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The importance of optimal balance of calcium, phosphorus and vitamin D and adequate physical activity during the period of growth and development on bone health

Значај оптималног биланса калцијума, фосфора и витамина Д и адекватне физичке активности током периода раста у развоја на коштано здравље

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Значај оптималног биланса калцијума, фосфора и витамина Д и адекватне физичке активности током периода раста у развоја на коштано здравље

SUMMARY
Bones are mineralized connective tissue that provides to body anti-gravity support, enables movement with the help of muscles, and protects internal organs. Individual skeletal quality, as a result of genetic, hormonal and external factors, such as nutrition, physical activity and others, is achieved during the period of growth and development. Peak bone mass is attained by the end of the second decade of life and is maintained until age 40–50, then gradually decreases without the possibility of rebuilt. It is therefore clear that the lack of adequate bone mass building during the development period, in addition to the immediate consequences, represents a high risk of osteoporosis and its complications in later life, especially in old age. The purpose of this article is to review the importance of optimal calcium, phosphorus and vitamin D balance and adequate physical activity during growth and development in achieving maximizing peak bone mass.
Keywords: bone health; children; adolescents

САЖЕТАК
Кости су минерализовано везивно ткиво које телу пружа антигравитациони ослонац, омогућава кретање уз помоћ мишића и штити унутрашње органе. Индивидуални квалитет скелета, као резултат генетских, хормоналних и спољашњих фактора, као што су исхрана, физичка активност и други, постиже се у периоду раста и развоја. Врхунска коштана маса се постиже крајем друге деценије живота и одржава се до 40–50 године, а затим постепено опада без могућности обнављања. Стога је јасно да изостанак адекватне изградње коштане масе у периоду развоја, поред непосредних последица, представља висок ризик од остеопорозе и њених компликација у каснијем животном добу, посебно позном. Сврха овог чланка је да се сагледа значај оптималног баланса калцијума, фосфора и витамина Д и адекватне физичке активности током раста и развоја у постизању максималне вршне коштане масе.
Кључне речи: коштано здравље; деца; адолесценти

INTRODUCTION

Bones are specialized mineralized and multifunctional connective tissue composed of minerals (60–70%), primarily hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], collagenous and non-collagenous proteins (20–40%), cells (osteoblasts, osteoclasts and osteocytes) and a small portion of water and lipids [1]. Osteoblasts induce the formation of new bone by secreting collagen fibers, which is then mineralized, while osteoclasts dissolve bone by secreting enzymes and acids. Osteocytes arise from osteoblasts after finished secreting matrix. They secrete soluble factors that influence osteoclastic and osteoblastic activity and play a central role in bone remodeling in response to mechanical stress.

According to their formation, structure and function, bones are divided into long, flat, short, irregular and sesamoid. Long bones include bones in the upper and lower limbs, and flat, bones skull, face, thoracic cage and the pelvis. Short bones are present in the wrist and ankle, and the patella as a sesamoid bone within the ligament of the quadriceps femoris muscle.

Long bones, along with short bones and the patella, support the body's weight and enable movement, while flat bones protect internal organs of the head, face, thorax and pelvis [2]. In addition, within the flat bones is red bone marrow [2]. The vertebrae, the irregular bones of the spinal column, support the head, neck, and body, allowing them to move and protecting the spinal cord [2]. In addition, bones are an endocrine organ, reservoir of calcium and phosphorus, and a significant participant in the regulation of acid-base homeostasis of the body [2]. The hormonal role of bone is reflected in the production of fibroblast growth factor-23 (FGF-23), osteocalcin and sclerostin. FGF23, which originates from osteocytes and osteoblasts, enhances renal phosphate excretion directly through inactivation of sodium/phosphate cotransporter (NaPi)-2a and -2c in the proximal tubules and indirectly by suppressing 1,25$(OH)_2D_3$ synthesis and promoting 1,25$(OH)_2D_3$ conversion to inactive 24,25$(OH)_2D_3$ [2, 3, 4]. Osteocalcin, produced by osteoblasts, participates in the regulation of energy metabolism, glucose tolerance, testosterone production and bone resorption, while sclerostin, a product of osteocytes, is a suppressor of osteoblast differentiation [2].

