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CERTAIN ASPECTS OF OSTEOPOROSIS IN GONADAL DYSGENESIS

Summary. *Osteoporosis — a metabolic disease of the skeletal system associated with a reduced bone density and deterioration of bone tissue microarchitecture. The article describes the basic mechanisms of formation and clinical and diagnostic aspects of osteoporosis in children with gonadal dysgenesis.*
Key words: *Turner's syndrome, osteoporosis, children, gonadal dysgenesis, hormones.*

Relationship between the reproductive and skeletal systems is the subject of search of many sientiests. It was established that during menarche under the influenced of sex hormones, inhibition of bone growth in length due to the blockade of growth zones begins. In reproductive age due to cyclical secretion of estrogen and progesterone to 18–20 years is forming the peak bone mass, which is under the influence of various factors. In adolescence and reproductive age, especially during the formation of the peak bone mass, the dominant influence of sex hormones on bone tissue is determined. Therefore, the deficiency of sex hormones couses disrupted formation of peak bone mass and may develop osteopenia and osteoporosis [2, 3, 5].

Osteoporosis is a metabolic disease of the skeletal system, accompanied by a decreased density of bones and deterioration of micro-architectural bone tissue due to insufficient increase of bone mineral density (BMD) in adolescence (lack of peak bone mass) or its excessive loss of in adulthood (postmenopausal and eyelid-induced osteoporosis) [9, 10, 14, 15]. Bone fragility, as a result of osteoporosis, increases the risk of fractures, wich are the most typical and often a single clinical sign of its manifestation [1].

Predictors leading to the development of osteoporosis are:

1) genes that control calcium homeostasis;

2) genes that control hormonal homeostasis;

3) genes responsible for the development and regulation of the metabolic activity of osteoblasts and osteoclasts;

4) genes that encode components of the extracellular matrix;

5) genes of lipoprotein metabolism [1].

Normal skeletal maturation takes place against the background of a sufficient functioning of the endocrine system, so any hormonal dysfunctions leads to disruption of the accumulation of peak bone mass and, occasionally, skeletal abnormalities [2, 8]. Many researchers point to various violations of the skeletal system, that accompany a number of chromosomal disorders, including Turner's syndrome [7].

Complex of symptoms that consist of a low growth and gonadal dysgenesis was marked in 1922 by Robert Ressle and was named as «sex dwarfism». More details the syndrome of stunting, sexual infantilism, alary folds on the neck and valgus deformity of elbows was described by Henry Turner in 1938. In 1959, Ford and colleagues found violations as part of sex chromosomes — namely, the absence of one X chromosome, which determines the typical clinical picture of the syndrome. Most fetuses with karyotype 45 X0 (true monosomy) are dying prenatal that's why the prevalence of the pathology among newborn girls is only 1: 2500–5000 [3, 6, 21]. Turner's syndrome is characterizing by the following changes in the skeletal system: growth retardation, violation of maturation and differentiation of skeleton and abnormalities of bone development [19]. Patients have a decreased BMD and a high risk of osteopenia and osteoporosis [17, 20, 21]. The controversial question is whether the decrease of bones mineral density in this case is the result of the deficit caused by the sex hormones or is provoked by chromosomal abnormalities in combination with hypoestrogenemia [23, 29]. In 1997 was opened a gene-SHOX (short stature homeobox), which is localized on the short arm of pseudoautosomal area of Y and X-chromosome and is responsible for the development of growth retardation in this syndrome [25]. It is believed that this gene inhibits fusion of the growth plates and skeletal maturation of distal parts of extremities,

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while as in haploid insufficiency of gene, the fusion of plate is accelerated, explaining bone disproportion at a syndrome. Also was determined that estrogens stimulate maturation of distal skeletal tissues in which takes place accelerated fusion of the growth plates because of insufficiency of haploid gene SHOX, therefore the onset of spontaneous or induced puberty skeletal deformations in patients may not manifest itself [25]. The second X chromosome in female karyotype carries in itself not only determinants of the formation of ovaries, and also determinants of growth in length [8].

The main increase of the bone mass, its density and strength occurs in children from 10 to 14 years [14, 15]. Indicators of structural and functional condition of the skeletal system, normally, in puberty have a positive dynamics [2, 8, 29], and in girls with Turner's syndrome is observed growth retardation [7] and the risk of fractures persists throughout their life [26].

