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O.I. Nishkumay[1], Mike K.S. Chan[2], Yu.I. Nalapko[2], H.V. Mostbauer[1], O.O. Alekseenko[1], O.D. Nikitin[1], I.A. Kordubailo[1]

[1]Bogomolets National Medical University, Kyiv, Ukraine

[2]European Wellness Academy, Edenkoben, Germany

Osteoporosis, arterial calcification, and kidney stone disease: modern anti-aging modalities (literature review)

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Abstract. ***Background.*** The problem of osteoporosis as well as a cardiovascular disease remains one of the leading in the statistics of morbidity and mortality due to the aging of the population throughout the world. Recent publications accentuate the new viewpoint to an association of this statistic with the mechanism of the "calcium paradox". These processes can have common risk factors when endothelial cells of different organs have been modified to osteoblasts-like bone cells and become intensive capture calcium crystals. This pathological process results in bone and vessel fragility and nephrocalcinosis. This pathogenesis is complex and common but not fully understood mechanisms. ***The purpose*** was to analyze the current literature data on reasons and molecular mechanisms of bone remodeling and vascular calcification according to a literature review over the past 5 years. ***Materials and methods.*** An analytical review of literature data was conducted using the information analysis of Medline (PubMed), Web of Science and Scopus databases, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) for 2018–2023 using the keywords "osteoporosis", "atherosclerosis", "vascular calcification", "stem cells", "exosomes", "kidney stones diseases". ***Results.*** The literature analysis underlines the multiplay pathogenetic mechanisms as common lifestyle risk factors (calcium and vitamin D, K_2 deficiency smoking), as an osteosarcopenia, immunoaging, and stem cell senescence. ***Conclusions.*** In order to solve the problem prevention of the "calcium paradox", it is necessary to access the correction of multiple mechanisms: calcium and vitamin D, K_2 deficiency, reasons causing secondary hyperparathyroidism, falling, osteosarcopenia, immunoaging, and senescence of stem cells, microRNA and exosomes. A new understanding of the problem opens up opportunities for influencing all the known links and new perspectives of treatment.

Keywords: arterial calcification; osteoporosis; osteopontin; stem cells; exosomes; kidney stone disease

Introduction

Osteoporosis remains one of the leading causes in the statistics of morbidity and mortality due to the aging of the population throughout the world [1]. A progressive decrease in bone mineral density (BMD) is more typical for postmenopausal women [2]. Men aged 65 years and older also have a decreased BMD. However, in recent years there has also been an increase in cases of secondary osteoporosis due to the influence of concomitant pathologies and drugs on the state of bone tissue. For example, COVID-19, rheumatic diseases, etc. were associated with the intake of glucocorticoids and other drugs [3]. Another problem of poor compliance in the prevention and treatment of osteoporosis is the inadequate intake of calcium supplements and calcium-containing foods. According to statistics, many such patients have calcium and vitamin D deficiency [4]. The problem of insufficient calcium intake is exacerbated by the fear of both patients and doctors of the possible side effect of calcium preparations, such as vascular calcification (VC), and the occurrence of urolithiasis. Indeed, the aging of the body is accompanied not only by the fragility of the bones but also by a decrease in the elasticity of blood vessels. Increased vascular stiffness is one of the factors of poor cardiovascular prognosis as well as the progression of chronic kidney disease in the presence of urolithiasis [5]. Unfortunately, both morbidity and mortality due to cardiovascular

Для кореспонденції: Нішкумай Ольга Іванівна, доктор медичних наук, професор кафедри внутрішньої медицини № 2, Національний медичний університет імені О.О. Богомольця, бульв. Т. Шевченка, 13, м. Київ, 01601, Україна; e-mail: nishkumay@ukr.net; тел.: +380509178460

For correspondence: Nishkumay O.I., MD, PhD, Professor of the Internal Medicine Department 2, Bogomolets National Medical University, Shevchenko boulevard, 13, Kyiv, 01601, Ukraine; nishkumay@ukr.net; tel.: +380509178460

Full list of authors' information is available at the end of the article.

diseases (CVD) are progressively increasing [6]. Recent publications increasingly point to an association between bone loss and vascular calcification [7–9].

