosemide on renal excretion of calcium **(slide 15)**

3. Skeletal handling of calcium **(slide 16)**

c. Role of calcium in cell biology (slide 5)
1. Calcium channels
2. Intracellular messenger
a. Know that calcium is an intracellular second messenger
3. Neurotransmission
a. Know that calcium is important for neural function, particularly at the neuromuscular junction, and that decreased extracellular calcium concentration causes increased neuromuscular excitability, accounting for many of the symptoms of hypocalcemia **(slide 5, 22)**

2. Phosphate
a. Mechanisms of absorption, excretion, and compartmentalization
1. Kidneys (for regulation by PTH, see II.B.1.c.(1)) **(slide 15)**
a. Know that phosphate homeostasis is regulated predominantly by the kidney

2. Bone **(slide 6)**
a. Recognize that phosphate is a major constituent of bone mineral

3. Intracellular exchange
a. Recognize that phosphate shifts between extracellular and intracellular compartments and know which factors influence this movement

- Shifts between intracellular and extracellular compartments
    - In body fluids, most phosphate is intracellular as HPO_4^{2-}
    - Conditions that move phosphate into cells
        - Respiratory alkalosis (by activating phosphofructokinase and stimulating intracellular glycolysis which leads to phosphate consumption)
        - Carbohydrate intake
        - Osmotic diuresis
        - Catecholamines/beta receptor agonists

3. Magnesium
a. Components (slide 7)
1. Know that serum magnesium is composed of free and protein-bound components

b. Intestinal absorption (slide 14)
1. Understand that magnesium is actively absorbed in the intestinal tract

c. Renal handling of magnesium (slide 15)
1. Understand that the kidney acts to conserve magnesium during magnesium depletion

d. Effect of PTH secretion, action
1. Know how hypomagnesemia can affect parathyroid secretion and action **(slide 7, 53)**

2. Know that hypocalcemia may be refractory to therapy when serum magnesium concentration is decreased **(slide 56)**
3. Recognize the suppressive effect of hypermagnesemia on parathyroid hormone secretion **(slide 7, 55)**

B. The calciotropic hormones
1. PTH
a. Glandular origin (slide 8)
1. Anatomy and embryology
a. Recognize the embryonic derivation of the parathyroid glands
b. Biochemistry, physiology (slide 8)
1. Synthesis and secretion
a. Know that PTH is derived from proteolytic processing of pre-pro-PTH
b. Know that the classical bioactivity of PTH resides in the first 34 N-terminal amino acid structure
c. Know that calcitriol can directly suppress parathyroid hormone synthesis **(Slide 13)**
d. Know that PTH secretion is regulated by extracellular ionized calcium via G-protein-coupled calcium-sensing receptors in parathyroid cells **(slide 9)**

2. Mechanism of action **(slide 10)**
a. Know that PTH acts through the PTH/PTHrP receptor and that this receptor is a seven-transmembrane receptor that signals through Gs to increase cAMP

3. Metabolism **(slide 9)**
a. Recognize that PTH is rapidly cleaved after secretion into amino- and carboxy-terminal fragments

c. Effect on target organs
1. Kidney
a. Know that PTH inhibits phosphate reabsorption in the proximal renal tubule and increases Ca reabsorption in the distal tubule **(slide 15)**
b. Recognize that PTH is an important stimulus to renal 1 alpha-hydroxylase activity and synthesis of calcitriol **(slide 10)**

2. Bone **(slide 16)**
a. Know mechanisms by which PTH increases calcium resorption from bone by activating osteoclastic activity
b. Know that PTH is involved in the recruitment and differentiation of osteoclasts from monocytic cells

3. Intestinal tract **(slide 14)**
a. Recognize that PTH effects upon intestinal calcium absorption are mediated indirectly by its stimulation of calcitriol synthesis

d. Measurement of PTH (slide 8)
1. Region specific assays

a. Understand the physiologic and diagnostic importance of PTH assays which are specific for the N-terminal, C-terminal and mid-region fragments and intact molecule
2. Cytochemical assay
3. Ancillary studies (cyclic AMP, urine calcium)
a. Know the uses and limitations of assays for PTH and vitamin D metabolites and other calciotropic hormones **(slides 8, 10)**
b. Know that nephrogenous cyclic AMP, assessed by measuring plasma and urinary cyclic AMP, is a measure of parathyroid hormone activity **(slide 9)**

e. PTH-related abnormalities
1. PTH insufficiency or resistance
a. Primary hypoparathyroidism **(slides 24, 25, 26)**
1. Be aware that congenital hypoparathyroidism may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive trait
2. Know the syndromes associated with hypoparathyroidism **(see cram sheet)**
3. Know that acquired hypoparathyroidism may be a complication of thyroid surgery or, rarely, radioactive iodine therapy

- Acquired hypoparathyroidism
    - After parathyroidectomy
    - Can be a complication of thyroid surgery or (rarely) radioactive iodine therapy
    - Part of APS-1, the APCED syndrome due to AIRE mutations
    - Iron deposition in gland
    - Copper deposition in gland
    - Gram-negative sepsis
    - Toxic shock syndrome
    - HIV infection

