Ministry of health Republic of Belarus
Establishment of education "Gomel state medical university"

Department of histology, cytology and embryology

MANUAL
for 1-st year students of faculty of foreign students on gynecology

Topic: 10:
HISTOPHYSIOLOGY OF SKELETAL TISSUES

Duration 4 hours

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THE MOTIVATIONAL CHARACTERISTIC OF THE THEME

Cartilage and bone tissue unite the term "skeletal". The bone tissue together with cartilage bears the basic mechanical loading in an organism. Properties of this tissue (elasticity, hardness, etc.) are connected with features of a structure of their intercellular substance which can vary under influence of hormones thyroid and others.

THE PURPOSE

Studying of classification, development, structure and histophysiologies of cartilage and bone tissues.

PROBLEMS

The student should know:

1) Histophysiologies features of cartilage and bone tissues.
2) Difference of a lamellar bone from coarse-fibred.
3) Histophysiologies features of lamellar and coarse-fibred bone tissues.
4) Basic stages histogenesis of both regenerations and bone.
5) Microscopic both ultramicroscopic structure and function of cartilage and bone tissues.

The student should be able:

1) To define versions cartilage on structural features of their intercellular substance.
2) To distinguish a lamellar bone from coarse-fibred.

REQUIREMENTS TO THE INITIAL LEVEL OF KNOWLEDGE

For full mastering a theme it is necessary for student to repeat from medical biology and genetics questions on the general cytology and from normal human anatomy.

CONTROL QUESTIONS FROM RELATED SUBJECTS

1) Functions organelles of cells
2) The anatomic structure of flat and tubular bones

CONTROL QUESTIONS ON THE THEME

1) The general characteristic of cartilage.
2) The structure of cartilage (the characteristic of cells and intercellular substance).
3) Classifications of cartilage
4) Development, growth, regeneration and age changes of a cartilage.
5) The general characteristic of a bone.
6) The structure of a coarse-fibred bone (the characteristic of cells and intercellular substance.
7) The structure of a lamellar bone.
8) The structure of a bone as body: a spongy and compact bone.
9) Blood supply of bone
10) The Straight line ontogenesis.
11) Development of a bone on a place of a cartilage.
12) The mechanism of growth of bones.
13) Cellular mechanisms of reorganization of a bone.

THE PRACTICAL PART

1) The General characteristic of cartilage- to fill the table (Exercise № 1 in album).

2) Intercellular substance of cartilage – to study the table (Exercise № 2 in album).

3) The Scheme of the structural organization of a bone – to enter designations . (Exercise № 3 in album).

4) To study structure of intercellular substance to give the characteristic of its organization in a coarse-fibred and lamellar bone (Exercise № 7 in album).

5) To represent cells of a bone tissue and to enter their functions (Exercise №9 in album).

7) To study the scheme of development of a bone on a place of a cartilage (Exercise № 12 in album).

8) Microscopy and a sketch in an album of histological preparations (Exercise № 3, 4, 5, 8, 10,11and 12. in album).

9) Studying diagrams

SLIDES

1) Hyaline cartilage.
2) Elastic cartilage
3) Fibrous cartilage
4) Bone cells

QUESTIONS FOR SELF-CHECKING KNOWLEDGE

1) Fill the table 1 describing the structural organization, function and a source of development of cells of a bone tissue.

Table 1 – Structural organization, function and a source of development of bone tissue cells

Cells	The Version	Functions	The Source of Development
Osteocyte Osteoblast Osteoclast			

HISTOPHYSIOLOGY OF SKELETAL TISSUES

Skeletal tissue dividing to bone and cartilage.

Cartilage

Cartilage is a skeletal connective tissue characterized by firmness and resiliency. It forms most of the fetal skeleton and persists in sites where its mechanical properties are needed. Most fetal cartilage eventually becomes bone.

Characteristics of cartilage

1. Low level of metabolism.
2. Don’t have blood vessels.
3. Groth all time.

4. Strong and elastic [1 – 4].

Like all connective tissues, cartilage is composed of cells, fibers, and ground substance.

