Bone Tissue
Chapter 7

- Tissues and organs of the skeletal system
- Histology of osseous tissue
- Bone development
- Physiology of osseous tissue
- Bone disorders
Bone Tissue

- Bone is alive and continuously changing.
- Bone tissue (osseous tissue) is a type of connective tissue with cells, vessels, nerves and a matrix hardened by minerals (mostly calcium phosphate).
- Bones are units of the skeletal system
  - individual bones are made up of bone tissue, marrow, cartilage and periosteum
- Functions of the skeletal system include
  - support, protection, movement, blood formation, calcium and phosphate reservoir, pH balance
Compact Bone does not have any spaces or hollows in the bone matrix that are visible to the eye. Compact bone forms the thick-walled tube of the shaft (or diaphysis) of long bones, which surrounds the marrow cavity (or medullary cavity). A thin layer of compact bone also covers the epiphyses of long bones.

Spongy Bone (also called trabecular bone or cancellous bone) consists of a delicate network of trabeculae which branch and intersect to form a sponge-like tissue. The ends of long bones (or epiphyses) contain mainly spongy bone.
Compact Bone and Spongy Bone

- Spongy Bone
- Compact Bone
Features of Long Bones

• **Diaphysis** (shaft) is a cylinder of compact bone containing the marrow cavity (medullary cavity)
  – Diaphysis covered with periosteum

• **Marrow Cavity** contains hematopoietic tissue

• **Epiphyses** (enlarged ends) are spongy bone covered with a thin layer of compact bone
  – enlarged ends strengthen joint and provide attachment of tendons and ligaments

• **Joint Surface** is covered with articular cartilage (smooth, low friction hyaline cartilage and synovial fluid)
Features of Long Bones
Periosteum is a layer of vascular, innervated, dense connective tissue surrounding the non-articular surfaces of bone. **Perforating Fibers** (also called Sharpey’s fibers) are collagen fibers that connect the periosteum to the bone matrix. The **endosteum** is a thin layer of connective tissue that lines the inside of the marrow cavity and any canals passing through the compact bone. Both the periosteum and the endosteum membranes are **osteogenic** — they contain cells that can produce bone. During growth or following injury, osteogenic cells can differentiate into bone-forming osteoblasts.
Structure of a Flat Bone

- External and internal surfaces of flat bone are composed of compact bone.
- Middle layer is spongy bone and it is also called the **diploe**.
- An impact to the skull may fracture the outer layer and crush the spongy bone, but not harm inner compact bone or the underlying brain.
Osteogenic Cells

- **Osteogenic Cells** are found in the endosteum and periosteum.
  - arise from embryonic mesenchymal cells
  - multiply continuously and differentiate into osteoblasts in response to stress or fractures
- **Osteoblasts** produce an extracellular matrix of about 35% collagen fibers and 65% mineral (mostly calcium phosphate).
- **Osteocytes** are osteoblasts that have completely surrounded themselves with the extracellular matrix they produce.
- **Spicules** are isolated, newly formed pieces of bone.
Osteocytes are completely surrounded by **bone matrix**.

- **Lacunae** are the pits in the matrix occupied by the cells.
- **Filopods** (also called pseudopods, cytoplasmic extensions, dendritic processes) are long thin extensions of the osteocytes that produce bone matrix around the cell.
- Filopods are inside tiny canals in the matrix called **canaliculi**.
Osteocytes are arranged in rings called lamellae that are around a central canal that contains blood vessels and nerves. Tips of filopods absorb nutrients from the central canal. Adjacent osteocytes are inter-connected with gap junctions at the tips of the filopods. Osteocytes transfer nutrients from one cell to another through gap junctions.
• Some stem cells in bone marrow develop into macrophages white blood cells called **macrophages**. Some macrophages leave the blood and move into bone tissue. In the bone, 3-50 of these macrophages can merge into giant, multinucleated cells called **osteoclasts**. A single cell formed by the fusion of several cells is called a **syncitium**.

