I. Bone Introduction

A. Like other connective tissues, bone consists of cells, fibers, and ground substance but differs because the extracellular matrix is calcified.

B. The rigid extracellular matrix has several functions:
   1. provides an internal support for the body and attachment for muscles and tendons
   2. protects vital organs of the cranial and thoracic cavity, and encloses the blood forming elements of the bone marrow
   3. provides a reservoir of ionic calcium essential for many cellular processes of the body

II. Macroscopic Structure of Bone

A. Diaphysis: shaft of the bone
B. Epiphysis: end of a long bone
C. Metaphysis: area between the diaphysis and the epiphysis
D. Epiphyseal plate (growth plate)
E. Medullary cavity: central cavity of bone occupied by bone marrow
F. Trabeculae: irregular lattice of thin columns of bone surrounded by bone marrow
G. Articular cartilage: hyaline cartilage covering joint surfaces
H. Periosteum: external covering of bone
I. Endosteum: internal covering of bone

III. Bone Cells

A. Osteoprogenitor cell
   1. A mesenchymal stem cell that can undergo mitotic division and differentiate into an osteoblast.
   2. Osteoprogenitor cells are located in the inner cellular layer of the periosteum, the endosteum and lining osteonic canals.
   3. These cells are most active during bone growth, but large numbers are reactivated in adult life in repair of fractures.
4. They also differentiate into osteoblasts during the continuous process of bone remodeling.

B. Osteoblasts

1. Cells that are derived from osteoprogenitor cells and are responsible for the synthesis of the organic components of bone matrix, which is called osteoid.
2. They are located on the surface of bone tissue and resemble epithelium. When the cells are active they have a cuboidal appearance; and when their activity declines, they flatten.
3. They have the structure expected of cells that are actively engaged in protein synthesis, such as extensive rough ER, well developed Golgi complex and numerous secretory vesicles.
4. The cells have cytoplasmic processes that bring them in contact with neighboring cells.

C. Osteocytes

1. When an osteoblast has completely surrounded itself and its cytoplasmic processes with matrix, the cell is now termed an osteocyte.
2. The space in which the cell resides is termed the lacuna. The thin cylindrical spaces that house cytoplasmic processes are called canaliculi. Canaliculi also contain extracellular fluid carrying nutrients to nourish the osteocytes.
3. Processes of adjacent cells make contact via gap junctions, which allow ions and small molecules to travel from cell to cell.

D. Osteoclasts

1. Large, motile, multinucleated, bone-resorbing cells derived from blood monocytes that occupy depressions in the bone matrix in bone undergoing active resorption
2. The portion of the osteoclast directly in contact with the bone can be divided into two regions.
   a) Ruffled border: This is the region of the cell directly involved in the resorption of bone. It contains infoldings of the plasma membrane that increase surface area.
   b) Clear zone: This region of the cytoplasm surrounds the periphery of the ruffled border. It contains many actin microfilaments that help maintain contact between integrins of the clear zone plasma membrane and the bone matrix. This area is where the osteoclast firmly adheres to the bone matrix and assists in sealing off the acidic compartment adjacent to the ruffled border.
3. Osteoclasts adhere tightly to established bone matrix and acidify the surface by the use of a proton pump that actively transports H+ ions onto the surface of bone. Lysosomal enzymes are released by exocytosis and degrade the organic components of bone.
4. The degraded minerals and organic components are endocytosed by the osteoclast and delivered to nearby capillaries to enter the circulation.
5. Two hormones affect osteoclastic activity:
   a) Parathyroid hormone: A hormone produced by the parathyroid gland that increases osteoclastic activity and results in elevated blood calcium levels.
   b) Calcitonin: A hormone produced by the thyroid gland that decreases osteoclastic activity and results in reduced blood calcium levels.

Bone Cell Quiz

IV. Bone Coverings

A. Periosteum:
   1. The external covering of bone, except in areas where tendons and ligaments insert into bone and on the surfaces covered by articular cartilage.
   2. Consists of two layers
      a) outer fibrous layer: collagenous connective tissue that contains many blood vessels. Branches of the blood vessels penetrate the inner layer of periosteum to enter Volkman’s canals and eventually communicate with the vessels in the osteonic canals.
      b) inner cellular layer: layer that contains osteoprogenitor cells that have osteogenic potential
   3. Sharpey’s fibers: bundles of periosteal collagen fibers that penetrate the bone matrix and strongly adheres the periosteum to bone

B. Endosteum: thin layer of osteoprogenitor cells, osteoblasts and a small amount of connective tissue that lines all internal surfaces of cavities within bone including the osteonic canals and marrow spaces

V. Bone Matrix

A. Mature bone is made up of approximately 70% inorganic salts and 30% organic matrix by weight.
B. Collagen (mostly Type I) makes up over 90% of the organic component, which is called osteoid. The remainder of organic materials are ground substance proteoglycans and non-collagen molecules involved in the regulation of bone mineralization.

