Peculiarities Of The Hypofunction Of The Perthygroid Gland In Rats On The Morphological Formation Of Bone Tissue

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ABSTRACT
This study is dedicated to the study of the effect of changes in the active energy of the parathyroid glands on the morphological tension of bone tissue formation. Experimental modeling of hypoparathyroidism in laboratory rats (n = 30) was carried out and the dynamics of morphological changes in the process of bone tissue ossification was analyzed. On the basis of the results of morphological methods of study, the dynamics of the formation of tubular bones was revealed, and the patterns of ossification of bone tissue against the background of hypoparathyroidism were also set. As a result of the study, it was shown that it differs from the usual histological picture of hypoparathyroid individuals in the zones of elevation, just the basal layer of chondrocytes are vacuolated. The emergence of young osteoblasts is oriented by the spaces; they are located according to the type of multidirectional architectonics.

KEYWORDS: parathyroid gland; chondrocyte; hypoparathyroidism; hypocalcemia; hyperphosphatemia; tubular bones.

1. INTRODUCTION

Hypoparathyroidism in most cases is characterized by a decrease in the function of the parathyroid glands (PTG) and a decrease in the production of parathyroid hormone (PTH), but peripheral forms are also popular, resulting from the resistance of cells and tissues of the body under the action of PTH. Hypoparathyroidism of various origins is seen in 0.2-0.3% of the population [H. Singh, 2005]. More often, hypoparathyroidism in adults develops afterwards surgical removal or damage to the PTG, in fact, which often happens afterwards thyroidectomy on the pretext of thyroid cancer (TC) or Graves' disease (BG), repeated or extensive operations on the pretext of other diseases of the thyroid, cervical organs and the upper mediastinum, and even subsequently surgical interventions for the treatment of the initial or secondary hyperparathyroidism. Subsequently, operations on the thyroid gland on the pretext of BG, the incidence of transient hypocalcemia is within 3.1% [Roca-Cusachs A., 1997; Simonetti G., 2007], and persistent hypoparathyroidism occurs in 1% of cases [Basil M. 2001]. Among other popular reasons for hypoparathyroidism are:
1) abnormal formation of the PTG (congenital agenesis or hypoplasia of the glands);
2) deformation of the OSHD in autoimmune diseases;
3) a decrease in the function of the thyroid gland due to a violation of the secretion or production of PTH;
4) syndromes of resistance to PTH (hypomagnesemia, pseudohypoparathyroidism).

All described forms have a similar pathogenesis and clinical picture, differing only in etiological qualities.

The PTH defect, in its own turn, leads to an increase in the level of phosphorus in the blood, due to a decrease in the phosphaturic effect of PTH on the kidneys, and also to hypocalcemia due to a decrease in calcium absorption in the intestinal tract, a decrease in its mobilization from the bones and insufficient calcium reabsorption in the renal tubules. In the genesis of hypocalcemia, it makes sense to reduce the synthesis in the kidneys of an intensive metabolite of vitamin D - calcitriol, the production of which depends on PTH. The main clinical manifestations of hypoparathyroidism are justified by hypocalcemia and hyperphosphatemia, which in fact leads to an increase in neuromuscular excitability and joint autonomic reactivity [1,3].

All of the above establishes the need for further research on the intensity of osteogenesis in the morphological nuance in hypoparathyroidism and determines the relevance of the study.

Main objective of the study. Learn the effect of PTH deficiency on the morphological tension of the process of ossification of tubular bones.

Study tasks.

1. To determine the best experimental model of hypoparathyroidism in rats.
2. To reveal the dynamics of morphological individualities of longish tubular bones of rats at all possible ages of the control group.
3. To study the morphological configurations of the formation of tubular bones in hypoparathyroidism.
4. To qualify microanatomical configurations of the structure of tubular bones in hypoparaterioid rats.

2. MATERIALS AND METHODS

Experimental modeling of hypoparathyroidism in laboratory rats (n = 30) was carried out and the dynamics of morphological changes in the process of ossification of tubular bones was studied.

The materials used was the tubular bones of rats with parathyroid hypofunction.

