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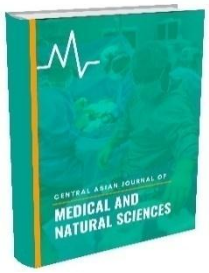

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Morphology and Structure of Bone

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Abstract: Connective tissue cells, including fibroblasts, cartilage and bone cells, are specialized in the secretion of fibrillar proteins (primarily collagens), which are used for building intercellular substance. The intercellular matrix is a complex substance found in the interstitial intracellular space (between cells). In connective, cartilage and bone tissue, the intercellular matrix occupies a significant volume and performs its main functions. Bone formation Cells of mesenchymal origin - fibroblasts, osteoblasts - synthesize and secrete collagen fibrils, which are in the matrix containing also proteoglycans and glycosaminoglycans. Mineral components come from the surrounding liquid phase, crystal lattice formation is induced by nucleation (three-chain collagen activates crystal formation).

Key words: bone structure and morphology, connective tissue cells, bone formation.

Introduction. Bone formation begins between collagen fibrils, where apatite structures line up (biomineralization occurs). The crystals become nucleation centers for hydroxyapatite deposition and collagen induces calcium deposition. Proteoglycans increase the extensibility of the collagen network and increase swelling. Bone formation occurs in the vicinity of osteoblasts. Degradation of protein-polysaccharide complexes is noted in the calcification zone. Growing crystals displace proteoglycans and water (formed bone is dehydrated). 20% of the bone mass and 40% of the volume is collagen. The structure of bone substance contains cell-lined haversacks that conduct blood vessels. Bone is a dynamic calcium depot, and the stability of the bone structure is ensured by the activity of osteoblasts and osteoclasts. The large contact surface of the crystals of the mineral components of the bone tissue with the intercellular fluid provides a rapid entry of various cations into the bone composition. The crystals are hydroxyapatites or carbonatapatites, which are the most important mineral component of the bone tissue and whose composition is reflected by the formulas Ca10(RO4)6(OH)2 and Ca10(RO4)6CO3. Bones contain carbonates of other alkaline-earth chemical elements. Apatite is a large complex cation Ca[Ca3(PO4)2]32+, which is surrounded by counterions OH-, CO32-, HPO42-, F-. The crystals are in the form of plates or sticks about 8¬15 °A thick, 20-40 wide, 200-400 long. In the crystal lattice of hydroxyapatite calcium can be replaced by other divalent cations. Anions are adsorbed to the surface, which form small crystals, or dissolve in the hydrate shell of the crystal lattice. Hydroxyapatite crystals are firmly bound to the protein (49 amino acid residues), containing three residues of γ-carboxyglutamic acid. This protein is involved in the regulation of calcium binding in bones and teeth.

Anatomy and bone structure

Anatomically, bones are divided into flat bones and long bones. Flat bones include the skull, lower jaw, scapula, pelvis, long bones - shoulder bones, forearm bones, femur bones, shin bones. In long bones, there are epiphyses (the two wide ends), diaphyses (the cylindrical middle part) and metaphyses (the transition between the diaphyses and the epiphyses). Between the metaphyses and the epiphyses, there are so-called growth plates, represented by a layer of epiphyseal cartilage. The outer (cortical) layer of the bone is very thin, dense and is a calcified tissue, which thins even more towards the metaphyses and diaphyses. The cortical layer also lines the inner medullary cavity in the diaphyses, which contains bone marrow (thus there is a periosteum and endosteum in tubular bone). The inner part (spongy, trabecular) of the bone is filled with calcified trabeculae. Bone marrow is located not only in the medullary cavity, but also in the peritrabecular spaces. Cortical and trabecular parts differ functionally and structurally, although they consist of the same cells and matrix. The cortical bone performs protective and mechanical functions; the trabecular bone performs metabolic functions. The cortical part is 80-90% calcified, while the trabecular part is 15-20% calcified. Cortical bone (mainly flat bones and diaphyses of tubular bones) accounts for 80% of skeletal volume. Vertebral bodies, pelvic bones, distal parts of femur bones mainly consist of trabecular tissue. Bone marrow, vessels, and connective tissue make up the rest of the bone. Bone consists of cellular elements, intercellular matrix, and mineral components closely related to each other. There are two types of bone tissue - coarse fibrous (immature) and lamellar (mature). Coarse fibrous (reticulofibrous bone tissue) in adults is found in the growth areas, in places where tendons are attached to bones, in dental alveoli, in the bone labyrinth of the inner ear, in the areas of cranial sutures overgrowth. It is also formed in inflammatory, neoplastic processes, metabolic disorders, in the process of treatment that stimulates bone formation. Its structure is characterized by the presence of disordered collagen bundles, a large number of proteoglycans, glycoproteins and, on the contrary, low content of mineral salts.