Thus, understanding the reasons, including molecular mechanisms of the occurrence of pathological extraosseous calcification is very important for the prevention of both bone mineral density and cardiovascular and renal diseases.

The purpose was to analyze the current literature data on reasons and molecular mechanisms of bone remodeling and vascular calcification according to a literature review over the past 5 years.

Materials and methods

An analytical review of literature data was conducted using the information analysis of Medline (PubMed), Web of Science and Scopus databases, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) for 2018–2023 using the key words "osteoporosis", "atherosclerosis", "vascular calcification", "stem cells", "exosomes", "kidney stone disease".

Risk factors for osteoporosis and vascular calcification

The risk factors for osteoporosis and vascular calcification are very similar. ***Aging*** is a common cause that leads to loss of bone density, and degenerative changes in valves and blood vessels. Bone tissue aging begins with the mechanisms of senescence of stem cells. That is why an impaired capability of osteogenic differentiation, senescence of mesenchymal stem cells (MSCs), genetic (expression of osteoporosis-associated genes runt-related transcription factor 2 (RUNX2), lipoprotein receptor-related protein 5 (LRP5), collagen type 1 alpha 1) and microenvironment imbalance and disordered immunoregulation also promote OP [10]. As markers of vascular aging, both medial and intimal calcification as a progression of atherosclerosis (plaque calcification) should be noticed. Perhaps, taking into account the simultaneous aging of both bone tissue and the vascular wall, there are common pathogenetic links. Observational studies reported an association between vitamin D deficiency and OP risk, hypertension, atherosclerosis, and heart failure [11]. That is why fracture prevention and improvement of vascular elasticity can be achieved by vitamin D correction [12]. In general, scientists study the mechanism of simultaneous aging of bones and blood vessels in order to prevent the deterioration of two pathogenetic processes by the minimal amount of drugs.

The goal of ***cardiovascular risk prevention*** is to minimize the occurrence of myocardial infarction, stroke, and cardiovascular death by assessment of the patient's risk factors [13].

However, in the prevention of osteoporosis, the most important thing is the ***prevention of fractures***, and not just the increase in bone mineral density. Statistical data show that the presence of a fracture of the radius increases the risk of subsequent fractures by 2 times, while vertebral fractures by 5 times, and the neck of the femur in 2 times increases the risk of death. Therefore, prevention of falls is the prominent goal. Bone fractures lead to immobilization of patients, which also complicates the clinical course of cardiovascular pathology. It leads to pulmonary embolism, progression of heart failure, and eventually death [14, 15].

The increased risk of falls, especially in the elderly, may be caused by several reasons. One of them is a decrease in the strength and amount of muscle mass, the so-called sarcopenia [16]. It is also important to decline cognitive and mental functions. In total, it increases the risk of falls and consequently, the risk of fractures. Another important risk factor for fractures is increased bone fragility. It may be due to a decrease in both bone mineral density and bone mineralization and its quality [17]. Bone mineralization is greatly influenced by both calcium and vitamin D deficiency. Both mechanisms may be associated with the development of hyperparathyroidism. Also, hyperparathyroidism, both primary and secondary, contributes to progressive vascular calcification [18].

Genetic predisposition is an important unmodified risk factor for both osteoporosis and CVD. Therefore, when interviewing the patient, we have to pay attention both to the history of fractures in relatives (especially the femoral neck), and past heart attacks and strokes [19, 20].