The experiments were carried out on 30 snow-white rats weighing 135 ± 1.2 g. Taking into account the significant effect on the position of animals of the exchange of minerals, weight, their age and the composition of the food menu, we observed identical circumstances during the experiments.

Experimental studies were carried out in two series: series I - animals of the control group, series II - animals with hypoparathyroidism. For each series, 15 rats were used. The trait of the starting animals of the individual series of the experiments performed is reflected in table.

Number of the initial group of rats

Experiment stages	Стартовые крысы	
	quantity, pcs.	weight, g
Control Group I	10	130±1,2
Hypoparathyroidism II	30	140±1,3
Total	40	135±1,2

In 1 control series, the morphological structure of the bone tissue of the tubular bones was studied in animals. In series 2, hypoparathyroidism was induced in animals with surgical electrocoagulation of the upper grains of the parathyroid gland.

All rats were in the same vivarium criteria. The circumstances of the experiment and the decapitation of animals corresponded to the provisions of order No. 742 of November 13, 1984 "On the use of experimental animals", as well as the international rules "Guide for the Care and Use of Laboratory Animals".

Study methods. The hypoparathyroidism model was induced by the method of removing the upper grains of the parathyroid gland. For histological examination, pieces of tissue from all possible constituents of the long bones of rats were noted in Carnoy water and in a 12% solution of neutral formalin, dehydrated in alcohols of growing concentration and embedded in paraffin. Sections 5-8 microns wide were stained with hematoxylin eosin and according to the Van Gieson method.

For histological examination, pieces of tissue from all possible constituents of the long bones of rats were noted in Carnoy water and in a 12% solution of neutral formalin, dehydrated in alcohols of growing concentration and embedded in paraffin. Sections 5-8 microns wide were stained with hematoxylin eosin and according to the Van Gieson method. Neutral mucopolysaccharides were detected by the CHIC reaction, and acidic ones by toluidine blue color.

An experimental tissue taken from the constituents of the tubular bones in control rats and in experimental hypoparathyroidism was subjected to morphological studies [5,7,8].

Research and creation of experimental models of skeletal destruction contribute to the search and implementation of effective methods for early detection and treatment of this pathology. Meanwhile, this requires a clear understanding of the usual structure of bone formation structures in morphological nuance. We conducted our own studies on rat pups.

Histological examination of all control animals in the epiphyses of tubular bones orientated the space of attachment of the articular bag, where the fibrous capsule and the components of the synovial membrane are perfectly detected.

The synovial layer of the capsule is characterized by an uneven width, in fact, which is justified by the growth of granulation tissue of different maturity, rich in blood vessels. The walls of blood vessels are clearly oriented, of uniform thickness. It contains endotheliocytes of different maturity.

In some substances, the synovial membrane is built of fibrous connective tissue structures, spaces with rather short villi. Collagen fibers without swelling symptoms adhere tightly to each other.

