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The Practicability of the Application of Vitamin D in Combination with Vitamin K for the Improvement of Bone Tissue Metabolism

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ABSTRACT

This work is dedicated to the explication of practicability of application of vitamin D in combination with vitamin K for the improvement of bone tissue metabolism. Actuality of this work is justified by the growth of number of low energy fractures in patients with osteopenic syndrome caused by the decrease of bone tissue mineral density (BTMD). Silent continuous epidemic of osteoporosis leads to more profound consideration of bone tissue metabolism, looking for application points of pharmacological substances for the prevention and treatment of BTMD. Vitamin D improves the absorption of calcium, increases its excretion by the kidneys, but vitamin K is necessary for following effective inclusion of ions of Calcium into the bone tissue matrix. Gla-protein obtains ability to bind calcium as a result of K-dependent carboxylation thereby maintaining and increasing density of bone tissue. The conclusion based on results of the research can be made about the rationality of combination of vitamin D and vitamin K for positive influence on the bone tissue metabolism and for decline of risk of low energy fractures development in patients with osteopenic syndrome.

Keywords: Vitamin D, Vitamin K, Bone Tissue Mineral Density, Osteocalcin, Bone Tissue Metabolism.

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INTRODUCTION

The decrease of bone tissue mineral density (BTMD) in the group of patients of old age is the important factor of risk for low energy fractures on the basis of osteopenia or osteoporosis. Osteoporosis is the systematic metabolical illness of skeleton characterized by the decrease of bone mass and infraction of microarchitectonics of bone tissue. Osteopenia is characterized by clinical, laboratory and radiological manifestations of bone tissue loss when the index of BTMD is lowered, constituting from 1.0 to 2.5 SD, which is lower than in cases of young representatives of healthy population (T-criteria from 1.0 to 2.5), but which does not reach the level of osteoporosis. Based on the data by the USA National fund of osteoporosis it is known that the osteoporotic fracture can occur to every 3rd woman older than 50, demanding hospitalization, long-term nursing and rehabilitation. In Russian Federation osteoporosis is determined in 34% of women and in 27% of men among the population at age of 50 and older, and the frequencies of osteopenia are 43% and 44% accordingly. The frequency of osteoporosis increases with age [1]. Thus there are 14 mln. people in Russia struggling with the osteoporosis and there are 20 mln. more people with lower BTMD corresponding to osteopenia [2]. An enormous number of factors such as genetic predisposition, style of life, hormone status, presence of comorbid conditions, excessive body mass or obesity, accumulation of combined deficit of microorganisms and vitamins, individual aging rate and lifespan contribute to the decrease of BTMD [3]. The decrease of level of accustomed physical activity with the rate of aging creates conditions for the decrease of general level of metabolism. Also the absence of regular muscular contractions leads to the decrease of microcirculation and lymph circulation as well as to the increase of loss of bone calcium with age.

The insufficiency, deficit of vitamin D representing the pandemia especially, also makes contribution to the decrease of BTMD. It is noted that the prevalence of vitamin D deficit in the group of elderly patients with the presence of osteoporotic syndrome can reach 100% [4]. Statistically significant improvement of bone tissue condition among patients receiving additional vitamin D isn't determined by results of meta-analysis published in 2018. It made us to analyze the metabolism of bone tissue and to look for possible ways of increasing the effectiveness of pharmacotherapy by vitamin D. Preparations of vitamin D are used most often with the preparations of calcium [5]. It is known for a long time that vitamin D is necessary for the maintenance of metabolism of bone tissue and calcium phosphoric exchange throughout whole lifespan. Vitamin D enters the organism in the form of predecessors. Vitamin D2 – ergocalciferol – is formed in cells of plants from ergosterol. Vitamin D2 enters the body with the food, and then it is absorbed in small intestine. The necessary condition for the absorption of vitamin B2 is sufficient quantity of fat in food and the presence of bile which helps to include it in the structure of chylomicrons transporting it by the lymphatic system into the venous bloodstream. The disorder of secretion and bile excretion during illnesses of liver and biliary tracts makes absorption of vitamin D in the intestines significantly difficult. Cholecalciferol (Vitamin D3) is synthesized in skin under the influence of ultraviolet rays as a result of non-enzymatic reaction of photolysis dependent on ultraviolet light with the length of wave from 290 to 315 nm. Predecessors of Vitamin D are also contained in fat kinds of fish (salmon, mackerel, herring), mushrooms, nettle, parsley and some sorts of animal origin (egg yolk, liver, creamy butter, cheese, cottage cheese). Cholecalciferol vitamin D3 in the form of chylomicrons is transported to the liver for the transformation into the biologically active form and for

subsequent hydroxylation in the position 25. As a result, 25-OH of vitamin D is formed, and subsequently hydroxylation takes place in kidneys with the formation of active metabolite 1.25(OH)2D. The absorption of 30-40% of calcium takes place in small intestine with normal concentration of vitamin D provided, while in the condition of deficit only 10-15% are absorbed [6].

