6.5 Bone Development

- Ossification (osteogenesis) is the process of bone tissue formation
  - Formation of bony skeleton begins in month 2 of development
  - Postnatal bone growth occurs until early adulthood
  - Bone remodeling and repair are lifelong

Formation of the Bony Skeleton

- Up to about week 8, fibrous membranes and hyaline cartilage of fetal skeleton are replaced with bone tissue
- Endochondral ossification
  - Bone forms by replacing hyaline cartilage
  - Bones are called cartilage (endochondral) bones
  - Form most of skeleton
- Intramembranous ossification
  - Bone develops from fibrous membrane
  - Bones are called membrane bones

Formation of the Bony Skeleton (cont.)

- Endochondral ossification
  - Forms essentially all bones inferior to base of skull, except clavicles
  - Begins late in month 2 of development
  - Uses previously formed hyaline cartilage models
  - Requires breakdown of hyaline cartilage prior to ossification
  - Begins at primary ossification center in center of shaft
    - Blood vessels infiltrate perichondrium, converting it to periosteum
    - Mesenchymal cells specialize into osteoblasts

Formation of the Bony Skeleton (cont.)

- Five main steps in the process of ossification:
  1. Bone collar forms around diaphysis of cartilage model
  2. Central cartilage in diaphysis calcifies, then develops cavities
  3. Periosteal bud invades cavities, leading to formation of spongy bone
    - Bud is made up of blood vessels, nerves, red marrow, osteogenic cells, and osteoclasts

Formation of the Bony Skeleton (cont.)

- Five main steps in the process of ossification:
4. Diaphysis elongates, and medullary cavity forms
   - Secondary ossification centers appear in epiphyses
5. Epiphyses ossify
   - Hyaline cartilage remains only in epiphyseal plates and articular cartilages

Formation of the Bony Skeleton (cont.)
- **Intramembranous ossification**: begins within fibrous connective tissue membranes formed by **mesenchymal cells**
  - Forms frontal, parietal, occipital, temporal, and clavicle bones

Formation of the Bony Skeleton (cont.)
- Four major steps are involved:
  1. Ossification centers are formed when mesenchymal cells cluster and become osteoblasts
  2. Osteoid is secreted, then calcified
  3. Woven bone is formed when osteoid is laid down around blood vessels, resulting in trabeculae
    - Outer layer of woven bone forms periosteum
  4. Lamellar bone replaces woven bone, and red marrow appears

Postnatal Bone Growth
- Long bones grow lengthwise by interstitial (longitudinal) growth of epiphyseal plate
- Bones increase thickness through appositional growth
- Bones stop growing during adolescence
  - Some facial bones continue to grow slowly through life

Growth in Length of Long Bones
- Interstitial growth requires presence of epiphyseal cartilage in the epiphyseal plate
- Epiphyseal plate maintains constant thickness
  - Rate of cartilage growth on one side balanced by bone replacement on other
- Epiphyseal plate consists of five zones:
  1. **Resting (quiescent) zone**
  2. **Proliferation (growth) zone**
  3. **Hypertrophic zone**
  4. **Calcification zone**
  5. **Ossification (osteogenic) zone**
Growth in Length of Long Bones (cont.)
1. **Resting (quiescent) zone**
   - Area of cartilage on epiphyseal side of epiphyseal plate that is relatively inactive
2. **Proliferation (growth) zone**
   - Area of cartilage on diaphysis side of epiphyseal plate that is rapidly dividing
   - New cells formed move upward, pushing epiphysis away from diaphysis, causing lengthening

Growth in Length of Long Bones (cont.)
3. **Hypertrophic zone**
   - Area with older chondrocytes closer to diaphysis
   - Cartilage lacunae enlarge and erode, forming interconnecting spaces
4. **Calcification zone**
   - Surrounding cartilage matrix calcifies; chondrocytes die and deteriorate

Growth in Length of Long Bones (cont.)
5. **Ossification zone**
   - Chondrocyte deterioration leaves long spicules of calcified cartilage at epiphysis-diaphysis junction
   - Spicules are then eroded by osteoclasts and are covered with new bone by osteoblasts
   - Ultimately replaced with spongy bone
   - Medullary cavity enlarges as spicules are eroded