The lamellar bone tissue is a result of further development of the coarse-fiber bone tissue - saturation with minerals, ordering of the structure, increasing strength. The main structural and functional unit of lamellar bone tissue is an osteon, which consists of a layer of osteoblasts, osteocytes, a system of interconnected bone plates surrounding a central canal in which blood and lymphatic vessels and nerves are located. It takes about 79 days for the osteon to form in an adult. Osteon is a dynamic structure: when the load increases, the number of plates increases and the lumen of the canal decreases; when the load decreases, the opposite process is observed. This data demonstrates the extent to which physical activity is important for the condition of bone tissue. Three groups of osteons are distinguished: growing, mature, resorption. Their transformations (restructuring) continue throughout human life. The number and size of osteons decrease with age. Between the osteons there is a tissue called the "bone plate". Cellular elements of bone are represented by osteoblasts, osteocytes, osteoclasts. They make up 2% of bone tissue (Table 1.1). The origin of bone cells is not definitively established: it is supposed that preosteoblasts first differentiate from mesenchymal stem cells, then osteoblasts and osteocytes. From monocytes (representing hematopoietic stem lineage) differentiate preosteoclasts, osteoclasts. Osteoblasts are located on the surface of the bone and form it. They are polygonal cells of medium size (15¬-40 μm) with a developed Golgi complex, endoplasmic network, a significant number of ribosomes, polysomes, high actin content. Histochemical marker of osteoblasts is alkaline phosphatase (ALP), biochemical - osteocalcin. A distinction is made between immature and mature, active and inactive (resting) osteoblasts. Active osteoblasts (large cubic or cylindrical cells with thin processes) secrete alkaline phosphates, synthesize proteins, and form the osteoid. Taking into account the peculiarities of their functioning three types of osteoblasts are distinguished. Osteoblasts secrete matrix vesicles (contain calcium, phosphatases) that calcify the osteoid, walling up the cell. Osteoblasts may pass into a quiescent state or into osteocytes. The main function of osteoblasts is protein synthesis, formation of collagen network, production of organic matrix components, matrix

