Chapter 8

# Pathophysiology of bones and joints

## 8.1  Introduction

The skeleton has several functions in the organism: it forms the supporting framework of the body, protects the organs, and forms cavities where the bone marrow is localized. From pathophysiological point of view however, the most important function of skeleton is that it serves as a rich reservoir of mineral ions, above all of calcium, phosphate, magnesium and sodium. Under physiological conditions all these functions operate in well balanced mutual interaction. Under pathological conditions the participation of bones in maintainance of chemical homeostasis (e.g. during calcium deficiency) may lead to progressive bone demineralization which can negatively influence the supportive function of the skeleton. The complicated relations between the bone and extracellular milieu being mediated mainly by hormones, enable the development of a large variety of pathological conditions where the initiating factor may be any component involved (e.g. kidney, GIT, endocrine gland, bone).

### 8.1.1  Remarks to the anatomy and physiology of bones

The bone consists of a firm organic matrix (30 per cent) strengthened by deposition of calcium salts (70 per cent). The organic matrix contains mainly the collagen fibers with high content of glycine, proline and hydroxyproline. The collagen fibers are arranged in the direction of the pressure forces acting on the bone. They ensure the bone elasticity. The rest of organic matrix is the homogeneous ground substance containing, above all, the vitamin K- dependent protein osteocalcin (Gla- protein) binding the calcium, the phosphoprotein osteonectin forming the connection between collagen and calcium, and other proteins and lipids in less quantity. The ground substance serves as medium for exchange of nutrients, oxygen, minerals, and waste products of metabolism between the bone tissue and blood. It is supposed that it participates also in the regulation of inorganic salts deposition into the bone matrix.

The **inorganic component** of bone containing mainly the calcium and phosphate in form of hydroxyapatite crystals is localized in close proximity to the surface of collagen fibers and among them. The ratio Ca/P changes according to the nutrition conditions in adults being about 1.67. The hydroxyapatite crystals provide the bones with extraordinary strength. On the surface of hydroryapatite crystals a brisk exchange of ions occurs. Therefore they could be considered to some degree as a ion exchanger or buffer system. The inorganic bone component is completed by magnesium, sodium and potassium ions but they have not been identified in crystalline form. It seems that they conjugate with hydroxyapatite. The property to conjugate with bone crystals have also the ions foreign for the human body e.g. lead, strontium, gold or radioactive substances. Deposition of radioactive substances in bones leads to prolonged irradiation with the risk of development of neoplasms in bones.

The bones are throughout the life constantly remodelled by two alternating processes: continuous bone resorption and formation. After the end of growth period both processes function in equilibrium. The continuity of bone remodelling is important from two points of view, at least:

1. it ensures optimal stability of skeleton during changing external conditions by prompt adaptation response to the magnitude and direction of the load exerting its action on the bone

2. by continual release and reuptake of calcium into the mineral component of bone tissue it contributes to the maintainance of calcium blood level stability.

The bone formation and resorption are performed by bone cells. The **osteoblasts** are present on the outer bone surface and in the bone cavities. They are responsible for the bone new-formation. They secrete the collagen monomers and proteoglycans of the ground substance. The collagen monomers rapidly polymerize forming collagen fibers. In few days the calcium salts begin to precipitate on the surface of collagen fibers. Small agglomerations of precipitates grow and increase quickly in number. The elementary amorphous substance of the precipitate is a mixture of various salts. During weeks or even months it is changed into hydroxyapatite crystals by substitution and addition of atoms and by complicated processes of reabsorption and reprecipitation. It is very important for the organism that about 25 per cent of salts remain permanently in the amorphous form. Only in this form they can be deposited or released to maintain constant calcium level in ECF. The response is in so far prompt that the release or uptake of the necessary quantum of ions from blood occurs actually during a sole blood flow trough the bone. Total amount of in this way available calcium represents 5 to 10 g.

The activity of osteoblasts results in osteoid formation. Osteoblasts remain in osteoid permanently changing functionally and morphologically (in shape and function) into **osteocytes** localized in the osseous lacunae. The osteocytes do not form new bone substance. They communicate with one another and with osteoblasts via long processes forming a dense network (so called osteocytic membrane system) in bone canaliculi. Since they are in close connection with capillaries and in immediate contact with the bone fluid rich in nutritive substances they participate actively in transfer of minerals in the lacunar wall. They can be reactivated into osteoblasts if need arises.