Insufficient intake of calcium and vitamin D. As mentioned above, low calcium intake is the basis for bone density deficiency. Numerous studies confirm an increase in vascular calcification due to the occurrence of secondary hyperparathyroidism as a cause of calcium and vitamin D deficiency [21–23]. Some observational and clinical trials of calcium supplementation have suggested to be potential for cardiovascular harm. Therefore, calcium supplementation is used cautiously, striving for recommended intake of calcium predominantly from food sources. Currently, the available evidence demonstrates that vitamin D and calcium supplements are not harmful to cardiovascular health [24]. Based on the results of a recent meta-analysis conducted in 2010, 15 studies showed that calcium supplementation without vitamin D was associated with an increased risk of myocardial infarction (relative risk (RR) = 1.27; 95% confidential interval (CI): 1.01–1.59; p = 0.038). A non-significant increase in the risk of stroke was also found (RR = 1.20; 95% CI: 0.96–1.50; p = 0.11), early death (RR = 1.18; 95% CI 1.00–1.39; p = 0.057) and global risk of death (hazard ratio = 1.09; 95% CI 0.96–1.23; p = 0.18). But, it should be noted that in 13 of these 15 studies, calcium preparations were used as monotherapy compared with the placebo group. Only one study compared calcium monotherapy with combination therapy (calcium and vitamin D). This does not give grounds to extrapolate the results of a study on calcium monotherapy to its combined intake with vitamin D [25].

Estrogen deficiency is the main cause of postmenopausal osteoporosis in women since normal estrogen levels have a protective effect on the cycle and speed of bone remodeling [26]. A normal level of estrogen is also a protection against the development of atherosclerotic damage to the intima of the arteries [27]. It is a well-known fact that a fertile woman is less susceptible to the development of cardiovascular disease. In menopause, the CVD incidence reaches the same level as men due to dyslipidemia [28]. However, taking into

account the cardiovascular risk, hormone replacement therapy (HRT) in menopause is recommended in case of significant severity of menopausal syndrome with a low risk of venous thromboembolism. According to the recommendations of the International Menopause Society 2016, HRT is indicated taking into account the patient's age and/or time after menopause, the presence of comorbidities. HRT, which is recognized on time, can reduce all-cause mortality and cardiovascular disease. Even more than other methods of primary prevention of cardiovascular diseases, such as lipid-lowering therapy. Complications associated with HRT are rare in this case (< 10 events/10,000 women), and are comparable with other medications. Hormone replacement therapy is a sex-specific and time-dependent primary CVD prevention therapy that concomitantly reduces all-cause mortality, as well as other aging-related diseases with assessment of risk. And prevention strategies must be personalized [29, 30].

Smoking, alcohol abuse, obesity, sedentary lifestyle are common risk factors for both osteoporosis and cardiovascular disease, with increased osteoclasts activity and a rise the myocardial infarction. Stroke also occurs due to endothelial dysfunction [31–34].

Male gender and *hypertension* are known risk factors for coronary events and death. Although studies have recently been published that an increase in blood pressure is associated with a decrease in BMD [35, 36].

Thus, the association of bone fragility and vascular calcification can be called the "calcium paradox" [37]. Understanding the reasons for the loss of calcium compounds by bone tissue and their increased uptake and accumulation by endothelial cells and vascular media is the actual problem. Since the interruption of the activation pathways of this process can contribute to both improving the condition of bone tissue, and elasticity and blood vessels. What we need to know in this complex mechanism?

First of all, we should understand the principles for diagnosing osteoporosis. It is based on the evaluation of the T-score by X-ray absorptiometry of BMD of lumbar vertebrae and the femoral necks. According to the World Health Organization (WHO) definition, menopausal women, men aged more the 65 years old with a T-score less than –2.5 standard deviation (SD) value are diagnosed as having OP. T-score of –1 to –2.5 SD of the value is categorized as having osteopenia. Normal BMD is evaluated in T-score more than –1 SD. Also, the WHO Fracture Risk Assessment Tool (FRAX) is considered to be efficient in estimating the risk of fracture [38].