Sex hormones play a central role in the regulation of bone remodeling, development and maturation of skeleton and maintenance of the bone mass, so the study of bone tissue metabolism and features of bone status at hypogonadism, associated with abnormalities of sex chromosomes, are the subject of study of many researchers [6, 18, 27]. The gene of estrogen receptors and mutations in it, leading to its inactivation, are studied. In patients with Turner's syndrome is determined the reduction of peak bone mass and violation of bone remodulation with demineralization of bone tissue, which is due to estrogen deficiency [7, 8]. Osteoblasts and osteoclasts contain highly specific estrogen receptor and are the target cells to estrogen. Estrogens can influence on osteoclasts directly — reducing their activity, in particular by reducing their secretion of lysosomal enzymes, and indirectly — suppressing the secretion by osteoblasts of osteoclast-stimulating factors — interleukins (IL-1, IL-3, IL-6, IL-11), tumor-necrotizing factors (TNF-α and -β), macrophage-colony stimulating factor, granulocyte-macrophage-colony stimulating factor, stromal cell factor, annexin II and prostaglandins and increasing their osteoclasts inhibiting factors — interferon, transforming growth factor β, interleukins (IL-4, IL-10, IL-13), opsonin M [14, 20]. By acting directly on osteoblasts, estrogen stimulates their proliferation and differentiation, activate intramembraine ossification [14]. In addition, estrogens help to increase the number and sensitivity of intestinal receptors to calcitriol and promote excretion of excess calcium [14, 15]. Activating effect of estrogen on endochondral ossification is provided by their effect on receptors of cartilages, causing increased production of messenger RNA and protein for insulin-like growth factor (IGF) [15]. Negative consequences of estrogen deficiency for bone tissue are increased activity of osteoclasts and reduction of calcitonin and calcitriol, which naturally reduces calcium absorption in the gastrointestinal tract, inhibits the secretion of prostaglandins and increases the sensitivity of bone to parathyroid hormone [16, 20].

For girls with Turner's syndrome is typical not only estrogen deficiency, but progestogens and androgens, which play an important role in the development of osteoporosis [27]. Androgens inhibit the processes of differentiation and activation of osteoclasts, and activate protein biosynthesis in osteoblasts [20], carrying out an independent impact on achieving peak bone mass. The level of free IGF-1 in Turner's syndrome is decreased with normal level of total IGF-1. However, total IGF-1 decreases along with the binding protein 3 IGF-1 and the ratio of IGF-1 and IGF-1 and SAT-3 are decreased, which leads to reduction of the skeleton area and BMD [23].

Progestins also have modulating effect on bone metabolism — they stimulate intramembrane ossification, exhibit anabolic effect by stimulating the biosynthesis of protein in osteoblasts, act as competitors of glucocorticoid binding to corticosteroid receptors on bone tissues [16, 20].

It was found that in girls with Turner's syndrome, which appeared spontaneous puberty, bone formation is not broken [24] and remains a normal BMD [18, 24], although they stay stunted. For achieving an optimal peak bone mass in girls with Turner's syndrome is necessary treatment by estrogens [29], which helps to normalize the metabolism of bone and increase bone mass, which leads to the conclusion in favor of hormonal causes of disorders of the bone metabolism. At the same time, those patients who at the time of puberty BMD was sufficient, even against the background of hormone replacement therapy cannot achieve normal peak bone mass [23]. There are data on improvement of BMD in patients with Turner's syndrome during the treatment by growth hormone, but the duration of observation was insufficient [26].

An important factor that determines the development of osteoporosis in gonadal dysgenesis, is a disturbance of bone remodeling [14, 16]. The beginning of the process activation depends on desquamation of covering cells, which are formed by osteoblasts and cover all bone surfaces. On the bare surface are fixed mononuclear osteoclast precursors, which fuse together and form differentiated osteoclasts. The causes and mechanisms of remodeling activation in certain areas are not clear. Multiple units of remodeling are activated in different parts of the skeleton in random order. Possible reasons for activation of some loci are release of local factors from old bones or signals from osteocytes and coating cells. Activated osteoclasts resorb insignificant amount of bone for 1–2 weeks, after which they disappear from the surface and are replaced by mononuclear cells that promote the training of lacunar surfaces to formation of new bone and/or migration of osteoblast precursors to sites of bone resorption. During this so-called «switch phase», when resorption changes on bone formation, can be selected the factor of linking these two processes. The nature of the signal remains unclear: it may be paracrine factor or combination of factors that are produced inside and outside of the lacunaes, that are in a state of resorption or switching phase. Likely candidates for this role are mitogens of insulin-like growth factor type II or transforming growth factor, which are produced by osteoblasts and transferred to the matrix. After the release, these factors under the influence of active osteoclasts can stimulate the replication and differentiation of osteoblasts in areas of resorption. Osteoblasts that appear begin to fill the cavity by the organic matrix or osteoid that is mineralized in 25–30 days. The complete cycle of remodeling is going on for several months

and leads to the formation of new structural units in spongy and cortical bone tissue [16].

Thus, violation of remodeling at any stage leads to a decrease of bone mass. In case of Turner's syndrome against the backdrop of estrogen deficiency bone loss occurs primarily in trabecular bone tissue, which is represented in the bodies of the vertebrae, calcaneus and metaphysis of long tubular bones [16].