The cells are chondrocytes, chondroblast, chondroklast.

The extra cellular matrix predominates and determines cartilage's mechanical properties. Type II collagen is a characteristic cartilage matrix component, and the abundant ground substance is firm and gel-like. Cartilage cells are termed chondrocytes. Under the light microscope, chondrocytes appear rounded, with an eccentric nucleus, a prominent nucleolus, and basophilic cytoplasm. With Electron Microscopy, chondrocyte surfaces exhibit characteristic projections and enfolding. The RER and Golgi complex are well developed, the Golgi complex enlarges as the cell grows, and its crastae fill with secretory material. Some lipid droplets are typically found in the cytoplasm.

There are the 3 types of cartilage: **hyaline cartilage, elastic cartilage, and fibrocartilage.**

Hyaline Cartilage

Hyaline cartilage, the most common type in both fetus and adult, is white and translucent when fresh, with a firm, gel-like consistency. Hyaline cartilage matrix contains thin fibrils of type II collagen. Their small size and their refractive index (close to that of the ground substance) make them difficult to distinguish with the light microscope. Ground substance, the predominant tissue component, comprises the following:

GAGs, mostly chondroitin sulfates and hyaluronic acid, with smaller amounts of keratan sulfate and heparin sulfate, Proteoglycans, core proteins with GAG side chains,

Proteoglycan aggregates, proteoglycans covalently linked to long chains of hyaluronic acid by link protein;

Glycoproteins, which attach various matrix components to oneanother and cells to the matrix, including link protein, fibronectin, chondronectin

Tissue fluid, an ultra filtrate of blood plasma [1 – 5].

The consistency of hyaline cartilage results from extensive cross-linking among its components. The chondrocytes are embedded in the matrix either singly or in isogenous groups of 2 8 cells derived from one parent cell. The potential space occupied by each chondrocyte called a lacuna, is visible only after the cell s death or after shrinkage during tissue processing. The Chondrocytes at the core of a tissue mass are usually spheric those at the periphery are flattened or elliptic. The matrix immediately surrounding the chondrocytes called the capsular (territorial) matrix, is more intensely basophilic and Periodic Acid ShifflPAS positive than the intercapsular (in-terterritorial) matrix owing to the higher concentration of sulfated GAGs and lower concentration of collagen. Except for articular (joint) cartilage all hyaline cartilage is surrounded and nourished by perichondrium.

Histogenesis. All cartilage derives from embryonic mesenchyme.

Cartilage grows by 2 distinct processes. Both involve mitosis and the deposition of additional matrix. Matrix synthesis is enhanced by growth hormone, thyroxine, and testosterone and is inhibited by estradiol and excess cortisone.

Interstitial growth involves the division of existing chondrocytes and gives rise to the isogenous groups. It is important in the formation of the fetal skeleton and continues in the epiphyseal plates and articular cartilages [5 –7].

Appositional growth involves the differentiation into chondrocytes by chondroblasts and stem cells on the inner surface of the perichondrium. It is responsible for con-

tinued increase in the girth of the cartilage masses.

Repair of cartilage fractures involves invasion of the breach by mesenchymal stem cells from the perichondrium, which then differentiate into chondrocytes. If the gap is large, a dense connective tissue scar may form.

Function and location. Its ability to grow rapidly while maintaining its rigidity makes hyaline cartilage an ideal fetal skeletal tissue. As fetal cartilage is replaced by bone, hyaline cartilage remains in the epiphyseal piates at the ends of long bones, allowing these bones to lengthen between birth and adulthood. At all ages, hyaline cartilage without a perichondrium (articular cartilage) covers the articular surfaces of bone, where its resistance to compression and its smooth texture make it a good cushion and low-friction surface. Hyaline cartilage is the most abundant and widely distributed cartilage type in the body. The costal (rib) cartilages, most of the Iaryngeal cartilages, the cartilaginous rings supporting the trachea and the irregular cartilage plates in the walls of the bronchi are hyaline cartilage [6, 7].