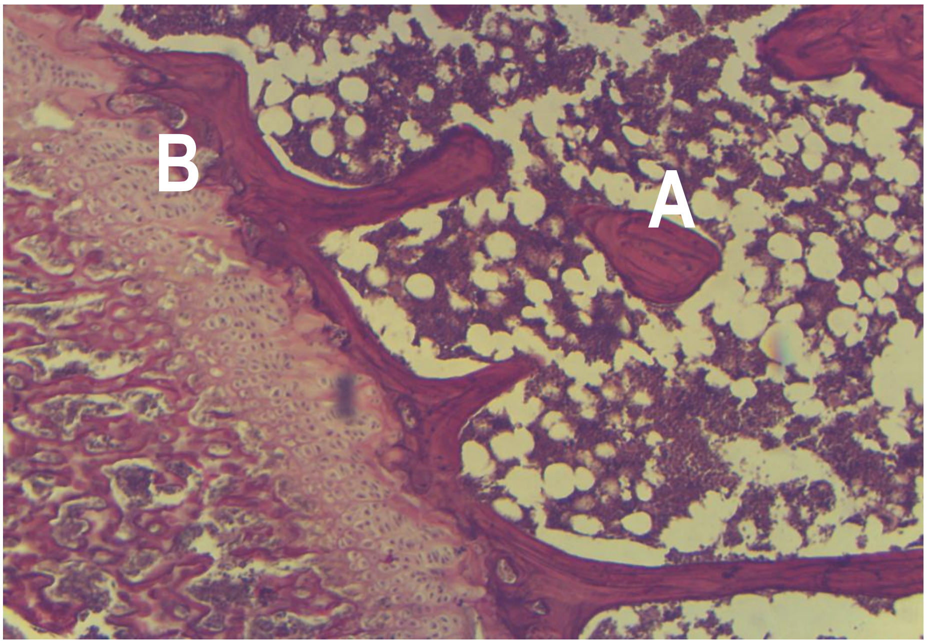

Figure: 1 Bone plate (A) and bone marrow (B).
Staining by Van Gieson. Uv. 10 × 40

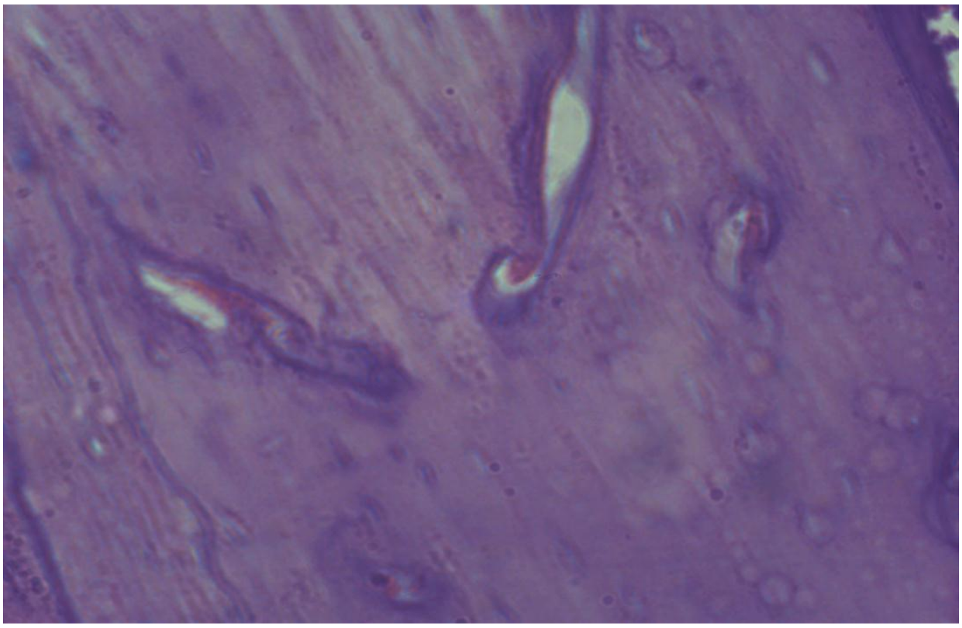

Figure: 2 Periosteum of the femoral head.