Simultaneously with bone formation the bone resorption occurs performed by the activity of **osteoclasts**. Osteoclasts are large phagocytic cells derived from monocytes of bone marrow. Under physiological conditions they operate in small groups on less than 1 per cent of bone surface. The resorption is performed by amply ruffled border of osteoclasts releasing proteolytic enzymes (from lysosomes) and acids e.g. lactic and citric acids (from mitochodria). The enzymes dissolve the organic matrix and the acids dissolve the inorganic salts. The result of osteoclast activity is a tiny cavity or canaliculus (Howship's lacuna) with the length of some few millimeters and diameter of about 1 millimeter. They are immediately occupied by osteoblasts and the bone formation starts again. Considering the functional point of view the above mentioned processes are termed: **basic multicellular unit**, BMU. It is a functional unit in which every cycle is characterized by osteoclast activation leading to bone resorption and by subsequent activation of osteoblasts performing the bone formation. Since the osteoblastic bone formation is associated with precedent osteoclastic bone resorption (osteoblasts need place for their action) the remodelling rate is determined by the osteoclast activation rate. The close coupling of bone resorption and formation processes indicates that between both types of cells i.e. the osteoblasts and osteoclasts exchange of information occurs. The mechanism of this communication is not known however several, mainly local factors (e.g. prostaglandins, growth factors and even the partly decomposed components of osteoid) participate in this process.

Continual remodelling performed by balanced interaction of osteoblasts and osteoclasts enable the bone to change its architecture in response to mechanical load. During the exposure of the bone tissue to the load action its new formation increases. That is why the bones of hard working people and of sportsmen are substantially heavier. On the contrary the bones of immobilized limbs become during several weeks lighter by 30 per cent. Thus the permanent physical load stimulates the osteoblastic activity and calcification of the bone.

The overload of bone elasticity and firmness causes **fracture**. Periost and the blood vessels of the bone marrow, compact bone tissue and neighboring soft tissues become disrupted. Haematoma develops along the medullar cavity, among the broken ends of the bone, and under the periost. The bone tissue in the immediate proximity to the fracture is affected by necrosis. stimulating an intense inflammatory re-

sponse characterized by vasodilatation, plasma exsudation and infiltration with leukocytes and mast cells. After 48 Hs the blood vessels from surrounding tissues and bone marrow begin to infiltrate the inflammatory focus and the blood circulation restores progressively. The activated cells of periost, endosteum and bone marrow produce subperiostal procallus bridging the fracture surfaces and forming the non osseal connection. Osteoblasts of procallus synthesize collagen and other components of matrix which begin to mineralize and to form callus (in about 3 weeks). As the healing process continues the unnecessary callus is resorbed. New bone trabeculae are formed arranged in the direction of pressure forces action. This process lasts for weeks to months.The healing duration can be negatively influenced by several factors. To the general factors belong the advanced age, insufficient nutrition, (starving or malabsorption leading to protein, calcium, vitamin D and C deficiency). As the most frequent local factors should be mentioned the incorrect apposition of the broken bone ends and insufficient immobilization which can lead owing to the repeated moving to formation of fibrotic connection – the pseudoarthrosis. Further local causes of retarded healing may be the infection and insufficient blood supply given also by anatomic localization of the fracture e.g.:

- the nutrient artery enters the bone far from the site of fracture, or it is impaired by the fracture (head of femur, carpal scaphoid bone)

- fracture is localized in region where periost is absent (collum femoris)

- minimal amount of adjacent soft tissue (tibia)

The process of healing is retarded also in pathologic fractures. This term is used in cases of fractures caused by preexisting bone disease. It occurs in diseases with decreased bone density: osteoporosis, Paget's disease, osteogenesis imperfecta, and tumours of bone. In these cases due to decreased bone density or alterations in bone tissue composition lower, in extreme cases minimal external force is sufficient to disrupt the bone continuity.

## 8.1.2  Hormones influencing the bone tissue

Constant calcium and phosphate levels in blood are critically important for vital functions. Responsible for their maintainance are, above all, the hormones influencing the reservoir of these ions (bones) and the organs of ion intake (GIT) and excretion (kidneys). Dominant role in hormonal regulation play parathormone and calcitriol.

