Pediatric Metabolic Bone Disorders

SPAP Annual CME Conference – September 13, 2019

Courtney Bishop MPAS, PA-C
Department of Orthopaedics
Nationwide Children’s Hospital - Columbus, Ohio
Metabolic Bone Disorders

- Fibrous Dysplasia
- Osteogenesis Imperfecta
- Osteomalacia
- Osteopenia
- Osteopetrosis
- Osteoporosis
- Paget disease of bone
- Rickets
- Scurvy
Bones

Functions:
- Locomotion
- Support and protection of soft tissues
- Phosphate storage
- Harboring of bone marrow

Sometimes bones are broken. I like to fix bones. Sometimes I break bones to fix bones. Sometimes I put screws in bones. Sometimes I put plates on bones. Sometimes I put wire around bones. Bones. I like to take broken bones and make them straight. Unless it is not a straight bone. Then I do not like to make it a straight bone.

"Guys! I found some bones in here!"

The lungs confuse me. The heart confuses me. Kidneys confuse me. The pancreasconfuses me. Bones do not confuse me. Unless it is the skull. That confuses me. Teeth confuse me. They are bones. I do not like them as much. Ancef is good. I like when anesthesia gives it. Sometimes gentamicin is good too. Not as good as bones. I like bones.
Bone remodeling is necessary for skeleton growth/adaptation, fracture healing, and calcium homeostasis.

Bone remodeling cycle:
- Initiation of bone resorption by osteoclasts
- Transition from bone resorption to bone formation
- Bone formation by osteoblasts

Most metabolic bone disorders secondary to errors in bone remodeling cycle:
- Excessive resorption = osteoporosis
- Excessive formation = osteopetrosis
Bone Metabolism

4 cell types involved in bone metabolism/remodeling cycle

- Osteoblasts
- Bone Lining Cells
- Osteocytes
- Osteoclasts
Bone Metabolism

- **Osteoblasts**
  - Located along bone surface
  - 4-6% of bone cells
  - Derived from mesenchymal stem cells
  - Synthesize type I collagen
  - Mature cells can become osteocytes or bone lining cells, or undergo apoptosis
  - Have receptors for PTH (release secondary messenger to stimulate osteoclast activity) & 1,25 dihydroxyvitamin D (stimulates matrix, alkaline phosphatase synthesis and production of bone proteins)

- Bone Lining Cells
- Osteocytes
- Osteoclasts
Bone Metabolism

- Osteoblasts
- Bone Lining Cells
  - Flat-shaped osteoblasts that cover bone surfaces where neither bone resorption or formation occurs
  - Prevent direct interaction between osteoclasts and bone matrix when resorption should not occur
  - Involved in osteoclast differentiation
- Osteocytes
- Osteoclasts
Bone Metabolism

- Osteoblasts
- Bone Lining Cells
- **Osteocytes**
  - Comprise 90-95% of total bone cells; most long lived (~25 years)
  - Derived from osteoblasts, are ‘trapped’ in matrix to create intracellular matrix
  - Detect mechanical pressures and loads, allow bone to adapt to daily mechanical forces → guide bone remodeling & regulate osteoblast & osteoclast activities
  - Directly stimulated by calcitonin and inhibited by PTH
  - Control extracellular concentration of calcium and phosphorus
- Osteoclasts
Bone Metabolism

- Osteoblasts
- Bone Lining Cells
- Osteocytes
- **Osteoclasts**
  - Originate from mononuclear cells of hematopoietic stem cell lineage
  - Resorb bone
  - Synthesize tartrate-resistant acid phosphatase
  - Bind to bone surface via integrin proteins
  - Receptors for calcitonin (inhibit bone resorption)
Minerals, Vitamins, & Hormones Required for Normal Bone Metabolism

- Calcium
- Phosphate
- Parathyroid Hormone
- Vitamin D
- Calcitonin
- Estrogen
- Corticosteroids
- Thyroid Hormone
- Growth Hormone
Minerals, Vitamins, & Hormones Required for Normal Bone Metabolism
Calcium

- 99% stored in bone
- Necessary for muscle and nerve function
- 50% unbound in plasma, 50% bound to albumin
- Absorbed in duodenum by active transport that is regulated by $1,25\text{(OH)}_2\text{vit D}$ and by passive transport in jejunum
- Resorbed in proximal tubules of kidney
- Dietary requirements:
  - Children: 600mg/d
  - Adolescents 1300mg/d

- Regulators of calcium
  - PTH: increases calcium, decreases phosphate levels
  - $1,25\text{(OH)}_2\text{vit D}$: increases calcium and phosphate levels
Phosphate

- 85% stored in bone
- Unbound in plasma
- Resorbed in proximal tubules of kidney
- Dietary requirements:
  - 1000-1500mg/d
Parathyroid Hormone

