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HYPOVITAMINOSIS D AND OSTEOPENIA OF PRETERM INFANTS: RISK FACTORS AND MECHANISMS OF FORMATION

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ГИПОВИТАМИНОЗ D И ОСТЕОПЕНИЯ НЕДОНОШЕННЫХ ДЕТЕЙ: ФАКТОРЫ РИСКА И МЕХАНИЗМЫ ФОРМИРОВАНИЯ

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The article presents a literature review on the effect of vitamin D deficiency on the body of premature newborns. According to the results of numerous studies, insufficient intake of vitamin D in the fetus increases the risk of developing bronchopulmonary dysplasia, lower respiratory tract infections, and neonatal sepsis. There is evidence that hypovitaminosis D negatively affects physical and neuropsychic development. One of the most important biological effects of vitamin D, namely its participation in the regulation of phosphorus-calcium metabolism and bone remodeling, is discussed. The mechanisms of the influence of parathyroid hormone (PTH) and calcitonin (CT) on the regulation of phosphorus-calcium homeostasis are also described. Increasing the survival rate of extremely low birth weight and very low birth weight infants increases the incidence of pediatricians and neonatologists with diseases such as osteopenia – a metabolic bone disease of preterm infants, characterized by impaired bone mineralization due to a lack of vitamin D, calcium and phosphorus. The review examines the causes, clinical manifestations, diagnosis, treatment and prevention of this disease.

Keywords: vitamin D, vitamin D deficiency, preterm neonate, parathyroid hormone, calcitonin, osteopenia of preterm neonates

Обзор посвящен влиянию дефицита витамина D на организм детей, рождённых раньше срока. Согласно результатам многочисленных исследований, недостаточное поступление в организм плода витамина D повышает риск развития бронхолёгочной дисплазии, инфекций нижних дыхательных путей, а также неонатального сепсиса. Имеются данные, подтверждающие негативное влияние гиповитаминоза D на физическое и нервно-психическое развитие. Обсуждается один из важнейших биологических эффектов витамина D, а именно – его участие в регуляции фосфорно-кальциевого обмена и ремоделировании костной ткани. Также описаны механизмы влияния паратиреоидного гормона (ПТГ) и кальцитонина (КТ) на регуляцию фосфорно-кальциевого гомеостаза. Повышение выживаемости новорожденных с экстремально низкой массой тела и очень низкой массой тела увеличивает частоту

встречаемости с таким заболеванием, как остеопения – метаболическое заболевание костей недоношенных новорождённых, характеризующееся нарушением минерализации костной ткани вследствие нехватки витамина D, кальция и фосфора. Рассматриваются причины, клинические проявления, диагностика, лечение и профилактика данного заболевания.

Ключевые слова: витамин D, недостаточность витамина D, недоношенный новорождённый, паратиреоидный гормон, кальцитонин, остеопения недоношенных

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CT – calcitonin
ELBW – extremely low birth weight
IGF-1 – insulin-like growth factor-1
PTH – parathyroid hormone

To this day, the study of vitamin D, its calcium and multi-vector noncalcemic effects, remains the focus of attention of the medical scientific community. It is one of the most important vitamins necessary for maintaining the body from infancy to old age [1, 2].

The history of the discovery of vitamin D began in 1913, when E. V. McCollum and his colleagues found a «fat-soluble growth factor» in fish oil that has antirachitic effects. American biochemist Harry Stenbock showed in 1923 that certain types of food that were exposed to ultraviolet rays helped in the treatment of rickets. A. Hess and M. Weinstock in 1924 obtained ergosterol – vitamin D1 from vegetable oils. In 1928 A. O. R. Windaus, who described the structure of vitamin D, received the Nobel Prize for the discovery of the precursor of vitamin D, 7-dehydrocholesterol [3].

The peculiarity of this vitamin is that it enters our body not only with food (ergocalciferol) but is also produced under the action of ultraviolet rays of sunlight on the skin (cholecalciferol). In both cases, vitamin D is not considered biologically active until two hydroxylation processes have taken place [4]. The first occurs in the liver with the participation of the enzyme 25-hydroxylase (CYP3A4), which promotes the formation of 25-hydroxyvitamin D-25(OH)D. The level of this metabolite is a standard biomarker of the body's supply of vitamin D. The second stage of activation occurs in the kidneys under the influence of 1a-hydroxylase (CYP27B1), where 25(OH)D is transformed into the most active form of the vitamin – 1.25-dihydroxyvitamin D (calcitriol) [5]. It is calcitriol that is transported in the bloodstream by the vitamin D-binding protein VDBR.

The activation of VDR receptors by calcitriol is the most important way of realizing the biological effects of vitamin D through non-genomic and genomic mechanisms [1, 2]. Non-genomic mechanisms are carried out by the action of vitamin D on signaling pathways in the cells of the nervous and immune systems, followed by regulation of the activity of phospholipase C(PLC), adenylate cyclase, tyrosine kinase (SRC), MARSS protein, and protein kinase C(PKC). Genomic mechanisms involve the interaction of the VDR with genomic DNA (Fig. 1) [6].

There are 6 groups of specific proteins specifically associated with the regulation of gene expression through the VDR receptor: mitochondrial proteins, zinc finger proteins involved in gene expression, NAD dehydrogenases, ubiquitin-regulated proteins, interleukins that regulate immunity and inflammation, and proteins of calcium homeostasis.