Osteoporosis diagnosis

The problem of studying of the structural and functional condition of the skeletal system at gonadal dysgenesis constantly attracts attention of researchers due to marked changes in the skeletal system on the background of hormonal dysfunction. To diagnose osteoporosis, it has a great importance to collect detailed medical history to identify risk factors for developing of the disease. On physical examination the anthropometry is necessarily performed, because the most patients with Turner's syndrome have a lag behind their peers in growth from the first year of life, and puberty increasing of growth is less than 3 cm and occurs in 15–16 years [13]. To confirm the diagnosis are using instrumental methods: bone X-ray and measurement of bone density using densitometry. Radiography — method of research to assess anatomical peculiarities of bones and bone's structure. The disadvantage of this method is its low sensitivity, which allows to determine the decrease of bone mass in case of the degree of mineralization reduction of up to 20–40 %. For earlier diagnosis of osteoporosis roentgenometric methods, that can diagnose osteoporosis at 5–10 % of loss of bone mass, are used. Significant distribution received ultrasound examination that can detect osteoporosis at 3–5 % of loss of bone mass [5]. In patients with Turner's syndrome are described these changes like hypertrophic osteoporosis with defect in the form of cysts with clear boundaries, and changed shape of the vertebral bodies [5, 7]. The dependence of structural and functional state of the bone system from the patients body weight, height, body mass index and age at the beginning of the appointment of hormonal therapy and its duration were found.

The «gold standard» in diagnosis of osteoporosis is BMD measurement using two-energy X-ray absorbption (DXA), which determines bone metabolism and calcium homeostasis. The most sensitive and informative are the following criteria: bone projection plane (A, cm^2), bone mineral mass (g), BMD (g/cm^2), volumetric bone mineral density (vBMD, g/cm^3). These figures are measured in bones of the lumbar spine, proximal femur and forearm.

For the purpose of differential diagnosis of primary osteoporosis and metabolic diseases of the skeleton, and before prescribing pharmacological therapy is recommended to determine the level of calcium and inorganic phosphorus in blood and urine, GAG in blood, oxyproline level, uronic acids or the ratio of calcium to creatinine in urine [4, 9, 12]. The rate of formation or destruction of the matrix of bone tissue can be assessed either by changing the activity of specific enzymes of ossification or bone destruction cells (alkaline and acid phosphatase), or by identifying of components that enter into general circulation during the synthesis or bone resorption, based on breach of communication between processes of bone resorption and reparative bone formation [12]. Markers of bone formation are used to characterize the different functions of osteoblasts. Thus, production of N-terminal propeptide procollagen I (PINP), participating in collagen genesis, characterizes the early stages of bone formation, while production of N-terminal propeptide procollagen III (PIIINP) reflects extra-bone collagen formation. Bone alkaline phosphatase and osteocalcin characterize the function of osteoblasts.

An important indicator of the state of bone tissue is hydroxyproline wich is released in the destruction of collagen [12, 15]. There is evidence about increasing urinary hydroxyproline concentration in different types of osteoporosis [15, 23]. In the study of biochemical markers of bone tissue metabolism in patients was defined accelerated bone metabolism by using bone remodulation indicators: reduction of bone phosphatase with normal levels of total osteocalcin in plasma, PIIINP and PINP. Such markers of bone resorption as C-terminal telopeptide of type I collagen in blood and N-terminal telopeptide of type I collagen in urine relative to creatinine can rise to 21–23 % [11, 13]. It was indicated the decrease of 1,25-hydroxyvitamin D_3 and calcium that points violation of the metabolism of vitamin D.

Thus, Turner's syndrome is characterizing by a decrease of BMD and bone area, due to the relative hypoestrogenemia, low IGF-1 level and typical skeletal abnormalities. Reducing of the bone size is a factor of determining changes of BMD, and is indicating by the decline of vBMD.

Comprehensive study of the state of skeleton, bone metabolism and calcium homeostasis using dual energy X-ray absorptiometry, evaluation of bone markers, growth factors and sex hormones are the main methods to assess the effectiveness of prevention and treatment measures of osteoporosis.

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ОКРЕМІ АСПЕКТИ ОСТЕОПОРОЗУ ПРИ ДИЗГЕНЕЗІЇ ГОНАД

Резюме. Остеопороз — метаболічне захворювання кісткової системи, що супроводжується низькою щільністю кістки та погіршенням мікроархітектоніки кісткової тканини. У статті викладено основні механізми формування та клініко-діагностичні аспекти остеопорозу при дизгенезії гонад у дітей.

Ключові слова: синдром Шерешевського — Тернера, остеопороз, діти, дизгенезія гонад, гормони.

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ОТДЕЛЬНЫЕ АСПЕКТЫ ОСТЕОПОРОЗА ПРИ ДИСГЕНЕЗИИ ГОНАД

Резюме. Остеопороз — метаболическое заболевание костной системы, сопровождающееся низкой плотностью кости и ухудшением микроархитектоники костной ткани. В статье изложены основные механизмы формирования и клинико-диагностические аспекты остеопороза при дисгенезии гонад у детей.

Ключевые слова: синдром Шерешевского — Тернера, остеопороз, дети, дисгенезия гонад, гормоны.