- Synthesized and secreted from chief cells of parathyroid glands
- Regulates plasma calcium
- Activates osteoblasts → stimulate osteoclasts
- Modulate renal phosphate filtration
- Decreased calcium levels stimulate release of PTH that acts at intestines, kidneys and bone
Vitamin D

- Steroid that is naturally occurring; activated by UV irradiation (sunlight) or from dietary intake
- Hydroxylated in liver to 25-(OH)₂ vitamin D³
- Hydroxylated again in kidney to 1,25-(OH)₂ (active) and 24,25-(OH)₂ (inactive)
- 1,25-(OH)₂ works at intestines, kidneys and bone
  - Increases serum calcium and increases serum phosphate
Calcitonin

- Created from clear cells in thyroid gland
- Inhibits osteoclasts from resorbing bone → decreases serum calcium
- Increased serum calcium levels stimulates release of calcitonin
Patient #1

- 8 month male with 1 month persistent cough presents to ED
- Chest XR consistent with viral disorder v. reactive airway disease
- PTH: 434
- Vit D 25 hydroxy: <4
- Ca: 9.5
- Phos: 4.2
Rickets
• Spectrum of rare bone disorders
• Failure of mineralization leading to changes at physis resulting in weak bones & deformities
  • Vitamin D
  • Calcium
  • Phosphorus
• Most cases of rickets are secondary to nutritional deficiencies but can also be due to genetic or metabolic issues
Rickets

- First described in the 1640’s by English physician Dr. Daniel Whistler
- During the winter of 1918-1919, German pediatrician Dr. Kurt Huldschinsky demonstrated that rickets could be treated with UV lamps.
- Dr. Edward Mellanby demonstrated the role of diet in rickets between 1918-1920.
- In 1923, Dr. Harry Steenbock demonstrated that irradiating milk and other foods with UV light increased their vitamin D content.
- Fortification of milk with vitamin D beginning in the 1930s decreased incidence in the US, with near elimination by 1945.
Rickets

Types

- Vitamin D deficient
  - Nutritional
- Familial hypophosphatemic
  - Vitamin D resistant
  - Most common genetic form; renal problem
- Vitamin D dependent
  - Types 1 and 2
  - Rare genetic disorder, clinically similar to vitamin D deficient type but more severe
- Renal osteodystrophy
  - Renal failure
- Hypophosphatasia
  - Rare metabolic bone disorder due to deficiency of alkaline phosphatase
Patient #2

14 mo female presented to ED with refusal to WB after fall from crib

Labs:
- Vit D 25 hydroxy <4
- PTH 333
- Ca 8.5
- Phos 2.4
- Alk Phos 1389
Rickets – Vitamin D Deficient

- Secondary to low vitamin D intake
- Highest incidence in premature infants, children with dark skin >6 months of age that are breastfed, children with malabsorption, Asian immigrants, those with dietary restrictions
- Risk factors: lifestyle/clothing habits, prolonged breastfeeding, vegan diet, maternal vitamin D deficiency during pregnancy, prolonged use of medications that modify metabolism – anticonvulsants and antiretrovirals, malabsorption syndromes
- Can also be caused by drugs that change the metabolism of vitamin D
- Most commonly presents between 6-24 months of age
- Relatively rare in US after addition of vitamin D to milk
Rickets – Vitamin D Deficient

Pathophysiology

- Vitamin D promotes gut absorption of calcium and maintains serum calcium and phosphate
- Low vitamin D leads to altered serum calcium and phosphate
  - Poor calcification of cartilage matrix of long bones
  - Interferes with physeal growth and mineralization of bones
- Results in deformities as child grows

Similar pathophysiology for nutritional hypocalcemia and hypophosphatemia
Rickets – Vitamin D Deficient

Clinical Features

- Generalized muscle weakness
- Lethargy & irritability
- Short stature (<3%)
- Delayed milestones
- Delayed dentition, enamel defects, multiple carries
- Frontal bossing & suture line enlargement
- Ligamentous laxity
Rickets – Vitamin D Deficient

Orthopedic Features

- Bowing abnormalities of lower limbs
  - Type of bowing depends on age of onset (due to overgrowth of natural bow at age)
    - 1-2 years → varus
    - 2-4 years → valgus
- Elbow, wrist, knee, and/or ankle enlargement
- Chest abnormalities – costal cartilage enlargement & indentation of lower ribs
- Spinal kyphosis
- Higher risk for fractures
Rickets – Vitamin D Deficient

Radiographic Features

- Physeal irregularities – widening, splaying, or cupping
- Osteopenia – more apparent in metaphysis
- Thin, indistinct cortices
- Femoral and/or tibial bowing
- Looser’s Zone – insufficiency fracture on compression side of bone
Rickets –**Vitamin D Deficient**