• The surface of an osteoclast facing bone is folded into a **ruffled border** that releases **lysosomes** that contain **enzymes and acids** that erode bone matrix and produce pits in the matrix called **resorption bays** (also called Howship’s lacunae).
Osteoclasts

Four multinucleated osteoclasts producing resorption bays (Howship’s lacunae) in the blue-stained bone matrix. The ruffled border of the osteoclasts is facing the bone matrix. Dissolved components of the bone matrix (calcium and amino acids) accumulate in the interstitial space and are reabsorbed into the blood.
Bone Matrix

- Bone Matrix is about 35% organic and 65% inorganic
- Bone Organic matter consists of:
  - collagen
  - glycosaminoglycans (chondroitin sulfate)
  - proteoglycans
  - glycoproteins
- Bone Inorganic matter consists of:
  - 85% hydroxyapatite (calcium phosphate crystals)
  - 10% calcium carbonate
  - 5% other minerals (fluoride, sulfate, potassium, magnesium)
- Combination of organic and inorganic materials makes bones both strong and resilient
  - minerals resist compression
  - collagen give some flexibility
  - Bone matrix is similar to fiberglass that is composed of strong glass fibers embedded in a flexible polymer
Bone Matrix

© Courtesy of Trent Stephens

Without mineral

Without collagen
Compact Bone

- Osteon (Haversian system) is the basic structural unit of bone.
  - Osteons are cylinders of bone tissue formed from layers (concentric lamellae) of osteocytes and matrix arranged around a central (Haversian) canal.
  - Central Canal is lined with endosteum and contains a neurovascular bundle.
  - Neurovascular Bundles contain an artery, vein, nerve and lymphatic vessel.
  - Osteocytes are connected to each other and their blood supply by thin pseudopods within canaliculi.

- Perforating Canals (Volkmann’s canals) are perpendicular branches of the central (Haversian) canal.

- Circumferential lamellae ring the outer circumference and the marrow cavity.

- Bony trabeculae branch off the compact bone surrounding the marrow cavity, filling the cavity with spongy bone.
Osteon = Haversian System

Circumferential lamellae

Osteon

Haversian canal

Periosteum

Perforating fibers

Blood vessel

Endosteum

Lacuna

Trabeculae

Spongy bone

Perforating canal
Histology of Compact Bone
Osteon = Haversian System

- Lacunae
- Canaliculi
- Haversian (central) Canal
- Concentric Lamellae
Perforating (Volkman’s) Canal

Central (Haversian) Canal
Development of an Osteon

Spongy Bone

• Spongelike appearance formed by rods and plates of bone called trabeculae
  – spaces among the trabeculae are filled with bone marrow

• Light weight but strong
  – trabeculae develop along bone’s lines of stress
Bone Marrow

- Bone Marrow is a soft tissue that occupies the medullary cavity of long bones and the spaces among the trabeculae of spongy bone
- Red Marrow
  - looks like thick blood
  - bone marrow is the adult hemopoietic tissue that produces blood cells and platelets
  - found in vertebrae, ribs, sternum, pelvic girdle and proximal heads of femur and humerus in adults
- Yellow Marrow
  - fatty marrow in shaft of long bones in adults
- Gelatinous Marrow
  - reddish, jelly-like marrow in old individuals
Red Bone Marrow
Two types of Bone Development

- **Intramembranous Ossification** produces the flat bones of the skull.
- **Endochondral Ossification** produces most of the other bones of the skeleton including the long bones of the extremities (arms and legs).

The principal difference between intramembranous bone formation and endochondral bone formation is what is replaced during development.

The tissue replaced during development in intramembranous ossification is embryonic CT. The tissue replaced in endochondral ossification is hyaline cartilage.

The two processes can occur side by side, and do, in the case of fracture healing and in the development of the the mandible and the clavicle which develop partially from intramembranous ossification and partially from endochondral ossification.
Intramembranous Ossification

- Produces flat bones of skull
- Steps of the process:
  1) Mesenchyme condenses into a sheet of vascular, soft tissue
  2) Some mesenchymal cells develop into osteoblasts that form osteoid tissue (uncalcified bone matrix). Other mesenchymal cells develop into fibroblasts that form the periosteum membrane. Calcium is deposited in the matrix and it hardens. Osteoblasts develop into osteocytes as they become surrounded by bone.
  3) Bony trabeculae form spongy bone.
  4) Spaces between trabeculae fill with bone in the surface layers forming compact bone that is covered with periosteum
Intramembranous Ossification of the Skull
1. Condensation of mesenchyme into soft sheet permeated with blood capillaries.

