Bone Pathology
MHD II 2018-19

Brief Review

- Bone is a
  - Connective tissue
  - Normally mineralizes
    - Inorganic (65%)
      - Calcium hydroxyapatite
    - Organic (35%)
      - Cells
      - Protein
        - Type I collagen

Review

- What is unmineralized bone called?
Review
- Which cells
  - Synthesize, transport, arrange proteins of bone matrix?
  - Initiate mineralization?
  - Have cell surface receptors which bind numerous hormones (PTH, Vitamin D, Estrogen)?

Review
- Osteoblasts once surrounded by matrix are called?

Review
- Which cells are responsible for bone resorption?
Enchondral Bone Formation
Formation of cartilage matrix replaced by bone

Most bones formed by enchondral bone formation
Mechanism for long bone growth
Intramembranous Bone Formation
Formation of bone without pre-existing cartilage matrix. Bone formation occurs within membrane-like mesenchymal condensations.

Flat bones of skull, mandible, rib cage

Lecture Topics
- Bone Fracture
- Osteoporosis
- Rickets/Osteomalacia
- Hyperparathyroidism
- Paget Disease of Bone
- Genetic Diseases
  - Osteogenesis Imperfecta
  - Achondroplasia
- Avascular Necrosis
- Bone neoplasms

Fractures
- Common condition affecting bone
- Bone is able to repair itself
  - Callus

Fractures
- Common condition affecting bone
- Bone is able to repair itself
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Why do bones break?

- Trauma
- Nontraumatic
- Pathologic fracture = break occurs in bone already altered by a disease process
  - Osteoporosis
  - Vitamin D deficiency
  - Hyperparathyroidism
  - Osteogenesis Imperfecta
  - Paget Disease
  - Neoplasm

Osteoporosis

- Most common bone disease in humans

- Osteoporosis
  - Decreased bone mass
  - Increase risk of fracture

- Normal bone
- Osteoporosis bone

Osteoporosis

- US - >1 million fractures/year secondary to osteoporosis
- $$$ - complications
- Loss of independence
- Death
- Prevention critical
Osteoporosis

- Generalized
  - Primary
    - Postmenopausal, senile
  - Secondary

- Localized
  - Disuse

Understanding Osteoporosis

- Peak bone mass
- Bone remodeling
  - Associated cytokines
    - RANK, OPG
“Bone remodeling”

- Replacement of old bone with newly formed bone
- Enables bone to
  - adapt to mechanical stress
  - maintain strength
  - regulate calcium homeostasis

Bone remodeling
tightly regulated process of bone turnover

Bone resorption & formation in remodeling are coupled and controlled by systemic factors and local cytokines
Bone Multicellular Unit

Key signaling pathways

NFκB – transcription factor key for osteoclast generation, survival
RANK-signaling activates NFκB
RANK ligand = RANKL

Osteoprotegerin (OPG) – "decoy receptor" made by osteoblasts that bind RANKL, prevent interaction with RANK

OPG and RANKL oppose each other

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4th Decade – bone resorption > formation

Bone loss in men

Bone loss in women

0.2-1% loss per year

At menopause 2% loss cortical bone; 9% cancellous bone
Osteoporosis

- Pathology
  - Bone decreased in quantity
  - Entire skeleton affected
    - Greatest vertebra, wrist, ribs, pelvis
  - Thinned trabeculae

Osteoporosis

![Compression fracture](image)

Osteoporosis
Osteoporosis

- Clinico-pathologic correlation
  - Fractures
    - Minimal “trauma”
  - Vertebral fractures
    - Loss of height, kyphoscoliosis, Dowager's hump
  - Pain
  - Associated complications
    - Pulmonary embolism, pneumonia

- Not detectable on X-Ray until 30-40% bone mass lost

- Blood calcium, phosphorous, alkaline phosphatase levels not diagnostic

- Screening, diagnosis: Bone densitometry - dual energy x-ray absorptiometry (DXA) scans

- Prevention/Treatment
  - Exercise
  - Calcium and vitamin D
  - Bisphosphonates
  - Estrogen replacing agents
  - Recombinant PTH
  - RANK ligand inhibitor (denosumab)
Secondary Osteoporosis

- Hyperthyroidism: accelerated turnover of bone and increased osteoclastic activity
- Hypogonadism:
  - women: estrogen deficiency
  - men: anabolic androgens
- Hyperparathyroidism: osteoclast recruitment and increased osteoclastic activity
- Corticosteroids: inhibit osteoblastic activity (suppress expression)
- Alcohol: direct inhibitor of osteoblasts, may inhibit calcium absorption
- Malabsorption: impaired absorption of calcium, phosphate, and vitamin D
- Multiple myeloma: secretion of osteoclast activating factor