Laboratory Findings

- Serum vitamin D (25 & 1,25): Low
- Serum Calcium: Low (or normal)
- PTH levels: High
- Alkaline phosphatase: High
- Phosphorus: Low
- Urinary Calcium: Low
Rickets – Vitamin D Deficient

Treatment

- Pharmacologic
  - Oral vitamin D
    - Cholecalciferol (D3), ergocalciferol (D2), calcitriol (vitamin D analogue)
    - Dosing depends on age/weight
    - Resolves most deformities

- Orthopedic referral for deformities that do not correct with vitamin D correction
Rickets – Familial Hypophosphatemic

- Vitamin D resistant
- Most common form of heritable rickets
  - X linked dominant
- Manifests in early childhood
- Lower extremity deformities common
- Short stature
- 1.7-4.8/100,000 children affected; females more common
Patient #3

- 15 y female with X-linked familial hypophosphatemic rickets
Renal tubule inability to absorb phosphate and decreased renal production of vitamin D
  • Genetic mutation affects phosphate regulating gene on X chromosome
  • Causes increased production of fibroblast growth factor 23, which leads to less phosphate reabsorption in renal tubule and decreased renal production of vitamin D

• Decreased production of vitamin D results in poor mineralization of long bones
Clinical Findings
  • Delayed growth, short stature
  • Lower limb deformities

Radiographic Findings
  • Osteopenia
  • Irregular, widened physis

Laboratory Findings
  • Serum phosphorus: Low
  • Alkaline phosphatase: High
  • Serum vitamin D: Low or normal
Rickets – *Familial Hypophosphatemic*

Treatment

**Pharmacologic**
- Calcitriol + phosphate replacement
- Treatment adjusted based on therapeutic outcomes
- Typically continued until adulthood

**Surgical**
- Orthopedic referral for deformity correction
Rickets – 

Vitamin D Dependent

- Rare
- Clinically appears similar but is more severe than vitamin D – Deficient Rickets
- Type 1: cannot convert vitamin D to active form
- Type 2: defect in vitamin D intracellular receptor
Scurvy
Scurvy

- Deficiency of vitamin C (ascorbic acid)
- Leads to decreased chondroitin sulfate synthesis → defective collagen growth and repair → impaired intracellular hydroxylation of collagen peptides
- S/Sx: fatigue, bleeding gums, joint effusions
- Effects bone formation in metaphysis
  - Zone of provisional calcification in physis is widened
- Patients with limited resources highest risk
- Treatment: vitamin C supplementation
Osteoporosis
**Juvenile Osteoporosis**

- Decreased bone density – either secondary to deficiency in formation or too much resorption
  - Osteoporosis common in elderly individuals especially females

- Rare in pediatric patients
  - Generally caused by underlying cause (secondary)
    - Medications
    - Disease
    - Idiopathic osteoporosis

- Especially problematic because occurs during ‘bone building’ years (bone mass peaks ~late 20’s)
Secondary Juvenile Osteoporosis

**Medications**
- Anticonvulsants
- Corticosteroids
- Immunosuppressants

**Behavioral**
- Inactivity/immobilization
- Nutritional
- Excessive exercise

**Underlying medical disorders**
- JIA
- Diabetes
- OI
- Hyperthyroidism
- Hyperparathyroidism
- Cushing syndrome
- Anorexia
- Renal disorders
• When able:
  • Treat underlying condition
  • Change medications if effective and/or ensure dose is lowest effective dose

• Ensure diet has sufficient calcium and vitamin D

• Encourage physical activity as able
  • Unless excessive exercise is playing role – then need activity modifications
Idiopathic Juvenile Osteoporosis

- Primary condition with no known cause
  - Diagnosis of exclusion

- Generally presents before onset of puberty in otherwise healthy children
  - Average age at onset is 7 years, but case reports of 1 year – 13 years

- Most children recover completely
Clinical Findings:
- Pain: low back, hips, and feet; knee and ankles less common but possible
- Difficulty walking/limp
- Lower extremity fractures
- Kyphosis
- Growth retardation or loss of height
- Sunken chest

Imaging:
- Plain radiographs:
  - Low bone density
  - Collapsed vertebrae
- DEXA
  - Low bone mass (Z-score)
Idiopathic Juvenile Osteoporosis

Treatment

• No standard treatment
• Sometimes spontaneous remission
• Therapy, protective support (bracing), and activity restrictions may be beneficial
• Ensure diet has sufficient calcium and vitamin D
  • Recommended intake of calcium for 9-18y: 1300mg/d
    • 10% girls and 25% boys meet this
• When severe and long lasting, bisphosphonates may be beneficial
  • Experimental at this time
Osteogenesis Imperfecta
Osteogenesis Imperfecta

- Connective tissue disorder that causes skeletal dysplasia
  - Also known as ‘brittle-bone disease’, ‘blue-sclera syndrome’, and Lobstein disease