Hematoxylin-eosin staining. Uv. 10 × 40

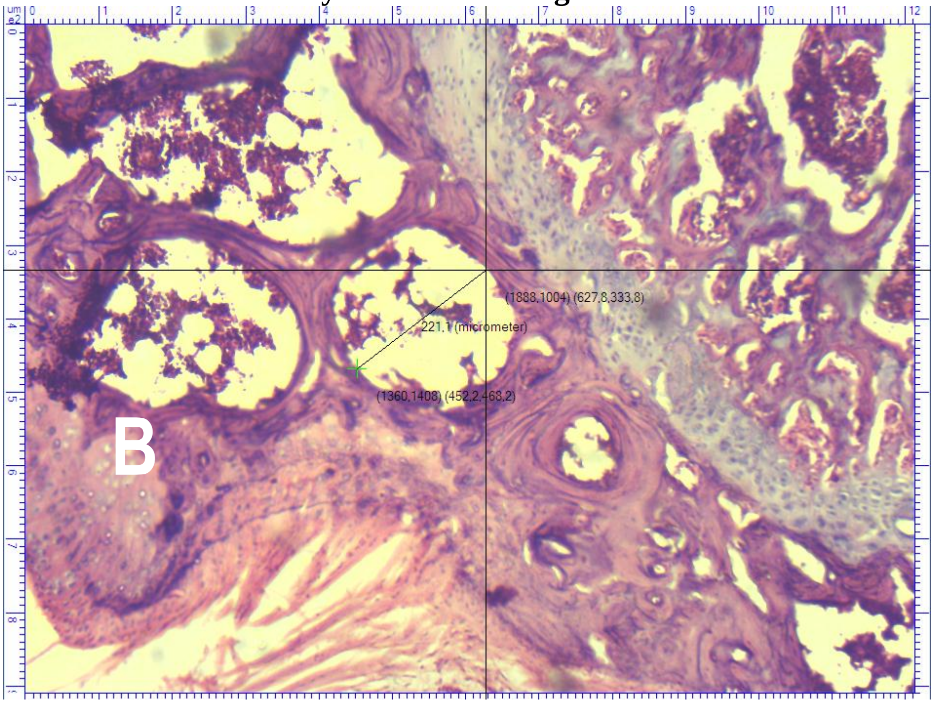

Figure: 3 The cartilaginous part of the femoral head with well-stained basophilic chondrocytes (A) and a dense fibrous connective tissue capsule (B).

Hematoxylin-eosin staining. Uv. 7 × 10

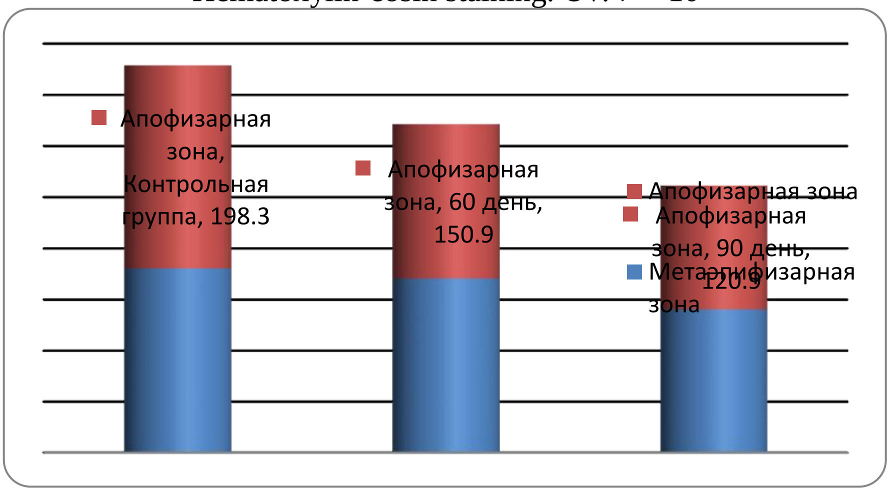

Figure: 4 The width of the medullary canal.

The lobe of the epiphysis (head) of the femur is formed from cartilaginous tissue, which is produced from chondrocytes located in a plane perpendicular to the columns. In the depths, they lie in longitudinal nests, and on the periphery, young cartilaginous cells with basophilic nuclei are visible. The head is surrounded by an impermeable connective tissue capsule.

In the area of the metaphysis, there is a zone with perfectly colored cellular substances. Osteoblasts and newly formed bone supports are placed along the edge. An impenetrable capsule (fibrous bursa) and a synovial membrane are formed around a piece of the coming bone (Figure 3.4). The intercellular substance is homogeneous, more actively colored towards the center.

In the proper zone, the compilation of the bone beams is traced, growing towards the periphery. There is perichondral and enchondral ossification. This means that the entire species corresponds to ordinary osteogenesis, i.e. bone formation instead of cartilage. Osteoblasts and osteocytes are clearly oriented in the supports.