Elastic Cartilage

Elastic cartilage is yellowish when fresh. It is more flexible than hyaline cartilage. Elastic cartilage is structurally identical to hyaline cartilage except that it contains, in addition to type II collagen fibers, a dense network of branching and anastomosing elastic fibers. This network is densest at the core of the cartilage mass and when stained with elastic stains (eg, Verhoeff or Weigert's), may obscure the organization of the tissue. The chondrocytes characteristically occur in isogenous groups.

A perichondrium surrounds the elastic cartilage mass.

Histogenesis and growth. Elastic cartilage develops from a primitive connective tissue containing wavy bundles of fibrils that differ in protein composition from both elastin and collagen. Ftbroblasts eventually secrete elastin, and the fiber bundles are transformed into branching elastic fibers. The development of chondrocytes and production of the other matrix materials is the same as in hyaline cartilage Further growth resembles that of hyaline cartilage

Function and location. Elastic cartilage provides flexible support. It occurs alone and with hyaline cartilage, the two may grade into each other in a single cartilage mass. In humans, elastic cartilage is found in the auricle of the external ear, the wails of the external auditory canals and auditory tubes, the epiglottis, and the corniculate and cuneiform cartilages of the larynx [1 – 4].

Fibrocartilage

Fibrocartilage is intermediate in character between hyaline cartilage and dense connective tissue. Fibrocartilage is characterized by abundant type I collagen fibers, at low magnification, it closely resembles dense connective tissue. The ground substance contains equal amounts of chondroitin sulfate. The matrix immediately surrounding the chondrocytes resembles that of hyaline cartilage and contains some type II collagen. The chondrocytes .are distributed in columnar isogenous groups between the densely packed type I collagen bundles. There is no distinguishable perichondrium.

Histogenesis and growth. At sites where strong mechanical stresses occur, fibrocartilage develops from dense regular connective tissue

through the transformation of fibroblasts or fibroblast-like precursors into chondrocytes. Fibrocartilage growth has not been closely examined.

Function and location. Fibrocartilage is always associated with dense connective tissue, and the border between the two is usually indistinct. Its combination of cartilaginous ground substance and dense collagen bundles allows fibrocartilage to resist deformation under great stress, it is important in attaching bone to bone and providing restricted mobility. Sites in humans include the annulus fibrosus the intervertebral disks, the symphysis pubis, and certain bone-ligament junctions [1 – 3].

Vascular supply

Most cartilage is enveloped by a layer of dense connective tissue, the perichondrium, which contains the vascular supply and fibroblast-like stem cells from which additional chondrocytes may arise Few blood vessels (or found within cartilage, thus the composition of the ground substance is crucial to the percolation of nutrients and oxygen to chondrocytes from the surrounding vessels.

Intervertebral disks

The intervertebral disks act as cushions between the vertebrae, allowing limited movement of the vertebral column. They are bound to the vertebrae by ligaments. Each disk has 2 parts:

Annulus fibrosus. This outer ring is composed mainly of fibrocartilage and is covered on its outer surface by the dense connective tissue of associated ligaments. The fibrocartilage is arranged in concentric layers, with the collagen bundles of each layer oriented at right angles to those in the next. This organization may appear as a "herringbone" pattern when seen through a fight microscope at low power. Nucleus pulposus. This structure forms the center of the disk and derives from the embryonic notochord, It is composed of mucous connective tissue, with a few fibers and rounded cells embedded in syrupy, hyaluronic acid-rich ground substance. The nucleus pulposus smaller in adults than in children, because it is partially replaced by fibrocartilage [3].

Bone

Bone is the main constituent of the adult skeletal system. Like cartilage, it is a connective tissue specialized for support and protection.

Mature bone tissue has cells (osteocytes, osteoblasts, and osteoclasts), fibers (type I collagen), and ground substance. It differs from other connective tissues primarily in having large quantities of inorganic salts in its matrix, accounting for its hardness.