C. The inorganic portion of bone is composed mainly of calcium and phosphorus in the form of hydroxyapatite crystals.

D. Hydroxyapatite crystals are deposited in the gap regions of the collagen molecules and are also present in the overlap regions.

VI. Types of Bone

A. Primary bone (woven bone, immature bone)
   1. Immature bone that is the first type of bone formed during fetal development or during the repair of a fractured bone.
   2. Characteristics of primary bone are abundant osteocytes, a low mineral content, and an irregular array of collagen fibers.
   3. It is temporary and is replaced by secondary bone tissue.

B. Secondary bone (mature bone, lamellar bone):
   1. Secondary bone characteristically contains collagen fibers arranged in lamellae that are parallel to each other or concentrically organized around a vascular channel.
   2. Compact bone:
      a) Lamellae are arranged into osteons (haversion systems) around a haversion canal
      b) Collagen fibers are parallel to each other within a lamella, but collagen fibers in adjacent lamellae lie perpendicular to one another providing the bone with great strength.
      c) Lacunae containing osteocytes are found between and occasionally within the lamellae.
      d) Canaliculi house cellular processes belonging to osteocytes and permit communication between lacunae and with the osteonic canals.
      e) Organization of lamellae
         (1) outer circumferential lamellae: lamellae that are deep to the periosteum and form the outermost region of the diaphysis
         (2) inner circumferential lamellae: lamellae that completely encircle the marrow cavity
         (3) osteons: lamellae arranged around an osteonic (haversion) canal
         (4) interstitial lamellae: triangular or irregularly shaped groups of parallel lamellae leftover by osteons destroyed during growth and remodeling
   3. Spongy bone (cancellous bone or trabecular bone)
      a) Branching bone trabeculae project out from the internal surface of compact bone into the marrow cavity. Spongy bone typically does not contain osteons.
      b) Trabeculae are only a few cell layers thick and contain irregularly arranged lamellae.
c) The lamellae contain lacunae housing osteocytes, which are nourished by diffusion of nutrients that travel through canaliculi from the marrow cavity.

VII. Development of Bone:

A. Bone can be formed in two ways.

1. Intramembranous ossification: Direct mineralization of matrix secreted by osteoblasts

2. Endochondral ossification: Deposition of bone matrix on pre-existing cartilage matrix

3. In both processes the bone tissue that appears first is woven bone (a.k.a. primary or immature bone).

4. Both forms of ossification can result in the formation of both spongy bone and compact bone.

B. Intramembranous ossification

1. This type of ossification is responsible for the formation of most flat bones including bones of the cranial vault.
2. This process takes place in highly vascularized mesenchymal tissues.
3. Groups of mesenchymal cells differentiate into osteoblasts.
4. The osteoblasts secrete bone matrix, which is quickly followed by calcification. The region of initial osteogenesis is termed the primary ossification center.
5. As the osteoblasts produce matrix, some become surrounded and trapped by the newly formed matrix and are now called osteocytes.
6. Islands of developing bone are formed; these are termed spicules. The collagen fibers in the developing spicules are randomly oriented (primary bone).
7. The remaining connective tissue among the spicules is penetrated by growing blood vessels and the undifferentiated mesenchymal cells give rise to bone marrow cells.
8. The ossification centers grow radially and finally fuse replacing the original connective tissue.
9. The portion of bone that does not undergo ossification becomes the periosteum and endosteum.
C. Endochondral ossification