4. Know the pathophysiological consequences of hypoparathyroidism
5. Know that hypocalcemia that occurs in hypoparathyroidism is partly due to decreased synthesis of calcitriol
6. Recognize the characteristic laboratory abnormalities in hypoparathyroidism
7. Know the clinical features of hypoparathyroidism including ectopic (particularly intracranial) calcification
8. Know the differential diagnosis of hypoparathyroidism
9. Know that functional hypoparathyroidism can result from activating mutations or antibody-mediated stimulation of the calcium-sensing receptor of the parathyroid cells
10. Know which medications are used to treat children with hypoparathyroidism and how to adjust doses **(slide 28)**

- Therapy of hypoparathyroidism/PTH resistance (pseudohypoparathyroidism 1a)
    - Calcium (doses between 20-100 mg/kg of elemental calcium day)
    - Calcitriol (doses between 10-40 ng/kg/day)
    - Adjust doses based on serum calcium, urine calcium excretion (usually measured by spot urine calcium/creatinine ratio)

b. Resistance to PTH (pseudohypoparathyroidism) **(slide 25, 26, 28)**
1. Recognize the phenotype known as Albright hereditary osteodystrophy(AHO) that occurs in PHP I
2. Distinguish between PHP I and PHP II
3. Recognize the findings in patients with pseudohypoparathyroidism and in patients with progressive osseous heteroplasia
4. Recognize that PHP IA is due to a mutation in the gene encoding Gs-alpha, which is involved in PTH receptor signal transduction, and that PHP IB is due to abnormal imprinting of Gs-alpha
5. Know that maternal inheritance of inactivating Gs-alpha mutations leads to AHO plus resistance to various hormones, whereas paternal inheritance leads to AHO alone
6. Recognize the laboratory findings, including gene analysis, in patients with pseudohypoparathyroidism
7. Know how to treat children with pseudohypoparathyroidism

2. Hyperparathyroidism
a. Etiology **(slide 35)**
1. Be aware that hyperparathyroidism may occur sporadically or as an inherited trait, particularly in MEN I or MEN IIA
2. Know the causes of hyperparathyroidism

- Secondary hyperparathyroidism (disease of parathyroid glands caused by another disease)
    - Seen in conditions of low calcium intake or absorption
    - Seen in renal insufficiency (Stage V) – initially due to low levels of 1,25D, phosphorus retention, decrease in CaSR activation, skeletal resistance to PTH –also high FGF-23 (d/t high serum phos) suppresses 1,25-OHD leading to high PTH; eventually leads to hypocalcemia and secondary hyperparathyroidism
        - Renal osteodystrophy
            - Associated with high turnover: osteitis fibrosa
            - Associated with low turnover: mixed uremic osteodystrophy
        - Can use calcimimetic agents (cinacalcet) that activate the CaSR to decrease PTH release (can help with osteitis fibrosa but can precipitate hypocalcemia)

b. Familial hypocalciuric hypercalcemia **(slide 38)**
1. Be familiar with the diagnosis of familial hypocalciuric hypercalcemia and know how to distinguish it from other forms of hypercalcemia
2. Know the molecular cause and inheritance pattern for familial hypocalciuric hypercalcemia and its relationship to severe neonatal hyperparathyroidism

c. Treatment **(slide 39,40)**
1. Know the appropriate treatments for hyperparathyroidism
2. Recognize the biochemical profile consistent with "hungry bone syndrome" after parathyroidectomy for severe hyperparathyroidism

2.Vitamin D
a. Biochemistry, physiology
1. Biosynthesis (slide 10)

a. Photosynthesis in skin
1. Know that vitamin D is produced in the skin by the action of ultraviolet light on 7-dehydrocholesterol
2. Know that the photocatalyzed conversion of 7-dehydrocholesterol to vitamin D proceeds faster in light-skinned persons than dark-skinned persons
3. Know that ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) can be derived from plant and animal dietary sources respectively and that the two molecules are metabolized similarly

b. Hydroxylation in liver
1. Know that the liver is the site of 25-hydroxylase activity

c. Hydroxylation in kidney
1. Understand the regulation of 1-alpha hydroxylase activity by phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D

d. Synthesis in inflammatory tissue **(slide 37)**
1. Know that 1-alpha hydroxylase activity exists in some neoplastic and inflammatory monocytes and in macrophages, particularly in sarcoidosis

2. Circulating metabolites
a. Know that serum 25-hydroxyvitamin D concentrations primarily reflect vitamin D nutritional status **(slide 10)**
b. Know that 1,25-dihydroxyvitamin D concentrations may be elevated in children with rickets due to phosphate or vitamin D deficiency **(slide 29, 43)**
c. Know that 25-hydroxyvitamin D can cross the placenta from mother to fetus **(slide 63)**

3. Mechanism of action (slide 11)
4. Effects on target tissues (slide 11)
a. Binding sites
1. Know that 1,25-diydroxyvitamin D binds to a ~~cytoplasmic~~ nuclear receptor that is a member of the steroid receptor superfamily and that the receptor binds to promoters to alter transcription of the target genes

b. Intestine
1. Recognize that 1,25-dihydroxyvitamin D is the primary stimulator of intestinal calcium transport
c. Bone
d. Kidney

5.Vitamin D-related disorders

a. Vitamin D deficiency (nutritional) (slide 29, 63)