Functions. Bone is second only to cartilage in its ability to withstand compression and second only to enamel in hardness. It supports and protects the more fragile tissues and organs, harbors hematopoietic tissue and forms a system of levers and pulleys that multiply and focus the contractile forces of muscle. The constant turnover of bone tissue results from a balance between the activities of the bone-forming osteoblasts and the bone-resorbing osteoclasts and allows bone matrix to function as an important storage site for calcium and other essential minerals.

Types of bone tissue. Bone tissue is classified according to its architecture as spongy or compact and according to its fine structure as primary (woven) or secondary (lamellar). All bone tissue begins as primary bone, but after all is eventually replaced by secondary bone. The term "bone" refers both to bone tissue and to an individual named element of the adult skeleton – a bone. A bone is an organ composed largely of bone tissue but also containing other connective tissues, as well as bone marrow, blood vessels, and nerves.

Bones are classified by their shape (eg, long bones, fiat bones) and the process by which they form (endochondral bones, membrane bones). Most exhibit protuberances that

serve as attachment sites for muscles, tendons, and ligaments. A double-layered coat of connective tissue, the periosteum, covers the outer surfaces of bones. The outer or fibrous layer of the periosteum is dense connective tissue; the inner or osteogenic layer is a looser tissue containing bone cell precursors. Sharpey's fibers are periosteal collagen fibers penetrate bone matrix and anchor the periosteum to the bone. The internal surfaces of bones are covered by a thinner, condensed re-ticular connective tissue called endosteum that contain bone and blood cell precursors. The endosteum lines the marrow cavity and sends extensions into the Haversian canals. Most bones of the arms and legs (eg, the femur) are termed long bones, and knowledge of their parts is important to the study of regional differences in bone histology. The diaphysis is the shaft of a long bone, and the epiphysis is its bulbous end. In adults, the diaphysis is cylindric with walls of compact bone and a central marrow lined with endosteum. Each of the 2 epiphyses contains mostly spongy bone. Where bones contact other bones to form movable joints, their surfaces are covered by articular cartilage [4, 8].

Bone is a connective tissue composed of cells, fibers, and ground substance Bone matrix, containing abundant mineral salts, is the predominant tissue component The hardness of bone makes it difficult to section. Special techniques for obtaining thin sections include grinding bone slices until they become translucent or demmerahzing fixed bone by immersion in solutions of dilute acid or calcium-cheiating agents (eg, EDTA). Demmeralized bone can be sectioned and stained by standard histological methods.

Bone cells

Osteoprogenitor cells are stem cells found in the endosteum and periosteum. These spindle-shaped cells have ovoid to elongate nuclei and unremarkable cytoplasm. Two types are distinguishable with the electron microscope one gives rise to osteoblasts, the other to osteoclasts. Osteoblast precursors derive from embryonic mesenchyme and have sparse RER and Golgi complexes. Osteoclast precursors derive from blood monocytes and have abundant free ribosomes and mitochondria.

Osteoblasts, the major bone forming cells, are typically cuboidal, each with a large, round nucleus and basophilic cytoplasm. They form one-cell thick sheets resembling simple cuboidal epithelium on surfaces where new bone is being deposited Osteoblasts exhibit high alkaline phosphatase activity and have the well-developed RER and Golgi complex typical of protein-secreting cells. They synthesize and secrete all the organic components of bone matrix and may be involved in bone mineralization. Once surrounded by matrix, osteoblasts are considered mature and called osteocytes

Osteocytes are terminally differentiated bone cells found in cavities in the bone matrix called lacunae. Their long, thin cytoplasraic processes, called filopodia, radiate from the cell body in fine extensions of the lacunar cavity called canaliculi Osteocytes are isolated from one another by the impermeable bone matrix and contact one another at the tips of their filopodia, often through gap junctions. This arrangement provides limited cytoplasmic continuity between the cells and explains how osteocytes obtain nutrients and oxygen and dispose of wastes at relatively great distances from the blood vessels. While incapable of mitosis, osteocytes retain some synthetic and resoiptive capacity whereby they turn over and maintain nearby bone matrix. The death of osteocytes results in bone breakdown, or resorption. Osteocytes recently derived from osteoblasts are located near bone surfaces in rounded lacunae, older cells are found farther from the surface in flattened lacunae