vesicles, cytokines, growth factors (FR). These cells also synthesize collagenases, glycoproteins, osteonectin, osteocalcin, bone sialoprotein, osteopontin, plasminogen activator, etc. The newly formed tissue, consisting of collagen fibers and proteoglycans synthesized by osteoblasts, subsequently undergoes mineralization (deposition of hydroxyapatite crystals). Bone mineralization is the result of the synthesis of matrix products and the production of matrix vesicles. Under the influence of parathyroid hormone (PTH), cytokines, osteoblasts release factors that activate osteoclasts. Osteoblasts (osteocytes) can carry out resorption of intercellular substance with the formation of lacunas, resorption sinuses. They influence differentiation of osteoclasts from progenitor cells. Inactive osteoblasts take part in bone tissue metabolism (Aaron J.E., 1976). 2¬8% of the bone surface is occupied by active osteoblasts, 80¬-92% by inactive ones (they are mainly located near the sinus of the medullary canal). Osteoblast cells carry receptors and produce factors that regulate bone remodeling. Osteoblast cells carry receptors for PTH, PTH-related proteins, 1,25-dihydroxycholecalciferol (calcitriol) - 1,25-(OH)2D3, GCs, estrogens, androgens, progestins, thyroid hormones, retinoids (vitamin A), prostaglandins (PG)E, PGF2b , insulin-like growth factor (IGF)-1 and -2, insulin, fibroblast growth factor (FGF), transforming growth factor (TGF)-β, bone morphogenetic protein (BMP), epidermal growth factor (EGF), platelet-derived growth factor (TRGF)-A and -B, interleukins (IL)-1, -3, -4, -6, -8, -11, tumor necrosis factor (TNF)-α, leukemia inhibitory factor (LIF), endothelin. The function of osteoblasts is influenced by IPFR, TFR and TrFR, as well as FRF, PG. Osteoblasts respond to the load with increased work. Lack of physical activity, decrease in body weight cause a decrease in bone formation. The mechanical signal originates in the matrix, is transmitted to the cells, and is transformed into biochemical signals. Osteocytes immersed inside the bone are involved in the reception and transformation of mechanical stimuli. Besides mechanical stimuli, systemic and local factors (sex hormones, GC, anabolic steroids, 1,25-(OH)2D3, PTH, IL-1, PGE, etc.) regulate bone formation. Osteocytes originate from osteoblasts: the tissues they produce (collagen, proteoglycans) are mineralized towards the osteoblast and it becomes lodged, calcified. They are located in osteocyte lacunae filled with collagen fibrils. Depending on the functional activity of osteocytes there are 5 types of lacunas. Cellular lacunae connect to the tubules and form the so-called lacunar-channel system. The fluid contained in the lacunar-channel system differs from blood plasma in its composition. Periosteocyte spaces (between cytoplasmic membranes and matrix) contain interstitial fluid, calcium ions (lower concentration of calcium ions compared to blood plasma ensures its inflow). In mature individuals, osteocytes make up 90% of the osteogenic cells of the skeleton. Metabolically, osteocytes are not active. With the help of long processes they contact each other, forming a network of canals in the bone matrix, allowing intra- and extracellular transport of minerals, nutrient substrates (Aaron J.E., 1976). A distinction is made between canals (central, punctate, connective) containing vessels. The main function of osteoclasts in contact with calcified surfaces is bone resorption (resorption). These large (giant) multinucleated dome-shaped cells have a lifespan of 2 to 20 days and secrete lysosomal enzymes (including acid phosphatase) that allow them to perform their primary function. They originate from hematopoietic granulocytic-macrophage colony-forming units, the precursors of monocytes/macrophages. Preosteoclasts (mononuclear cells) are also involved in bone resorption. Among the factors influencing the formation of osteoclasts, IL, 1,25-(OH)2D3, TNF (osteoprotegerin suppresses osteoclastogenesis) are noted (Dedukh V.N., 2002b). Resorption is modulated by increased proliferation of osteoclastic cells and increased activity of mature osteoclasts. Bone destruction involves lactate, H+-ions that are formed from H2CO3 due to the action of carboanhydrase with the participation of adenosine triphosphatase (ATPase) (osteoclastic H+-pump), proteolytic enzymes. Decrease in the activity of carboanhydrase and H+-ATPase is accompanied by inhibition of bone resorption. To the resorbable surface belongs the so-called resorbable rim. In this place an osteoclastic resorption lacuna is formed. On the cytoplasmic membrane there are receptors for calcitonin, the effects of which are mediated through cyclic adenosine monophosphate (cAMP). Functional activity of osteoclasts is regulated by osteoblasts, systemic (PTH,

