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THE SIGNIFICANCE OF VITAMIN D IN THE REGULATION OF BONE METABOLISM IN TERM AND PREMATURE INFANTS

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ЗНАЧЕНИЕ ВИТАМИНА D В РЕГУЛЯЦИИ КОСТНОГО МЕТАБОЛИЗМА У ДОНОШЕННЫХ И НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

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Improvements in neonatal care for premature babies have led to significant improvements in survival rates for low and very low birth weight infants. Due to the characteristics of calcium-phosphorus homeostasis and bone metabolism, neonatologists often encounter skeletal system pathology in premature newborns. This condition is a metabolic disease of premature infants' bones based on a deficiency of calcium, phosphorus, and vitamin D, resulting in impaired growth and mineralization of the growing skeleton. Vitamin D is one of the most important regulators of bone metabolism. On the one hand, it stimulates the absorption of Ca2+ and P3- in the small intestine, and on the other hand, it has a direct effect on bone tissue cells (osteoblasts, osteocytes, osteoclasts, and chondrocytes) through the vitamin D receptors located in them. Risk factors for developing bone metabolism disorders in term and premature newborns, as well as the correlating role of vitamin D in skeletal formation and maintaining homeostasis, were considered.

Keywords: bone tissue, bone metabolism, newborns, premature babies, vitamin D, parathyroid hormone, calcitonin

Совершенствование неонатальной помощи недоношенным детям привело к значительному повышению выживаемости младенцев с очень низкой и экстремально низкой массой тела. Из-за особенностей кальций-фосфорного гомеостаза и костного метаболизма врачи-неонатологи нередко сталкиваются с патологией костной системы у недоношенных новорожденных. Данное состояние представляет собой метаболическое заболевание костей недоношенных детей, в основе которого лежит дефицит кальция, фосфора и витамина D, что приводит к нарушению роста и минерализации растущего скелета. Витамин D является одним из важнейших регуляторов костного метаболизма. С одной стороны, он стимулирует абсорбцию Ca^{2+} и P^{3-} в тонком кишечнике, а с другой – оказывает непосредственное воздействие на клетки костной ткани (остеобласты, остеоциты, остеокласты и хондроциты) через расположенные в них рецепторы витамина D. В обзоре представлены особенности минерализации костной ткани у доношенных и недоношенных новорожденных. Рассмотрены факторы риска развития нарушения метаболизма кости, а также коррелирующая роль витамина D в скелетообразовании и поддержании гомеостаза.

Ключевые слова: костная ткань, костный метаболизм, новорожденные, недоношенные дети, витамин D, паратгормон, кальцитонин

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Ca^{2+} – calcium
CT – calcitonin
FGF – fibroblast growth factor
OB – osteoblasts
OC – osteoclasts
OPG – osteoprotegerin
P^{3-} – phosphorus
PTH – parathyroid hormone

Vitamin D deficiency is a global problem today, and the study of the role of 25(OH)D in human health remains in the spotlight. The relationship between hypovitaminosis D and impaired bone mineralization has long been established [1].

Given the steadily increasing survival rate of premature babies, who are more likely to develop skeletal abnormalities, diagnosing vitamin D deficiency-related diseases is essential. Newborns, including preterm infants, constitute a high-risk group for developing 25(OH)D deficiency [2–4].

From the 5th week of intrauterine development, there is the laying of bone tissue followed by the gradual replacement of the cartilage skeleton with bone, which lasts several years after birth [5, 6]. The bone tissue of the newborn has a coarse fibrous structure, contains a lot of water and little dense substance, and is therefore easily deformed. In addition, it is reconstructed from a rough fiber structure into a plate [6, 7]. During this period, bone tissue is characterized by increased sensitivity to adverse effects, especially the lack of calcium and other essential micronutrients (phosphorus, magnesium, zinc, etc.) [5–8].

The skeletal system undergoes constant self-renewal due to two multidirectional but co-occurring processes: bone formation by osteoblasts (OB) and resorption of existing bone tissue by osteoclasts (OC) [5, 9].