The role of calcium in the organism is difficult to overestimate. Its distribution is not even: about 99% is deposited in bone tissue and only 1% is contained in other issues. But this 1% has vital significance. The level of calcium in blood has to be held in strict limits (Normative values 2,3-2,8 mmol/l0 [7]. Ion of Ca^{2+} serves as one of the most important intracellular signal factors. The sustenance of necessary concentration of calcium in cytoplasm of cells of different types is provided by the work of membrane enzymes – Ca-ATPase or Ca2+pumps of plasmatic membrane and sarcoplasmic reticulum which are able to transport two ions of Ca2+ through membrane against its concentration gradient due to the hydrolysis of one molecule of ATP and also to the work of systemic Na+/Ca2+-exchange [8]. Calcium is necessary for the realization of intercellular contacts, the functioning of cell membranes, transfer of neural impulse and muscular contraction, regulation of heartbeat. Calcium demonstrates expressive anti-inflammatory and antiallergenic effect, increases sensibility of central nervous system, enhances effect of vasopressin, which regulates the tone of blood vessels. The decrease of intracellular calcium in cells of blood vessel's wall leads to the decrease of vessel's tone. Calcium is the component of cascading mechanism of blood coagulation. Calcium in the form of mineral hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ gives strength to the bone tissue, which is one of types of connective tissue [9]. Bone tissue plays role of calcium depot in the organism. Calcium itself is faintly absorbed in small intestine. The influence of bile acids and hydrochloric acid in sufficient quantity is necessary for the conversion of calcium into more digestible condition. The malapsorbtion in small intestine can be caused by such diseases as atrophic gastritis, enteritis, disorder of secretory function of the pancreas, diseases' of biliary tracts, htpatitis, and cirrhosis of the live. The presence in food of large number of saturated fatty acids that can be found in lamb and beef meat and cooking fats also leads to the disorder of calcium absorption. Unsaturated fatty acids and magnium and phosphorus contained in them in relevant numbers improve absorption of calcium [10]. Organic salts namely calcium citrate and calcium malate are considered to be more bio accessible, nonorganic salts namely calcium carbonate and calcium gluconate are considered less bio accessible. It is generally known that parathyroid hormone, calcitonin, and metabolites of vitamin D influence the exchange of calcium. But recent researches determined the influence of one more additional factor of exchange processes of bone tissue, namely vitamin K.

GOAL

To conduct an analysis of Russian and foreign literature sources concerning the influence of vitamin K on bone tissue metabolism, including cases of patients with osteopenia syndrome.

RESULTS AND DISCUSSION

Vitamin K.

Vitamins are the group of organic compounds with low molecular weight that can't be synthesized by human's organism at all or can be synthesized by the intestine's microflora in limited quantities. Vitamins don't realize structural function and realize its effect through the involvement in the catalysis as conferment or as compounds that control the enzymes activity and their production.

Vitamin K – is the name of the group of lipophilic (fat soluble) and hydrophobic vitamins. In 1920s Carl Peter Henrik Dam, biochemist and physiologist from Denmark, was performing the research of cholesterol that had been discovered by him. Henrik Dam completely deprived laboratory chicken of fats, i.e. deprived of cholesterol for the determination of its biological role. Hemorrhages started to appear in tissues of animals after several weeks of experiment and insignificant wounds led to mortal bleeding. The scientist tried to give to one group of chicken the purified cholesterol but that didn't save from mortal loss of blood. Directly proportional and dose dependent positive effect was achieved by the feeding of chicken with dried spinach. As a result the conclusion was made about the existence of fat soluble substance that is necessary for normal progress of processes of blood coagulation. Henrik Dam called this compound koagulationsvitamin – "vitamin for coagulation" [11]. Almost at the same time Edward Adelbert Doisy, American biochemist, faced the same phenomenon of hemorrhage during the lack of fats. He was able to help chicken adding rotten fish instead of spinach to the food. Fresh food didn't cause any healing effect. This fact allowed making a conclusion that vitamin K can be produced by some bacteria in the process of their life activity. In 1939 Edward Doisy received vitamin K in its pure form and deciphered the structure of its molecule. In 1943, in the midst of the Second World War, the Nobel Committee awarded Edward Doisy with Nobel Medicine Prize for the research and discovery of vitamin K. After that, vitamin K was considered only the factor of coagulation for a long time.

