The skeletal system has important functions as protection and support during movements, for the mineral balance, blood production and the storage of triglycerides. In this process, bones (Latin: os, greek: ost-, oste- or osteo-) give us stability and shape. Now, how many bones do humans have? This is easily answered numerically, 206. However, for exams, it is more important for physicians to understand the structure and composition of bones than the amount.

Structure and Function of Bone

The macroscopic bone structure of single bone segments can be assessed and described by closer examination of long bones (e.g. humerus or femur). A hollow bone or long bone is longer than it is wide and is composed by the following elements:
A typical long bone shows the gross anatomical characteristics of bone.
Bone Formation

Collagen deposition ⇒ Ground substance ⇒ Crystal seeding ⇒ Maturation

Each bone contains a small organic and a larger inorganic part. A bone consists of the following parts:

<table>
<thead>
<tr>
<th>Component (% by weight)</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic (30 %)</td>
<td>Cells (2 %)</td>
</tr>
<tr>
<td></td>
<td>Collagen + Type I (93 %)</td>
</tr>
<tr>
<td></td>
<td>Ground Substance (5 %)</td>
</tr>
<tr>
<td>Inorganic (70 %)</td>
<td>( \text{Ca}^{2+} ) and ( \text{PO}_4^{3-} )</td>
</tr>
</tbody>
</table>

Cells, blood vessels, nerves, ground substance and a dense network of collagen forms the organic substance. Calcium phosphate is the main part of inorganic substance. Calcium carbonate and magnesium salts are found in large amounts, while there are numerous further minerals and trace elements found in smaller amounts.

Considering the minerals calcium, phosphate and magnesium, bones represent by far the largest storage organ of the human body. Approximately 1.2 kg or 98% of the entire body’s calcium is stored in our bones.

Diaphysis

The diaphysis is the major part of the bone, long and cylindrical in nature. It consists of a bony sheath made up of layers of bone lamellae and compact bone, also known as cortical bone, which is dense and rigid. These parts come together to enclose on a large hollow space known as the Medullary Cavity. It is the innermost cavity of the bone shafts, storing two types of bone marrow; red and yellow. The former being vascular in nature and the latter made of adipose tissue.

Epiphysis

The epiphyses are the proximal and distal ends of a bone. They are covered with cartilage. The epiphysis of a long bone should NOT be confused with the endocrine gland epiphysis (pineal gland) of the brain.

The transition area between the ends of the diaphysis and each epiphysis is also referred to as growth plate, epiphyseal plate, and metaphysis.

The epiphyses also have an outer sheath of compact bone better known as spongy bone, which consists of delicate trabeculae and lamellae, making it appear spongy. The bone trabeculae are not arranged randomly, but follow lines of pressure to provide the bone with maximum stability. The resulting hollow spaces of the spongy bone make room for the hematopoietic bone marrow.

The special conformation of the spongy bone, consisting of numerous hollow spaces such as the large medullary cavities, contributes considerably to reducing their weight. The strength and resilience of bone remain despite this “lightweight construction”.

Metaphysis

The metaphysis consists of one layer consisting of hyaline cartilage, which is responsible for the longitudinal growth of the diaphysis. At the age of approximately 18-21 years, bones stop growing. During this time the cartilage of the epiphyseal plate is
replaced with bone and the resulting line is referred to as an epiphyseal line.

Articular cartilage

The articular cartilage (cartilago articularis) consists of a thin layer of hyaline cartilage, which covers the end of each epiphysis thus forming a joint. The main function of the articular cartilage is to absorb impact forces on the joints as well as to reduce friction between bones.

Periosteum

The periosteum covers the bone in places where it is not protected by articular cartilage. It consists of thin, irregular connective tissue. The periosteum consists of dense irregular connective tissue divided into an outer “fibrous layer” and inner “cambium layer” (or “osteogenic layer”). The fibrous layer contains fibroblasts, while the cambium layer contains progenitor cells that develop into osteoblasts. The periosteum is responsible for growth in diameter, as bone-forming cells ordinarily can only make a bone thicker but not longer. Therefore, the periosteum serves to protect the bone, to maintain support during fracture repair, to supply nutrition to the bone and to provide insertion for tendons and ligaments.

Medullary cavity

Inside the hollow space of the diaphysis is the medullary cavity, which contains the hematopoietic bone marrow. Starting from early adulthood, the bone marrow slowly converts into fatty tissue due to excess capacity and the red bone marrow becomes yellow fatty tissue. The yellow fatty marrow has similar properties as red marrow as it provides nutrients and protection. However, under special circumstances e.g. large blood loss or leukemia, it can be converted back to red bone marrow. It is important to mention that red bone marrow does not take on any functions of the immune system but serves only as the site of blood formation.