Growth in Length of Long Bones (cont.)
- Near end of adolescence, chondroblasts divide less often
- Epiphyseal plate thins, then is replaced by bone
- *Epiphyseal plate closure* occurs when epiphysis and diaphysis fuse
- Bone lengthening ceases
  - Females: occurs around 18 years of age
  - Males: occurs around 21 years of age

Growth in Width (Thickness)
- Growing bones widen as they lengthen through appositional growth
  - Can occur throughout life
- Bones thicken in response to increased stress from muscle activity or added weight
- Osteoblasts beneath periosteum secrete bone matrix on external bone
- Osteoclasts remove bone on endosteal surface
- Usually more building up than breaking down which leads to thicker, stronger
bone that is not too heavy

**Hormonal Regulation of Bone Growth**

- **Growth hormone**: most important hormone in stimulating epiphyseal plate activity in infancy and childhood
- **Thyroid hormone**: modulates activity of growth hormone, ensuring proper proportions
- **Testosterone (males) and estrogens (females) at puberty**: promote adolescent growth spurts
  - End growth by inducing epiphyseal plate closure
- **Excesses or deficits of any hormones cause abnormal skeletal growth**

**6.6 Bone Remodeling**

- **About 5–7% of bone mass is recycled each week**
  - Spongy bone replaced ~ every 3-4 years
  - Compact bone replaced ~ every 10 years
- **Bone remodeling** consists of both **bone deposit** and **bone resorption**
  - Occurs at surfaces of both periosteum and endosteum
  - **Remodeling units**: packets of adjacent osteoblasts and osteoclasts coordinate remodeling process

**Bone Deposit**

- **New bone matrix is deposited by osteoblasts**
- **Osteoid seam**: band of unmineralized bone matrix that marks area of new matrix
- **Calcification front**: abrupt transition zone between osteoid seam and older mineralized bone

**Bone Deposit (cont.)**

- **Trigger for deposit** not confirmed but may include:
  - Mechanical signals
  - Increased concentrations of calcium and phosphate ions for hydroxyapatite formation
  - Matrix proteins that bind and concentrate calcium
  - Appropriate amount of enzyme alkaline phosphatase for mineralization

**Bone Resorption**

- **Resorption** is function of **osteoclasts**
  - Dig depressions or grooves as they break down matrix
  - Secrete lysosomal enzymes and protons (H⁺) that digest matrix
  - Acidity converts calcium salts to soluble forms
Bone Resorption (cont.)
• Osteoclasts also phagocytize demineralized matrix and dead osteocytes
  – Digested products are transcytosed across cell and released into
    interstitial fluid and then into blood
  – Once resorption is complete, osteoclasts undergo apoptosis
• Osteoclast activation involves PTH (parathyroid hormone) and immune T cell
  proteins

Control of Remodeling
• Remodeling occurs continuously but is regulated by genetic factors and two
  control loops
  1. **Hormonal controls**
     • Negative feedback loop that controls blood Ca\(^{2+}\) levels
     • Calcium functions in many processes, such as nerve transmission, muscle
       contraction, blood coagulation, gland and nerve secretions, as well as cell
       division
     • 99% of 1200–1400 gms of calcium are found in bone
     • Intestinal absorption of Ca\(^{2+}\) requires vitamin D
  2. **Response to mechanical stress**

Control of Remodeling
1. **Hormonal controls**
   – **Parathyroid hormone (PTH):** produced by parathyroid glands in
     response to low blood calcium levels
     • Stimulates osteoclasts to resorb bone
     • Calcium is released into blood, raising levels
     • PTH secretion stops when homeostatic calcium levels are reached
   – **Calcitonin:** produced by parafollicular cells of thyroid gland in response to
     high levels of blood calcium levels
     • Effects are negligible, but at high pharmacological doses it can lower
       blood calcium levels temporarily

Clinical – Homeostatic Imbalance 6.1
• Even minute changes in blood calcium levels can cause severe
  neuromuscular problems
  – **Hypocalcemia:** low levels of calcium cause hyperexcitability
  – **Hypercalcemia:** high levels of calcium cause nonresponsiveness
  – Sustained high blood calcium levels can lead to deposits of calcium salts
    in blood vessels or kidneys and formation of kidney stones
Control of Remodeling (cont.)