1. Understand that nutritional vitamin D deficiency occurs only if there is both insufficient dietary intake of vitamin D and insufficient sun exposure
2. Recognize that nutritional vitamin D deficiency can cause rickets, and less commonly, hypocalcemia
3. Recognize that anticonvulsant therapy may be associated with vitamin D deficiency
4. Know the typical pattern of biochemical abnormalities in vitamin D deficiency rickets
5. Know how to treat nutritional vitamin D deficiency

- Deficiency
    - Treat vitamin D deficiency – with enteral doses of vitamin D ranging from 2000 IU/day up to 50,000 per week (no standard approach although Munns et al 2016 have a table of suggested doses)

6. Recognize the high prevalence of subclinical 25-hydroxyvitamin D deficiency in U.S. children and its association with increased levels of parathyroid hormone

b. Vitamin D deficiency (gastrointestinal etiology) (slide 30)

1. Understand the importance of the intestinal mucosa, biliary tract, and pancreatic enzymes in the absorption of dietary vitamin D, and that vitamin D metabolites undergo enterohepatic circulation
2. Recognize the gastrointestinal causes of childhood vitamin D deficiency: short-bowel syndrome, celiac disease, biliary obstruction, and other causes of fat malabsorption
3. Know how to treat vitamin D deficiency due to malabsorption

Can use vitamin D sublingual, transdermal, IM injection, higher doses of oral vitamin D, or calcitriol (no 25-OHD currently available in US)

c. Vitamin D abnormalities in renal insufficiency (slide 31)

1. Understand the pathophysiology of the secondary hyperparathyroidism that accompanies renal insufficiency

Initially due to low levels of 1,25D, phosphorus retention, decrease in CaSR activation, skeletal resistance to PTH –also high FGF-23 (d/t high serum phos) suppresses 1,25-OHD leading to high PTH; eventually leads to hypocalcemia and secondary hyperparathyroidism

2. Recognize that 1,25-dihydroxyvitamin D values are decreased in patients with chronic renal insufficiency and understand the pathophysiological basis for the decreased concentrations
3. Understand the rationale for use of calcimimetic agents **(slide 39)**

d. Deficient 1 alpha-hydroxylase activity (slide 31)

1. Know that deficiency of calcidiol 1 alpha-hydroxylase results in rickets (previously termed Vitamin D-dependent rickets type 1) which is inherited in an autosomal recessive pattern
2. Recognize the laboratory abnormalities in 1 alpha-hydroxylase deficiency
3. Know the treatment for 1 alpha-hydroxylase deficiency. Calcitriol and calcium

e. Hereditary resistance to vitamin D (slide 32)

1. Know that vitamin D insensitivity is associated with mutations in the gene encoding the vitamin D receptor
2. Recognize that insensitivity to calcitriol causes vitamin D-dependent rickets type 2 (hereditary vitamin D-resistant rickets) and know the phenotype of that condition, which includes alopecia

	Vitamin D Deficient	Vitamin D Dependent Type 1	Vitamin D Dependent Type 2	X-Linked Hypophosphatemic Rickets (Vit D resistant)	Renal Disease
Problem	Nutritional Poor UV exposure	1-alpha hydroxylase deficiency	End Organ resistance -VDR mutation	Defect of renal tubular reabsorption of phos	Defect of Phosphate excretion
Calcium	normal/↓	↓	↓	normal	↓
Phosphate	↓	↓	↓	↓	↑
Alkaline Phosphatase	↑	↑	↑	↑	↑
iPTH	↑	↑	↑	normal	↑
1,25 Vitamin D	normal/↑	↓	↑	normal/↓	↓
25 Vitamin D	↓	normal	normal	normal	
Treatment	Vitamin D and Ca	Calcitriol	Difficult to treat	Calcitriol and phos; burosumab	Variable

f. Hypervitaminosis D (slide 35)

1. Recognize various causes of Vitamin D excess

Vitamin D intoxication

1. 400 IU/ml vs 400 IU/drop (1 ml = 20 drops)
2. Excess fortification of milk
3. Topical calcipotriol or calcipotriene used for psoriasis has been associated with systemic vitamin D excess

25 OH D has a very long half-life (2-3 weeks); stored in adipose tissue

4. Excess calcitriol but less likely since it lasts only 1-2 days (half-life 5-12 hours)
5. Rare LOF mutation of CYP24A1 gene (decrease in 24 hydroxylase enzyme)

2. Recognize the clinical and laboratory manifestations of hypervitaminosis D

High serum Calcium, high serum Phosphorus, low PTH, elevated 25 OH Vitamin D

3. Calcitonin

Calcitonin is a polypeptide secreted by parafollicular cells. Its action is primarily antiresorptive.