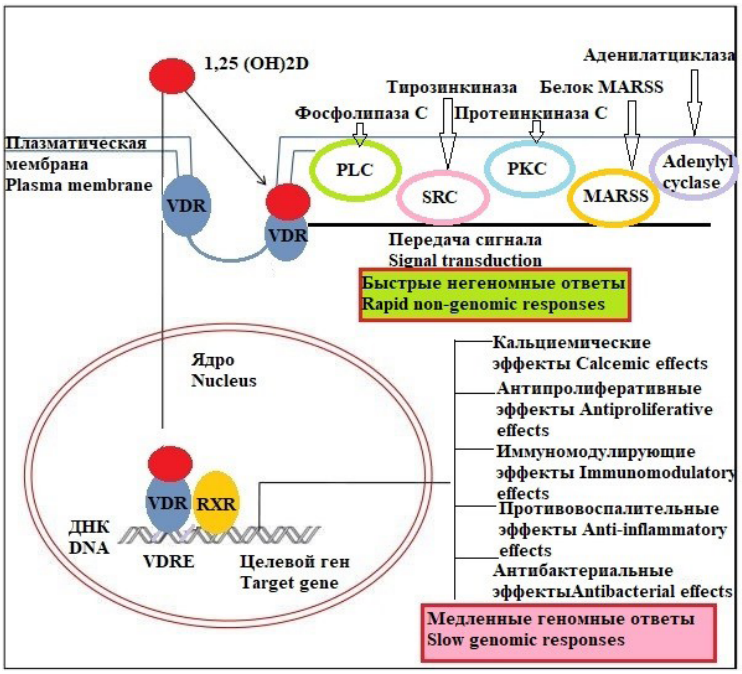

Fig. 1. Genomic and non-genomic mechanisms of regulation of the biological effects of vitamin D [6]

In newborns, both maturely and prematurely born, there are peculiarities of the metabolism of vitamin D. From the mother through the placenta, 25(OH)D is supplied using passive or lightweight transport, while from the 24th week of gestation, the fetal kidneys begin to metabolize 25(OH)D in $1.25(OH)_2D$ [7, 8]. After birth, possibly due to the need to stimulate the absorption of calcium in the intestine, the synthesis of $1.25(OH)_2D$ is activated [9].

In preterm infants, due to the immaturity of the expression of 24-hydroxylase CYP24A1, insufficient conversion of vitamin D into the form $24.25 (OH)_2 D$ occurs, which allows them to maintain a higher concentration of $1.25 (OH)_2 D$ to ensure active skeletal growth [7, 9].

For a long time, the metabolic effects of vitamin D have been analyzed exclusively from the standpoint of an antirachitic agent. However, the discovery of receptors in various organs and tissues has significantly expanded the

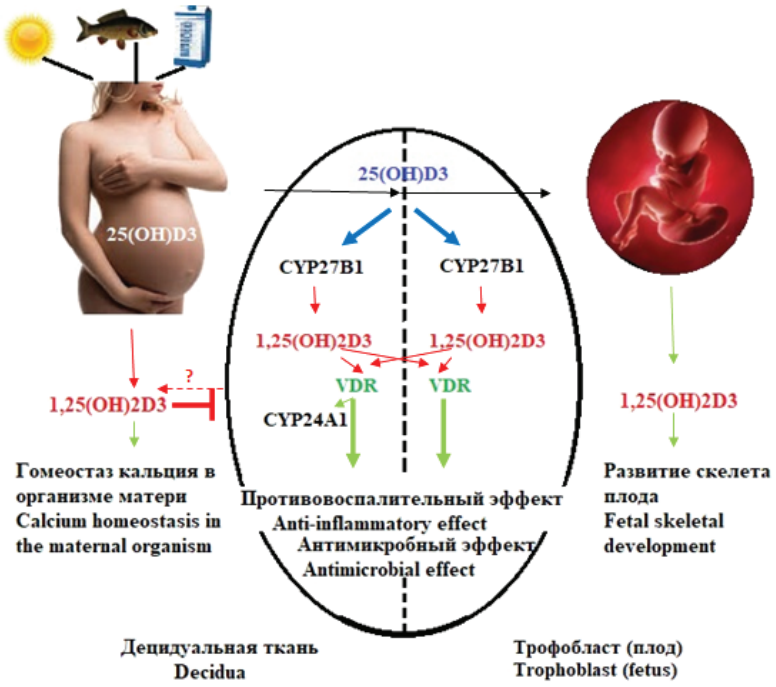

Fig. 2. Metabolism and the role of vitamin D in the mother-placenta-fetus system [10]

understanding of the spectrum of its biological properties [1]. According to the results of numerous studies, vitamin D deficiency increases the risk of metabolic disorders, diseases of the endocrine, immune, cardiovascular, reproductive and other systems (Fig. 2) [10, 11].

One of the most susceptible to hypovitaminosis D population groups are newborns, regardless of gestational age [12]. Their provision with calcidiol depends directly on its level in the mother's body. In the umbilical cord blood of a child, the concentration of 25(OH)D is 50–80 % of the level of maternal calcidiol [7, 8]. Deficiency of vitamin D can lead to the development of symptomatic hypocalcemia and hypocalcemic seizures [13].

Vitamin D metabolites have a positive effect on the development of lung tissue, on the synthesis of surfactant, reduce the need for oxygenation, especially in preterm infants and, thereby, reduce the risk of developing respiratory distress syndrome and respiratory tract infections [14, 15].