**Parathormone (PTH)** secretion from parathyroid glands is extremely sensitive to changes in blood concentration of calcium ions. The secretion of PTH rises when the calcium ion concentration in blood falls and vice versa (negative feedback mechanism). The end- effect of PTH action is the calcium blood level elevation achieved by influencing the:

1. absorption of calcium and phosphates from bones

2. excretion of calcium and phosphates via kidneys

3. calcitriol

**ad 1)** The effect of PTH is realized in two phases. During the **fast phase** lasting some minutes PTH stimulates existing osteoblasts and osteocytes equipped with receptors for PTH to reabsorb the calcium salts. Binding of PTH to the receptors induces the rise in cAMP concentration via adenylcyclase activation and subsequent phosporylation of regulative proteins. These processes result in enhanced permeability of osteocyte membrane to calcium. Calcium present in the bone fluid enters the osteocyte governed by the steep concentration gradient. The transfer of calcium from cells into the extracellular fluid (ECF) is performed by Ca-pumps. The calcium concentration in the bone fluid decreases. To maintain the equilibrium the surrounding amorphous salts are dissolved. Such a process – the osteocytic osteolysis – does not cause resorption of the organic matrix of bone (see the figure 8.1).

During the **slow phase** lasting days to weeks PTH induces an indirect activation of osteoclasts which are not equipped whith PTH receptors. It is supposed that the activated osteoblasts and osteocytes emit a till unknown signal inducing activation of present osteoclasts and simultaneous formation of new osteoclasts. The result is an increased rate of osteoclastic resorption of the whole bone tissue i.e. of
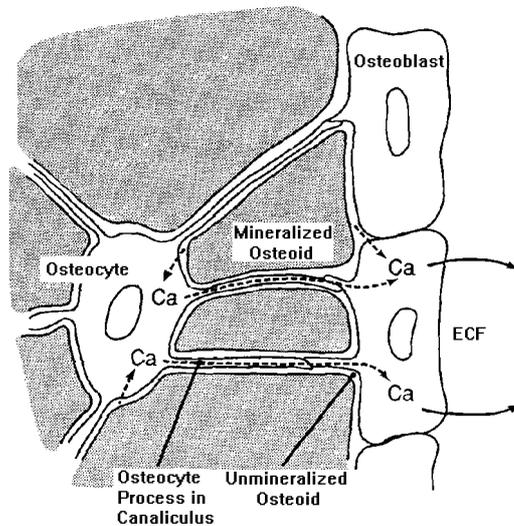
Figure 8.1: Osteolytic osteolysis

both components: the mineral salts and organic matrix.

Skeleton contains about thousand times more calcium than is its total amount present in ECF. That is why even the maximal increase in calcaemia induced by PTH does not lead to evident alterations in bones. Long-term duration of PTH hyperproduction (months to years) however, leads to osteoporosis characterized by presence of large cavities filled with osteoclasts. Progressive bone resorption results in secondary stimulation of osteoblasts, nevertheless the resorption prevails over the bone formation.

**ad 2)** PTH increases in kidneys the tubular calcium reabsorption (ascending limb of Henle's loop, distal tubule and collecting tubule) and simultaneously it inhibits the phosphate reabsorption in the proximal tubule. By combination of these effects PTH enables to increase the calcium level and to excrete simultaneously excess of phosphates released from bone minerals (should the product of calcium and phosphate remain constant, the increase in concentration of one ion entails the fall of the other and vice versa).

**Calcitriol (1,25–dihydroxyvitamin $D_3$)** Active hormonal form of vitamin $D_3$ the calcitriol – is be-

sides the parathormone the second most effective regulator of bone metabolism. Vitamin $D_3$ – cholecalciferol is formed in the skin from endogenous precursor by the action of ultraviolet radiation (sunlight). Vitamin D in small amount is ingested in food as ergocalciferol ($D_2$) differing from vitamin $D_3$ only in the length of the side chain. The biologically inert cholecalciferol is transported via blood flow into the liver where it is oxidized to an intermediate product – 25-hydroxyvitamin $D_3$ exhibiting low biologic activity. After being released into the blood it is metabolized (1-alpha-hydroxylation) in the cells of renal proximal tubule to thousand times more active calcitriol. Calcitriol fulfills criteria to be considered as hormone from more than one points of view, above all, because it acts in a manner characteristic of steroid hormones i.e. it binds to a specific intracellular receptor in the target cells.