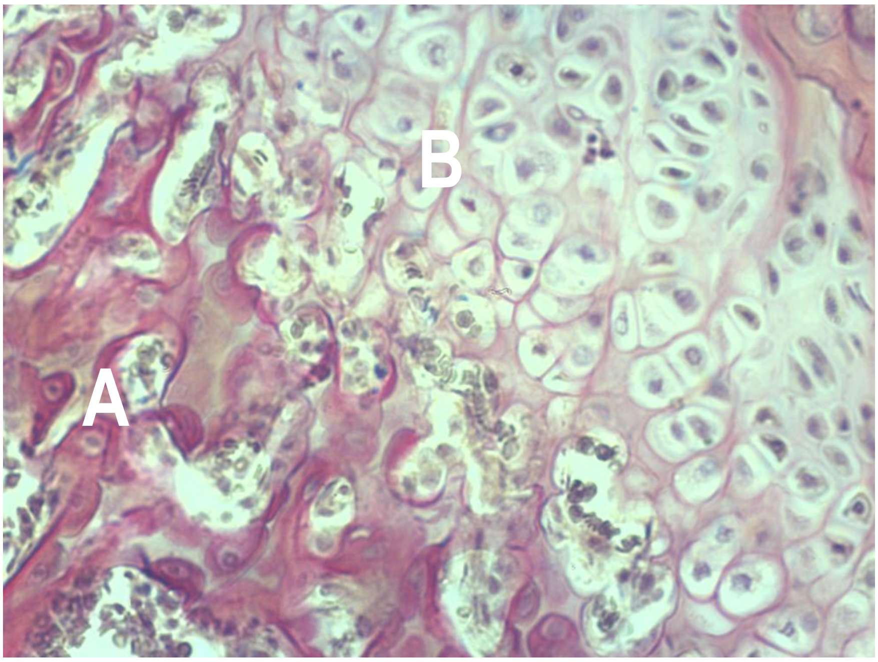

Figure 3.5 Cartilaginous part of the femoral head.

Hematoxylin-eosin staining. Uv. 10 × 40

The results of histochemical studies have recommended, in fact, that in the hyaline cartilage of the head of the leg and the glenoid cavity, both acidic, for example, neutral mucopolysaccharides, are present in significant numbers.

Glycogen is found in the solid zones of the cartilage, which, most likely, is associated with the intensity of metabolic processes in these zones and is considered the initial product in the synthesis of chondrothin sulfate.

The predominant localization of acidic mucopolysaccharides is still present in solid zones, in fact, which is explained by the diffusion of high-calorie preparations, in the lead, through these zones. The synthesis of chondrocytes with mucopolysaccharides in the articular cartilage is indicated by the presence of an abundant number of components in a specific proximity to the cell.

In this way, the main physicochemical properties of cartilage are associated with the state of the protein-polysaccharide matrix assemblies. The localization of the identified groups in the leader corresponds to the distribution of mucopolysaccharides in the cartilaginous and bone tissue of the head of the leg and the glenoid cavity. Probably, all processes in the articular cartilage are performed by protein-polysaccharide assemblies.

Scientific novelty. On the basis of the results of morphological methods of study, the dynamics of the formation of tubular bones was revealed, and for the first time the regularities of ossification of tubular bones against the background of hypoparathyroidism were set.

As a result of a thorough analysis of morphological changes, practical advice was prepared for the development of preventive and healing events in the destruction of the limbs against the background of a reduced function of the parathyroid gland.