Two general representatives of this group are distinguished. These are vitamin K1 (phylloquinone), which is met in leafy green plants, and vitamin K2 (menaquinone), which is endogenously synthesized by intestinal bacteria. Vitamin K2 (menaquinone) belongs to the group of chemical compounds that have naphtoquinone ring and lateral chain of different length. The chemical formula of K2 vitamin is MK_n (from MK-2 to MK-14), where "n" is the quantity of remaining chains of isoprenoid. Although the majority of these isoprene residues are desaturated, some forms of menaquinone produced by bacteria have saturated prenyl links [12]. Small amount of MK-4 is found in products of animal origin such as eggs, meat and liver. MK with long chain such as MK-7, MK-9 can be found in fermented food products. These MK are bacterial products that are contained in fermented products [13]. But in modern realities it is not reasonable to rely on the complete coverage of organism' daily need in vitamin K by its own microflora's production. Small intestine, where the absorption of fat soluble substances is highly limited, is the main place of vital activity of vitamin K-producing microflora. Also the productive potential of micrbiota can be lowered by the wide usage of antibiotics in population, insufficiently various food

rations, fiber depleted but abundant with carbohydrates. Vitamin K acts as a cofactor to -glutamyl carboxylase (GGCX), thus the biochemical role of vitamin K is in the carboxylation provision of residue of glutamic acid's proteins. As a result, these proteins (K-dependent proteins) obtain the ability to bind calcium [14]. There are 16 vitamin K-dependent proteins found in the organism of human (Gla-proteins) [15]. Osteocalcin, bone (matrix) Gla-protein (bone-Gla-protein, BGP), is one of these proteins. It is main noncollagenous protein of extracellular bone matrix and consists of 49 amino acids with summarized mass of 5800Da being predominantly secreted by osteoblasts and odontoblasts. Continued metabolical processes and remodeling take place in bone tissue as well as in any other.

Continuous metabolic processes and renovation take place in bone tissue as well as in every other organ. The continuous metabolism and renovation of bone tissue structure are both provided by coordinated effect of osteoblasts and osteoclasts. All processes of mineralization and resorption of bone tissue are balanced in grown up healthy man under 40 years old. The positive calcium balance is observed among children before definitive calcification. The negative calcium balance is observed after 40 years old. As a result of work of osteoclasts old bone beams and mineralized bone are leased, and the bone matrix stays unchanged. Subsequently osteolblasts begin work in this place. Osteoblasts are young bone-forming cells which are differentiated from mesenchymal stem cells. Two main factors of differentiation of osteoblasts are RUNX-2 and core-binding factor alpha-1 (CBFA1). Osteoblats synthesize intercellular substance – the matrix. As the intercellular substance is accumulated osteoblasts are walled up in it becoming osteocytes in the result of the final stage of differentiation. The effective work of osteocalcin is necessary for the formation bone matrix and its strengthening. Transcription and translation of osteocalcin gene are regulated by 1,25 $(OH)_2 D_3$ [16], but its ability to bind with ions of calcium is dependent on vitamin K which answers for γ-carboxylation of three residues of glutamic acid in positions 17, 21 and 24 of OC molecule [17]. Thus carboxylated osteocalcin is metabolically active form. In absence of bone ostocalcin's carboxylation during the deficit or lack of vitamin K, uncaborxylated osteocalcin is accumulated and calcium can't adjoin the bone matrix, and as a result BTMD decreases [18]. Thus, calcium stays in bloodstream. But the necessity for sustenance of constant of calcium level in blood blocks reabsorption of calium in renal canals which leads to the increase of calcium excretion with urine.

Matrix Gla-protein (MGP) is another K-dependent protein that has opposite effect and takes part in the inhibition of vessel's calcification. MGP is represented by small secretory protein (14 kDa) which is primarily secreted by cells of smooth muscles of blood vessels in the arterial wall. MGP contains five residues of glutamic acid, that need carboxylation to be activated and execute their function of calcification's inhibition. This stage of carboxilation is also vitamin K-dependent post-translation reaction. Through peripheral distribution in low density lipoproteins, VK2 exercises its effect by activating various VKDPs including the soft-tissue calcification inhibitor MGP [19]. The accumulation of uncarboxylated matrix Gla protein occurs in the condition of vitamin K deficit, which leads to the adjoining of calcium that was unable to take part in bone tissue metabolism and has not yet been excreted with urine or excrement. The role of prescription drugs namely Vitamin K's antagonists such as Warfarin of coumarin's line in the acceleration of atherosclerotic calcification and in the evocation of vulnerable plaques phenotype has already been shown by a number of researches [20].

CONCLUSION

It is important to note that considering worldwide significance of osteopenia and osteoporosis problem the complex approach to the prevention of bone tissue mineral density decrease is necessary. The special place in this matter is taken by individual and group work with patients of risk groups and people of old age with the purpose of healthy habits formation, lifestyle change, and low phusical activity and sarcopenia prophylactics. The control of normal functioning of gastrointestinal tract and various food rations is also important. But provided data shows practicability of influence on all chains of calcium exchange with the purpose of bone tissue metabolism improvement. Vitamin K is not only the agent that not influences BTMB increase but it is also factor influencing decrease of the calcification of arterial type blood vessels, which is independent risk factor of cardiovascular complications.

All aforesaid lets making the conclusion about the rationality of combination of vitamin D and vitamin K for effective prevention of BTMD decrease, for decline of risk of low energy fractures development and also for complement of complex of rehabilitating measures among patients with osteopenic syndrome.

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