1. **Hormonal controls (cont.)**
   - Other hormones play a role in bone density and turnover
     - **Leptin**
       - Hormone released by adipose tissue
       - May play role in bone density regulation by inhibiting osteoblasts
     - **Serotonin**
       - Neurotransmitter regulates mood and sleep; also interferes with osteoblast activity
       - Most serotonin made in gut
       - Secreted into blood after a meal
       - May inhibit bone turnover after a meal, so bone calcium is locked in when new calcium is flooding into bloodstream

2. **Response to mechanical stress**
   - Bones reflect stresses they encounter
     - Bones are stressed when weight bears on them or muscles pull on them
     - **Wolf’s law** states that bones grow or remodel in response to demands placed on them
       - Stress is usually off center, so bones tend to bend
       - Bending compresses one side, stretches other side
         - Diaphysis is thickest where bending stresses are greatest
         - Bone can be hollow because compression and tension cancel each other out in center of bone

Control of Remodeling (cont.)

- Wolf’s law also explains:
  - Handedness (right- or left-handed) results in thicker and stronger bone of the corresponding upper limb
  - Curved bones are thickest where most likely to buckle
  - Trabeculae form trusses along lines of stress
  - Large, bony projections occur where heavy, active muscles attach
    - Weight lifters have enormous thickenings at muscle attachment sites of most used muscles
  - Bones of fetus and bedridden people are featureless because of lack of stress on bones

Control of Remodeling (cont.)

- Mechanical stress causes remodeling by producing electrical signals when bone is deformed
  - Compressed and stretched regions are oppositely charged
Compression/tension changes fluid flows within canaliculi, which may also stimulate remodeling.

Hormonal controls determine whether and when remodeling occurs in response to changing blood calcium levels, but mechanical stress determines where it occurs.

6.7 Bone Repair

- **Fractures** are breaks
  - During youth, most fractures result from trauma
  - In old age, most result from weakness of bone due to bone thinning

**Fracture Classification**

- Three “either/or” fracture classifications
  - Position of bone ends after fracture
    - *Nondisplaced*: ends retain normal position
    - *Displaced*: ends are out of normal alignment
  - Completeness of break
    - *Complete*: broken all the way through
    - *Incomplete*: not broken all the way through
  - Whether skin is penetrated
    - *Open (compound)*: skin is penetrated
    - *Closed (simple)*: skin is not penetrated

- Can also be described by location of fracture, external appearance, and nature of break

**Fracture Treatment and Repair**

- Treatment involves **reduction**, the realignment of broken bone ends
  - *Closed reduction*: physician manipulates to correct position
  - *Open reduction*: surgical pins or wires secure ends
  - **Immobilization** of bone by cast or traction is needed for healing
    - Time needed for repair depends on break severity, bone broken, and age of patient

**Fracture Treatment and Repair (cont.)**

- Repair involves four major stages:
  1. *Hematoma formation*
  2. *Fibrocartilaginous callus formation*
  3. *Bony callus formation*
  4. *Bone remodeling*
1. Hematoma formation
   - Torn blood vessels hemorrhage, forming mass of clotted blood called a hematoma
   - Site is swollen, painful, and inflamed

Fracture Treatment and Repair (cont.)
2. Fibrocartilaginous callus formation
   - Capillaries grow into hematoma
   - Phagocytic cells clear debris
   - Fibroblasts secrete collagen fibers to span break and connect broken ends
   - Fibroblasts, cartilage, and osteogenic cells begin reconstruction of bone
     • Create cartilage matrix of repair tissue
     • Osteoblasts form spongy bone within matrix
   - This mass of repair tissue is called fibrocartilaginous callus

Fracture Treatment and Repair (cont.)
3. Bony callus formation
   - Within one week, new trabeculae appear in fibrocartilaginous callus
   - Callus is converted to bony (hard) callus of spongy bone
   - Bony callus formation continues for about 2 months until firm union forms

Fracture Treatment and Repair (cont.)
4. Bone remodeling
   - Begins during bony callus formation and continues for several months
   - Excess material on diaphysis exterior and within medullary cavity is removed
   - Compact bone is laid down to reconstruct shaft walls
   - Final structure resembles original structure
     • Responds to same mechanical stressors