calcitonin, 1,25-(OH)2D3) and local factors. Calcitonin inhibits the proliferation and differentiation of osteoclast precursors. One of the mechanisms of action of estrogen and testosterone to inhibit resorption is a decrease in IL-6 production. PTH, 1,25-(OH)2D3 stimulate differentiation of precursors and also increase resorptive activity of osteoclasts. Among the local factors, bone tissue resorption is enhanced by: IL-1, -3, -6, -11; TNF-α, -β; macrophage colony stimulating factor (M-CSF); granulocyte-macrophage colony stimulating factor (GM-CSF); stem cell factor; PG. Interferon (IFN)-γ; TDF-β; IL-4, -13 inhibit bone resorption. Cytokines can be produced by osteoblastic lineage cells, indicating a functional relationship between these two cell types. Osteosclerosis" or "marbled bone disease" occurs due to genetic dysfunction of osteoclasts. Osteosclerosis develops in patients with a defect in the gene encoding carboanhydrase II, which causes deficiency of this enzyme. In patients with this pathology, osteoclasts cannot completely resorb bone tissue, and the bones become obesogenic. Radiography reveals generalized osteosclerosis, narrowing of the medullary spaces, and pancytopenia. In early childhood, a malignant form of the disease develops, leading to the death of patients in a short time. In the case of benign course patients survive until adulthood. In the malignant form in children bone marrow transplantation is used, which contains normal osteoclasts.

Bone tissue matrix

As noted above, a significant part of the bone tissue is the intercellular matrix (intercellular substance - 98%), which performs the main functions. It is conventionally divided into organic and mineral. The inorganic mineral components of bone comprise 70%, and the remaining part is represented by the organic matrix (20%) and water (10%). The organic matrix of bone includes proteins and lipids. Collagens form the basis of the organic matrix (95%). In the human body, collagen is the predominant protein in quantitative terms: it constitutes 25% of total protein. It has an unusual amino acid composition: 1/3 is glycine, about 10% is proline, as well as hydroxyproline and hydroxylysine. The length of the entire collagen molecule is about 300 nm. Collagen of type I is 90%, types III, IV, V, XI, and XII are 5%. Thus, the strength of bones against stress and tension is provided by collagen type I, around the fibers of which mineralization occurs. A collagen molecule consists of three polypeptide chains of different types (α-helices) twisted in the form of the right triple helix (Kolman J., Rem K., 2000). Polypeptide chains are constructed of frequently repeated fragments with the characteristic - Gly-X-Y- sequence. Every third amino acid residue is glycine. Proline is often found at the X-position; the Y-position can be occupied by either proline or 4-hydroxyproline. The collagen molecule also contains 3-hydroxyproline and 5-hydroxylysine residues. A characteristic feature of collagen is the presence of hydroxyamino acid residues in the polypeptide chain. Proline and lysine residues are hydroxylated after their incorporation into the polypeptide chain (posttranslationally). Hydroxylation of proline and lysine residues in the procollagen molecule is catalyzed by procollagen hydroxylases containing iron atoms in the active center. Ascorbic acid serves as a coenzyme. One end of collagen molecule is cross-linked by cross-links formed by side chains of lysine residues. As the body ages, the number of cross-links increases. Depending on the combination of polypeptide α-chains, there are 12 types of collagen. Collagen type I has a long filamentous molecule with a molecular weight of 285 kDa. Collagen molecules are capable of spontaneous aggregation to form more complex structures - microfibrils, fibrils, meshes, ligaments. Fibrils have a cylindrical shape and diameter from 20 to 500 nm. The components of the intercellular matrix are bound by adhesive proteins: laminin, fibronectin, elastin. Adhesive proteins, interacting with cell receptors (integrins), fix cells in the intercellular space. The peculiarities of fibronectin structure provide them with the properties of a "molecular glue", since fibronectin subunits subdivided into different domains are capable of binding to cell receptors, collagens, fibrin and proteoglycans. The intercellular substance contains organic acids that form complexes with calcium. Non-collagen proteins (osteocalcin, osteonectin, bone sialoproteins, phosphoproteins, morphogenetic protein (MSP), proteolipids, glycoproteins, proteoglycans) make up 5% of intercellular substance. Proteoglycans act as a filler and make up the main substance of the