Skeletal quality, as a result of both genetic, hormonal and external factors, such as diet, physical activity and others, is attained by the end of the second decade of life. Peak bone mass achieved during that period is maintained until age 40–50, then bone density gradually irreversibly decreases leading, if not at an adequate level, to various consequences both during that period and later [5–11]. Also, in numerous diseases, both hereditary and acquired, various pathogenetic mechanisms lead to serious disruption of the integrity of the skeletal bone system [3, 12, 13, 14].

The aim of this review is to highlight the importance of meeting optimal calcium, phosphorus and vitamin D needs and maintaining adequate physical activity during growth and development to achieving maximizing peak bone mass as essential components of health both during this period and in later life.

CALCIUM

Calcium is the fifth most abundant element in the human body. It is predominantly (99%) found in the hydroxyapatite of bones and teeth, and only 1% in other tissues [15, 16, 17]. It is present in serum at concentrations of 2.12–2.62 mmol/L, both in ionized and non-ionized form, and in intracellular fluid at 100–200 nmol/L [15, 18]. Calcium homeostasis is carried out at the level of the gastrointestinal tract, kidneys and skeleton under the influence of 1,25$(OH)_2$D and parathyroid hormone (PTH) [15, 16, 19, 20]. A standard diet, with an optimal balance of vitamin D, meets the body's calcium needs [15, 16]. It is most abundant in milk and dairy products, as well as in green leafy vegetables [15, 16]. Calcium is absorbed in the small intestine, mainly by active transport and partly by passive diffusion [15, 16, 20]. The main stimulator of intestinal absorption is 1,25$(OH)_2$D, which induces enterocyte expression of calcium channels, calbindin, $Ca2^+$ATPase (calcium pump), and $3Na^+/Ca2^+$ ion exchangers [16]. The utilization of calcium from food is favorably affected by low chyme pH, lactose, lactic and citric acids, some amino acids PTH, growth hormone, prolactin, estrogen, and insulin-like growth factor, while luminal phosphates, oxalate, phytate, tannin, iron, rapid intestinal transit, glucocorticoids, calcitonin, and fibroblast growth factor-23 (FGF-23) have an unfavorable effect [15, 16, 21]. The main route of elimination of calcium from the body is the kidney. The majority of calcium filtered by the glomerulus is reabsorbed along the nephron, mostly (>60%) from the proximal tubule, so daily calciuria in a healthy child does not exceed 4 mg/kg [16, 20]. A precise insight into the calcium balance in the body is obtained by determining the ratio of calcium to creatinine in the urine (CaUmg/CrUmg), which normally is 0.1–0.2 [15]. Due to low creatinuria, the upper reference value of CaUmg/CrUmg in a child in the first year is higher (up to six months 0.8, and from 6 to 12 months 0.6) [16, 22]. The main stimulators of tubular calcium reabsorption are 1,25$(OH)_2$D and PTH, and the inhibitors are hyperphosphaturia, metabolic acidosis and polyuria [16, 23]. In a state of negative calcium balance, due to insufficient intestinal reabsorption and/or tubular reabsorption, maintenance of its serum and intracellular concentrations is provided by the skeleton [20]. The inducers of this process are PTH and 1,25$(OH)_2$D. [2].

Table 1 shows the recommendation of the Institute of Medicine (USA) for reference intakes of calcium in the diet during the period of growth and development, and Table 2 shows the calcium content in the diet, the percentage of absorption and the net amount absorbed [15, 24].

For children aged 0 to 12 months, the AI is equivalent to the average calcium intake of a healthy and optimally nourished breastfed infant, whereas at age 7–12 mots, the AI assumes 120 mg calcium from human milk plus 140 mg calcium from complementary food, while the RDAs for older children and adolescents are based on intakes associated with bone accumulation and positive calcium balance [15].

As can be seen in Table 2, the calcium content in food and the degree of its absorption are highly variable. Milk, yogurt and cheese are the best sources of calcium [15, 24]. The degree of calcium absorption from breast milk compared to cow's milk, due to the better ratio of calcium to phosphorus (1.7:1 vs 1:1), as well as the higher lactose content (7 g/dl *vs*. 4.7 g/dl), is 2.5 times higher [25, 26]. Phytates and oxalates, present in spinach, cucumber, potatoes and beans, inhibit calcium absorption by forming insoluble calcium salts in the gastrointestinal tract [15]. On the other hand, the bioavailability of calcium from broccoli, kale and cabbage, which do not contain these compounds, is relatively high [15]. However, due to the low utilization in the former case and the low content in the latter, these foods are much weaker sources of calcium compared to milk and dairy products [15, 24]. Therefore, people with lactose intolerance, milk protein allergy, and those who avoid dairy products (including vegans) are at high risk of inadequate calcium intake [27, 28]. The prerequisite for covering the need for calcium, regardless of its origin, is an optimal status of vitamin D [6, 15]. In general, the degree of absorption of calcium is relatively high if its content in food is low, as well as during the period of growth and development, especially in the phases when it is the most intense, i.e. in the first three years after birth and puberty [15]. The recommended daily amount of plain milk, yogurt or sour milk that, along with other standard nutrition, provides an optimal calcium balance for a child in their second year is 500 ml, from 2–8 years 625 ml and from 9–18 years 750 ml [29].