Osteoclasts are bone-resorbing ceils that He on bony surfaces in shallow depres-

sions termed Howship's lacunae. They are large and multi- nucleated (2-50 nuclei per cell), with acidophilic cytoplasm containing abundant lysosomes and mitochondria and a well-developed Golgi complex. The osteoclast surface facing the depression exhibits a ruffled border of plasma-membrane infoldings, which form many isolated compartments between the cell and the bone surface .The cells release acid, collagenase, and other lytic enzymes into the compartments, these break down bone matrix and release minerals, a process called bone resorption. Osteoclasts respond to Parathyroid hormone (PTH) by enlarging their ruffled borders and increasing their activity, resulting in increased blood calcium levels The effect of PTH may be indirect and mediated by a signal from the osteoblasts. Calcitonin, which decreases blood calcium, reduces surface raffling and osteoclast activity. While their immediate precursors are found in the endosteum and periosteum, Osteocfasts ultimately derive from the fusion of blood monocyte derivatives and are considered components of the mononu-clear phagocyte system.

Bone matrix. Bone matrix contains organic components, or **osteoid,** and inorganic components, or bone mineral.

Organic components. Osteoid constitutes about 50% of bone volume and 25% of bone weight. It is composed of fibers and unmineralized ground substance.

Fibers.Type I collagen fibers constitute 90-95% of the osteoid. The overlapping pattern of staggered tropocollagen results in periodic gaps(lacunar regions), which may contain up to 50% of the hydroxyapatite crystals (mineral) in bone.

Ground substance. Hydroxyapatite crystals and collagen fibers are embedded in the acidic ground substance, which is composed of proteins, carbohydrates, and small amounts of proteoglycans and lipids. The proteins are glycoproteins, phosphoproteins, sialoproteins. The carbohydrates (glycosaminoglycans) include chondroitin sulfates and keratan sulfate. Some ground substance components may be nucleation sites for hydroxyapatite crystals [3, 8].

Inorganic components. Bone mineral makes up about 50% of bone volume and 75% of bone weight. It is composed primarily of calcium and phosphate, with some bicarbonate, citrate, magnesium, and potassium and trace amounts of other metals. Calcium and phosphate form needJelike crystals of hydroxyapatite, $Ca_{ш}(PO_4)б(OH)_2$

Hydrated ions at the crystal surface form an enveloping hydration shell, through which ions are exchanged between the crystal and surrounding body fluids. Adult bone occurs in 2 basic organizational types, spongy and compact.

Spongy bone, also called **cancellous bone,** forms a fine 3-dimensional lattice with many open spaces. The branching and anastomosing slips of bone between the spaces, termed trabeculae or spicules, align along the lines of stress to which the bones are subjected, maximizing the weight-bearing capacity of this bone tissue. Spongy bone is found at the core of the epiphyses of mature long bones, at the core of short bones (eg, phalanges), and between the thick plates, or tables, of the flat bones of the skull, where it is called the diploe. It may be composed of either primary or secondary bone.

Compact bone, also called **dense bone or cortical bone,** lacks the large spaces and trabeculae. It forms the thick diaphyseal cylinder of long bones, a thin covering over the epiphyses, and the tables of the flat bones of the skull. Compact bone is always composed of secondary bone [4].

Histogenesis, Remodeling, Growth, and Repair Primary bone. The first bone tissue to appear during the formation of new bone or in the repair of fractures is termed pri-

mary bone, or **woven bone.** This immature bone, which is always spongy, is later replaced by secondary bone except near the skull sutures and in alveolar bone of the mandible and maxilla. Its collagen fibers do not form concentric rings but, rather, exhibit an irregular "woven" appearance. It is less mineralized than secondary bone, making it more radiolucent (penetrable by X-rays), and it has a higher osteocyte-to-matrix ratio. Primary bone can form by either intramembranous or endochondrai bone formation [8, 9].