intercellular matrix. They are large molecules (over 2-106 Da) with protein (5%) and carbohydrate (95%) components (Kolman J., Rehm K . ., 2000). Protein monomers carrying a large number of polysaccharide chains are associated with the axial molecule of hyaluronic acid. The polysaccharides found in proteoglycans refer to glycosaminoglycans. The basic structural unit of various glycosaminoglycans is a disaccharide link consisting of uronic acid (glucuronic, iduronic, galacturonic) and N-acetylhexosamine. Noncollagen proteins affect mineralization, bone formation, and collagen synthesis. Such processes as intercellular interactions (fibronectin, sialoprotein, osteopontin, thrombospondin), bone tissue remodeling (osteocalcin), mineralization (phosphoproteins, proteolipids, osteonectin) depend on them. 10% of non-collagen proteins are proteoglycans, which influence the formation of collagen fibrils, their relationship with the crystal phase and mediate FR. The collagen-proteoglycans-crystals complex provides the mechanical qualities of bone tissue. Bone glycoproteins include alkaline phosphate, osteonectin, thrombospondin, fibronectin, vitronectin, osteopontin, and bone sialoprotein. They create conditions for mineralization processes, cell proliferation, cell adhesion, etc., which are necessary for the development of the cellular matrix. S and Gla-proteins, cytokines (IGFR-1 and -2, TrFR, colony-stimulating growth factor) are found in organic matrix. Noncollagen matrix proteins are unevenly located in the matrix (their location has not been sufficiently studied). Osteopontin is located in the newly synthesized mineralized bone tissue near the osteoblasts, in the zone of osteocyte lacunae, in the zone of cell-osteoid contacts. Sialoprotein is located inside the interfibrillar openings and regulates the initiation of calcification. The collagen fibers of the bone matrix are oriented in one direction. Collagen filaments are surrounded by crystals (lamellar, spindle-shaped) oriented in the same direction as the fibers. Together, they create a lamellar bone structure. The laminae are arranged parallel or concentric, depending on the nature of the bone surface and the presence of channels. In the calcification, fixation of hydroxyapatite crystals an important role is played by the main substance, consisting of glycoproteins and proteoglycans. Proteoglycans act as a filler - the basic substance. They bind cations and the bulk of water due to their polar nature and strong negative charge. The matrix contains osteocalcin (γ-carboxylated proteins), proteins containing osteopontin, fibronectin. Osteocalcin is represented by 50 amino acid residues (3 of them bind calcium) and makes up 15% of noncollagen proteins. It is secreted by osteoblasts and participates in bone tissue mineralization. Its secretion is regulated by the active metabolite of vitamin D, calcitriol (1,25-(OH)2D3). The concentration of osteocalcin in the blood is a biochemical marker of bone metabolism. Osteocytes and osteoblasts interact (via integrin and other receptors) with collagens type I and II, collagen fibers, osteopontin, osteonectin, fibronectin, fibrinogen, thrombospondin, laminin. Rapid and slow changes in the organic matrix ultrastructure are distinguished. The former are caused by external factors - physical and neurohumoral loads, diseases, extreme factors. Slow changes are thought to be caused by metabolic changes in the course of natural aging (regarded as the result of the cumulative effect of external conditions during life). Among the mineral compounds in the inorganic matrix calcium phosphates predominate (95% of them are hydroxyapatite, which is constantly being rearranged). The inorganic matrix includes apatites, magnesium, fluorides, sodium, potassium, chlorides, trace elements (about 30, including copper, lead, radium, strontium, barium), amorphous calcium phosphate, CaCO3, Mg3(PO4)2, etc. The mineral matrix contains about 98% of all inorganic substances of the body (99% of calcium, 87% of phosphorus, 58% of magnesium, 46% of sodium, 20% of trace elements). The major components of the mineral matrix are the crystalline hydroxyapatite Ca10(RO4)(OH)2 and the amorphous calcium phosphate Ca3(RO4)2. The crystalline structures are believed to be apatite because they do not contain free OH-groups. Crystallization nuclei, which are a layer of calcium phosphate, are located between collagen fibrils and gradually increase, filling the interfibrillar spaces (Fratzl P. et al., 1991). The structure of the crystals depends on the conditions of crystallization. It is assumed that precursors in the formation of apatite in pathological conditions (at acidic pH) are dicalcium hydrophosphate and octacalcium phosphate. The least soluble hydroxyapatite is formed in a neutral and basic environment. Amorphous calcium