Bone (osteoclasts) – inhibits resorption

Kidney – inhibits phosphate and calcium reabsorption
Lowers serum calcium and phosphate levels
There are no known diseases of deficiency or excess of calcitonin. Salmon calcitonin is used pharmacologically for hypercalcemia but has associated tachyphylaxis.

a. Physiology -- effects on target tissue
1. Bone
a. Know that calcitonin, given pharmacologically, inhibits bone resorption

C. Other clinical disturbances of mineral homeostasis
1. Hypocalcemia (slide 22, 23)
a. Neonatal
1. Clinical recognition
a. Know the symptoms of infantile hypocalcemia

2. Early onset
a. Recognize that early onset neonatal hypocalcemia frequently reflects intrauterine and postnatal insults such as type 1 diabetes, toxemia of pregnancy, or premature or traumatic delivery

3. Late onset
a. Know that late onset neonatal hypocalcemia may be due to excessive phosphate intake, hypomagnesemia, or congenital hypoparathyroidism

4. With hypomagnesemia **(slide 53)**
a. Know that hypomagnesemia is associated with hypocalcemia and decreased secretion of PTH
b. Know that, in patients with hypomagnesemia, eucalcemia is achieved by administration of magnesium

5. Maternal hypercalcemia
a. Know that maternal hypercalcemia can cause neonatal hypocalcemia and the mechanism involved

6. Transient
a. Recognize that hypoparathyroidism in the newborn and early infancy periods may spontaneously abate, particularly when it is caused by maternal ~~hypocalcemia~~ hypercalcemia

b. Nutritional calcium deprivation
1. Know that hypocalcemia can be due to inadequate calcium intake, particularly in infants

c. Evaluation of hypocalcemia

1. Know the various causes of hypocalcemia and how to determine the etiology of hypocalcemia by clinical and laboratory evaluation **(slide 27)**
2. Recognize the signs and symptoms of hypocalcemia **(slide 22)**

d. Treatment **(slide 28)**
1. Know appropriate therapy for individual causes of hypocalcemia
2. Know the available therapies for children with hypoparathyroidism and their potential adverse effects
3. Recognize the therapeutic usefulness of various forms of vitamin D (vitamin D, calcidiol, 1-alpha hydroxyvitamin D, calcitriol, and dihydrotachysterol), including vitamin D metabolites or analogs which do not raise serum calcium

	AKA	What is this (analog)?	Brand names
Vitamin D	Ergocalciferol (D2) Cholecalciferol (D3)	NA	Many preparations available; can also get D3 from sun exposure Some useful ones • Drisdol drops 8000 IU/ml (contains propylene glycol) • Chewable (Replesta®) 14,000 or 50,000 IU • Capsules: 50,000 IU
Dihydrotachysterol	DHT	Synthetic vitamin D analog - once activated in liver does not require renal hydroxylation to activate	
25 (OH) vitamin D	calcidiol		Calderol, Didrogyl, Dedrogyl, Hidroferol
1,25 $(OH)_2$ vitamin D	calcitriol		Rocaltrol, Calcijex
1-alpha hydroxyl vitamin D	alfacalcidiol; doxercalciferol	Binds to VDR, reduces PTH with less risk of hypercalcemia	Alfarol, one-alpha, einsalpha, etalpha, alpha D3, hectorol
1,25 OH2 – 19- nor-dihydroxy vitamin D	Paracalcitol	Binds to VDR, reduces PTH with less risk of hypercalcemia	Zemplar

https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

4. Know the indications for intravenous administration of calcium

2. Hypercalcemia
a. Malignancy associated (slide 37)
1. Know the various mechanisms by which malignant diseases increase serum calcium concentrations
2. Know that PTH-related peptide is a major cause of humoral hypercalcemia of malignancy

b. Williams syndrome (slide 35)
1. Know that Williams syndrome is associated with developmental delay, supravalvular aortic stenosis and a characteristic facies
2. Know that Williams syndrome is caused by a contiguous gene deletion
3. Know that Williams syndrome is associated with infantile hypercalcemia that usually resolves spontaneously

c. Hypervitaminosis A (slide 35)
1.Know that vitamin A causes hypercalcemia by increasing bone resorption

d. Immobilization (slide 35)
1.Know that immobilization can cause hypercalcemia because of increased bone resorption

e. Evaluation (slide 36)
1. Know the various causes of hypercalcemia and how to determine the etiology of hypercalcemia by clinical and laboratory evaluation
2. Recognize the signs and symptoms of hypercalcemia **(slide 36)**

f. Management (slide 39)
1. Be able to appropriately treat hypercalcemia
2. Recognize the importance of correcting dehydration in acute hypercalcemia

3. Hypophosphatemia
a. Recognition (slide 42, 43, 44, 45, 46)
1. Know that hypophosphatemia is most often due to renal phosphate wasting
2. Recognize the association of hypophosphatemic rickets and mesenchymal tumors of bone and soft tissue (oncogenic osteomalacia) and understand the clinical and pathophysiological similarities between this disorder and X-linked hypophosphatemic rickets
3. Know what is meant by the "Fanconi syndrome" and recognize its causes

- Fanconi syndrome
    - Renal proximal tubular disorder leading to phosphaturia, amino aciduria, glycosuria, tubular proteinuria, electrolytes in urine, and proximal RTA
    - Genetic causes include: cystinosis, Dent disease, galactosemia, hereditary fructose intolerance, Lowe oculorenal syndrome, mitochondrial myopathies, Tyrosenemia type 1, Wilson disease

- Acquired causes
  - Drugs: aminoglycosides, cisplatin, ifosfamide, desfirasirox, and valproic acid
  - Heavy metals: cadmium, lead, mercury