Rickets/Osteomalacia

- Etiology = Vitamin D deficiency
- Bone mineralization defect
- Accumulation of osteoid
Vitamin D Deficiency

1. Hydroxylation
2. 25 (OH) D
3. 1a-hydroxylation
4. Calcium absorption
5. Mobilization of Ca and P
6. Phosphorus absorption
7. Serum Ca x P (product)
8. Poor bone remodelling

Soft bones = weak bones
Bone modeling/remodeling abnormal
Osteomalacia - Adults

- Loss of skeletal mass (density)
  - Osteopenia
- Fractures & microfractures
  - Vertebral bodies, femoral neck
- Bone pain

Rickets - Children

- Excess unmineralized matrix
- Affects GROWING BONES

Rickets

- Growth plate not adequately mineralized
  - Osteoclasts do not resorb growth plate cartilage
    - Growth plate irregular, thickened, lobulated
Rickets

- Enlargement of costochondral junction
  - "Rachitic Rosary"

Rickets

- Enlarged joints
- Bowing of legs due to poorly mineralized bone

Rickets

- Soft skull bones
  - Occipital bones flattened
  - Parietal bones buckled inward
- Frontal bossing/squared appearance of head
  - (excess osteoid)
Rickets/Osteomalacia

- How common?
  - VERY
- Treatment = Vitamin D

Hyperparathyroidism

- Increased parathyroid hormone (PTH) level
  - Sensed by osteoblast receptors
  - Release mediators of osteoclastogenesis
  - Increased osteoclast activity
  - Bone resorption

Hyperparathyroidism

- Osteoclasts bore into center of bone trabecula
  - Dissecting osteitis
  - railroad tracks

- Bone loss leads to microfractures
Hyperparathyroidism

- "Brown tumors"
  - NOT Neoplasm
  - Hemorrhage from bone microfractures
  - Influx of macrophages
  - Extensive repair with ingrowth of fibrous tissue

"Brown" because of vascularity, hemorrhage, hemosiderin

SEVERE Hyperparathyroidism

- Osteitis fibrosa cystica
  - Increased osteoclast activity, fibrosis, cystic brown tumors, degenerating brown tumors

Hyperparathyroidism

- Clinico-pathologic correlation
  - How common?
    - Decreased bone mass
    - Pain
    - Fractures
      - Stress fractures
  - Control of hyperparathyroidism - bone changes can regress
Check:
A 38-year-old woman has severe systemic lupus erythematosus with renal complications. She is treated with long-term corticosteroid therapy. Which of the following bone diseases is she most likely to develop?
A. Rickets
B. Osteoporosis
C. Osteomalacia
D. Osteitis fibrosa cystica

Paget Disease of Bone
- Disease caused by osteoclast dysfunction
- Excessive bone resorption followed by disorganized, excessive bone formation

Paget Disease
- Etiology
  - Slow virus infection – Paramyxovirus (remains an hypothesis)
  - Induces IL-6 secretion, increased RANK expression?
    - Stimulate osteoclast activity
  - Genetic
    - Gene mutations leading RANK mediated osteoclast stimulation
    - Mutations in RANKL and RANK/OPG
Paget Disease

- Three “stages”
  - Osteolytic
  - Osteolytic-osteoblastic
  - Osteosclerotic

Paget Disease

Mosaic pattern of bone

Prominent cement lines
Paget Disease

- Begin mid-adulthood
- Axial skeleton, proximal femur involved up to 80% of patients

Paget Disease

- Can be an incidental finding
- Pain in affected bone(s)
  - Microfractures
  - Bone overgrowth compressing nerves, spinal roots
- Platymbasia
  - Flattening of the skull base impinging on foramen magnum
- Leontiasis ossea
- Secondary arthritis

Paget Disease

Thickened skull
Paget Disease
Bowing of tibia

Hypervascular Pagetic bone

High output heart failure
- Cardiac output is high
  - Elevated resting cardiac index beyond normal range of 2.5 to 4.0 L/min per m²
  - Normal systolic function
- Causes
  - Anemia
  - AV fistulas (shunting of blood to venous system)
  - Hyperthyroidism
  - Thiamine deficiency (beri-beri)
Paget Disease

- Sarcoma Development
  - 5-10% patients
  - Osteosarcoma, fibrosarcoma

Paget Disease

- Diagnosis
  - Radiographs
  - Bone scan (increased Osteoblast Activity)
  - “Chalk-stick” type fracture

Paget Disease

- Elevated serum **alkaline phosphatase**
  - Serum calcium, phosphorous unaffected