In the mineral composition of bone, calcium is the most important, 99 % of which is in the bones. The calcium residue circulating in the blood regulates the most essential functions of the body [10, 11].

Along with Ca^{2+}, phosphorus (P^{3-}) is also a particularly significant macronutrient. Eighty-five percent of it is concentrated in bone tissue, which regulates several metabolic processes [10, 12].

In the period of intrauterine development, Ca^{2+} and P^{3-} actively accumulate in the fetus's body only after 33–34 weeks of pregnancy [13–15]. Thus, premature newborns are more likely to disrupt bone mineralization than children [16, 17].

Bone is a target organ for many hormones (PTH, calcitonin, sex hormones, D-hormone, and others) that regulate bone metabolism [18–20]. In addition, it performs an endocrine function, producing at least two hormones, osteocalcin and fibroblast growth factor 23 (FGF23) [21, 22].

Osteoblasts synthesize osteocalcin, the most essential, vitamin K-dependent, and non-collagenous bone protein. Not all the produced osteocalcin is deposited into the bone matrix, some entering the bloodstream. This is the level of circulating osteocalcin, which is the primary marker of bone formation. However, when the bone is destroyed, it is released and enters the blood, but in this case, it will serve as a resorption marker [21, 23].

Osteocytes produce FGF23 and are responsible for phosphorus metabolism. Its main action is to reduce the concentration of P^{3-} in the blood by inhibiting the reabsorption of phosphates and the synthesis of 1,25(OH)2D in the kidneys. Thus, high levels of FGF23 circulating in the blood lead to hypophosphatemia and pathology of the skeletal system, while a deficiency leads to hyperphosphatemia and tissue calcification. However, under physiological conditions, this protein acts according to the body's phosphate needs [24, 25].

Bone tissue, together with the intestines and kidneys, is part of the central systems that maintain a constant calcium concentration in the blood serum [26, 27].

Vitamin D provides bone mineralization by stimulating the absorption of Ca^{2+} in the small intestine and maintaining calcium and phosphate levels in the blood necessary for the body. The lack of 25(OH)D leads to a decrease in the expression of the CALB1 and TRPV6 genes, which contributes to a significant reduction in the absorption of Ca^{2+} and P^{3-} in the intestine (Fig. 1) [27, 28].

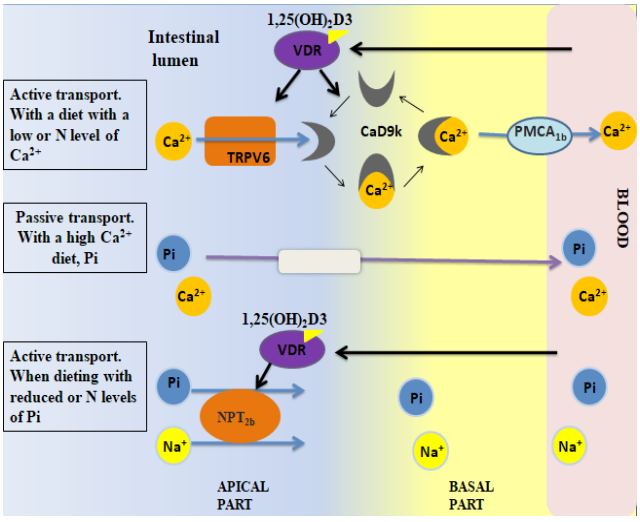

Fig. 1. The role of vitamin D in the active and passive transport of phosphate and calcium in the small intestine [27, 28]

It also takes part in osteosynthesis in another way – through VDR, it directly affects chondrocytes, osteocytes, OB, and OC [28, 29].

OBs are the main target for 1,25(OH)2D [9, 30]. According to studies, these cells can independently synthesize 1,25(OH)2D under the control of interleukin-1b, interferon-γ, and TNF-α [30, 31].

The primary regulator of OB differentiation is Cbfα1, the nuclear binding factor-α1, which regulates genes involved in producing bone proteins such as osteopontin, sialoprotein, type 1 collagen, and osteocalcin [32].