The formation of calcitriol is under physiological circumstances strictly controlled by PTH. Parathormone induces enhancement of calcitriol formation by stimulation of the 1-alpha-hydroxylation in kidneys. Further regulating factor of calcitriol formation are the levels of ionized calcium and inorganic phosphate in blood. Hypocalcaemia (acting directly on kidney and indirectly mediated by PTH effects) and hypophosphataemia also stimulate the calcitriol formation.

Calcitriol increases the concentration of ionized calcium and in a less degree the phosphate concentration in blood by its action on the target organs i.e. intestine, kidney and bone. It enhances the calcium absorption and in a less degree also the phosphate absorption by increasing the permeability of the brush border, the calcium binding protein synthesis, and the active transport across the basolateral cell membrane in the intestinal wall.

Calcitriol stimulates the calcium reabsorption in kidneys mediated by specific receptors for calcitriol in distal parts of nephron.

In the bone calcitriol stimulates the osteoclastic bone resorption in the same way as does PTH in slow phase of its action: it augments the number and the activity of osteoclasts. Since the osteoclasts lack the specific calcitriol receptors, it probably stimulates the differentiation of mononuclear precursor cells to the mature osteoclasts. The activity of osteoclasts is simultaneously modulated by neighbo-

ring osteoblasts equipped with specific intracellular calcitriol receptors.

Calcitriol is inevitably necessary for initiation and regular continuation of osteoid mineralization. This effect is realized probably by influencing the calcium ion transport through the membranes of osteoblasts and osteocytes. It supports indirectly the bone mineralization increasing the calcium and phosphate absorption in the intestine. Calcitriol and PTH realize their effects on bone by an evidently common final mechanism. Evidence of it is given by the fact that during calcitriol deficiency the responsiveness of the bone to PTH is reduced and on the contrary in PTH deficiency even hundred times more calcitriol is needed to calcium and phosphate mobilization.

Besides both mentioned major hormones there are further hormones and local modulatory factors influencing the bone metabolism. However their physiological function is still not well understood. Their effect on bone becomes manifest only under certain circumstances.

**Calcitonin** is a hormone secreted by C-cells of parathyroid gland. Effects of calcitonin on plasmatic levels of calcium are in contrary to those of PTH and calcitriol. Calcitonin achieves the decrease in plasmatic calcium level by acting on the bone tissue.

1. It immediately suppresses the resorbing activity of osteoclasts by binding to the specific receptors and influences simultaneously the osteocytic membrane system resulting in calcium deposition into the rapidly exchangeable amorphous salts. This effect of calcitonin is evident only when high metabolic turnover in bones is present e.g. in growing period or in Paget's disease (see further).

2. By long-lasting effect calcitonin decreases the new-formation of osteoclasts. Because the osteoclastic bone resorption leads to secondary stimulation of osteoblastic activity reduced numbers of osteoclasts result in reduced numbers of osteoblasts. Resulting effect of long-term calcitonin action is the bone remodelling retardation.

**Estrogens** influence positively the bone metabolism. Decrease in, or absence of estrogen secretion leads to the loss of the bone mass. The action of estrogens on the bone is directly mediated by specific receptors, or indirectly by:

1. stimulation of calcitonin

2. inhibition of bone resorption induced by PTH

3. positive influence on calcitriol activation in kidneys

**Androgens** are responsible for the achievement of peak bone mass in men. Androgens together with estrogens and growth hormone influence the growth and the epiphyseal closure.

**Glucocorticoids** are in physiological doses important regulators of bone growth. Glucocorticoids influence both, the osteoclasts and the osteoblasts. In excess however, they reduce the bone mass density (osteoporosis). This final effect results from their direct action on bone (inhibition of replication and differentiation of osteoblasts and increase in numbers and activity of osteoclasts) and from indirect action (inhibition of intestinal calcium absorption and stimulation of calcium excretion via kidneys).

The mechanism of thyroxine effects on bone is not well understood. Nevertheless it is well known that the untreated thyrotoxicosis may lead to osteoporosis and the hypothyroidism on the contrary is associated with decreased metabolic turnover in the bones.