The pathogenesis of OP is based on the decreased bone density as a result of the imbalance between the bone formation by osteoblasts and bone resorption due to osteoclast over-activity. As a result, the bone becomes brittle due to decreased mineral density. Also, the degree of mineralization of the bone is of great importance. This process is largely affected by calcium and vitamin D deficiency, as well as secondary hyperparathyroidism, which occurs as a consequence. Impaired mineralization also leads to reduced bone quality. This can be determined using the densitometry (trabecular bone score) [39]. However, the trigger for the violation of the structure and quality of bone tissue construction, as well as aging, can be due to the senescence of the mesenchymal stem cells.

The bone life starts from the osteogenic differentiation of MSCs, while the multipotent bone marrow stem cell is able to differentiate into osteoblasts, adipocytes, myocytes, or chondrocytes under the influence of a large number of immune intra- and extracellular regulators. Activation of factors such as RUNX2, and osterix, promote the osteoblasts proliferation of MSCs. The antagonist of osteoblast formation is peroxisome proliferator-activated receptor gamma. Such activation can shift osteogenesis to adipocyte formation. It is known that the main senescence of the osteogenic differentiation capacity of MSCs, which is one of the reasons for osteoporosis is the increasing activity of adipogenesis. The bone morphogenetic protein 2 (BMP) signaling pathway is generally acknowledged to play an important role in regulating the adipogenic and osteogenic differentiation of MSCs in the direction of osteoblast formation. Production of the type I collagen-deficient extracellular matrix also causes adipogenic differentiation [40].

The osteoclasts formation occurs from another precursor — hematopoietic stem cells — monocytes and macrophages. One of the ways of osteoclastogenesis starts with osteoblasts expression of receptor activator of nuclear factor kappa B ligand (RANKL) [41]. Being banded with its receptor, osteoprotegerin (OPG) as the natural inhibitor of RANKL reduces the osteoclasts activity. OPG is synthesized in various organs, including bones, heart, arteries, lungs, kidneys, and intestine. OPG binds with a soluble substrate of RANKL and prevents the formation of osteoclasts and bone resorption by inhibiting the interaction of RANKL-RANK receptors [42]. OPG inhibits the extensive calcifications of the aortic, carotid, femoral, mesenteric, hepatic, and renal arteries induced by treatment with warfarin or toxic doses of vitamin D [43]. Patients with osteoporosis, as with vascular calcification, have a lower OPG/RANKL ratio [44].

The mechanisms of vascular calcification

Regarding VC, it must be clarified that there are 3 main types: intimal calcification (most common for atherosclerotic damage), medial (kidney disease, hyperparathyroidism), and valvular calcification. Each species has its own pathogenic mechanisms of development and disease. For example, intimal calcification is more characteristic of an atherosclerotic process. Medial is typical for chronic kidney disease and hyperparathyroidism. Valve calcification is due to common factors, which we will discuss below [45].

Arterial stiffness increases during senescence [46] and in various pathological conditions, including obesity, diabetes, smoking, and dyslipidemia [47]. It reflects the health of the cardiovascular system. Increased stiffness of arteries contributes to hypertension, especially its isolated form, which is characterized by an increase in pulse pressure. Also, the increase in arterial stiffness reduces the coronary perfusion pressure and increases the afterload of the left ventricle, contributing to its remodeling and dysfunction [48]. Finally, high pulse pressure deteriorates the microcirculation of target organs, such as the kidneys and brain, while the paren-

chyma of such organs is exposed to high blood pressure and mechanical stress [49].

The main reason for vascular calcification, as well as the reason for OP development, is the imbalance between calcification inhibitors and their promoters. Calcification promoters activation are RANKL, Wnt ways, mitochondrial dysfunction, hyperparathyroidism, vitamin D and calcium deficiency, hypercalcemia, genes RUNX2, and low-density lipoproteins (LDL). Also, the VC can be induced due to decreases activity of calcification inhibitors, like Wnt inhibitor, osteopontin (OPN), OPG, fetuine, high-density lipoproteins (HDL), Klotho, BMP, fibroblast growth factor (FGF), matrix Gla protein (MGP), etc. [50, 51].