- Primarily caused by mutations in COL1A1 and COL1A2 genes
  - Novel mutations more common than inherited
  - Changes in all tissues that utilize type 1 collagen
    - Bone, ligaments, dentin, & sclera
  - Other mutations may cause similar syndromes and are often considered subtypes of OI

- Autosomal dominant
  - If inherited 50% risk of subsequent pregnancies having OI
  - If novel mutation - unknown risk for future pregnancies
Musculoskeletal
- Fractures
- Limb deformities
- Scoliosis
- Joint laxity
- Growth retardation
- Barrel chest

Other
- Blue sclera
- Triangular facies
- Macrocephaly
- Hearing loss
OI

Skeletal changes

• Epiphysis and physis are broad and irregular
• Disorganized proliferative and hypertrophic zones with loss of normal columnar arrangement
• Zone of calcified cartilage thinning
• Deficiency of primary spongiosa of metaphysis
• Delay of secondary centers of ossification in epiphysis

• Vertebral bodies are wedged, translucent, & shallow
• Thin skull & Wormian bones in skull – multiple ossification centers
OI

Epidemiology

- 1:20,000 live births
  - Believed to be higher due to mild forms being underdiagnosed
- Can present at any age
- Equal male:female
- No racial predilection
<table>
<thead>
<tr>
<th>Type</th>
<th>Bone Fragility</th>
<th>Bone Deformity</th>
<th>Height</th>
<th>Teeth</th>
<th>Sclera</th>
<th>Spine</th>
<th>Skull</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - A</td>
<td>Variable, less severe</td>
<td>Moderate</td>
<td>Average</td>
<td>Normal</td>
<td>Blue</td>
<td>20% with scoliosis and/or kyphosis</td>
<td>Wormian bones</td>
<td>Fair</td>
</tr>
<tr>
<td>I - B</td>
<td>None</td>
<td>None</td>
<td>Average</td>
<td>Dentinogenesis imperfecta</td>
<td>White</td>
<td>No increased risk</td>
<td>No involvement</td>
<td>Good</td>
</tr>
<tr>
<td>II</td>
<td>Very severe</td>
<td>Multiple fractures</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Blue</td>
<td>Unknown</td>
<td>Wormian bones with absence of ossification</td>
<td>Perinatal death</td>
</tr>
<tr>
<td>III</td>
<td>Severe</td>
<td>Progressive bowing of long bones and spine</td>
<td>Short</td>
<td>Dentinogenesis imperfecta</td>
<td>Bluish at birth, white in adults</td>
<td>Kyphoscoliosis common</td>
<td>Hypoplastic wormian bones</td>
<td>Non-ambulatory, wheelchair bound</td>
</tr>
<tr>
<td>IV - A</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Average</td>
<td>Normal</td>
<td>White</td>
<td>Kyphoscoliosis common</td>
<td>Hypoplastic wormian bones</td>
<td>Fair</td>
</tr>
<tr>
<td>IV - B</td>
<td>None</td>
<td>None</td>
<td>Average</td>
<td>Dentinogenesis imperfecta</td>
<td>White</td>
<td>No involvement</td>
<td>Good</td>
<td></td>
</tr>
</tbody>
</table>

V, VI, VII, and VIII – have been described but are not incorporated into the INCO
- 3 year old female; OI type 3
OI - Workup

Labs
• In OI usually normal, but can help rule out other disorders

DNA testing
• 60-94% accuracy
- Respiratory infections
- Basilar impression/invagination
- Anesthesia complications
  - High basal metabolism
- Child bearing
  - Antepartum hemorrhage, abruptio placentae, intrauterine growth restriction, preterm
• Consider supposed mechanism of injury
• Type of fracture
  • Metaphyseal corner fractures are rare in OI

• Evaluate for non-skeletal issues
  • Retinal hemorrhage, hematomas, abdominal trauma – more consistent with NAT
OI or IJO?

- Most children with OI have secondary osteoporosis
- OI patients may also have ligamentous laxity, tinted sclera, or family history (65%)
- Bone biopsy or genetic testing may be necessary
Bracing
Adaptive Devices
Surgical
Pharmacologic
• IV Bisphosphonates:
  • Synthetic analogues of pyrophosphate – binds to hydroxyapatite and inhibits osteoclast mediated bone resorption on endosteal surface → new bone formation via osteoblasts without concurrent bone destruction → increased cortical thickness of bone → decreased fracture incidence & increased bone density
  • Given IV every 4-6 months
  • Especially beneficial in OI types III & IV
  • Side effects: febrile reactions, hypocalcemia (mild), leukopenia, scleritis
Patient #4

Power Chair
AFOs
Walker
PT & OT
Zoledronic Acid infusions
Support for Families

http://www.oif.org/site/PageServer?pagename=Informationcenter