2. Deposition of osteoid tissue by osteoblasts on mesenchymal surface; entrapment of first osteocytes; formation of periosteum.

3. Honeycomb of bony trabeculae formed by continued mineral deposition; creation of spongy bone.

4. Surface bone filled in by bone deposition, converting spongy bone to compact bone. Persistence of spongy bone in the middle layer.
This is a cross section of fetal skull bone developing by intramembranous ossification. The irregularly shaped pink areas are developing spicules of bone.
Embryonic connective tissue (ECT) is gradually replaced by trabeculae (T) of bone that develops around blood vessels in Haversian canals (HC). Osteoblasts (Ob) cover the developing trabecular bone (T) and become osteocytes (Oc) once completely surrounded by matrix. Multinucleated osteoclasts (Ocl) demineralize and remodel the bone matrix.
Endochondral Ossification

- Long Bones form from endochondral ossification as a hyaline cartilage model that is gradually replaced by bone.
- Endochondral Ossification proceeds as follows:
  - a primary ossification center forms in the cartilage model
  - cartilage becomes hypertrophic (chondrocytes swell as they form the primary ossification center).
  - hypertrophic cartilage is removed by macrophages
  - primary marrow space is formed as cartilage is removed
  - blood vessels and nerves grow into the marrow space
  - osteogenic cells (mesenchymal-like fibroblasts) from the perichondrial/periosteal membrane invade the spaces created by the macrophages and transform into osteoblasts
  - osteoblasts deposit osteoid tissue and calcified matrix
Ossification Centers

- The **primary ossification center** forms as cartilage in the center of the cartilage model becomes hypertrophic from a growing blood supply.
- Hypertrophic cartilage calcifies and dies.
- Osteoclasts remove of the dead hypertrophic cartilage and then blood vessels, nerves and osteoblasts grow into that space.
- The same process begins in each epiphysis forming **secondary ossification centers** that will develop into spongy bone.
Figure 9.16  Endochondral bone formation. **A.** Mesenchyme cells begin to condense and differentiate into chondrocytes. **B.** Chondrocytes form a cartilaginous model of the prospective bone. **C, D.** Blood vessels invade the center of the cartilaginous model, bringing osteoblasts (black cells) and restricting proliferating chondrocytic cells to the ends (epiphyses) of the bones. Chondrocytes toward the shaft side (diaphysis) undergo hypertrophy and apoptosis as they mineralize the surrounding matrix. Osteoblasts bind to the mineralized matrix and deposit bone matrices. Later, as blood vessels invade the epiphyses, secondary ossification centers form. Growth of the bones is maintained by proliferation of chondrocytes in the growth plates (Fig. 9.16D). Langman's.
Ossification Centers

- Hyaline cartilage model
- Primary ossification center
- Perichondrium
- Secondary ossification center
- Primary marrow space
- Blood vessel
Cartilage proliferates, becomes hypertrophic, calcifies, dies and is removed and is replaced with new bone tissue.
Zones of Ossification

A) **Zone of Reserve Cartilage** is a layer of resting hyaline cartilage

B) **Zone of Cell Proliferation** is a layer of chondrocytes that multiply forming columns of flattened lacunae

C) **Zone of Cell Hypertrophy** is a region of swollen chondrocytes

D) **Zone of Calcification** is where the cartilage matrix mineralizes and the chondrocytes die

E) **Zone of Bone Deposition** is where mineralized cartilage matrix is replaced by bone. Voids are filled with osteoblasts and blood vessels forming Haversian canals and osteons
Metaphysis is cartilaginous tissue between the primary and secondary ossification centers. The **epiphyseal plate (growth plate)** is a temporary layer of cartilaginous tissue between the spongy bone of the medullary cavity (marrow cavity) and the spongy bone in the epiphyses that persists until growth of the bone is complete.
Secondary Ossification Centers