Endosteum

The endosteum (endon = within) surrounds the medullary cavity and consists of a thin membrane. It contains a small amount of connective tissue and consists of a simple layer of bone-forming cells.
The Histology of Bony Tissue

Bony tissue is a type of connective tissue in the body. The formation and maintenance of normal connective tissue only need one single type of cell, the fibrocyte or rather, fibroblast.

The bone requires one more cell type for the degradation of the organic matrix and the dissolving of inorganic calcium phosphate crystals (apatite). This happens in the course of a continuous conversion process.

The following types of bone cells can be differentiated:

- Osteoblasts
- Osteocytes
- Osteoclasts

**Remember:** “Osteoblasts build bones.”

Osteoblasts are cells that build bones and are needed especially for the formation of the extracellular matrix. Osteoblasts are found mainly within the outer and inner surface of the bone, integrated in the cambium layer of the periosteum. They synthesize and secrete collagen fibers and other organic components. They are also important to initiate calcification. A high concentration of participating ions is necessary to produce calcium phosphate for the process of calcification. This is achieved by the protein osteocalcin and by membrane-surrounded vesicles outside the osteoblasts, which contain enzymes that can split off phosphate. These matrix vesicles are extracellular round spherical bodies of about 100 nanometres in size which act as initial sites for hydroxyapatite crystal deposition. Crystals are formed with the help of calcium ions that have already been gathered inside the osteoid (organic ground substance). Further apatite crystals are accumulated until the whole osteoid is calcified.

With time, enough extracellular matrix accumulates around the osteoblasts until they are embedded in it and develop into osteocytes.

**Remember:** “Osteocytes maintain the tissue.”

Osteocytes are the main cells of bony tissue. They carry out their daily metabolism by
exchanging nutrients with the blood. Just like osteoblasts, the mature bone cells are not able to divide.

**Remember:** “Osteoclasts chew bones.”

Their task is to degrade the extracellular matrix. This is a process that goes hand in hand with the coordination of osteoblasts since they also secrete a series of messenger substances. This is part of the normal development, maintenance, and repair process of bones.

Osteoclasts are specialized macrophages or giant cells. They are concentrated inside the endosteum and consist of up to 50 monocytes. The second essential function of osteoclasts is the maintenance of the calcium serum level. When degrading bones, the bound calcium and phosphate are released and their serum levels increase.

**What Are Osteons?**

Bones have numerous small gaps between their cells and the components of the extracellular matrix (among others, collagen fibers, water, electrolytes, and glycosaminoglycans). As we have learned, bone consists of periosteum, compact bone, spongy bone, endosteum, and bone marrow.

The smallest units of bones are found inside the compact bone. Through the concentrated arrangement of bone lamellae, several thin long cylinders are formed. These are called **osteons or Havers’ system.**

The concentrated lamellae proceed around a recess along the longitudinal axis of the bone, which is referred to as the Haversian canal or **central canal (canales centrales).** Inside this centrally located Haversian canal, blood vessels and single nerves proceed through the bone surrounded by a bony sheath. These bony sheaths contain osteocytes that are necessary for maintaining the structure. Perpendicular to the Haversian canals is the Volkmann’s canals (canales perforantes). They contain arteries, veins, and nerves from the periosteum, which proceed to the center of the osteons.
Stability of the Compact Bone

Lacunas (lacunae = small lake) are small gaps between the lamellae that contain osteocytes. From the lacunas, which are filled with extracellular fluid, small canals (canaliculi) radiate in all directions. Finger-shaped extensions of osteocytes are located inside the canaliculi, which connect the lacunas and the central canals. Neighboring osteocytes communicate via so-called gap junctions. These are a complicated network of tiny, interconnected canals, found across the whole bone. This network forms a network for the supply of nutrients and oxygen as well as the removal of metabolic products.

The stability of a compact bone is achieved through continuously repeating units, the osteons, which consists of a central canal with arranged lamellae, lacunas, osteocytes and canaliculi. Osteons of a long bone can be compared to a tree trunk. An immense amount of strength is required to break through a tree trunk, attributed to their well-formed circular structure made of hard material. The same is found in the system of bones and osteons. To meet the requirements of continuous stress like running or weight lifting, the load line of bones change and the bone reconfigures itself to match the stress lines.