Intrainembranous bone formation occurs within membrane-like mesenchymal condensations. The cells in such connective tissue membranes differentiate into osteoblasts and begin to synthesize and secrete os-teoid, which later becomes mineralized. This initial site of bone formation is termed the primary ossification center. The osteoblasts surround themselves with bone matrix, forming spicules that eventually fuse into a spongy lattice of primary bone. The mesenchyme between the spicules may participate in bone marrow development. Only a few human bones form entirely in this way, most of these are flat and are called membrane bones. Membrane bones of the skull are the frontal and parietal bones, the mandible, and the maxilla. The term "membrane bone" also refers to the tissue type formed by this mechanism. Membrane bone also forms parts of other bones, such as the temporal and occipital bones of the skull and the periostea! bone collar of endochondrai bones. Endochondrai **bone formation** involves the replacement of cartilage by bone and occurs in ai! except membrane bones. **Basic steps in the formation of an endochondrai bone:**

I, Cartilage model In the embryo, a hyaline cartilage model, which resembles the bone to be formed, is laid down.

The periosteal bone collar. Capillaries penetrate the perichondrium, and mesenchymal cells on its inner surface become osteoprogenitor cells. Some of these differentiate into osteoblasts and secrete bone matrix, creating primary bone spicules just inside the perichondrium (now the periosteum). The spicules eventually fuse to form a thin periosteal bone collar of membrane bone around the cartilage model.

Proliferation. While the periosteal bone collar is forming, structural and functional changes begin in the cartilage model. The chondrocytes near the collar undergo rapid proliferation, forming long columns (isogenous groups) of flattened cells oriented parallel to the long axis of the bone.

4.Hypertrophy. The chondrocytes hypertrophy rapidly into large, rounded cells that are not separated by matrix. The result is tube-like super lacunae filled with columns of hypertrophic chondrocytes,which secrete type X collagen.

5.Calcification. As hypertrophy progresses, the long strips of cartilage matrix between the tubular cavities begin to calcify. Thus oxygen, nutrients, and cellular wastes can no longer diffuse through the matrix, and the hypertrophic chondrocytes die.

6.Formation of the primary marrow cavity. Dead chondrocytes and part of the calcified cartilage matrix are removed by chondroclasts (large, multinucleaied cells resembling osteoclasts). Tunnels at the center of the developing bone, stimulate proliferation and hypertrophy of condrocytes and enlarged by chondroclasts, become the bone's primary marrow cavity.

7.The periosteal bud is a small cluster of blood vessels and perivascular tissue from the periosteum that penetrates the primary marrow cavity. This bud and its branches invade the tunnels left by the dead chondrocytes. Osteoprogenitor cells and bone marrow stem cells, delivered by the invading blood vessels, are deposited on the surface of the calcified cartilage matrix.

8.Ossification. This is term whose interpretation requires attention to context. In its broadest sense, ossification is synonymous with bone formation [1 –3]

Here, in a more restricted connotation, it refers to the final steps in the process, including the deposition of osteoid followed by mineralization. The osteoprogenitor cells divide and differentiate into osteoblasts, which deposit primary bone on the surface of the calcified cartilage matrix strips. The primary bone and the residual calcified cartilage are later resorbed and replaced by secondary bone.

Ossification centers. The above steps may occur more than once in forming a bone. In long bones, the process occurs first near the middle of the diaphysis, forming the primary ossification center. The secondary ossi fication centers form later, by the same process, in the epipbyses. The region between a primary and a secondary ossification center is termed a me-taphysis. The ossification centers enlarge until all that is left between them is a thin plate with resting cartilage at its center, the epiphyseal plate. In humans, the first bone to ossify is the clavicle.

5 overlapping zones characterize the microscopic structure of the metaphyses of developing endochondral bones:

1.The zone of resting cartilage is composed of typical hyaline cartilage and is farthest from the primary marrow cavity

2.The zone of proliferation contains columns (isogenous groups) of flattened chondrocytes

3. the zone of hypertrophy, the chondrocytes in the columns are enlarged and rounded.