3. RESULTS AND DISCUSSION

The results of the study done will serve as the basis for the transformation of the existing classification and research criteria for hypoparathyroidism. The revealed symptoms of negative monitoring at the early stages of the disease proves the need to take into account the variant of the onset and course of JA when choosing a strategy for the treatment of patients.
The main manifestation of hypoparathyroidism is considered hypocalcemia, which is associated with the fact that the lack of PTH leads to insufficient mobilization of calcium from the bones, a decrease in calcium reabsorption in the kidney tubules, and also to a decrease in calcium absorption in the intestinal tract.
The serum ionized calcium level is in direct proportion to PTH and 1.25 (0H) 203. The rate and extent of changes in the concentration of serum ionized calcium are guided by extracellular calcium-sensitive sensors (CaBIV), which have the highest density in the tissue of the parathyroid glands. With a decrease in the value of serum calcium, a homeostasis maintenance device is turned on, which manifests itself in an increase in PTH secretion. Conversely, when calcium levels increase, PTH secretion is inhibited. PTH initiates bone resorption, which supplies calcium and phosphorus into the bloodstream. In the kidney, PTH initiates calcium reabsorption and promotes phosphate release. PTH also activates 1 - hydroxidation 25 (OHp, i.e. 1.25 (0H) 203 -active metabolite vitamin O appears, which, like PTH, affects the absorption of calcium in the intestinal tract. Harmoniously, these moments restore calcium homeostasis In case of non-compliance with the effect of PTH, associated either with its inadequate level, or with a decrease in the sensitivity of peripheral target cells, the functioning of all links of the chain of maintaining calcium homeostasis in the body is disrupted, which actually leads to the appearance of hypocalcemia, hyperphosphatemia and hypercalciuria.
The leading space between the bases of the formation of hypoparathyroidism (up to 95%) is occupied by postoperative hypoparathyroidism, in fact, which is often justified by damage or removal of the parathyroid glands during surgery, as well as hemorrhage in them or the development of fibrotic processes in the operation space in the long term.
The incidence of postoperative hypoparathyroidism associated with constructive interventions on the thyroid gland, according to various authors, ranges from 0.5 to 50%. Almost all points affect the incidence of postoperative hypoparathyroidism: the doctor's skill, the size of the surgical intervention, the artel size of the thyroid gland, reoperation, and the inability to qualify all 4 parathyroid glands during the operation.
Distinguish between transient and persistent (6 months or more after surgery) postoperative hypocalcemia. The prevalence of transient hypocalcemia, according to various creators, makes up 20-40%, persistent - 5-7%.
The development of hypocalcemia is characteristic after operations on the parathyroid glands on the pretext of hyperparathyroidism. In these cases, hypoparathyroidism is associated with the removal of a more intense tumor tissue, with this depressive vigor of the remaining parathyroid glands leads to a sharp drop in the value of PTH and serum calcium. The concomitant pathology of the skeletal system contributes to the development of the syndrome of "hungry bones", in fact, which leads to increased absorption of calcium and phosphate by the bones, in fact, that, including the intact remnant of the parathyroid glands, is not able to compensate for these changes.

Idiopathic hypoparathyroidism can still be an integral part of a number of hereditary syndromes: APS like 1, Erns-Sayra, Annie-Effie, Di Georgie and a number of others.
In accordance with the medical picture, APS is divided into types: 1, 2, 3 (a, b, c), 4. Only APS-1 is mixed with hypoparathyroidism, other main components are acquired generalized granulomatous candidiasis (candidiasis of the skin and mucous membranes) and an initial adrenal deficiency. Less common are initial hypothyroidism, initial hypogonadism, acquired active hepatitis, malabsorption syndrome, vitiligo, autoimmune gastritis, alopecia, steatorrhea [2,3,6].
Exceptional studies of hypoparathyroidism are associated with iron deposits in hemochromatosis or with transfusion-dependent thalassemia, copper deposits in Wilson-Konovalov disease, and, in rare cases, with foreign tissue replacement in case of damage to the parathyroid glands associated with granulomatosis and metastasis.
The extensive use of radioactive iodine for the treatment of diffuse toxic goiter or thyroid cancer suggests, in fact, that the parathyroid glands are usually resistant to radiation, but in some painful ones, hypoparathyroidism subsequently appears after a specific time.
A decrease or excess of magnesium has the ability to lead to hypocalcemia and, as a consequence, to active hypoparathyroidism. Magnesium is needed for the secretion of PTH and the activation of the PTH receptors by the ligand. With hypo-magnesium, the degree of PTH is low or is located at the lower limit of the usual spectrum, in the presence of insignificant hypocalcemia. Magnesium, like calcium, has the ability to activate extracellular calcium-sensitive sensors and suppress PTH secretion. The loss of magnesium is due to gastrointestinal disorders, as well as alcoholism.
Subsequently, adjusting the value of magnesium, the capacity for PTH secretion by the parathyroid glands and affectation to it are restored.
In all PTH resistance syndromes against the background of an increased PTH value, there is hypocalcemia and hyperphosphatemia associated with the resistance of target tissues to the action of PTH. As a consequence, they are referred to by the collective term "pseudohypoparathyroidism". Normalization of the calcium value in pseudohypoparathyroidism usually leads to a decrease in the PTH value, but does not eliminate the resistance of the target tissues to PTH. An attack of tetany appears suddenly or is provoked by mechanical or acoustic irritation or hyperventilation. Obvious tetany is often preceded by paresthesias in the fingers and around the mouth. Involuntary muscle contractions are painful. Tetania develops not only with hypocalcemia, but also with hypomagnesemia and metabolic alkalosis.
Insignificant neuromuscular excitability is characterized by latent tetany, which is indicated by the flattering signs of Khvostek and Trousseau. The sign of Khvostek appears when tapping with a finger in the exit space of the facial nerve (at a distance of 2 cm from the earlobe below the zygomatic process) and there is a decrease in facial muscles (twitching of the upper lip, corner of the mouth). Trousseau's sign (tonic convulsion of the hand) is caused by compression of the brachial nerve by the doctor's hand or by the inflated cuff of the tonometer in the direction of 3 minutes. A positive symptom is the appearance of sick wrist spasms ("obstetrician hand").
With acquired hypocalcemia due to hypoparathyroidism, exostoses and foci of calcification appear in pliable tissues. Periarticular calcium deposits are often accompanied by chondrocalcinosis and pseudogout.
Bone costs in the peripheral skeleton are initially detected in the terminal sections of tubular bones due to the dominance of cancellous bone here. Endosteal resorption plays a major role in HPT. The result of this is the expansion of the medullary canal with a thinning of the cortical layer. Previously, it was actually that a more characteristic manifestation of bone loss was considered generalized fibrocystic osteitis, which was detected in 50% of cases.