- Treatment
  - Acetaminophen, NSAIDS
  - Inhibitors of osteoclast function
    - Bisphosphonates
    - Calcitonin
Musician who began to lose hearing at age 28; Complete loss of hearing by 44

Metabolic Summary

Genetic Bone Disease
- Osteogenesis Imperfecta
- Achondroplasia
Osteogenesis Imperfecta

- “Brittle bone disease”
- Defect in extracellular structural protein
  - Type I collagen
    - Not just in bone
      - Joints, eyes, ears, skin, teeth

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Osteogenesis Imperfecta

- Autosomal dominant
- Autosomal recessive
- New mutations

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Osteogenesis Imperfecta

- Multiple fractures of multiple bones
- Accordion-like shortening of limbs
- Blue sclera
- Small mis-shaped
  - Blue-yellow teeth
### Osteogenesis Imperfecta

**Do not memorize**

- Type I – mildest form  
  - Autosomal dominant
- Type 2 – lethal, perinatal disease  
  - Autosomal recessive
- Type 3 – progressive, most severely deforming type  
  - Usually autosomal dominant
- Type 4 – similar to type 1 (normal sclerae)  
  - Autosomal dominant

### Osteogenesis Imperfecta

- **Goals of treatment**
  - Maximize mobility/function
  - Minimize fracture risk
  - Pain control
  - Psychosocial
- Ways to improve collagen synthesis?
- Clinical trials
  - Osteoprogenitor cells for bone marrow transplantation
  - Growth factors
  - Gene therapy

### Achondroplasia

- Defect in signal transduction system
  - Mutation in FGF receptor 3
- Most common disease of growth plate
- Dwarfism
Achondroplasia

- Activating mutation of FGFR3
  - FGFR3 formally inhibits cartilage proliferation
  - Mutation leads to constant activation
  - Inhibits chondrocyte differentiation and proliferation
  - Retards growth plate development
- Autosomal dominant
  - 80% new mutations

Achondroplasia

- Trunk of relatively normal length
- Shortened proximal extremities
- Enlarged head
- Bulging forehead
- Depression of root of nose

Thanatophoric Dwarfism

- Lethal form of dwarfism
  - Perinatal death
- Underdeveloped thorax
  - Respiratory insufficiency
  - Craniofacial abnormalities
Osteonecrosis (Avascular necrosis)

- Bone death (infarction)
  - Bone and bone marrow

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Osteonecrosis

- **Pathogenesis**
  - Ischemia
  - Mechanical (fracture)
  - Thrombosis/embolism
  - Vessel injury
  - Vascular compression

- **Etiology**
  - Trauma
  - Corticosteroids
  - Infection
  - Dysbarism
  - Radiation therapy
  - Connective tissue disorders
  - Vasculitis
  - Sickle cell anemia
  - Tumors
  - Gaucher Disease

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Osteonecrosis

- Dead bone – empty lacunae

- Subchondral wedge shaped pale yellow area
Osteonecrosis

- Subchondral infarcts
  - Pain
  - Collapse
  - Secondary arthritis
    - >10% of joint replacements/year for AVN
- Medullary infarcts
  - Majority clinically silent

“Bone Tumors”
Neoplasms
Topics

- General
- Osteogenic neoplasms
  - Osteoid osteoma (benign)
  - Osteogenic sarcoma (malignant)
- Chondrogenic neoplasms
  - Osteochondroma (benign)
  - Chondrosarcoma (malignant)
- Metastases
  - Ewing Sarcoma (self study)

Primary Bone Neoplasms

- Uncommon
- Children & adolescents > adults
- Benign or malignant
- Age, location, radiographic appearance, tissue examination

Primary Bone Neoplasms

- Hematopoietic 40%
- Chondrogenic 22%
- Osteogenic 19%
- Histiocytic
- Fibrogenic
- Vascular
- Lipogenic
- Neurogenic
- Unknown origin 10%
Bone Forming Neoplasms (Osteogenic)

Osteoid Osteoma
- Benign
- Osseous tissue tumor nidus surrounded by halo of reactive bone formation

Haphazard bone and osteoid rimmed by osteoblasts
Stroma - loose connective tissue, vascular
Osteoid Osteoma

- Arises in cortex of femur, tibia
- Less than 2cm

Osteoid Osteoma

- Clinico-pathologic correlation
  - Men <25 years old (5-25)
  - PAIN
    - Prostaglandin E2
    - Nocturnal
    - Relieved with aspirin
  - Therapy – Radiofrequency ablation, surgery

Osteosarcoma (Osteogenic Sarcoma)

- MALIGNANT
- Most common primary malignant bone tumor
- Site
  - Medullary cavity, metaphysis, long bones
Osteosarcoma