Calcidiol has an immunotropic effect by stimulating the formation of antimicrobial peptides, namely β_2 -defensins and cathelicidins, which have bactericidal activity, helping to reduce the incidence of neonatal sepsis [16, 17].

There are data confirming the linear dependence of the dynamics of neurocognitive development in children on the provision of vitamin D in the antenatal period. Vitamin D has neuroprotective and neurotrophic effects, is a neurosteroid and an integral element of the neuroendocrine regulation of the development of the nervous system, starting from the prenatal period [8].

Despite the variety of noncalcemic mechanisms, one of the most important biological effects of vitamin D throughout life is its participation in the regulation of phosphorus-calcium metabolism and bone remodeling [4, 18]. Calcitriol stimulates the synthesis of transport proteins by enterocytes of the small intestine, such as the calcium-binding protein calbindin – CaBP-9k, CaBP-28k and others, which bind calcium, magnesium and phosphate ions, then transport them to the lymphatic and then to the circulatory system [19]. Calcitriol interacts with VDRs located on osteoblasts, which increase the production of alkaline phosphatase and non-collagen proteins (osteonectin, osteocalcin, osteopontin) [9, 19, 20].

$1.25(OH)_2D$ also stimulates the differentiation of osteoclasts from progenitor cells and promotes the acceleration of bone resorption with the release of mineral components into the vascular bed. Thus, the process of bone tissue remodeling, and maintenance of normal blood calcium levels is carried out [20].

Bone tissue, which performs metabolic, protective and support functions in the human body, is a type of connective tissue [21]. Bone metabolism is a combination of two oppositely directed processes – bone formation with the help of osteoblasts and bone resorption by osteoclasts [21, 22].

Osteoblasts are bone cells that actively synthesize and secrete extracellular substance. They have a well-developed granular endoplasmic reticulum and the Golgi complex. Osteoblasts synthesize type 1 procollagen, containing the N-terminal and C-terminal domains. Under the action of special peptidases, these molecular fragments are cleaved from the procollagen. The C-terminal peptide contains the alpha form of aspartic acid, which is then converted to the beta form – β-cross-laps. In the process of bone resorption, β-cross-laps enters the vascular bed and is a marker of type 1 collagen degradation [22].

Osteoclasts are large multinucleated cells that, by synthesizing alkaline phosphatase and collagenase, cause the destruction of the bone matrix [22, 23].

In the period of intrauterine development, the dominance of bone mineralization in relation to bone growth is noted. Thus, at the birth of a mature newborn, the bone tissue has sufficient density. And already in the postnatal period, the bones begin to grow intensively by increasing the length and diameter, which is accompanied by a decrease in density in the cortical layer [24]. In preterm infants, a decrease in bone density is more often detected due to more pronounced violations of bone mineralization, compared with linear bone growth [25].

The main micronutrient involved in the formation of the bone tissue matrix is calcium (Ca^{2+}). Most of Ca^{2+}, about 90–95 % is in the bone, and the rest is involved in the regulation of several important functions (activation of the secretion of endo- and exocrine glandular cells, participation in ensuring adequate neuromuscular excitability, as well as muscle contractility, regulation of secretion enzymes, proteins, etc.) [26].

Calcium enters the body with food (dairy products, sesame seeds, nuts, dried fish) in the form of calcium phosphate and is absorbed in the proximal parts of the small intestine, with the participation of calcium-binding protein. In serum, the level of total calcium is represented by three fractions: in a complex with proteins (about 40 % of the total level), mainly with albumin; in the form of ionized Ca^{2+}, which is about 50 % of the total calcium; associated with anions (about 5–10 % of the total), such as citrate, phosphate, carbonate, sulfate.

Along with calcium, magnesium is also an essential micronutrient for bone tissue. In addition, it regulates many intracellular processes, takes part in electrolyte and energy metabolism, is important in the synthesis of protein molecules, inhibits excitation processes in the central nervous system, and causes relaxation of skeletal muscles.

Another important micronutrient in the formation of bone tissue is phosphorus (P^{3-}), which is required for the synthesis of hydroxyapatite due to the binding of extracellular calcium in composite mineralized bone structures [27].

In mature infants, 99 % calcium and 80 % phosphorus at birth are in the skeleton, while in preterm infants there is a deficiency of most nutrients, up to 33–34 weeks of gestation, the accumulation of Ca^{2+} and P^{3-} is very low [26]. It was found that during the third trimester the daily intake of calcium is 90–150 mg/kg/day [28], according to other sources – 10–130 mg/kg/day, phosphorus – up to 60–70 mg/kg/day [29].

A decrease in the intake of calcium, phosphorus, magnesium and other micronutrients by 3–3.5 times is facilitated by disturbances in the maternal-placental and placental-fetal blood flow [30]. Thus, bone mineralization in preterm infants with extremely low birth weight (ELBW) is 25–70 % lower than in mature infants, which significantly increases the risk of subsequent disorders of bone metabolism [31].

In addition to calcitriol, PTH and CT are involved in the regulation of calcium-phosphorus metabolism [32, 33].

PTH was first isolated in 1970 by H. D. Nayel et al. in bovine parathyroid glands. The molecule is represented by a polypeptide chain consisting of 84 amino acid residues. According to the literature, this hormone is synthesized mainly by oxyphilic cells of the gland. With a decrease in the level of Ca^{2+} in the blood, the synthesis of PTH increases, as a result of which the resorption of bone tissue and the release of calcium from the bone into the blood increase, in parallel, the reabsorption of Ca^{2+} and the excretion of P^{3-} in the renal tubules increase, the absorption of Ca^{2+} in the intestine is enhanced by the method induction of QD synthesis [34].