4. Know that hypophosphatemia may be due to acute redistribution of phosphate
5. Recognize that hypophosphatemia can be caused by primary or secondary hyperparathyroidism
6. Recognize the clinical signs and symptoms of hypophosphatemia
7. Be familiar with X-linked autosomal dominant and autosomal recessive hypophosphatemic rickets, including clinical characteristics, mode of inheritance, biochemical characteristics, pathophysiology, and molecular genetic etiology
8. Understand that, in patients with X-linked hypophosphatemic rickets, there is both urinary phosphate wasting and decreased 1-alpha hydroxylation, often resulting in a 1,25-dihydroxyvitamin D level that is inappropriately normal in the presence of hypophosphatemia
9. Be familiar with hereditary hypophosphatemic rickets with hypercalciuria and understand how the phosphaturia causes increased 1-alpha hydroxylation that leads to increased calcium absorption and hypercalciuria
10. Understand the role of increased FGF-23 in disorders of phosphate
11. Understand the role of increased FGF-23 function in disorders of phosphate wasting, such as autosomal dominant hypophosphatemic rickets or McCune-Albright syndrome

b. Evaluation (slide 46)
1. Know the various causes of hypophosphatemia and how to determine the etiology of hypophosphatemia by clinical and laboratory evaluation
2. Understand the concepts of reabsorbed fraction of filtered phosphate and the renal phosphate threshold

c. Therapy (slide 47)
1.Understand the treatment of hypophosphatemic disorders and recognize renal calcification and secondary hyperparathyroidism as complications of therapy

Inherited Form	Molecular Genetics	Clinical Characteristics	Biochemistry	Pathophysiology	Rx
X-linked dominant	PHEX mutations	Hypophosphatemia, slow growth, rickets, dental abscesses, enthesopathy	Low phosphorus; normal calcium; normal to high PTH; high alk phos; inappropriately normal 1,25 D	PHEX mutations indirectly change degradation and production of FGF23	As per talk – calcitriol and phos or burosumab
Autosomal Dominant Hypo-phosphatemic Rickets (ADHR)	Mutations in Klotho/ FGF-23	As above with incomplete penetrance and dominant inheritance pattern – eg. can see transmission from father to son		Activating mutations in FGF23 lead to high FGF23 concentrations; KLOTHO mutations are associated with hyperparathyroidism	calcitriol and phos; some cases resolve spontaneously

Autosomal Recessive Hypo-phosphatemic Rickets	Mutations in DMP1 or ENPP1	As above with recessive inheritance pattern		DMP-1 associated with high FGF23 levels	Calcitriol and phos
Hereditary Hypo-phosphatemic Rickets with Hypercalciuria (Autosomal Recessive)	Mutations in renal NaPi-IIc trans-porter	Hypophosphatemia, slow growth, hypercalciuria	Low phosphorus; normal calcium; normal to high PTH; high alk phos; **high normal or high 1,25 D (since FGF23 low)**		Phos alone

4. Hyperphosphatemia

a. Neonatal (slide 49)

1. Know the causes of increased serum phosphate concentrations in the neonate

b. Renal insufficiency

1.Recognize the relationship between calcium and phosphate in renal disease

2.Understand the pathogenesis and clinical manifestations of renal osteodystrophy including the role of hyperphosphatemia, decreased 1,25-dihydroxyvitamin D, and secondary hyperparathyroidism

- In renal disease
    - When phosphate rises, calcium falls (and then PTH can rise)
    - Can be associated with renal osteodystrophy (see secondary hyperparathyroidism)

c. Idiopathic (tumoral calcinosis) (slide 50)

1. Recognize different causes of hyperphosphatemia, including the syndrome of tumoral calcinosis

2. Understand the role of decreased FGF-23 function, such as in the syndrome of tumoral calcinosis

3. Understand the increased role of decreased FGF-23 function, such as in the syndrome of tumoral calcinosis

d. Hypoparathyroidism (slide 49)

1. Recognize that hypoparathyroidism causes hyperphosphatemia

e. Phosphate loading (slide 49)

1.Endogenous

a. Recognize that hyperphosphatemia can be a cause of hypocalcemia

b. Know that acute hyperphosphatemia and hypocalcemia can be caused by massive cell lysis, either neoplastic cell lysis (due to cytotoxic therapy) or lysis of normal cells (eg, rhabdomyolysis, hemolytic anemia, crush injuries, etc)

2. Exogenous

a. Know that acute hyperphosphatemia and hypocalcemia can be caused by phosphate administration (intravenous, oral, or rectal)

f. Evaluation

g. Treatment (slide 51)
1. Know when to use a low phosphate diet and phosphate-binding agents to treat hyperphosphatemia

5. Hypomagnesemia
a. Clinical presentation
1. Recognize the clinical consequences of hypomagnesemia **(slide 53)**

b. Etiology
1. Know the causes of hypomagnesemia **(slide 54)**

Congenital

1. IDM, infant of mom with preeclampsia, prematurity, IUGR,
2. Hypomagnesemia with secondary hypocalcemia (TRPM6)
3. Gitelman and Bartter syndrome

   Gitelman syndrome: NaCl cotransporter mutation – hyperreninemia, metabolic alkalosis, hypokalemia, hypomagnesemia, HYPOcalciuria. Typically presents at a later age (adolescence, adults)

   Bartter syndrome: Mutation of chloride channel. Classically presents before age 6 with polyuria, polydipsia, FTT. hyperreninemia, metabolic alkalosis, mild hypomagnesemia, HYPERcalciuria.
4. Autosomal dominant hypocalcemia – activating mutation of CaSR in kidney. Low calcium, low mag, inappropriately normal PTH, HYPERcalciuria. Right shift set point of PTH secretion.