phosphate is converted into apatite, and its calcium/phosphorus ratio is relatively constant at 1.5. The longitudinal axis of the crystals is parallel to the axis of the fibrils. The stereochemical calcium/phosphorus ratio in apatite ranges from 1.37 to 1.67. Up to 50% of the mineral salts are in the amorphous phase. In the crystal lattice of hydroxyapatite Ca2+ can be replaced by other divalent cations, while anions other than phosphate and hydroxyl are either adsorbed on the crystal surface or dissolved in the hydrate shell of the crystal lattice. A feature of the bone matrix is the high concentration of citrate: about 90% of its total amount in the body is contained in bone tissue. It is necessary for mineralization of bone tissue, forms complex compounds with calcium and phosphorus salts. There is a close relationship between calcium and citric acid metabolism. In addition to quite firmly bound calcium in the form of hydroxyapatite, bones contain a readily usable supply of calcium (about 100 g) in the form of citrates and carbonates. In bone tissue cells, the process of glucose breakdown can be switched to citrate formation. Vitamin D apparently inhibits the oxidation of citric acid. In addition to citrate, succinate, fumarate, malate, lactate and other residues or salts of organic acids are found in bone tissue. The bone matrix contains lipids, which are a direct component of bone tissue, involved in the mineralization process, rather than being an impurity as a result of insufficient removal of lipid-rich bone marrow In osteoporosis, the size and properties of hydroxyapatite crystals change. In bone resorption (under both physiological and pathological conditions), a simultaneous "resorption" of both mineral and organic bone tissue structures is noted. Organic acids and their residues, including lactate, play a certain role in the removal of mineral salts from bone. A change in pH to the acidic side accounts for the dissolution and removal of minerals. Lysosomal acidic hydrolases are involved in the resorption of the organic matrix. The resorption of collagenous fibers occurs after preliminary exposure to collagenolytic enzymes. About 8% of bone tissue, including 11% of cortical layer of tubular bones and up to 44% of ribs is renewed on the average in 1 year. Average values of indicators of the amplitude of variations in the content of mineral matrix phosphates in the cortical layer of diaphysis of long bones are 2%, the rate of their exchange between blood and mineral matrix is 1%, the thickness of the cortical layer on the radiograph is 5%, its optical density is 19%. The authors concluded that only significant physical and neurohumoral influences cause clinically detectable changes in the stable macrostructure of the bone matrix.

Structural and functional features of bone The structural and functional unit of cancellous bone tissue is a bone trabecula subjected to neurohumoral regulation, the main form-forming factor of which is the load vector. Being a dynamic system, bone tissue is constantly undergoing remodeling based on resorption and bone formation: in normal conditions there are interrelated processes - osteoclastic resorption and osteocytic osteolysis with formation of new bone tissue in the resorption sites. In the process of remodeling in an adult person from 2 to 10% of bone mass is renewed annually (Canalis E., 1993) preserving initial external parameters of bone (they change in growing bones). Human bone tissue is almost completely rebuilt every 10 years. The rate of bone formation (compared to resorption) is lower. The intensity of metabolic processes is more significant in trabecular bone. Disturbance of remodeling processes is observed in osteopenia, osteoporosis. There are units of remodeling: basic multicellular unit (BMU); bone remodeling unit (BRU); bone structural unit (BSCU). BME includes a complex of cells involved in resorption (local) and bone formation. The number of new BMUs decreases with age, and the time required for their formation increases. As a result, the intensity of remodeling decreases and the bone-mineral balance is disturbed. CRE refers to the area of bone tissue in which resorption and bone formation occur. The CSE reflects the total remodeling activity. In compact bone, the KSE is the formation of secondary osteons of the haversal system; in cancellous bone, it is a 40¬-60 μm surface with an area of 0.5¬1 mm2. The time required for resorption and recovery of the CSE complex is 3¬5 months (Revel P.A., 1993; Kanis J.A., 1994): resorption occurs within 30 days, replacement by new tissue - 90 days. Longer (40¬-50 days) period of resorption in cancellous bone. At average age, the rate of skeletal renewal is 8% of bone mass per year, and it is