Inflammation plays an important role in various mechanisms of pathological calcification, as for vascular calcification so for kidney stones (KS) formation. One of the common mechanisms of VC, KS, and OP can be immune system influence through the activation of pro-inflammatory cytokines IL6, IL8, and OPG/RANK/RANKL system [52]. Chronic inflammation inducts stems to macrophages activation and provides osteoblastic transformation of vascular cells, including smooth muscle cells (SMCs) by tumor necrosis factor α and nuclear factor kappa B (an amplifier of the light chain of activated B cells) to activate the atherosclerosis development [53]. These mechanisms by which lipoproteins are taken up by MSCs mediate phenotypic switches toward the development of atherosclerosis and intimal calcification in the final stage [54]. The mechanism of interaction between low-density lipoproteins, which are pro-atherogenic lipids, and the Wnt/β-catenin calcification signaling pathway is known.

The Wnt/β-catenin is an intracellular signaling pathway that plays a key role in bone formation, regulating osteoblast activity. The phenomenon of vascular calcification means the conversion of the vascular smooth muscle cells (VSMCs) to an "osteoblast-like" phenotype when the process of mineralization takes place in the vessel [55]. Activation of Wnt/β-catenin pathway based on the Wnt ligand binding with their receptors, frizzled and LRP5/6 inactivating the glycogen synthase kinase 3 stabilizes β-catenin in the cytoplasm making possible their translocation into the nucleus and initiate the transcription of bone-forming genes. This regulates the pre-osteoblast differentiation through RUNX2 or/and OX induction. Inhibitors are able to block the Wnt/β-catenin pathway and decrease the osteoblast differentiation and activity, which will lead to loss of bone density.

The relationship between bone fragility and LDL was also proven in the experimental study. Hypercholesterolemia increased the fragility of the bones of experimental animals due to the disruption of mineralization processes [56].

A new receptor has recently been identified that can activate the "calcium paradox". It is the RANKL-receptors leucine-rich repeat-containing G-protein-receptor 4 (LGR4), also called G-protein-coupled receptor (GPR) 48. It is provided through RANKL-driven inhibition of osteoclastogenesis and the promotion of vascular calcification [57]. This receptor overexpression leads to increased responsibility for high parathyroid hormone (PTH) in uremic rats. *In vitro*, the silencing of the LGR4 gene in VSMCs was capable to prevent PTH-induced vascular calcification without changes in RANKL and OPG expression [58].

Metabolic disturbances in parathyroid hormone are also important in the pathological vascular calcification. Also, parathyroid hormone, phosphorus (P), calcium (Ca), FGF23, calcidiol, calcitriol and Klotho are involved in the processes of pathological calcification. This occurs through interaction with the RANK/RANKL/OPG system and Wnt/β-catenin. It is more typical in chronic kidney disease (CKD) [59].

Parathyroid hormone has an osteoblasts potential effect. The elevated level of PTH inhibits sclerostin and other Wnt/β-catenin pathway inhibitors. It also has a direct inhibitory effect on the Wnt/β-catenin pathway in osteoblasts through the induction of DKK (Wnt inhibitor Dickkopf protein) [60–62]. In particular, DKK3 is released by "stressed" tubular epithelial cells; DKK3 drives kidney fibrosis and is associated with a short-term risk of CKD progression and acute kidney injury. Thus, targeting the Wnt-β-catenin pathway might represent a promising therapeutic strategy in kidney injury and associated complications [63]. The effect of sclerostin on vascular calcification is controversial. Some studies show that its decrease is associated with an increase in calcification. Others — that with a decrease in its fraction isolated from the vessels, calcification also increases. A meta-analysis of randomized controlled trials found that the new osteoporosis drug romosozumab, which is an antibody that blocks sclerostin, does not significantly increase the risk of serious cardiovascular events (RR = 1.14; 95% CI: 0.83–1.57; p = 0.54) or cardiovascular death (RR = 0.92; 95% CI: 0.53–1.59; p = 0.71) [64].