Bone Formation

The process of bone formation is called ossification (os = bone, and fiacre = to make) or osteogenesis. It is differentiated between

- chondral (endochondral) ossification and
- desmal (membranous) ossification

They represent two different methods of bone development or ossification.

Chondral ossification – from cartilage to bone

In the case of chondral ossification, the formation of bones mainly starts after birth from preformed hyaline cartilage, which has been developed out of mesenchyme (embryonic connective tissue).

During growth and ossification of the cartilage of short and flat bones, which can be found among others at the wrist and tarsal bones as well as in the manubrium of the sternum, ossification occurs in two ways:

- perichondrally
- enchondrally
1. Phase: Perichondral ossification

In the case of **perichondral ossification**, the ossification starts from the outside, which means on the surface, with the formation of osteoblasts from **perichondral** connective tissue in the area of the **diaphysis**. Due to the extension towards the epiphyses, a bony shell is formed that encloses the cartilage matrix like a cuff or splint.

The cartilage is separated from its surroundings, which leads to the initiation of the conversion process of cartilage to bone (endochondral ossification). Finally, the perichondrium becomes the periosteum.
2. Phase: Endochondral ossification

In the case of **endochondral ossification**, the ossification process starts from the middle of the cartilage matrix inside the bone.

Blood vessels reach into the cartilage and are accompanied by mesenchymal cells. To gradually convert the cartilage tissue into bone, mesenchymal cells are changed into chondroclasts and chondroblasts.

**This type of ossification occurs in growing bones in the area of the epiphyseal plate and can be observed best in long bones.**

The longitudinal growth of a long bone starts in defined growth areas such as the epiphyseal plates (growth plates, physes), part of the metaphysis (remember, they are located between the diaphysis and the two epiphyses). Hyaline cartilage is produced inside the epiphyseal plate and after its “completion”, it is gradually shifted towards the diaphysis, which therefore gets longer. The primary centrum of ossification of a long bone is located in the diaphysis.

The newly built cartilage is initially arranged in columns to produce larger, bubble-shaped cells in the direction of the diaphysis. The “oldest” structures, the ones in the middle of the diaphysis start the process of ossification. This process has only been performed by cartilage but now deposition of calcium salts begins. Toward the end of puberty, the metaphysis changes into spongy bone, the growth plate ossifies and the inner structure of the diaphysis is reabsorbed, forming a medullary cavity. The cartilage degenerates and leaves hollow spaces behind that are expanded to the medullary cavities (see below).

While the bone matrix grows, the cartilage matrix is continuously degraded by chondroclasts and replaced with the help of osteoblasts.

The epiphyseal plate is an exception.

Until the end of puberty, calcium-free cartilage is only found in the epiphyseal plate, since the epiphyses themselves increasingly ossify. Due to the high serum growth hormone level during the growth spurt at the end of puberty, ossification is closed and no more physical growth is possible.
Desmal ossification - bone formation from mesenchyme

Desmal ossification is the easiest type of ossification.

In the case of this direct type of ossification, bones are not converted from preformed cartilage but built directly from embryonic connective tissue, the mesenchyme. During this process, the mesenchyme differentiates into osteoprogenitor cells, which mature into osteoblasts and form a preliminary stage of a bone, the so-called osteoid. Bone bridges are formed through the calcification of the osteoid, which finally results in the skeleton.

E.g. some cranial bones and the sternum are created this way.

Desmal ossification differs from chondral ossification, such as osteoblasts are created from progenitor cells of connective tissue (osteoprogenitor cells) instead of being created from chondroblasts. Apart from that, the mechanism of bone formation is mostly the same as the mechanism of chondral ossification.

Bone Remodeling
Bone remodeling cycle

<table>
<thead>
<tr>
<th>Signaling microdamage</th>
<th>Activation</th>
<th>Osteoclast precursor recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Osteocytes at the site of microdamage undergo apoptosis</td>
<td>Bone lining cells digest underlying osteoid to expose mineral and then lift off surface</td>
<td>Osteoclast precursors bind RANKL and coalesce to form an osteclast</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td><strong>Deposition</strong></td>
<td><strong>New bone</strong></td>
</tr>
</tbody>
</table>
Control and regulation of calcium and phosphorus

| Osteoclast digest minerals with acid, releasing Ca\(^{2+}\) and PO\(_4^{3-}\) | Osteoblast precursors become osteoblasts and lay down new osteoid. Osteoid mineralizes and forms new bone | Trapped osteoblasts become osteocytes and extend dendrites |

**Hematopoiesis (Formation of Blood Cells)**

**Note:** Hematopoiesis includes erythropoiesis, leukopoiesis, and thrombopoiesis. Blood cells and platelets have a limited lifespan so they need to be continually replaced. Hematopoiesis (hemopoiesis) occurs in the bone marrow. The hemopoietic stem cell (pluripotent stem cell) can differentiate into all the blood cell lineages.