**Somatotropin (STH)** action on bone is important mainly in the period of growth. It induces proliferation of chondrocytes. Experiments in vitro have shown that its effect is rather indirect, mediated by stimulation of the liver to form somatomedin (somatotropin mediator). This peptide circulates in blood firmly bound to proteins. Since its structure and activity is similar to insulin it is named recently – the insulin-like growth factor (IGF). It occurs in two forms:

- IGF1 strongly dependent on somatotropin

- IGF2 less dependent on somatotropin and more similar to insulin.

People which are resistent to the PTH effects e.g. Pygmies have a normal level of PTH but low level of IGF1 in blood.

**Vitamin C** participates in collagen and acidic mucopolysaccharide synthesis. **Vitamin K** is necessary for the biosynthesis of Ca-binding proteins (in plasma, kidney, liver), and for the osteocalcin biosynthesis in bones. **Vitamin A** sustains the osteoclastic bone resorption and by its action on the acidic mucopolysaccharides it influences the stage of calcification.

Various local factors contribute considerably to the maintainance of the tender balance in activities of single types of bone cells. Topically produced prostaglandins e.g. $PGE_2$ may directly act on the bone metabolism by stimulation of osteolytic processes or by inducing synthesis of further local factors (epidermal growth factor, platelet-derived growth factor). Interleukin-1 is a very effective substance stimulating the bone resorption. Similar to the interleukins is the osteoclast activating factor. Further cytokines e.g. the gamma interferon exert also topical regulative effects on bone tissue. By osteoblasts produced TGF beta (transforming factor beta) stimulates the mitogenesis and collagen synthesis. The majority of these factors is involved also in the healing and reparation of microfractures. Besides the hormones and topically acting factors the trophic influence of nervous system has a substantial importance in bone metabolism regulation. When the nervous system is excluded the bone formation is reduced and bone resorption enhanced (bone atrophy).

# 8.2  Generalized skeleton disorders

By evaluation the bone diseases the fact should be taken into consideration that in bones a continuous process of remodelling takes place. The bone remodelling does not occur however at identical velocity in all parts of skeleton. Therefore the disorder becomes manifest first in those parts of skeleton where the metabolic turnover is maximal. Intensity of remodelling has a declining tendency: mostly affected is the vertebral column, afterwards pelvis, ribs, lower extremities, shoulder girdle, upper extremities and at least the skull. Generalized process with identical manifestations in all parts of skeleton does not exist. The term – generalized process – indicates a biological process occurring at the molecular level, it does not indicate clinical manifestations. A metabolic disturbance induced mostly by hormonal or nutrition disorders is always involved. Specification as a process at molecular level is important because the bone affection assessed in clinical, radiological an even his-

tological examinations can be manifest only at one or more sites of the skeleton. Thus, the vertebral column alterations might have the look of local lesions, they however are indicative of generalized skeleton disease. The genuine real local disorders are caused by:

1. immobilization of one part of the skeleton leads to local atrophy developing the sooner the higher is the metabolic turnover in affected bone

2. disorder of circulation (local obliteration or obturation of blood vessel, or A-V anastomosis lead to trophic disorders of bone)

3. tumours of bones (every tumour of bone including the cyst whether it originates in bone or has been metastasized is substantially of local character, even if a multiple dispersion is involved because the bone among the metastases is normal).

## 8.2.1   Skeleton balance disorders

### 8.2.1.1   Negative balance of skeleton

**Osteoporosis**   The term osteoporosis is reserved for bone mass loss per bone volume unit. The composition of bone remains however normal as show the histological and biochemical findings.

The bone mass quantity is determined by mutual proportion of bone formation and resorption processes. Positive, neutral or negative bone balance are observed in various periods of life. In childhood and adolescence the bone formation preponderates evidently over the bone resorption. In adults are both processes in equilibrium (remodelling). The peak bone mass is attained in age of 30 to 35 years. In men are the peak values substantially higher than in women, so they are in black population in comparison to the white people. Genetic factors however predetermine the peak bone mass in every individual. Following five to ten years a slow decline in total bone mass begins. At the beginning the velocity of the decrease is identical in both sexes. Subsequent bone loss in women is during the menopause significantly accelerated. In advanced age is the rate of bone loss again identical in both sexes. The less the attained peak bone mass the sooner osteoporosis will develop.Therefore are the white postmenopausal women at greatest disadvantage.