The effect of PTH on bone is characterized by inhibition of the synthesis of type 1 collagen by active osteoblasts, osteocalcin, as well as an increase in the osteolytic activity of osteoblasts and osteocytes. As a result, the latter begin to secrete cytokines and insulin-like growth factor-1 (IGF-1), which stimulate the activity of osteoclasts [35].

It is important that, depending on the duration of action, PTH can affect the bone in different ways: a short intermittent effect promotes bone formation, and in the case of long-term continuous action (hyperparathyroidism), it is accompanied by osteodestruction and a decrease in bone mineral density [36].

In 1962, another important regulator of phosphorus-calcium metabolism, CT, was discovered [33]. This hormone is synthesized by the C-cells of the thyroid gland and consists of 32 amino acids. CT secretion depends on the serum calcium concentration: in response to an increase in Ca^{2+} in the extracellular fluid, an increase in CT production is noted. It is, on the one hand, the main antihypercalcemic, and hypophosphatemic hormone, on the other. CT performs its effects by disrupting the formation and suppression of the activity of osteoclasts, thereby reducing bone resorption. It also helps to reduce the synthesis of the biologically active metabolite of vitamin D – calcitriol, as a result of inhibition of the synthesis of α_1-hydroxylase. In the kidneys, CT reduces the reabsorption of Ca^{2+} and P^{3-}, while the absorption of Ca^{2+} in the intestine decreases in parallel [37].

Phosphorus-calcium homeostasis is influenced by several other factors. Micronutrients such as Mg and Al compete with calcium in the absorption process, vitamin A is a calcitriol antagonist in intestinal absorption. Glucocorticoids promote the leaching of Ca^{2+} into the blood and increase the risk of osteoporosis [38]. In turn, somatotrophic hormone (growth hormone) and androgens reduce blood calcium and increase calcium deposits in bones. Growth hormone stimulates the formation of insulin-like growth factor-1 (IGF-1), under the influence of which cartilage cells undergo increased division. Growth hormone, with the help of intracellular signaling systems, promotes the proliferation and maturation of mesenchymal precursors to osteoblasts and chondrocytes. Growth hormone has a depressing effect on osteoclasts by stimulating the production of osteoprotegerin with its subsequent accumulation, which leads to blocking of RANK and RANKL receptors.

The ligand-receptor system RANK/RANKL/OPG is one of the key links in bone tissue homeostasis, which regulates osteoclast differentiation and osteolysis. In certain situations, leading to the activation of osteoclastogenesis, the suRussian Federationace receptors RANK and RANKL begin to interact with each other. This facilitates the transformation of osteoclast precursors into mature active osteoclasts [23]. Osteoprotegerin, produced by osteoblasts and stromal cells, has an inhibitory effect on the binding of osteoclast precursors to RANK receptors, thereby exerting an antiresorptive effect [39].

Preterm infants have several significant features of calcium-phosphorus metabolism. During the first week after birth, they have hypocalcemia, then, as the postanal age increases, the calcium level gradually increases, but does not reach the indicators characteristic of mature infants [25, 27].

Extremely preterm infants are characterized by persistence of hypocalcemia until the 9–12th week of life. The development of this condition is possibly associated with a reduced secretion of PTH in infants born pretermly, due to the low sensitivity of their tissues to this hormone [27, 30, 32].

Another important reason is the increased secretion of CT, while the younger the gestational age, the higher the serum calcitonin level [40]. Also, functional immaturity of renal tissue in preterm infants contributes to a decrease in glomerular filtration, impaired absorption of calcium, phosphates and an increase in their excretion in the urine. The persistence of hypercalciuria throughout the neonatal period was revealed in preterm infants up to 32 weeks of gestation. An insufficient level of vitamin D contributes to impaired absorption of Ca^{2+} in the intestine and the development of hypocalcemia [10].

It should be remembered that preterm infants in utero do not have time to accumulate the required amount of minerals, sufficient levels of vitamin D, as a result of which the maturation of bone structures is insufficient [41]. In extrauterine life, they show increased growth, which is inevitably accompanied by an increase in the need for calcium, phosphorus and vitamin D. These features, inadequate environmental conditions for their development, increase the risk of bone mineralization disorders, which can lead to a decrease in bone density (Fig. 3) [42].

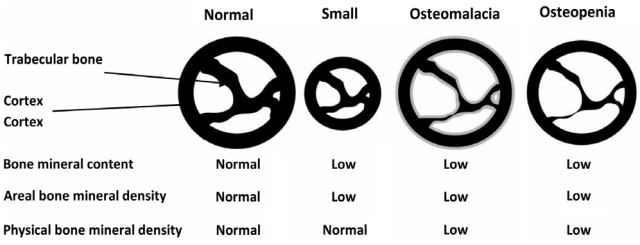

Fig. 3. Conditions affecting bone mineral density in preterm infants [42]

In the literature, this condition is referred to as osteopenia of prematurity, and its development is facilitated by both insufficient accumulation of P^{3-} and Ca^{2+} by the time of birth, and postnatal deficiency of micronutrients intake due to impaired absorption. Osteopenia is a metabolic

bone disease in preterm newborn infants, characterized by impaired bone mineralization and growth, which develops primarily due to insufficient intake of calcium and phosphorus after birth [43].