4.The zone of calcification is characterized by a more basophilic matrix. There is often a significant overlap between zones 3 and 4, which are sometimes referred to as a single zone of hypertrophy calcification.

5. The zone of ossification borders directly on the primary marrow cavity. It is characterized by intensely acidophilic osteoid, osteocytes within the bone matrix, and a monolayer of basophilic osteoblasts on the surface of the newly formed primary bone.

Secondary bone. In adults both dense and spongy bone are composed of secondary bone, or lamellar bone.

Secondary bone formation (remodeling)

Osteoclasts erode the primary bone matrix, blood and lymphatic vessels, nerves invade the cavity formed by the erosion, and osteogenic cells in the perivascular connective tissue are deposited on the walls of the cavity. Osteoblasts descended from these cells along with osteocytes released from their lacunae during resorption deposit the secondary bone in concentric layers, or lamellae, the oldest of which are farthest from the vessels. Owing to its greater organization, secondary bone is more efficient than the primary bone it replaces. Remodeling helps reshape growing bones to adapt to changing stresses and loads. It occurs continuously, even in adults, as secondary bone is eroded and replaced by new secondary bone. Secondary bone appears as a collection of densely packed bony cylinders, each with a central enuosieum-lined Haversian canal containing lymphatic and blood vessels, nerves, and some loose connective tissue, The cylinder surrounding each canal is composed of a series of concentric lamellae. The collagen fibers in each lamella are oriented parallel to one another and nearly perpendicular to those in adjacent lamellae, an arrangement that lends added strength to the tissue. Osteocytes lie between the lamellae in rows of lacunae, their filopodia lie in canaiicuH extending radially from each lacuna. Haversian canal, its contents, and the surrounding system of osteocytes and lamellae are

termed a Haversian system, or osteon. Vascular connections between osteons are established by Volkmann 's canals, which run perpendicular to Haversian canals and cut across the lamellae. Osteons may bifurcate, but they he roughly parallel to one another and are held together by cementing substance, which fills the spaces between the cylinders. Often an old osteon is only partially eroded before a new one begins to form, so that wedge-shaped portions of old lamellae appear between recently formed osteons .The lamellae of partially eroded osteons are called interstitial lamellae [1 – 5].

Bone growth. Bones increase in size from birth into early adulthood. During this growth, the bone tissue is continuously remodeled Growth occurs in 2 directions:

Growth in length of long bones is due primarily to the proliferation of chondrocytes in the resting cartilage and in the zone of proliferation of the epiphyseal plates, under the influence of growth hormone. Childhood levels of growth hormone cause cartilage to be produced in the epiphyseal plates as fast as it can be replaced by endochondral bone formation. At puberty, growth hormone levels decline and endochondral bone gradually overtakes and replaces the remaining cartilage, a process termed closure of the epiphyseal plates.

Growth in girth occurs by proliferation and differentiation of os-teoprogenitor cells in the inner layer of the periosteum and deposition of new ossified tissue on the outer surface of the bone [3, 8, 9].

Bone repair. Bone fractures tear vessels in the periosteum, en-dosteum, and haversian and Volkmann's canals, causing local hemorrhage and clot formation between the broken ends of the bone. The periosteum and endosteum provide macrophages and fibroblasts, the former remove the clot, and the latter fill the breach with fibrous connective tissue. Some of the connective tissue cells differentiate into chondrocytes. and the connective tissue eventually becomes a callus containing islands of fibrocartilage and hyaline cartilage that serves as a model for bone formation. The presence of cartilage in the callus is typical of endochondral bones (eg, long bones), whereas flat membrane bones (eg, the mandible) typically heal without cartilage formation Beginning in the subperiosteal region (as soon as 2 days after the injury in young people), the callus is gradually replaced by primary bone, which is subsequently remodeled and replaced by secondary bone The time required for complete healing depends on the site and extent of the injury and is longer in older people.