- White tumor filling medullary cavity
- Soft tissue mass (tumor infiltrated through cortex)

Osteosarcoma

- Anaplastic malignant tumor cells
- Neoplastic bone

Source: Robbins
Osteosarcoma

Codman triangle
Triangular shadow between cortex and raised ends of Periosteum
(tumor has broken through the cortex and lifted the periosteum resulting in reactive periosteal bone formation; Only the periosteum at the very margin of the lesion has time to ossify creating a triangular lip of new bone)

Osteosarcoma
- 70% of tumors with genetic abnormalities
  - Nonspecific ploidy changes, chromosomal aberrations
  - Tumor suppressor gene mutations
    - RB gene
      - Germline mutations
        - 1000x risk
      - Sporadic mutations
    - P53
      - Li-Fraumeni syndrome

Osteosarcoma
- Clinico-pathologic correlation
  - Men > women
  - Majority <20 years old
    - Older peak associated with predisposing conditions
      - Name a potential predisposing condition
  - Painful, enlarging mass
Osteosarcoma
- Aggressive
- Blood stream metastases
  - Lung
- Chemotherapy, limb sparing therapy
  - 60% - 70% 5 year survival
- Overt metastases, recurrent disease
  - 20% 5-year survival

Cartilage Forming Neoplasms

Osteochondroma
- Aka “exostosis”
- Benign
  - Most common BENIGN bone tumor
- Stalk of well-differentiated hyaline cartilage
Osteochondroma

- Arise from bones of enchondral origin
  - Metaphysis near growth plate of long tubular bones
    - Most commonly distal femur, proximal tibia, proximal humerus

- Late adolescence/early adulthood
- Men > Women 3:1
- Slow growing mass
  - Incidental
  - Pain if stalk fracture, nerve impingement
- Growth stops when growth plate closes
Chondrosarcoma

- Malignant

- Central portion of skeleton
  - Pelvis
  - Shoulder
  - Ribs

- Normal cartilage

- Malignant chondrocytes
**Chondrosarcoma**

- Grade 1 – Low grade
- Grade 2
- Grade 3 – High grade
  - Very hypercellular, pleomorphic, bizarre tumor giant cells

*Self-assessment time: what does tumor “stage” refer to?*

**Chondrosarcoma**

- Clinico-Pathologic Correlation
  - >40 years
  - Men > women
  - Painful enlarging masses
  - Metastases to lungs, skeleton
  - Prognosis related to grade, size
    - 5 year survival: 90% - Grade I; 43% - Grade 3
  - Surgery
    - Some variants chemotherapy

**Bone Metastases**
Bone Metastases

- Majority of bone neoplasms
- Any cancer, any bone
  - Red marrow of axial skeleton
  - Adults
    - Prostate, breast, kidney, lung
  - Children
    - Neuroblastoma, Wilm’s tumor, Rhabdomyosarcoma

Bone Metastases

- Direct extension
- Lymphatic or hematogenous spread
- Intraspinal seeding through venous plexus

Bone Metastases

- Radiography
  - Lytic
    - Prostaglandins, interleukins, parathyroid-hormone-related hormones
    - Osteoclast bone resorption stimulated
  - Blastic
    - Sclerotic response
      - WNT protein stimulates ostoblastic bone formation
    - Mixed lytic and blastic
via UIC Med School

- Lytic Bone Mets
  - Breast
  - Lung
  - Thyroid
  - Kidney
  - Multiple Myeloma

- Blastic Bone Mets
  - Prostate

Bone Metastases

Bone Metastases
Bone Metastases

Clinico-Pathologic Correlation
- Pathologic fractures
  - Prophylactic surgery to stabilized impending fractures
- Pain
  - NSAIDs
  - Bisphosphonates
  - Adjuvant treatments
    - Radiation Therapy
    - Opiates

Bone Metastases
EWING SARCOMA
Primitive Neuroectodermal Tumor (PNET)

EWING’S SARCOMA/PNET
- Malignant
- t(11;22)(q24;q12) ~90% carry specific chromosomal translocation
  - Resultant gene fusion EWS/FLI-1
    - Protein functions as transcription factor
- 80% patients <20 years old
- 10-15 years old
  - Boys > Girls
  - Rare in Asians and blacks
Ewings
Proiferation of uniform small round cell tumor cells

PNET
Home Wright Rosettes
Tumor cells around a central fibrillary space

Ewing Sarcoma/PNET

- Painful enlarging, destructive mass
  - Diaphysis of long bones
    - Femur
- Some patients have signs/symptoms which mimic infection
  - Fever; tenderness, warmth and swelling over tumor; leukocytosis; elevated ESR
- For patients with localized tumors 75% 5-year survival rate