Calcitriol, acting on OB, enhances their secretion of FGF23. In addition, it affects the renal tubules and enhances the production of the Klotho protein [33]. This protein is present in two forms: extracellular (performs an endocrine function in the extracellular space) and membrane (a co-receptor for FGF23, is involved in stimulating renal excretion of phosphates and suppressing the synthesis of 1,25(OH)2D) [34]. Thus, FGF23 is a factor aimed at suppressing the activity of vitamin D by increasing its catabolism due to the inhibition of 1-a-hydroxylase [25, 34].

In utero, 25(OH)D passes from mother to child through the placenta in a facilitated or passive way. From the 24th week of gestation, the fetus in the kidneys begins to metabolize 25(OH)D to 1,25(OH)2D (Fig. 2) [35, 36].

In the postnatal period, the synthesis of 1,25(OH)2D increases, probably due to the need to stimulate intestinal absorption of Ca^{2+} [37]. Due to the immaturity of the expression of 24-hydroxylase CYP24A1, insufficient conversion of vitamin D to the form 24,25(OH)2D is noted in premature newborns. Perhaps due to this, the concentration of 1,25(OH)2D is maintained at a high level, which is necessary for premature babies to develop the skeletal system rapidly [37, 38].

The regulation of phosphorus-calcium homeostasis of PTH in response to hypocalcemia consists in strengthening the intestinal and renal reabsorption of Ca^{2+} and in increasing the excretion of P^{3-} [39]. PTH, stimulating OB, increases RANKL expression, leading to osteoclast differentiation [40]. However, osteoprotegerin (OPG) produced by OB prevents their interaction, which is why the rate of preosteoclast differentiation depends on the RANKL/OPG ratio [41, 42]. As a result of the interaction of RANKL with RANK, transcription factors such as NFATc1 (nuclear factor of activated T-lymphocytes), c-fos, NF-kB, TRAF-6 (the sixth factor associated with the TNF receptor) are activated, which stimulates osteoclastogenesis [43]. PTH regulates the transcription of many genes in osteoblasts. One such gene is Mmp13, which is involved in remodeling and the early stages of endochondral bone formation [44].

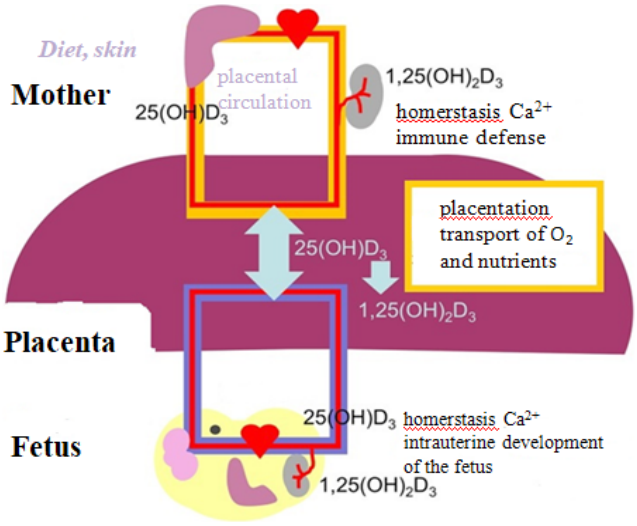

Fig. 2. Placental transport and the role of $25(OH)D_3$ and $1,25(OH)_2D$ in placental function and fetal development [35]

In addition, PTH affects the TC, releasing serum calcium from the bone [45]. In the kidneys, PTH stimulates 1-α-hydroxylase for the synthesis of active vitamin D. However, in premature infants, despite increased PTH synthesis, hypocalcemia may persist for a long time due to incomplete implementation of its effects, as tissues experience transient resistance to this hormone [46–48]. Under normal conditions, bone formation predominates over bone decay, including through the action of PTH, which is aimed at increasing the production of OPG-L on the surface of the OB and suppressing the synthesis of OPG [48, 49].