PHODPHORUS

Phosphorus is the sixth most abundant element in the human body. It is mostly found in the hydroxyapatite of bones and teeth, 15–20% in the intracellular space of soft tissues and 1% extracellularly [30, 31]. The intracellular concentration of organic phosphates varies from 5 to 70 mmol/L, and inorganic from 0.7 to > 2 mmol/L [30]. Its concentrations in the extracellular space are 0.8–1.4 mmol/L, about 85% in free form, 10% bound to proteins and 5% in complex with calcium or magnesium [30].

A normal diet for a healthy person meets their phosphorus needs [31, 32]. It is most abundant in protein-rich foods, such as meat, eggs, milk and dairy products, and legumes [31].

Phosphorus absorption is carried out in the small intestine by the active pathway via the $2Na^{+}/HPO42^{-}$ cotransporter (NaPi-2b), whose expression depends on the current needs of the organism and the stimulation of 1,25$(OH)_2$D [4, 31]. It is also partly absorbed paracellularly (passively) [4, 31]. The main regulator of phosphorus homeostasis is the kidney. About 80% of filtered phosphorus at the glomerular level is actively reabsorbed at the proximal tubule level via NaPi-2a and NaPi-2c cotransporters, so its renal clearance is normally only 10.8 ± 2.7 ml/min [4, 30, 31]. The most important stimulator of tubular phosphorus reabsorption is 1,25$(OH)_2$D, and the inhibitors are fibroblast growth factor 23 (FGF-23) and PTH [4, 31, 33].

Considering its high abundance in food, both plant and animal, and the efficient intestinal absorption (50–90%), phosphorus deficiency due to negative nutritional balance as a primary cause of skeletal hypomineralization is rare [32]. It is seen in hyperphosphaturia caused by excess FGF-25, such as X-linked, autosomal dominant and autosomal recessive hypophosphatemic rickets and tumor-induced osteomalacia or due to genetic defects of renal tubular phosphate reabsorption such as hypophosphatemic rickets with hypercalciuria [3, 4, 30, 34]. On the other hand, in calcipenic states, either due to insufficient intake and/or vitamin D deficiency, negative phosphorus balance and accompanying skeletal hypomineralization as a consequence of hyperphosphaturia caused by secondary hyperparathyroidism is a common associated phenomenon [35, 36].

VITAMIN D

Vitamin D, i.e., its active metabolite calcitriol [1,25$(OH)_2$D], is an important factor in calcium and phosphorus homeostasis and bone mineralization. In addition to calcium and phosphorus intestinal absorption and renal reabsorption, calcitriol, by activating the nuclear vitamin D receptor (nVDR), induces the transition of mesenchymal stem cells into mature osteoblasts and their production of type I collagen, osteopontin, osteocalcin and other extracellular bone matrix proteins necessary for the formation and maintenance of bone strength [6, 37]. In parallel with this, also through nVDR calcitriol has a suppressive effect on the differentiation and activation of osteoclasts, osteolytic cells of crucial importance in skeletal modeling, as well as in the removal of old or damaged bone tissue [16, 37]. Thus, the endocrine function of vitamin D is primarily directed to calcium and phosphorus intestinal absorption and renal reabsorption and skeletnu mineralization, except in conditions of hypocalcemia when, together with PTH, it induces osteoclasts in the mobilization of calcium from bones [6, 15, 37, 38].