The soluble Klotho is the antagonist of Wnt/β-catenin pathway activation through proteins interactions between him and extracellular activators of the Wnt/β-catenin pathway. In CKD, the loss of kidney function causes the reduction of renal Klotho gene expression. As Klotho depresses renal calcitriol production, its reduction could influence osteodystrophy in CKD patients, acting through the complex PTH-calcitriol-FGF23 axis modulating through a direct protein-protein mechanism. The interaction between the vitamin D receptor and β-catenin promotes the VC [65]. This mechanism is possibly related to vitamin D metabolism abnormality. It is known that vitamin D deficiency is an important risk factor for the development of not only metabolic diseases of bone tissue, but also hypertension, obesity, diabetes, and its additional intake can significantly reduce the frequency of heart attacks — vascular events [66]. The key link of these processes is probably the violation of the formation of the active metabolite of vitamin D. The kidneys are the target organs in hypertension. And when they are damaged, the synthesis of 1α-hydroxylase, the enzyme that helps 25-hydroxycholecalciferol ($25(OH)D_3$, calcidiol) in the kidneys is transformed into the active form of vitamin D_3 — 1,25 dihydroxycholecalciferol ($1,25(OH)_2D_3$, calcitriol — D-hormone) is destroyed [67].

Due to a deficiency of D-hormone, hypocalcemia develops. It leads to the development of secondary hyperparathyroidism, increasing the rate of bone tissue resorption. This increases the release of calcium from the depot and increases its absorption in the intestine and its entry into the

vessels. This mechanism provokes atherocalcinosis, as a kidney stone disease [68].

There is another mechanism for the formation of kidney stones. It involves OPN. Osteopontin mainly presents in the descending limb cells of the loop of Henle, in the papillary surface epithelium of the calyx. The trigger for OPN expression and stone formation is hyperoxaluria. After deposition of calcium oxalate crystals, OPN expression can be detected also in proximal tubules [69]. Osteopontin is a proinflammatory chemokine of the monocyte family (Kleinman et al., 1995). Damage to kidney cells produces the release of large amounts of OPN. It activates monocyte chemotaxis in the kidney and induces monocyte macrophages to differentiate into the pro-inflammatory M1 phenotype, leading to renal fibrosis. This is one of the many pathological mechanisms of nephrolithiasis. It is based on Randall's theory of plaque formation (calcified plaques that form on the surface of the renal papilla). This happens at the base of the thin legs of the loop of Henle on the surface of the renal papilla [70]. In experimental animal studies, crystal deposition in the kidney has been associated with oxidative stress, activation of inflammation, and increased expression of OPN molecules [71]. OPN is a secreted matricellular protein, that contains a calcium-binding domain and multiple phosphate sites. In acute and chronic inflammatory cytokine signals through integrin and CD44 receptors. It is very interesting different forecasts. For example, in an acute increase, it can attenuate vascular calcification, and promote postischemic neovascularization. In contrast, chronic increases in OPN are clinically associated with an increased risk for a major adverse cardiovascular event. That is why OPN expression is a strong predictor of cardiovascular disease independent of traditional risk factors [72]. Recent data have shown that only phosphorylated OPN can inhibit vascular calcification and promotes dissolution in cultured human vascular smooth muscle cells VSMCs. Moreover, in the absence of OPN, electrostatic repulsion and probably protein alignment increase. The distance between the filaments becomes larger and this leads to a decrease in stability and destruction. Recently, the influence of oxidized LDL in the promotion of proliferation and migration of human coronary artery SMCs via upregulation of OPN and matrix metalloproteinases was revealed [73].