In turn, calcitonin is the primary antihypercalcemic and hypophosphatemic hormone [50]. In response to an increase in calcium levels above normal, CT in the kidneys reduces the absorption of Ca^{2+} and P^{3-} and in parallel, reduces intestinal absorption, also has a suppressive effect on osteoclasts and, thereby, reduces bone resorption [50, 51]. Premature newborns are characterized by increased secretion of CT due to the need to conserve already reduced calcium stores [46, 49, 51].

The immaturity of renal tissue characteristic of premature children reduces glomerular filtration and leads to impaired reabsorption of phosphates and calcium. This is also a prerequisite for the vulnerability of calcium-phosphorus metabolism, on which adequate bone mineralization depends [52, 53]. The leading role of 25(OH)D in the formation of the skeletal system has been convincingly proven, and the most important mechanisms of the biological effects of vitamin D mediating osteogenesis and bone remodeling have been studied [54–56].

Insufficient intake of calcidiol to the fetus during the prenatal period may disturb the mineralization of bone tissue, further hindering the normal development and formation of the skeleton [57, 58]. Genetically determined mineral density of bone is programmed already in the period of intrauterine growth. Its achievement depends on a sufficient number of endogenous and exogenous factors [59, 60].

Conclusion. Early detection of risk factors and effective prevention of vitamin and mineral deficiency in pregnant women and premature children will significantly reduce the incidence of bone metabolic disease in children. Due to the correlative role of vitamin D, it has a complex effect on skeletal formation and homeostasis maintenance in newborns.

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THERAPEUTIC SCIENTIFIC MEDICAL SCHOOLS OF KUBAN: TO THE QUESTION OF FORMATION AND DEVELOPMENT IN THE FIRST HALF OF THE XX CENTURY

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ТЕРАПЕВТИЧЕСКИЕ НАУЧНЫЕ МЕДИЦИНСКИЕ ШКОЛЫ КУБАНИ: К ВОПРОСУ СТАНОВЛЕНИЯ И РАЗВИТИЯ В ПЕРВОЙ ПОЛОВИНЕ XX ВЕКА

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The article deals with the formation of therapeutic scientific directions and the further development of scientific schools in the Kuban Region in the first half of the 20th century. Historiographic, biographical, problem-chronological, descriptive, and comparative methods are applied within the framework of social and cultural, and axiological approaches. The contribution of professors N. N. Nizhibitsky, K. M. Rutkevich, E. M. Zhadkevich, P. I. Budarina, V. L. Einis, K. A. Patsevich, and others is considered in the implementation of scientific research on a wide range of nosologies related to the clinical course of internal diseases that were widespread among the population at that time. It is revealed that the first half of the 20th century in the Kuban Region was a period of formation of specific areas of research activities in internal diseases. These areas were the forerunners of the building and development of scientific therapeutic schools of the Kuban, as well as the allocation of other independent scientific areas in the framework of introducing new medical specialties.

Keywords: history of Kuban medicine, therapeutic research areas, scientific medical schools, Kuban State Medical University, socio-cultural environment

Рассмотрен процесс формирования терапевтических научных направлений и развития научных школ на Кубани в первой половине XX столетия. Применены историографический, биографический, проблемно-хронологический, описательный и сравнительный методы в рамках социокультурного и аксиологического подходов. Установлен вклад профессоров Н. Н. Нижибицкого, К. М. Руткевича, Е. М. Жадкевича, П. И. Бударина, В. Л. Эйниса, К. А. Пацевича и других в реализацию научных исследований по большому спектру нозологий, относимых к клинике внутренних болезней и широко распространенных среди населения в это время. Установлено, что первая половина XX столетия на Кубани стала периодом формирования в регионе конкретных направлений научно-исследовательской деятельности в области внутренних болезней. Данные направления выступили предшественниками процесса становления и развития научных терапевтических школ Кубани, а также выделения других самостоятельных научных направлений в рамках появления новых медицинских специальностей.

Ключевые слова: история медицины Кубани, терапевтические научные направления, научные медицинские школы, Кубанский государственный медицинский университет, социокультурная среда

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