- Secondary ossification centers begin to form in the epiphyses near time of birth.
- Bone development does not proceed all the way to the end of the bone. Hyaline cartilage remains over epiphysis as the articular cartilage of the joint surface.
- The metaphysis is at the junction of the diaphysis and epiphysis and forms an epiphysseal plate (also called a growth plate) until growth ends.
Growing Bone H&E

- epiphyseal plate
- epiphysis
- bone marrow
- bone trabeculae
The Fetal Skeleton at 12 Weeks stained red for bone tissue. Cartilage is unstained.
• Cranial ossification is incomplete at birth
• Soft regions of the skull called fontanels are regions of dense irregular connective tissue.
• There are usually 6 fontanels at birth
• Most fontanels close by 12 months and all are usually closed by 24 months.
Bone Growth and Remodeling

• Bones grow and remodel throughout life
  – exercise or manual labor increases density and mass of bone
  – pulling of muscle on periosteum stimulates bone growth on that side of the bone
  – osteoclasts are stimulated by increased pressure
  – osteoblasts are stimulated by decreased pressure

• Dental braces reposition teeth by creating greater pressure on the bone on one side of the tooth socket and less pressure on the other side of the tooth socket which remolds the jaw bone as the tooth moves
Factors Affecting Bone Growth

• 20 or more hormones, vitamins and growth factors affect bone and not all the mechanisms are known.

• Bone growth is especially rapid at puberty
  – growth hormones and sex hormones stimulate proliferation of osteogenic cells and chondrocytes in growth plate
  – adolescent girls grow faster than boys and reach their full height earlier (estrogen has strong effect on bone growth)
  – males grow for a longer time due to sustained high levels of testosterone resulting in larger average stature

• Growth ceases when epiphyseal plate “closes”
  – anabolic steroids may cause premature closure of growth plate producing short adult stature
Achondroplastic Dwarfism

- Achondroplastic dwarfism is a genetic disorder resulting in short stature but normal-sized head and trunk.
- Long bones of the limbs stop growing in childhood but other bones are unaffected.
Gigantism

• A pituitary giant can result from an excess of growth hormone during skeletal growth.

8' tall adult
Gigantism

Robert Pershing Wadlow in 1938, at age 20 with actresses Maureen O’Sullivan, left, and Ann Morris.

Smithsonian August 2005 p. 76.
Robert Pershing Wadlow, with his mother at his side, had grown to a record height of 8’11” by the time of his death at age 22.
There are over 200 different types of dwarfism, all of which involve bone growth disorders (osteodysplasia) that result in short stature (adult height less than 4 ft. 10 in. tall).

Primordial Dwarfism is a group of disorders in which growth is proportional but severely delayed, beginning in the womb. This results in some of the smallest people in the world.

The individual pictured has Majewski osteodysplastic primordial dwarfism (MOPD) Type II. Only about 100 individuals worldwide have been identified as having MOPD type II. Both males and females of all ethnic backgrounds are affected. Some families have more than one child with MOPD Type II, which suggests that the disorder is inherited in an autosomal recessive manner.

Mineralization of Bone Matrix

- Mineralization is a process in which ions (mostly calcium and phosphate) are removed from blood plasma and are deposited in the matrix of bone tissue.

- Steps of the mineralization process:
  - osteoblasts produce collagen fibers
  - fibers become encrusted with minerals

Image taken using a Scanning Electron Microscope showing collagen fibers produced by osteoblast cells on a polyurethane foam scaffold mimicking the bone matrix production and mineralization processes.

http://www.sciencewords.net/images/main.php?g2_itemId=157
Mineral Resorption

- Bone is dissolved by the osteoclast “ruffled border” and dissolved calcium and phosphate are released into the blood
  - pumps in the cell membrane secrete hydrogen ions into the space between the osteoclast and the bone and chloride ions follow forming hydrochloric acid (HCl)
  - hydrochloric acid with a pH of 4 dissolves bone minerals
  - an enzyme is also released that digests the collagen
Calcium Balance