In the United States back in the 90s, when modern nutritional support protocols were not introduced, the incidence of osteopenia was about 60–65 % in newborns weighing less than 1000 g, in children weighing less than 1500 g – 22–32 %, and fractures occurred in 10 % of newborns with VLBW [44]. According to S. Viswanathan et al., 31 % of preterm infants weighing less than 1000 g showed radiographic signs of metabolic bone disease, and the frequency of fractures was 10 % [45].

Among maternal factors that increase the risk of developing metabolic disorders in newborns, first, vitamin D deficiency in a pregnant woman is included [46]. Extragenital pathology, in particular, liver and kidney diseases, preeclampsia, etc. also contribute to a decrease in the synthesis of vitamin D-transport proteins, which can lead to the development of osteopenia in newborns [30].

A number of drugs with prolonged use also contribute to the violation of bone mineralization. It has been proven that glucocorticoids increase bone resorption, anticonvulsants induce the excretion of Ca^{2+} from the depot, diuretics lead to an increase in the excretion of Ca^{2+}, P^{3-} and other micronutrients in the urine [38, 47].

Pathology of the gastrointestinal tract in newborns, such as, in particular, short bowel syndrome, malabsorption syndrome, contributing to the disruption of the passive pathway of absorption of Ca^{2+}, P^{3-} ions.

The risk of developing steppe in preterm infants is the higher, the longer their hyperbilirubinemia is. This is since a high level of bilirubin prevents the conversion of vitamin D into a transport form [48]. Also, in premature newborns, bile salts are formed in an insufficient volume, as a result of which the absorption of fats is reduced. In the intestine, free fatty acids bind with calcium to form insoluble soaps and thereby cause impaired calcium absorption [49].

Long-term parenteral nutrition, without an adequate subsidy of necessary micronutrients, late started enteral nutrition with unfortified breast milk or a non-specialized formula for preterm infants significantly reduce the intake of Ca^{2+}, P^{3-} and other micronutrients, which is also a risk factor for the development of bone mineralization disorders [50, 51].

Clinical signs of osteopenia, characteristic radiological manifestations, and laboratory changes begin to appear between 6 and 12 weeks after birth [52–54]. Electrolyte disturbances underlying the disease are most often manifested by hypophosphatemia. Respiratory disturbances, dependence on respiratory support due to weakness of the respiratory excursion are clinically noted. Also characterized by a decrease in muscle tone, heart failure, depression syndrome, syndrome of vegetative-visceral disorders, dysphagia and even sudden death. Rib fractures are asymptomatic and are diagnosed accidentally on x-rays. Fractures of long bones are characterized by local tenderness and swelling, limited motor activity, and muscle hypotonia in the injured limb [55].

Possible late clinical manifestations include lagging behind peers in weight and height with reduced bone density and impaired bone mineral composition [56]. At the same time, the growth of the head is preserved, there are frontal tubercles, craniotabes, an increase in the large fontanelle with softening of the edges, and the divergence of the skull bones at the seams. Due to violations of the shape of the skull, myopia of preterm infants develops. Due to the high excretion of Ca^{2+} in the urine, the risk of developing dysmetabolic nephropathy and urolithiasis is high.

It is significant that changes characteristic of osteopenia appears on radiographs when bone mineralization is already reduced by 20–40 %. At the beginning, the changes are insignificant, then «worn out» epiphyses are revealed, and in severe cases – fractures of long bones and/or ribs [52].

Certain laboratory parameters allow us to indirectly assess the metabolism of bone tissue [57]. An increase in the bone isoenzyme of alkaline phosphatase (more than 500 U/L) may indicate a high risk of developing osteopenia [53]. At the same time, a simultaneous decrease in the level of phosphorus (in preterm infants the lower limit of P^{3-} is 1.3 mmol/l) and an increase in the level of alkaline phosphatase is an important condition for confirming the diagnosis [54]. The level of calcium is not a reliable sign, since its indicator in the body of a newborn can be within the normal range for a sufficient time, as a result of the mobilization of Ca^{2+} from the bone tissue (N – 1.8–2.6 mmol/l).

Primary prevention and treatment of osteopenia of prematurity first consists in providing the pregnant woman with the necessary level of vitamin D [45]. According to some data, the need of pregnant women for calcidiol ranges from 150 to 1000 IU/day [58], according to others, an increase up to 1500–2000 IU/day is possible [59].

Adequate intake of P^{3-} and Ca^{2+} into the body plays an important role in the formation and mineralization of bone tissue [29]. It is possible to provide a newborn, and even more so a preterm baby with the necessary level of trace elements by enriching breast milk, as well as using a specialized mixture for preterm infants. This type of nutrition allows prematurely born children to assimilate approximately 180–220 mg/kg/day of calcium and 100–130 mg/kg/day of phosphorus, which reduces the risk of metabolic disorders in bone tissue, and, if they occur, has a therapeutic effect. Preterm infants receiving parenteral nutrition should receive a parenteral supplement of calcium, phosphorus and vitamin D [44].

Physical activity plays an important role in stimulating bone growth, while daily mechanical stimulation using passive exercises for 5–10 minutes improves bone mineralization [60].

Conclusions. Thus, the problem of diagnosis and treatment of prematurity osteopenia requires close attention. It must be remembered that it is extremely important to prevent bone damage through the timely identification of risk factors. In the event of the development of the disease, timely diagnosis and treatment of calcium, phosphorus and vitamin D deficiency in newborns will significantly reduce the incidence of severe disorders of bone metabolism.