Ectopic calcification is also associated with impaired metabolism of two vitamin K-dependent proteins: osteocalcin (bone Gla protein) and Gla matrix protein (MGP). Osteocalcin and MGP are highly expressed in skeletal tissue. Osteocalcin is specifically expressed by osteoblasts. MGP is expressed in chondrocytes, as well as in vascular smooth muscle cells and epithelial cells [74]. Thus, increased expression of osteocalcin is a negative regulator of bone formation, while MGP has been shown to be an inhibitor of tissue calcification.

Vitamin K belongs to the group of fat-soluble vitamins. In 1929, it was discovered by the Danish biochemist Henrik Dam as a food component necessary for blood clotting [75]. Vitamin K comes in two forms — vitamin K_1 and K_2 [76]. Previously, vitamin K was best known for its key role in blood clotting. In recent decades, many different physiological functions have been discovered. Vitamin K has been found to play a significant role in cell growth and proliferation, apoptosis, oxidative stress, inflammation, and calcification. Vitamin K deficiency is linked to increased risk of cancer and heart disease [77]. Surprisingly, however, a recent study suggests that increased intake of vitamin K_2 may be associated with an increased risk of breast cancer and mortality in breast cancer patients [78].

The three forms of vitamin K differ inside chains and share a common naphthoquinone group. Vitamin K_3 does not have a hydrocarbon side chain and is therefore water soluble. In contrast, vitamins K_1 and K_2 carry hydrocarbon side chains that form a hydrophobic molecule. In addition, the side chain of vitamin K_2 can vary in the number of isoprenyl residues and hence in length. The classification of vitamin K_2 includes the designation for the number of isoprenyl residues, MK-n, where n denotes the amount [79]. Vitamin K_1 is found in green vegetables, including kale, spinach, and broccoli. Vitamin K_2 is found in meat, dairy products, and fermented soybeans [80].

Fat-soluble vitamin K exists in three different forms: vitamin K_1 (phylloquinone), vitamin K_2 (menaquinone), and vitamin K_3 (menadione) [81]. Vitamins K_1 and K_2 are compounds of natural origin, while vitamin K_3 is of artificial origin. Vitamins K_1 and K_2 are the main forms of human nutrition. Vitamin K_3, on the other hand, is only used in animal nutrition due to its relatively high toxicity. In the human body, vitamin K_1 is mainly found in the liver and is involved in the synthesis of blood coagulation proteins. Vitamin K_2 has a wider use in body systems.

The role of vitamin K in blood clotting is better known. It is due to its ability to act as a cofactor for the enzyme γ-glutamyl carboxylase (GGCX) [82].

This enzyme catalyzes the γ-carboxylation of glutamic acid (Glu) residues in vitamin K-dependent proteins. The consequence of this is the formation of γ-carboxyglutamic acid (Gla). This conversion promotes the binding of Ca2+, which is essential for blood clotting properties. Once taken up by the cell, vitamin K binds to the endoplasmic reticulum, where it acts as a cofactor for the carboxylation of GGCX. Prior to this, the dietary quinone form of vitamin K is reduced to the hydroquinone form by vitamin K reductase. GGCX-VitK then γ-carboxylates the glutamic acid residues of the Gla proteins, while vitamin K is converted to its epoxide form. Finally, vitamin K epoxide reductase reduces vitamin K to its quinone form. After conversion, vitamin K is involved in osteoblast differentiation and inhibits osteoclast differentiation, stimulates OPG expression, and inhibits RANKL expression [83].

However, the activation pathway of these numerous mechanisms of vascular calcification remains unclear. The possible significant influence of extracellular vesicles on the processes of activation of the dominant pathway of vascular calcification is being discussed more and more often.