Acquired

1. Malabsorption
2. Drugs –
   - Alcoholism
   - GI losses: PPI, laxatives
   - Renal losses: loop/thiazide diuretics, carboplatin, cisplatin, aminoglycoside, amphotericin B, cyclosporin

c. Evaluation
1.Know how to evaluate hypomagnesemia **(slide 56)**

- Check medication h/o, medical h/o.
- Labs – CMP, Ca, mg, phos, 25 OH D, PTH
- Urine Mg and calcium
  - Fractional excretion of magnesium

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

d. Treatment **(slide 56)**
1.Know how magnesium salts should be administered and the specific drawbacks of each route of administration

- Acutely can be associated with tetany, arrhythmia or seizures
  - Can give IV magnesium

- Note – when given IV ~50% given is quickly excreted in the urine d/t inhibition of renal magnesium reabsorption
- For chronic repletion give sustained-release preparations- can be associated with diarrhea

6. Hypermagnesemia (slide 55, 56)
a. Treatment
1. Know how to treat a hypermagnesemic patient
7. Disorders of other trace minerals

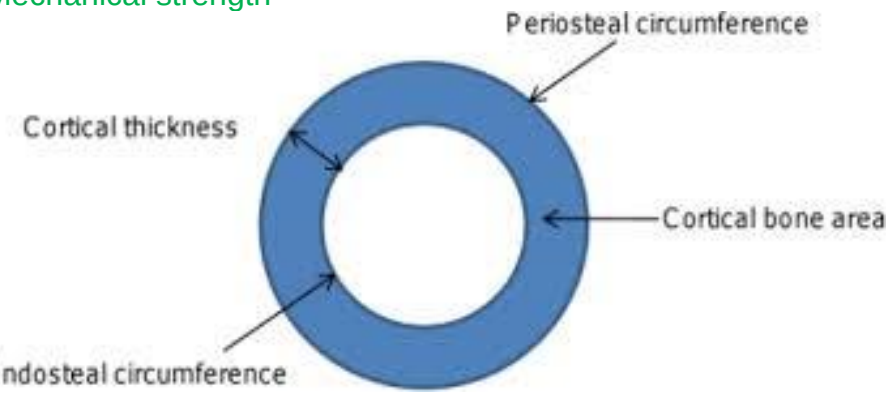
D. Bone biology
1. Anatomy and structure
a. Matrix
1. Know that the organic matrix of bone contains collagen (particularly type I) and osteocalcin and that unmineralized bone matrix is called osteoid

b. Mineral phase
1. Know that bone mineral is deposited in the matrix and consists principally of hydroxyapatite, which contains calcium and phosphate

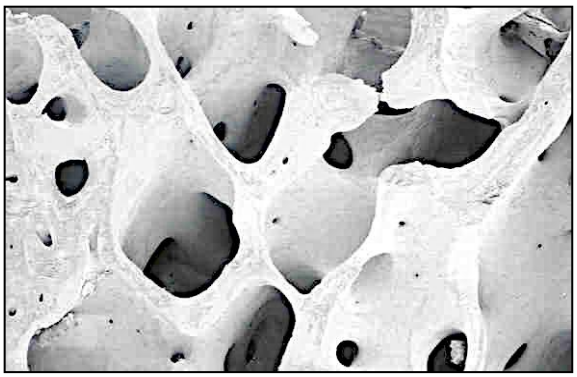
c. Bone cells
1. Understand the origins and roles of osteoblasts, osteoclasts, and osteocytes

d. Trabecular and cortical bone
1. Understand the differences between trabecular bone and cortical bone

- Types:
  - Cortical/compact (75%)
    - Outer surfaces of long bones, flat bones
    - Mechanical strength



  - Cancellous/trabecular (25%)
    - Inner core or ends of long bones, flat bones, vertebrae
    - Greater surface area, more dynamic



- Formation:
  - Flat bones – intramembranous bone formation
  - Axial, appendicular – endochondral bone formation

Most of the bone is compact or cortical that makes up the outer surfaces of long and flat bones. The inner core of the bones is composed of cancellous or trabecular bone. It has a greater surface area and more dynamic in its turnover.
Bone formation occurs via two different processes

1. intramembranous bone formation like in the flat bones of skull.
2. endochondral bone formation which primarily occurs at the ends of the long bones and vertebrae at the growth plate.