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References

1. Spirichev V. B. About the biological effects of vitamin D. *Pediatria.* 2011;6:113-119.
2. Kasyanova A. N., Dolbnya S. V., Kuryaninova V. A., Anisimov G. S., Abramskaya L. M. [et al.] Vitamin D and its biological role in the body. Message 3. Methods of prevention and drug correction of vitamin D deficiency. *Bulletin of the Young Scientist*. 2016;12(1):6-13.
3. Deluca H. F. History of the discovery of vitamin D and its active metabolites. *Bonekey Rep.* 2014;8(3):479. https://doi.org/10.1038/bonekey.2013.213

4. Wacker M., Holick M. F. Vitamin D – effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients.* 2013;5(1):111-148. https://doi.org/10.3390/nu5010111
5. Adams J. S., Rafison B., Witzel S., Reyes R. E., Shieh A. [et al.] Regulation of the extrarenal CYP27B1-hydroxylase. *J. Steroid Biochem. Mol. Biol*. 2014;144:22-27. https://doi.org/10.1016/j.jsbmb.2013.12.009
6. Ramagopalan S. V., Heger A., Berlanga A. J., Maugeri N. J., Lincoln M.R. [et al.] A ChIP-seq defined genome-wide map of vitamin D receptor binding: associations with disease and evolution. *Genome Res.* 2010;20(10):1352-1360. https://doi.org/10.1101/gr.107920.110
7. Maltsev S. V., Mansurova G. Sh., Zakirova A. M., Maltseva L. I., Vasilyeva E. N. The role of vitamin D in the mother-placenta-fetus system. *The practice of medicine.* 2016;1(93):26-31.
8. Zayachnikova T. E., Belan E. B., Krasilnikova A. S. Vitamin D deficiency in the «mother – placenta – fetus» system as a risk factor for disorders of physical and neurological development in premature infants. *Medical review.* 2019;5:20-25.
9. Hanson C., Jones G., Lyden E., Kaufmann M., Armas L., Anderson-Berry A. Vitamin D metabolism in the premature newborn: A randomized trial. *Clin. Nutr.* 2016;35(4):835-841. https://doi.org/10.1016/j.clnu.2015.07.023
10. Zakharova I. N., Maltsev S. V., Zubkov V. V., Kuryaninova V. A., Dmitriev A. V. [et al.] Vitamin D, low-weight, prematurely born and full-term newborns: time to change the paradigm. *Breast cancer. Mother and child.* 2020;3(2):142-148. https://doi.org/10.32364/2618-8430-2020-3-2-142-148
11. Zakharova I. N., Maltsev S. V., Zubkov V. V., Kuryaninova V. A., Dmitriev A.V. [et al.] The effect of vitamin D on the course of pregnancy and the health of newborns and young children: a modern view of the problem. *Breast cancer. Mother and child.* 2020;3(3):174-181. https://doi.org/10.32364/2618-8430-2020-3-3-174-181
12. Klimov L. Ya., Dolbnya S. V., Kuryaninova V. A., Alaverdyan L. S., Kasyanova A. N. [et al.] Vitamin D levels in newborns children of Stavropol Region. *Medical News of North Caucasus.* 2015;10(2):159-163. https://doi.org/10.14300/mnnc.2015.10037
13. Curtis E. M., Moon R. J., Dennison E. M., Harvey N. C. Prenatal calcium and vitamin D intake, and bone mass in later life. *Curr. Osteoporos. Rep.* 2014;12:194-204. https://doi.org/10.1007/s11914-014-0210-7
14. Narogan M. V., Ryumina I. I., Krokhina K. N., Zubkov V. V., Zakharova I. N. [et al.] Vitamin D in newborns and premature infants. *Neonatology: news, opinions, training.* 2018;3(21):134-138.
15. Zhuravleva L. N., Novikova V. I. Experience in the use of vitamin D in the complex therapy of pneumonia in premature newborns. *Reproductive health. Eastern Europe.* 2020;10(5):598-605. https://doi.org/10.34883/PI.2020.10.5.007
16. Zakharova I. N., Klimov L. Ya., Kasyanova A. N., Kuryaninova V. A., Dolbnya S. V. [et al.] Interrelationships between the incidence of infectious diseases and vitamin D deficiency: the current state of the problem. *Infectious diseases.* 2018;16(3):69-78. https://doi.org/10.20953/1729-9225-2018-3-69-78
17. Zakharova I. N., Klimov L. Ya., Kasyanova A. N., Kuryaninova V. A., Dolbnya S. V. [et al.] The relationship between infectious morbidity and vitamin D deficiency: the current state of the problem. *Infectious diseases.* 2018;16(3):69-78. https://doi.org/10.24110/0031-403X-2017-96-4-171-179
18. Holick M. F. Vitamin D: evolutionary, physiological and health perspectives. *Curr. Drug Targets.* 2011;12(1):4-18. https://doi.org/10.2174/138945011793591635
19. Fleet J. C., Schoch R. D. Molecular mechanisms for regulation of intestinal calcium absorption by vitamin D and other factors. *Crit. Rev. Clin. Lab. Sci.* 2010;47(4):181-195. https://doi.org/10.3109/10408363.2010.536429
20. Baldock P. A., Thomas G. P., Hodge J. M., Baker S. U., Dressel U. [et al.] Vitamin D action and regulation of bone remodeling: suppression of osteoclastogenesis by the mature osteoblast. *J. Bone Miner. Res.* 2006;21(10):1618-1626. https://doi.org/10.1359/jbmr.060714