Most of our vitamin D needs are met by cutaneous photolysis of 7-dehydrocholesterol under the action of sun ultraviolet-B rays of wavelengths 290-315 nm, while foods, excluding fish oil, fatty fish, liver, egg yolks, edible mushrooms treated with UV light, and fortified foods such as milk formulas, are poor sources of vitamin D [15, 38]. Serum 25(OH)D levels, whose half-life in circulation is about 15 days, represent a reliable indicator of vitamin D status in the body [1 = 15; 15]. According to criteria of the Institute of Medicine of the United States of America (IOM), optimal serum 25(OH)D levels considered adequate for bone and overall health in healthy individuals range from 20 ng/ml (50 nmol/L) to 50 ng/ml (125 nmol/L) [15]. A value lower than this causes numerous negative consequences, including optimal bone integrity, while a value over 125 nmol/L, apart from the risk of a toxic effect of vitamin D, has no evidence to support additional health benefits. Associations of the Nordic and DACH countries (Germany, Austria, and Switzerland), Australia and New Zealand, as well as the American Academy of Pediatrics and the Endocrine Society (ES) agree with the IOM guidelines regarding the lower limit of vitamin D adequacy based on serum 25(OH)D concentration [6, 39].

The required and upper levels of vitamin D intake in the absence of optimal sun exposure according to the IOM recommendations are given in table 3 [15]. The European Food Safety Authority and the ES agree with the IOM recommendations, as do the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the American Academy of Pediatrics [6, 40, 41].

PHYSICAL ACTIVITY

It is well known that physical activity with its stimulating effect during childhood and early adulthood plays a vital role in the development and achieved pick bone mass and thus the prevention of osteoporosis and its complications in later life [5, 7–11, 42]. Certainly, in order to preserve the acquired quality of the skeletal system, this practice, along with optimal intake of calcium, phosphorus, protein and other nutritional factors, as well as ensuring an adequate balance of vitamin D, should be continued in other stages of life [43–46].

The World Health Organization (WHO) guidelines on physical activity of children and adolescents are given in the table 4 [47, 48]. Identical recommendations also come from the US Department of Health and Human Services, 2018 [46].

CONCLUSION

Bone mass attained during growth and development is one of the most important determinants of lifelong skeletal health. Peak bone mass, which is attained by the end of the second decade of life, is maintained until age 40-50, and then gradually decreases without the possibility of being rebuilt. Optimal coverage of calcium, phosphorus and vitamin D needs and adequate physical activity during the developmental period are crucial for good bone health both at that age and in later life stages.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

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Table 1. Dietary Reference Intakes of Calcium (mg/d) [15]

Age (male & female)	Estimated average requirement	Recommended dietary allowance	Upper level
0–6 months	–	200 (AI)	1.000
7–12 months	–	260 (AI)	1.500
1–3 years	500	700	2.500
4–8 years	800	1.000	2.500
9–18 years	1.100	1.300	3.000

AI – adequate intake

Table 2. Dietary calcium content, percentage absorption, and net absorbed amount [24]

Type of food	Serving size	Calcium content (mg)	Estimated absorption (%)	Net Calcium absorbed (mg)
Cow milk	250 ml	310	32	100
White beans (cooked)	125 ml	85	22	18
Red beans (cooked)	125 ml	26	24	6
Whole wheat bread slice	35 g	26	82	21
Broccoli (cooked)	125 ml	33	20	20
Spinach (cooked)	125 ml	129	5	7
Almonds (raw, roasted)	60 g	97	21	21
Soy “milk” (unfortified)	125 ml	5	31	2

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Table 3. Dietary reference intakes of vitamin D for children and adolescents [15]

Life stage group (years)	**Recommended dietary allowance (IU/day)**	**Upper-level intake (IU/day)**
0–6 months	400*	1.000
6–12 months	400*	1.500
1–3 years	600	2.500
4–8 years	600	3.000
9–18 years	600	4.000

*adequate intake for infants 0–12 months of age is 400 IU/day

Table 4. World Health Organization guidelines on physical activity of children and adolescents [47, 48]

• Children 1–2 years of age should spend at least 180 minutes in a variety of types of physical activities at any intensity, including moderate-to vigorous-intensity physical activity, spread throughout the day; more is better.
• Children 3–4 years of age should spend at least 180 minutes in a variety of types of physical activities at any intensity, of which at least 60 minutes is moderate- to vigorous- intensity physical activity, spread throughout the day; more is better.
• Children and adolescents (aged 5–17 years) should do at least an average of 60 minutes per day of moderate- to vigorous-intensity, mostly aerobic, physical activity, across the week. Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, should be incorporated at least three days a week.