- Structure:
  - Osteoid – proteinaceous matrix (collagen, osteocalcin)
  - Mineral – calcium, phosphorus (hydroxyapatite)
  - Cell types:
  - Osteoblasts (derived from mesenchymal cells)
    - Bone forming cells, deposit bone mineral in the matrix
  - Osteoclasts (derived from macrophages)
    - Bone resorbing cells, release mineral, breakdown collagen
  - Osteocytes (derived from osteoblasts)
    - Support bone matrix turnover; make sclerostin, FGF-23; also related to mechano-sensing

2. Physiology
a. Bone formation
1. Know factors that stimulate bone formation (eg, mechanical load, GH/IGF-I, intermittent PTH) and factors that inhibit bone formation (eg, glucocorticoid) **(slide 63)**

b. Bone resorption
1. Know factors that stimulate bone resorption (eg, continuous PTH, thyroid hormone) and factors that inhibit bone resorption (eg, estrogen, androgen and calcitonin) **(slide 63)**

Bone remodeling is a continual process that happens throughout the lifespan. Modeling is a process that happens during childhood when there is growth and the shape and size of the bones are determined.
Peak bone mass is attained by early-mid 20s followed by a plateau and then decline especially in women post menopause.
Bone formation is stimulated by intermittent parathyroid hormone, mechanical loading, growth hormone, sex steroids, and vitamin D and inhibited by glucocorticoid therapy.
Bone resorption is stimulated by Continuous parathyroid hormone, hyperthyroidism, inflammatory markers like cytokines. Bone resorption is inhibited by sex steroids, calcitonin, bisphosphonates.

2. Understand the interplay among RANK, RANK ligand, and osteoprotegerin (OPG) in the regulation of osteoclast function **(slide 16)**

c. Bone mineralization **(slide 63)**
1. Know that bone mineralization requires sufficient extracellular calcium and extracellular phosphate and is promoted by osteoblasts
2. Know that alkaline phosphatase is an enzyme essential for normal mineralization of bone
3. Know that alkaline phosphatase in liver and bone are biochemically distinguishable and that bone alkaline phosphatase is a marker of bone formation

- Bone formation:
  - Osteocalcin (OC), Bone specific Alkaline Phosphatase (BSAP), amino-terminal propeptide of type I procollagen (PINP)
- Bone resorption:
  - Urinary N-telopeptide crosslink (NTX) and serum C-telopeptide crosslink (CTX)
- Alkaline Phosphatase – bone, liver, intestine - antigenically distinct
- Transient hyperphosphatasemia (benign) of infancy & childhood
  - Differential – primary bone disease, liver disease, renal osteodystrophy
- Bone formation markers are categorized as:
-
- **Matrix proteins:** Osteocalcin (OC), **Osteoblast enzymes:** Alkaline phosphatase (ALP) (total and bone-specific), **By-products of collagen synthesis:** Propeptides of type 1 collagen: (C-terminal: P1CP, N-terminal: P1NP)
-
- The bone resorption markers are categorized as follows:
-
- **Collagen degradation products:**
- Telopeptides of type 1 collagen (C-terminal: CTX-1 and CTX-matrix metalloproteinases [MMP], N-terminal: NTX-1)
- Alkaline phosphatase is important for bone mineralization and has antigenically distinct isoforms such as bone, liver, intestine, placenta. Benign transient 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.

d. Bone turnover

1. Be aware that bone is continually remodeled through the combined actions of osteoblasts and osteoclasts and that an imbalance between formation and resorption can lead to osteoporosis or osteopetrosis

- High or low rates of modeling/remodeling with an imbalance between resorption and formation can be associated with decreased or increased bone mass

e. Skeletal growth

1. Understand that longitudinal bone growth occurs at the growth plate by endochondral bone formation in which cartilage is created and then remodeled into bone tissue
2. Be familiar with the mechanisms of replacement of cartilage with ossification centers
3. Understand the process of longitudinal growth at the growth plate
4. Know that apoptosis is a mechanism of growth regulation
5. Know that growth in bone width occurs at the periosteum
6. Know that IL-1 alpha, TNF-alpha, and TNF-beta are potent stimulators of bone resorption and inhibitors of bone formation

Bone formation can occur via 2 methods:
Intramembranous – replacement of mesenchymal tissue directly by bone
Endochondral – intermediate step – cartilage production

- Normal bone growth
  - Longitudinal growth occurs at growth plate by endochondral bone formation
    - On epiphyseal side of growth plate cartilage is forming; on diaphyseal side this cartilage is ossified and bone grows in length
  - Endochondral ossification (at growth plate)
    - First mesenchymal cells condense
    - Then they differentiate into chondrocytes to make cartilage
    - Chondrocytes then proliferate – make bone model
    - Chondrocytes then stop dividing become hypertrophic
    - The cartilage is then invaded by blood vessels; chondrocytes die
    - Cells surrounding the model differentiate into osteoblasts
  - Bone also forms by intramembranous ossification (skull) (but this doesn't seem to be in specs)
  - Bone growth is regulated by apoptosis
  - Bone width increases at the periosteum
  - Bone resorption is stimulated by IL-alpha; TNF-alpha, and TNF-beta

E. Clinical disorders of the skeleton

1. Osteopenic disorders in childhood (slide 68)

a. Juvenile osteoporosis

1. Recognize idiopathic juvenile osteoporosis **(slide 69)**
2. Recognize the causes of acquired osteoporosis in childhood, particularly disuse and glucocorticoid therapy **(Slide 68)**
3. Know the treatment options for childhood osteoporosis **(Slide 72, 73)**

4. Know the foods rich in calcium so as to properly advise the optimal dietary calcium intake

- Foods rich in calcium – mostly milk products, fortified orange juice, some vegetables (spinach/broccoli – although calcium in vegetables less bioavailable).
    - Excellent resource: www.niams.nih.gov/health_info/bone/Bone_Health/Juvenile/default.asp

b. Osteogenesis imperfecta (slide 70, 71)