- Calcium levels outside of normal values cause:
  - hypocalcemia (deficiency of blood calcium)
    - causes excessive excitability of nervous system by increasing the gradient for diffusion of cations out of the cell which leads to:
      - muscle spasms, tremors or tetany
      - laryngospasm may cause suffocation
    - hypercalcemia (excessive of blood calcium)
      - depresses nervous system activity by decreasing the ionic gradient across the neuron membrane
- Calcium phosphate homeostasis depends on a balance of calcitriol, calcitonin and parathyroid hormone (PTH)
Calcitriol (Activated Vitamin D)

• UV radiation of epidermal keratinocytes converts a cholesterol derivative into \textbf{Vitamin D}_3 (\textbf{cholecalciferol}) which is absorbed into the blood.

• Liver and kidney enzymes convert Vitamin D\textsubscript{3} into the hormone \textbf{calcitriol}.

• Actions of \textbf{calcitriol} include:
  – stimulates the intestines to absorb calcium and phosphate
  – stimulates the kidneys to retain calcium
  – stimulates osteoclasts to release calcium from bone
Calcitriol Synthesis and Action

Ultraviolet light

7-dehydrocholesterol → Calcidiol → Calcitriol

Vitamin D3 (cholecalciferol)

Bone resorption
Reduced excretion of Ca^{2+}
Absorption of Ca^{2+} and phosphate
Calcitonin

• Secreted by C cells of the thyroid gland when calcium is abundant in the blood

• Functions:
  – reduces blood calcium levels
  – reduces osteoclast activity
  – increases the number and activity of osteoblasts

• Calcitonin has a powerful effect in children, but it is less effective in adults
  – calcitonin deficiency is not known to cause any disease in adults, but it may be useful in reducing bone loss in osteoporosis
Parathyroid Hormone (PTH)

- Secreted by the parathyroid glands when the calcium level is too low in the blood.
- Functions
  - promotes calcitriol synthesis
  - stimulates osteoclast multiplication and activity
  - inhibits collagen and bone matrix synthesis by osteoblasts
  - promotes calcium resorption by the kidneys
  - promotes phosphate excretion by the kidneys
Correction for hypercalcemia

- Blood calcium concentration
- Less bone resorption
- More bone deposition
- Reduced osteoclast activity
- Increased osteoblast activity
- Calcitonin

Correction for hypocalcemia

- Blood calcium concentration
- More bone resorption
- Less bone deposition
- Prevention of hydroxyapatite formation
- Conservation of calcium
- Increased osteoclast activity
- Reduced osteoblast activity
- More urinary phosphate excretion
- Less urinary calcium excretion
- Parathyroid hormone
Osteoporosis

- Most common bone disease
- Bones lose mass and become brittle due to loss of both organic matrix and minerals
  - increases risk of fracture of hip, wrist and vertebral column
  - hump results from deformed spine
- Best treatment is prevention: exercise and a recommended calcium intake of 1000 mg/day between ages 25 and 40.
Effects of Osteoporosis
Healing of Fractures

- Normally healing takes 8 - 12 weeks (longer in elderly)
- Stages of healing: see next slide
  1. *fracture hematoma* is a blood clot resulting from broken blood vessels
  2. *soft callus* of collagen and fibrocartilage is formed by fibroblasts and infiltrated by capillaries at site of break
  3. A soft callus is gradually replaced by a *hard callus* of spongy bone in about 6 weeks
  4. Remodeling occurs over 6 months as spongy bone is replaced with *compact bone*
Healing of Fractures

1. Medullary cavity
   - Hematoma
   - Compact bone

2. Fibrocartilage
   - Soft callus
   - New blood vessels

3. Hard callus
   - Spongy bone

4.
Fractures and Repairs
Fibrodysplasia Ossificans Progressiva

Trapped. Extra bone blankets the torso of this 12-year-old who has a genetic disease in which sufferers grow a “second skeleton.”
END