1. This type of ossification is responsible for the formation of short and long bones.
2. This process begins with a hyaline cartilage model whose shape resembles a small version of the bone to be formed.
3. Chondrocytes within the shaft of the cartilage model hypertrophy, which results in a reduction of the cartilage matrix to slender trabeculae. The cartilage matrix calcifies and the chondrocytes degenerate leaving large interconnecting spaces.
4. The first bone to be formed is by intramembranous ossification, which occurs within the perichondrium surrounding the diaphysis. The perichondrium of the shaft becomes vascularized and develops osteogenic potential. Osteogenic cells become osteoblasts that secrete bone, forming a bone collar. The perichondrium is now called periosteum.
5. The periosteum prevents diffusion of nutrients to the chondrocytes causing them to die which forms a central cavity in the cartilage.
6. Osteoclasts form holes in the bone collar allowing an osteogenic bud composed of osteoprogenitor cells, hematopoietic cells, and blood vessels to enter the concavities within the cartilage model.
7. Osteoprogenitor cells invade the area and differentiate into osteoblasts, which form a continuous layer over the calcified cartilage and secrete osteoid onto it.
8. The ossification center in the diaphysis is termed the primary ossification center and progresses in the direction of the epiphysis. Osteoclastic activity in the center of the forming bone forms the marrow cavity.
9. A secondary ossification center occurs in the epiphysis and progresses much like the diaphysis but a bony collar is not formed. Osteoprogenitor cells invade the cartilage of the epiphysis, differentiate into osteoblasts and secrete osteoid onto the cartilage matrix.
10. Cartilage remains in two places:
   a) articular cartilage: hyaline cartilage covering joint surfaces that remains throughout life.
b) epiphyseal plate: The cartilage of the epiphyseal plate continues to grow and is continuously replaced by newly formed bone matrix resulting in elongation of bone. Proliferation occurs at the epiphyseal aspect and replacement by bone occurs on the diaphyseal aspect. The epiphyseal plate is divided into zones.

1. resting zone: hyaline cartilage without morphological changes
2. zone of proliferation: chondrocytes dividing rapidly that from columns of stacked cells parallel to the long axis of the bone
3. zone of hypertrophy and calcification: large chondrocytes whose cytoplasm has accumulated glycogen and narrow areas of matrix between lacunae
4. zone of ossification: Osteoprogenitor cells invade the area and differentiate into osteoblasts, which secrete bone matrix onto the calcified cartilage matrix.

VIII. Bone growth

A. Bone length is dependent upon the activity that occurs in the epiphyseal plate. Bone growth stops when the cartilage of the epiphyseal plate ceases proliferation and bone development continues to unite the diaphysis and epiphysis.

B. An increase in bone width occurs by a process called appositional growth. Bone is produced by the periosteum (intramembranous ossification) on the external surface of the bone collar, and at the same time bone is removed from the internal surface causing the marrow cavity to increase in size.

C. During infancy and childhood the most important stimulus of epiphyseal plate activity is growth hormone (somatotropin), which is released from the anterior pituitary gland. Excessive amounts of growth hormone result in excessive height (pituitary gigantism) and deficits of growth hormone result in diminished height (dwarfism).

D. Normal bone growth is dependent on proper dietary intake of protein, minerals and vitamins. A deficiency of vitamin D prevents calcium absorption from the GI tract resulting in rickets (children) or osteomalacia (adults). Osteoid is produced but calcium salts are not deposited, so bones soften and weaken.
IX. **Bone Remodeling**

A. In a growing person bone deposition exceeds bone resorption.

B. In adulthood after the closure of the epiphyseal plates, bone deposition is balanced with bone resorption.
   
   1. Osteons are replaced by osteoprogenitor cells and osteoblasts from the periosteum.
   2. Trabeculae are replaced by Osteoprogenitor cells and osteoblasts from the endosteum.
   3. Bone resorption is accomplished by osteoclasts.
   4. If bone resorption exceeds bone deposition then osteoporosis will occur.

X. **Fracture Repair**

A. The bone matrix is destroyed and the bone cells adjoining the fracture die.

B. The damaged blood vessels form a blood clot.

C. The blood clot, damaged bone matrix, and dead cells are removed by macrophages.

D. Granulation tissue forms in the site of the blood clot and condenses into connective tissue and later into a fibrocartilagenous callus.

E. At the same time, osteoprogenitor cells of the periosteum are activated and become osteoblasts that begin to deposit new bone. The new bone, which is a meshwork of trabeculae of primary bone, forms a bone callus around the fracture site.

F. A similar activation of cells of the endosteum results in deposition of bone around the fibrocartilagenous callus that is slowly eroded away and replaced by bone (endochondral ossification).

G. The spongy bone uniting the bones is transformed into compact bone by osteoblastic deposition of bone matrix, which gradually obliterates the spaces among the trabeculae.

H. Resorption of excess bone by osteoclasts reestablishes the marrow cavity and the normal surface contours of the bone.

XI. **Key Points**

A. Understand the macroscopic structure of bone.

B. Know the origin, location, and function of bone cells.

C. Understand the structural and functional organization of periosteum and endosteum.

D. Know the components of bone matrix.

E. Be able to compare and contrast the different types of bone

F. Understand the process of intramembranous ossification and endochondral ossification.

G. Understand the differences between a bone growing in length and bone growing in width.

H. Understand the process of fracture repair

Reading:


Wheater’s Functional Histology. pp. 172-189