1. Recognize that osteogenesis imperfecta can be due to mutations of the type I collagen gene
2. Recognize the clinical features of osteogenesis imperfecta and the clinical spectrum of the disease
3. Know the treatment options for osteogenesis imperfecta **(Slide 73)**

2. Sclerosing disorders of childhood (slide 74)

a. Osteopetrosis

1. Primary

a. Know the various forms of osteopetrosis

b. Know that "malignant" osteopetrosis is a recessively inherited disorder of osteoclasts

- "Malignant" recessive form
    - Due to chloride channel 7 mutations – other forms related to mutations in RANK Ligand; Rank Receptor; TCIRG1, OSTM1, Carbonic anhydrase II
- "Benign" dominant form
    - Due to chloride channel 7 mutations
    - LRP5 mutations – NOT benign osteopetrosis – but former name of "autosomal dominant osteopetrosis type 1"
- Features
    - Increased bone density with "bone in bone" appearance of some long bones; "rugger jersey" spine
    - Fracture
    - Hypocalcemia
    - Frequent Infection; Osteomyelitis
    - Hydrocephalus, Optic nerve compression – blindness, Dental abnormalities (tooth eruption/caries)
    - Marrow failure

2. Secondary

a. Know the various forms of therapy for osteopetrosis (including calcitriol, bone marrow transplantation) **(slide 74)**

3. Rickets and osteomalacia (slide 62,63)

a. Features

1. Know the biochemical features of various types of rickets
2. Be able to recognize the clinical and radiographic features of rickets

3. Know the various causes of rickets and be able to determine the cause in a patient based on clinical and biochemical features
4. Know that rickets and osteopenia may occur in premature infants as a result of dietary phosphate and/or calcium deficiency **(slide 64)**
5. Know how to treat the various types of rickets

b. Associated Findings **(slide 65, 66)**
1. Know the principal clinical and biochemical manifestations of hypophosphatasia, an inherited deficiency of alkaline phosphatase leading to rickets-like bone disease and craniosynostosis
2. Know that distal type renal tubular acidosis may lead to rickets in childhood and eventually to dense nephrocalcinosis (see below)

4. Skeletal manifestations of systemic disease
a. Parenteral hyperalimentation **(slide 64)**
1. Recognize that aluminum toxicity may occur with parenteral nutrition of neonates
    - Neonates can have aluminum toxicity if on TPN due to additives in TPN (recommended threshold < 5 ug/kg/day)

2. Recognize that osteopenia may occur with parenteral nutrition

5. Miscellaneous

6. Investigation of bone disease
a. Assessment of bone mineral density **(Slide 58, 59, 60)**
1. Know the techniques used to assess bone mineral density in children (especially DEXA and quantitative CT)
2. Know the advantages and disadvantages of bone mineral density techniques
3. Be aware that bone density measured by DEXA scans should be interpreted using Z-scores (SD score for age) and not T-score (SD score compared to young adults) and that bone density by DEXA will appear artifactually low in a child with short stature

b. Biochemical markers of bone metabolism
1. Be able to distinguish between benign and clinically significant forms of hyperphosphatasemia
- Can be seen in disorders of high bone formation (e.g. rickets, Juvenile Paget's)
    - Begins in early childhood
    - Markedly elevated alkaline phosphatase
    - Expanded and bowed extremities, non-traumatic long bone fractures, kyphosis, macrocephaly, muscular weakness (wheelchair)
    - Radiographs: cortical thickening, osteosclerosis and osteopenia
    - Biallelic loss of function mutation of *TNFRSF11B* (encodes OPG)
    - Enhanced osteoclastic activity (coupled with osteoblastic activity)
- Also can be seen as a "transient benign" form usually in toddlers; may be after a viral illness; resolves over time

2. Know that bone formation and resorption can be assessed by serum and urinary markers (address above)

7. Miscellaneous disorders of mineralized tissue

a. Nephrolithiasis

1. Understand the pathophysiology of calcium-related kidney stones

- Nephrolithiasis
  - Stones form when crystals grow
  - Crystals form when urine is supersaturated with salts – including calcium oxalate and cysteine
  - Decrease risk of stones by
    - Increasing urine volume (dilutes salts)
    - Decreasing the amount of calcium or citrate in urine
    - Increasing the solubility of the stones by increasing urine ph (for uric acid/cysteine stones) or increasing the amount of inhibitors of crystal formation (citrate)
- Nephrocalcinosis
  - Distal type (type 1) RTA can lead to rickets in childhood and eventually nephrocalcinosis
  - Characterized by hypercalciuria, hypocitraturia, calcium phosphate stones

b. Soft-tissue calcification

1. Know the etiologies of soft-tissue calcification
2. Know the difference between soft-tissue calcification and ectopic bone formation

- Soft tissue calcification
  - Calcium hydroxyapatite (phosphate salt) deposition
  - Can be seen in chronic venous insufficiency, arterial calcification, tumoral calcinosis, metastases, scleroderma, dermatomyositis, pseudohypoparathyroidism,
- Soft tissue ossification (ectopic bone formation)
  - Bone formation in soft tissue
  - Seen in progressive osseous heteroplasia, fibrodysplasia ossificans progressiva, surgery/trauma