Histophysiology of Bone Calcium reserve. The skeleton contains 99% of the body's calcium, which serves as a cofactor for many enzyme systems and is important in muscle contraction, transmission of nerve impulses, blood clotting, and cell adhesion. Blood and tissue calcium concentrations must be maintained within narrow limits, and bone serves as the calcium reservoir, storing excess calcium and releasing it when it is needed.

Calcium mobilization. The release, or mobilization, of calcium occurs by 2 mechanisms. Rapid mobilization is simply the physical transfer of ions between hydroxyapatite crystals and the interstitial fluid along a concentration gradient. This occurs most readily where bone has a high surface-to-volume ratio, ie, around spicules of primary bone and in spongy secondary bone The second mechanism involves parathyroid hormone (PTH) and is also rapid, although slower than the first Cells of the parathyroid gland sense a decrease in blood calcium and release PTH, which increases the number of osteoclasts and activates existing ones The result is increased breakdown, or resorption, of bone and release of its calcium to the blood PTH also inhibits bone deposition by osteoblasts and reduces calcium

excretion by the kidneys. Excessive production of PTH (hyperparathy-roidisra) results in the depletion of bone calcium, elevation of blood calcium, and abnormal deposition of calcium in soft tissues, especially the kidneys and arterial walls.

Calcium deposition. The storage, or deposition, of calcium is promoted by calcitonin, a hormone secreted by the parafollicular C cells of the thyroid gland. Calcitonin has effects opposite those of PTH it enhances matrix synthesis by osteoblasts as well as deposition of calcium The rapid ion exchange described for calcium mobilization is also involved in calcium deposition [4, 5].

Osteoporosis is caused by decreased bone formation or increased bone resorption. Most often seen in chronically immobilized patients and postmenopausa! women, it is characterized by decreased bone mass and a normal mineral-to-matrix ratio. Do not confiise osteoporosis with osteo-malacia the mineral-to-matrix ratio is below normal

Nutritional factors

Protein deficiency causes reduced collagen synthesis, which inhibits bone growth and maintenance. Calcium deficiency leads to incomplete calcification of the bone matrix and, Jf prolonged, to bone resorption. In growing children, this causes rickets, ie, bone deformities, including bowing of the legs. In adults, it causes osteomalacia, ie, insufficient calcification of newly deposited bone, which weakens but does not deform the bones. Such bones are more susceptible to fracture and slower to repair than healthy bones. Osteomalacia may be exacerbated by pregnancy, because of the fetus s demand for calcium In this disease, the mineral-to matrix ratio is below normal. Vitamin D deficiency results in reduced blood calcium concentration, because vitamin D aids in the intestinal absorption of dietary calcium The effects are the same as those in dietary calcium deficiency. Vitamin A deficiency slows bone growth and affects the distribution of the bone cells. Poor coordination between the rates of skull and brain growth may cause abnormally high pressure on the brain and damage to the central nervous system.

Vitamin A excess slows cartilage growth and accelerates ossification An excess before birth, especially during the formation of the cartilage models, causes skeletal deformities and deletions. Excess in childhood or adolescence causes bone formation to overtake cartilage formation, resulting in premature closure of the epiphyses and small stature. Vitamin C deficiency inhibits bone growth and shows fracture repair, because ascorbic acid is required for normal collagen synthesis [3].

Hormonal factors

PTH and calcitonin, growth hormone, steroids (androgens and estrogens) have regulatory effects on bone formation. They influence the tune of appearance of the ossification centers and of the closure of epiphyses. Precocious sexual maturity owing to increased sex hormone synthesis by tumors may cause early closure of epiphyses and short stature. Conversely, sex hormone deficiency may delay puberty and closure of epiphyses, resulting in tall stature.

Joints, or arthroses, are complex connective tissue structures that join individual bones to form the skeletal system. There are 2 main types: Synarth roses These joints permit little or no movement. There are 3 subclasses:

In synostoses, the individual bones are fused and immobilized Example: between the bones of the skull in the elderly

In synchondroses, the individual bones are joined by cartilageand permit slight

movement. Example: between the ribs and sternum, in the pubic symphysis [8, 9].

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