However, in recent years, due to the more early diagnosis of the disease, fibrocystic osteitis is less and less frequent (10-15%). Demineralization of bones leads to destruction of the skeleton, pathological fractures, compression destruction of the spine, in connection with which there is a decrease in elevation by 2-4 cm, the appearance of neurological symptoms, manifested by radicular syndrome, paralysis of the muscles of the pelvic girdle, paresthesias, and decreased tendon reflexes. The characteristic configurations are visible on radiographs: erosion of the outer cortical plane, generalized demineralization, local destructive processes, often cystic. Histological examination of bone lesions reveals a decrease in the number of trabeculae, an increase in multinucleated osteoclasts, and replacement of cellular and bone marrow components with fibrovascular tissue. One of the more common spaces for the formation of cystic changes is the lower, less often the upper jaw.
In real time, three-energy X-ray absorptiometry (TERA) is considered a method for assessing and studying bone mineral density, this method is easy to use and contains a low radiation dose, in fact, which allows it to be performed repeatedly and to assess the dynamics of the state. It is the measurement of bone mineral density (BMD) that forms the basis for the diagnosis of osteoporosis and is considered one of the more significant and early characteristics of bone pathology, especially in connection with the increased risk of fractures with a decrease in BMD. In recent years, an important skill has been accumulated in the use of TERA in the study of osteoporosis and in predicting the risk of fractures in the joint population. In real time, with HPT, diffuse damage to bone tissue is most often revealed, which is not easy to distinguish in the power of age and gender of patients from postmenopausal osteoporosis. The definition of osteoporosis was created by WHO and is based on the determination of BMD at any point according to the T-criterion. The usual measure of BMD is T-score characteristics from +2.5 to -1 normal deviations from peak bone mass. Osteopenia - characteristics of the T-score -1 normal deviations and below. Difficult osteoporosis - T-score characteristics of -2.5 normal deviations or lower with a history of 1 or more fractures.

Conclusions: The lobe of the epiphysis (head) of the femur is formed from cartilaginous tissue, which is produced from chondrocytes located along the plane perpendicular to the columns. In the depths, they lie in longitudinal nests, and on the periphery, young cartilaginous cells with basophilic nuclei are visible. The head is surrounded by an impermeable connective tissue capsule.

In the area of the metaphysis, there is a zone with perfectly colored cellular substances. Osteoblasts and newly formed bone supports are placed along the edge. An impenetrable capsule (fibrous bag) and a synovial membrane are formed around a piece of the coming bone. The intercellular substance is homogeneous, more actively colored towards the center.