more significant (20%) in cancellous matter (4% in compact tissue). W.J. Marshall (2002) notes that the process of remodeling at any one time covers about 5% of the skeleton. Remodeling is coordinated by hormones, FRs and cytokines. In total, there are about 35 million CSEs in the bone system. Remodeling of cancellous tissue proceeds in several consecutive stages: osteoclast activation; resorption locus formation; osteoid formation; osteoid mineralization. Remodeling of compact bone is a synchronous process of resorption of the inner surface of the bone canal (remodeling occurs in the vascular canals) and formation of the osteoid by osteoblasts, which undergoes further mineralization. Remodeling is determined by the number of active cells, the balance of remodeling in the remodeling unit (remodeling balance is the ratio of the amount of resorbed and formed bone tissue). In practically healthy people at a young age, the ratio of resorbed tissue equals the amount of newly formed tissue. When resorption predominates, bone mass decreases, the structure is disturbed, the number and thickness of the plates decrease, and cavities increase. Disorder of remodeling with predominance of resorption is the cause of osteoporosis. Bone resorption is performed not only by osteoclasts, but also by osteocytes (osteocyte modeling is performed in the prelacunar region and is poorly understood). The mechanisms of mineralization of lamellar bone and rough fibrous tissue differ. Matrix vesicles (vesicles), released by osteoblasts and supplying hydroxyapatite crystals to the matrix, play an important role in the mineralization processes of cartilage and coarse fibrous tissue. In the first case, minerals are deposited within and between collagen fibrils. Bone homeostasis depends on mechanical stress: when it acts, a balance of resorption and bone tissue formation processes is observed (trabeculae that are not subject to mechanical stress are resorbed). In the bones of the skeleton, which bear the greatest load, there are phenomena of hypertrophy, bone thickening, occurring due to an increase in the content of bone protein, mineral elements. It is assumed that bone shaping is the result of the integration of the totality of external mechanical influences by means of bone tissue remodeling (V.S. Oganov, 1997). Bone deformations are decisive for the emergence of adaptive processes in bone. Mechanical influences cause changes at tissue and cellular levels. Lack of mechanical stimulation is accompanied by inhibition of activation, differentiation, proliferation of osteoblasts, loss of bone mass in endoste and trabecular bone, increase in intracortical porosity. Osteoporosis resulting from the lack of mechanical stimulation can be local, regional, and generalized. Bone mass loss, bone architectonics and structure, composition of the organic matrix, porosity, orientation of collagen fibers, the nature of the collagen-crystal bond and other factors are important for bone strength.

Conclusions: The above data indicate close and complex (not fully studied) functional relationships between the metabolism of minerals, trace elements, vitamins, hormones, enzymes, proteins, carbohydrates (both in each group and between group representatives). To maintain normal metabolism, regeneration of components of the mineral and organic matrix of bone tissue requires an adequate continuous comprehensive (balanced) supply of amino acids, vitamins, minerals, trace elements. Due to the inadequacy of the diet of the inhabitants of Ukraine for many nutrients it is also necessary to wider use preparations of vitamins, minerals, trace elements, bioantioxidants as supplements to the diet. Doses of ingredients in such complex preparations should correspond to the daily requirement for them.

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