6.8 Bone Disorders
• Imbalances between bone deposit and bone resorption underlie nearly every disease that affects the human skeleton.
• Three major bone diseases:
  – Osteomalacia and rickets
  – Osteoporosis
  – Paget’s disease

Osteomalacia and Rickets
• Osteomalacia
- Bones are poorly mineralized
- Osteoid is produced, but calcium salts not adequately deposited
- Results in soft, weak bones
- Pain upon bearing weight

### Rickets (osteomalacia of children)
- Results in bowed legs and other bone deformities because bones ends are enlarged and abnormally long
- Cause: vitamin D deficiency or insufficient dietary calcium

## Osteoporosis

### Osteoporosis
- Osteoporosis is a group of diseases in which bone resorption exceeds deposit
- Matrix remains normal, but bone mass declines
  - Spongy bone of spine and neck of femur most susceptible
    - Vertebral and hip fractures common

## Osteoporosis (cont.)

### Risk factors for osteoporosis
- Most often aged, postmenopausal women
  - Affects 30% of women aged 60–70 years and 70% by age 80
  - 30% of Caucasian women will fracture bone because of osteoporosis
  - Estrogen plays a role in bone density, so when levels drop at menopause, women run higher risk
  - Men are less prone due to protection by the effects of testosterone

## Osteoporosis (cont.)

### Additional risk factors for osteoporosis:
- Petite body form
- Insufficient exercise to stress bones
- Diet poor in calcium and protein
- Smoking
- Hormone-related conditions
  - Hyperthyroidism
  - Low blood levels of thyroid-stimulating hormone
  - Diabetes mellitus
- Immobility
- Males with prostate cancer taking androgen-suppressing drugs

## Osteoporosis (cont.)

### Treating osteoporosis
- Traditional treatments
  - Calcium
Osteoporosis (cont.)
- Vitamin D supplements
- Weight-bearing exercise
- Hormone replacement therapy
  - Slows bone loss but does not reverse it
  - Controversial because of increased risk of heart attack, stroke, and breast cancer

Osteoporosis (cont.)
- Other drugs for osteoporosis:
  - **Bisphosphonates**: decrease osteoclast activity and number
    - Partially reverse osteoporosis in spine
  - **Selective estrogen receptor modulators**: mimic estrogen without targeting breast and uterus
  - **Denosumab**
    - Monoclonal antibody shown to reduce fractures in men with prostate cancer
    - Improves bone density in elderly

Osteoporosis (cont.)
- **Preventing osteoporosis**
  - Plenty of calcium in diet in early adulthood
  - Reduce consumption of carbonated beverages and alcohol
    - Leach minerals from bone, so decrease bone density
  - Plenty of weight-bearing exercise
    - Increases bone mass above normal for buffer against age-related bone loss

Paget’s Disease
- Excessive and haphazard bone deposit and resorption cause bone to be made fast and poorly
  - Called *Pagetic* bone
  - Very high ratio of spongy to compact bone and reduced mineralization
- Usually occurs in spine, pelvis, femur, and skull
- Rarely occurs before age 40
- Cause unknown: possibly viral
- Treatment includes calcitonin and bisphosphonates

Developmental Aspects of Bone
- Embryonic skeleton ossifies predictably, so fetal age is easily determined from X rays or sonograms
- Most long bones begin ossifying by 8 weeks, with primary ossification centers
Developmental Aspects of Bone
Birth to Young Adulthood
- At birth, most long bones ossified, except at epiphyses
- Epiphyseal plates persist through childhood and adolescence
- At ~age 25, all bones are completely ossified, and skeletal growth ceases

Age-Related Changes in Bone
- In children and adolescents, bone formation exceeds resorption
  - Males tend to have greater mass than females
- In young adults, both are balanced
- In adults, bone resorption exceeds formation

Age-Related Changes in Bone (cont.)
- Bone density changes over lifetime are largely determined by genetics
  - Gene for vitamin D’s cellular docking determines mass early in life and osteoporosis risk at old age
- Bone mass, mineralization, and healing ability decrease with age beginning in fourth decade
  - Except bones of skull
  - Bone loss is greater in whites and in females