21. Kovacs C. S. Bone development and mineral homeostasis in the fetus and neonate: roles of the calciotropic and phosphotropic hormones. *Physiol. Rev.* 2014;94(4):1143-1218. https://doi.org/10.1152/physrev.00014.2014
22. Brunetti G., Papadia F., Tummolo A., Fischetto R., Nicastro F. [et al.] Impaired bone remodeling in children with osteogenesis imperfecta treated and untreated with bisphosphonates: the role of DKK1, RANKL, and TNF-α. *Osteoporos. Int.* 2016;27(7):2355-2365. https://doi.org/10.1007/s00198-016-3501-2
23. Brunetti G., Tummolo A., D'Amato G., Gaeta A., Ortolani F. [et al.] Mechanisms of enhanced osteoclastogenesis in alkaptonuria. *Am. J. Pathol.* 2018;188(4):1059-1068. https://doi.org/10.1016/j.ajpath.2017.12.008
24. Pereira-da-Silva L., Costa A., Pereira L., Filipe A., Virella D. [et al.] Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J. Pediatr. Gastroenterol. Nutr.* 2011;52(2):203-209. https://doi.org/10.1097/MPG.0b013e3181f8b295
25. Rauch F., Schoenau E. Skeletal development in premature infants. a review of bone physiology beyond nutritional aspects. *Arch. Dis. Child. Fetal Neonatal Ed.* 2002;86:82. https://doi.org/10.1136/fn.86.2.f82
26. Sethi A., Priyadarshi M., Agarwal R. Mineral and bone physiology in the foetus, preterm and full-term neonates. *Semin Fetal Neonatal Med*. 2020;25(1):101076. https://doi.org/10.1016/j.siny.2019.101076
27. Kovacs C. S. Calcium, phosphorus, and bone metabolism in the fetus and newborn. *Early Hum. Dev.* 2015;91(11):623-628. https://doi.org/10.1016/j.earlhumdev.2015.08.007
28. Greer F. R. Controversies in neonatal nutrition: macronutrients and micronutrients. Gastroenterology and Nutrition: Neonatology Question and Controversies. 2nd ed. / Ed. J. Neu. Philadelphia: Elsevier; Saunders; 2012:129-155.
29. Abrams S. A. Committee on Nutrition. Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics.* 2013;131(5):1676-1683. https://doi.org/10.1542/peds.2013-0420
30. Chinoy A., Mughal M. Z., Padidela R. Metabolic bone disease of prematurity: causes, recognition, prevention, treatment and long-term consequences. *Arch. Dis. Child Fetal Neonatal Ed.* 2019;104(5):560-566. https://doi.org/10.1136/archdischild-2018-316330
31. Faienza M. F., D'Amato E., Natale M. P., Grano M., Chiarito M. [et al.] Metabolic bone disease of prematurity: diagnosis and management. *Front. Pediatr.* 2019;12(7):143. https://doi.org/10.3389/fped.2019.00143
32. Wojda S. J., Donahue S. W. Parathyroid hormone for bone regeneration. *J. Orthop. Res.* 2018;36(10):2586-2594. https://doi.org/10.1002/jor.24075
33. Xie J., Guo J., Kanwal Z., Wu M., Lv X. [et al.] Calcitonin and bone physiology: in vitro, in vivo, and clinical investigations. *Int. J. Endocrinol.* 2020;10. https://doi.org/10.1155/2020/3236828
34. Sato E., Williams M. R., Sanford J. A., Sen G. L., Nakama T. [et al.] The parathyroid hormone family member TIP39 interacts with sarco/endoplasmic reticulum Ca^{2+} -ATPase activity by influencing calcium homoeostasis. *Exp. Dermatol.* 2017;26(9):792-797. https://doi.org/10.1111/exd.13294
35. Pittard W. B. 3rd, Geddes K. M., Hulsey T. C., Hollis B. W. Osteocalcin, skeletal alkaline phosphatase, and bone mineral content in very low birth weight infants: a longitudinal assessment. *Pediatr. Res.* 1992;31(2):181-185. https://doi.org/10.1203/00006450-199202000-00019
36. Moreira A., February M., Geary C. Parathyroid hormone levels in neonates with suspected osteopenia. *J. Paediatr. Child Health*. 2013;49(1):12-16. https://doi.org/10.1111/jpc.12052
37. Lerner U. H. Deletions of genes encoding calcitonin/alpha-CGRP, amylin and calcitonin receptor have given new and unexpected insights into the function of calcitonin receptors and calcitonin receptor-like receptors in bone. *J. Musculoskelet Neuronal Interact.* 2006;6(1):87-95. PMID: 16675892.
38. Ventura A., Brunetti G., Colucci S., Oranger A., Ladisa F. [et al.] Glucocorticoid-induced osteoporosis in children with 21-hydroxylase deficiency. *Biomed. Res. Int.* 2013;2013:250462. https://doi.org/10.1155/2013/250462
39. Boyce B. F., Xing L. Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res. Ther.* 2007;9(1):1. https://doi.org/10.1186/ar2165
40. Krokhina K. N., Smirnova I. E., Kucherenko A. G., Belyaeva I. A. Features of bone tissue formation in newborns. *Russian Pediatric Journal*. 2010;5:36-41.
41. Done S. L. Fetal and neonatal bone health: update on bone