**Several progenitor stem cell types arise from a hemopoietic stem cell (HSC)**

Two major colonies arising from the HSC are:

- **Common lymphoid progenitor cells**
  - Differentiate into T-cells, B-cells, and natural killer (NK) cells.

- **Common myeloid progenitor cells**
  - Differentiate into specific lineage-restricted progenitors under the influences of cytokines, growth factors including colony-stimulating factors (CSFs).
    - Megakaryocyte/erythrocyte progenitor (MEP)
    - Granulocyte/monocyte progenitor (GMP)

**Erythropoiesis (erythrocytes)**

The megakaryocytes/erythrocyte progenitor (MEP) provides erythrocyte committed progenitors.

**Stages of erythropoiesis**

1. Proerythroblast
2. Basophilic erythroblast
3. Polychromatophilic erythroblast
Orthochromatophilic erythroblast
4. Polychromatophilic erythrocyte or reticulocyte
5. Erythrocyte

Thrombopoiesis
The megakaryocyte has a multi-lobed nucleus and can measure 70 µm in diameter.
Platelets are derived from invaginations of the plasma membrane which initiates the shedding of these cytoplasmic fragments (platelets).

Granulopoiesis (granulocytes)
The granulocyte/monocyte progenitor (GMP) produces granulocytes and monocytes.

Stages of granulopoiesis, e.g. a neutrophil
1. Myeloblast
2. Promyelocyte
3. Myelocyte
4. Metamyelocyte
5. Band (stab) cell
6. Neutrophil

Bone Diseases
The entirety of bone and cartilage forms the skeletal system. Bones and joints perform hard labor and can be damaged by inactivity or wrong diet practices.
One well-known bone disease is osteoporosis.

Osteoporosis
In the case of osteoporosis (osteon = bone, poros = pore), the bone resorption dominates compared to the bone formation, which means that the body loses more calcium than it can be deposited in the bone. The state of a porous bone so to speak, where bone mass is reduced to such an extent, is when bones break more often and spontaneous fractures can occur.

Osteoporosis is found especially in the areas of hip, wrist and vertebral bodies. Height reduction of vertebral bodies, loss of body height, distortion of the spinal column or bone pain are results of this disease. People suffering from osteoporosis are usually of middle to old age and with women being more affected (ca. 80 %) since their bones are thinner than the bones of males. Also, women’s production of estrogen decreases rapidly during menopause. The male testosterone, however, only decreases slowly and slightly.

The activity of osteoblasts and the production of the extracellular bony matrix is stimulated by estrogens and testosterone.

Risk factors for a homeostatic imbalance can be a positive family anamnesis, European or Asian origin, thin physical build, little activity, smoking, alcohol, decreased vitamin D/calcium intake, as well as intake of certain medications.

In the case of increased risk factors of osteoporosis special emphasis should be put on prevention. Regular physical activity and continuous intake of calcium, particularly for younger women, have a better effect than medication or calcium substitution in older people alone.

Further Bone Diseases (Osteopathies) Are:

- Achondroplasia
- Fibrodisplasia ossificans progressiva
- Fracture
- Hypophosphatasia
- Bone marrow edema
- Morbus Ahlbäck
- Paget (Osteodystrophia deformans)
- Osteochondrosis dissecans
- Osteogenesis imperfecta
- Osteomyelitis (Inflammation of the bone)
- Spongy bone edema

Review Questions

Answers can be found below the references.

1. What is the area of a long bone/hollow bone called where longitudinal growth is initiated?
   
   A. Metaphysis  
   B. Epiphyseal plate  
   C. Diaphysis  
   D. Epiphysis  
   E. Periosteum

2. Which process is false?
A. Osteoblasts build bones  
B. Osteocytes maintain tissue  
C. Osteoclasts chew bones  
D. Osteons are small units of bones  
E. Canaliculi are narrow gaps

3. Which statement about ossification is true?

A. The process of bone degradation is called ossification  
B. Chondral ossification is part of desmal ossification  
C. Perichondral ossification is a phase of chondral ossification  
D. Desmal ossification describes the formation of bone from cartilage  
E. Chondral ossification is used to describe a direct way of bone formation

References


Correct answers: 1B, 2E, 3C

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