In the proper zone, the compilation of the bone beams is traced, growing towards the periphery. There is perichondral and enchondral ossification. This means that the entire species corresponds to ordinary osteogenesis, i.e. bone formation instead of cartilage. Osteoblasts and osteocytes are clearly oriented in the supports.

The results of histochemical studies have recommended, in fact, that in the hyaline cartilage of the head of the leg and the glenoid cavity, both acidic, for example, neutral mucopolysaccharides, are present in significant numbers.

Glycogen is found in the solid zones of the cartilage, which is most likely associated with the intensity of metabolic processes in these zones and is considered the initial product in the synthesis of chondrothin sulfate.

The predominant localization of acidic mucopolysaccharides is also observed in deep zones, which is explained by the diffusion of nutrients, mainly through these zones. The synthesis of chondrocytes with mucopolysaccharides in the articular cartilage is indicated by the presence of an abundant amount of components in the immediate vicinity of the cell.

Thus, the main physicochemical properties of cartilage are associated with the state of the protein-polysaccharide complexes of the matrix. The localization of the identified groups mainly corresponds to the distribution of mucopolysaccharides in the cartilage and bone tissue of the femoral head and glenoid cavity. Probably, all processes in the articular cartilage are carried out by protein-polysaccharide complexes.

The results of histological studies showed that in the collagen fibers of the fibrous capsule homogenization is noted, and in some places the cellular elements are not detected at all. Among the fibrous structures, the formation of the joint space takes place. The joint gap is narrowed due to the growth of connective tissue.

In some preparations, the proliferation of connective tissue, plethora and thrombosis of the vessels of the round ligament are noticeable. The femoral head consists of homogenized newly formed cartilage tissue with poorly stained chondrocytes. In most cartilaginous cells, there is hypochromia of the nuclei, and in some places - pictures of necrobiosis and necrosis. Places of attachment of fibrous structures to the head of the femur of loose fibrous tissue are traced.

Degenerative dystrophic changes in the cartilage of the greater trochanter are clearly defined. The cytoplasm of most chondrocytes is strongly vacuolated, necrobiosis and necrosis of chondrocytes are well defined. In the metaphysis zone, thin bone beams and cavities filled with fatty bone marrow are revealed. Bone beams are coarse-fibrous, located along the periphery, and the cavity of the medullary canal is determined inwardly. Consequently, the nature of the revealed changes indicates a lag in osteogenesis in the state of hypoparathyroidism in rats, which significantly affects the development of bone formation.

Histological studies revealed the detection in the cartilaginous covered femoral head with moderate vacuolar dystrophy. Along with well-stained chondrocytes, in most cartilaginous cells, nuclear hypochromia is noted, and in some places - a picture of necrobiosis and necrosis.

In the cartilage of the trochanter, cartilage cells with vacuolar degeneration, foci of necrobiosis and necrosis of chondrocytes are revealed.

In some preparations, the attachment points of fibrous structures to the femoral neck and foci of granulation tissue are traced.

Between the cartilaginous part of the head of the leg and the synovial membrane, the joint space reveals the synovial membrane with congested vessels and fatty material. Collagen fibers are loosened, homogenized. Along with the data, there is a space of enchondral ossification with newly formed bone supports and numerous congested vessels.
The results of the studies done make it possible to characterize the focal dystrophy of chondrocytes and inhibition of osteogenesis on the plane of the growth zone.
In a more distant period of the experiment, dedifferentiation of the surface and transitional layers of hyaline cartilage into fibrous material was revealed. In the solid layers of cartilage, symptoms of a decrease in proliferative processes and an increase in degenerative processes were noted, in fact, which led to a perversion of osteogenesis on the plane of the lifting zone.

The narrowing of the zone of enchondral elevation due to the disappearance of the layer of proliferating chondrocytes, most likely, preceded its early closure.
The revealed histological changes in the components of tubular bones have every chance to help predict the outcome of the healing of skeletal destruction, as well as their complications.
In experimental hypoparathyroidism, rapidly embodied configurations occur in the cartilaginous parts of the tremendous twist, manifested by vacuolization of chondrocytes.

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