growth and manifestations in health and disease. *Pediatr. Radiol.* 2012;42:158-176. https://doi.org/10.1007/s00247-011-2251-8
42. Rauch F., Schoenau E. Skeletal development in premature infants: a review of bone physiology beyond nutritional aspects. *Arch. Dis. Child Fetal Neonatal Ed.* 2002;86(2):82-85. https://doi.org/10.1136/fn.86.2.f82
43. Rustico S. E., Calabria A. C., Garber S. J. Metabolic bone disease of prematurity. *J. Clin. Transl. Endocrinol.* 2014;1(3):85-91. https://doi.org/10.1016/j.jcte.2014.06.004
44. Nehra D., Carlson S. J., Fallon E. M., Kalish B., Potemkin A. K. [et al.] A.S.P.E.N. Clinical guidelines: nutritional support of neonatal patients at risk for metabolic bone disease. *JPEN.* 2013;37(5):570-598. https://doi.org/10.1177/0148607113487216
45. Viswanathan S., Khasawneh W., McNelis K., Dykstra C., Amstadt R. [et al.] Metabolic bone disease: a continued challenge in extremely low birth weight infants. *JPEN J. Parenter. Enteral Nutr.* 2014;38(8):982-990. https://doi.org/10.1177/0148607113499590
46. Streym S., Moller U. K., Rejnmark L., Heickendorff L., Mosekilde L., Vestergaard P. Maternal and infant vitamin D status during the first 9 months of infant life-a cohort study. *Eur. J. Clin. Nutr.* 2013;67(10):1022-1028. https://doi.org/10.1038/ejcn.2013.152
47. Brunetti G., Faienza M. F., Piacente L., Ventura A., Oranger A. [et al.] High dickkopf-1 levels in sera and leukocytes from children with 21-hydroxylase deficiency on chronic glucocorticoid treatment. *Am. J. Physiol. Endocrinol. Metab*. 2013;304(5):546-554. https://doi.org/10.1152/ajpendo.00535.2012
48. Ruiz-Gaspà S., Martinez-Ferrer A., Guañabens N., Dubreuil M., Peris P. [et al.] Effects of bilirubin and sera from jaundiced patients on osteoblasts: contribution to the development of osteoporosis in liver diseases. *Hepatology*. 2011;54(6):2104-2113. https://doi.org/10.1002/hep.24605
49. Gomella T. L. Neonatology: Management, Procedures, OnCall Problems, Diseases, and Drugs. 25th ed. McGraw-Hill. 2013.
50. Christmann V., Gradussen C. J., Körnmann M. N., Roeleveld N., van Goudoever J. B., van Heijst A. F. Changes in biochemical parameters of the calcium-phosphorus homeostasis in relation to nutritional intake in very-low-birthweight. *Infants Nutrients.* 2016;8(12):764. https://doi.org/10.3390/nu8120764
51. Chin L. K., Doan J., Teoh Y. S., Stewart A., Forrest P., Simm P. J. Outcomes of standardised approach to metabolic bone disease of prematurity. *J. Paediatr. Child Health*. 2018;54(6):665-670. https://doi.org/10.1111/jpc.13813
52. Isojima T., Kushima R., Goishi K., Tsuchida S., Watanabe T. [et al.] Mineral status of premature infants in early life and linear growth at age 3. *Pediatr. Int.* 2015;57(5):864-869. https://doi.org/10.1111/ped.12657
53. Hung Y. L., Chen P. C., Jeng S. F., Hsieh C. J., Peng S. S. [et al.] Serial measurements of serum alkaline phosphatase for early prediction of osteopaenia in preterm infants. *J. Paediatr. Child Health.* 2011;47(3):134-139. https://doi.org/10.1111/j.1440-1754.2010.01901.x
54. Catache M., Leone C. R. Role of plasma and urinary calcium and phosphorus measurements in early detection of phosphorus deficiency in very low birth weight infants. *Acta Paediatr.* 2003;92(1):76-80. https://doi.org/10.1111/j.1651-2227.2003.tb00473.x
55. Rehman M. U., Narchi H. Metabolic bone disease in the preterm infant: Current state and future directions. *World J. Methodol.* 2015;5(3):115-121. https://doi.org/10.5662/wjm.v5.i3.115
56. Harrison C. M., Johnson K., McKechnie E. Osteopenia of prematurity: national survey and review of 5. Practice. *Acta Paediatr.* 2008;97:407-413. https://doi.org/10.1111/j.1651-2227.2007.00721.x
57. Rooz R., Genzel-Borovicheschi O., Prokitte G. Neonatologiya. Practical recommendations. M.: Meditsinskaya literatura, 2011:568.
58. Viljakainen H. T., Saarnio E., Hytinantti T., Miettinen M., Surcel H. [et al.] Maternal vitamin D status determines bone variables in the newborn. *J. Clin. Endocrinol. Metab*. 2010;95(4):1749-1757. https://doi.org/10.1210/jc.2009-1391
59. Holick M. F., Binkley N. C., Bischoff-Ferrari H. A., Gordon C. M., Hanley D. A. [et al.] Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011;96(7):1911-1930. https://doi.org/10.1210/jc.2011-0385
60. Stalnaker K. A., Poskey G. A. Osteopenia of prematurity: does physical activity improve bone mineralization in preterm infants? *Neonatal Netw*. 2016;35(2):95-104. https://doi.org/10.1891/0730-0832.35.2.95

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