Last recent publications very often mention the great role of exosomes in the pathogenesis and treatment of senescence bone cells that cause OP. Exosomes the extracellular vesicles (EVs) are the new theory of OP development. EVs are secreted by SCs and play an important role in cell-cell communication [84]. Besides the inhibition of the inflammatory response and

promoting vascularization, EVs have been found to promote bone formation by repairing the function of impaired which are similar to the effects of MSC transplantation. The diplex functions of bone-related cells-derived exosomes in OP. Exosomes secreted by osteoblasts and mesenchymal stem cells have bilateral effects in promoting and suppressing OP. Exosomes derived from myocytes and vascular endothelial cells mainly inhibit the process of OP [85].

Exosomes are nanovesicles 30–120 nm in size. They have been identified in many cell types, including stem cells. Their main function is to carry out effective intracellular communications. Exosomes deliver biologically active miRNAs, proteins, lipids, and other signaling molecules to recipient cells. Exosomes help cells communicate with each other, maintain cellular/tissue homeostasis, and respond to pathological stress. They regulate cell survival, cell proliferation and cell death. Thus, exosomes regulate biology and cell repair processes [86]. MicroRNAs that carry exosomes can influence resorption and bone formation. Exosomes can be detected by specific markers, such as CD63, CD81, and CD9 [87]. Some exosomes like tRF-25, tRF-38, and tRF-18 can be used for the diagnosis as biomarkers of osteoporosis [88].

The main mechanism of vascular calcification is the ability of endothelial cells to differentiate into osteoblast-like cells. They express transcription factors for osteoblastic differentiation and bone matrix proteins that help store calcium. Some cells may also differentiate into osteoclast-like cells. Some MSCs or precursors and macrophages have these properties. Thus, reducing the number of cells with a blast-like phenotype and increasing the number of cells that remove excess calcium may be a strategy for vascular calcification cell therapy [89, 90].

A decrease in MGP and fetuin-A increases the formation of calcified exosomes. The protein-lipid complex, which consists of phosphatidylserine and annexin, transforms exosomes into foci of calcification. These foci serve as sites for the start of calcium deposition. The deposition of calcium minerals is facilitated by their interaction with elastic proteins and collagen fibers in the matrix of endothelial cells [91]. Exosomes clean cells of excess calcium. This protects them from intracellular calcium overload. Over time, the activity of calcification inhibitors decreases [92]. An increase in the level of phosphates and calcium stimulates the release VSMCs of exosomes. The level of sphingomyelin phosphodiesterase 3 is also elevated. Some studies show that the first focus of calcification, which is formed by exosomes, is located near collagen and elastin fibers [93]. Recently, iron-based phosphate binders have been proposed in advanced CKD to treat hyperphosphatemia. Iron arrests further high phosphorus-induced calcium deposition through an anti-apoptotic action and the induction of autophagy on established calcified VSMC [94]. Studies have shown that exosomes are involved in vascular calcification, miRNA transport, and oxidative stress response [95].

Some studies have shown that exosomes can transport microRNAs (miRNAs) and proteins from various cells to GMCS. There are different miRNA profiles that are involved in coronary artery calcification [96]. Especially were increased miR-199b-3p, miR-27b3p, miR-130a-3p, miR-221-3p, and miR-24-3p in patients with asymptomatic carotid artery stenosis progression [97]. Known the promoters of VC, as miRNA-221, miRNA-222, miRNA-762, miRNA-714, miRNA-712, and miRNA-210 [70]. Conversely, several miRNAs are involved as calcification inhibitors, including miRNA-26, miRNA-30, miRNA-125b, and miRNA-204 [98].

A randomized study showed that sodium thiosulfate did not prevent the progression of abdominal aortic calcification, however, it had a positive effect on the process of calcification of the iliac arteries and heart valves [99, 100].

This evidence shows the possibility of treating calcification by exosome loading of substances that can reduce calcification [101–103]. For example, melatonin can reduce VC and aging through exosomal miR-204/miR-211 [104].

Conclusions

Thus, the pathogenesis of osteoporosis, vascular calcification, and nephrocalcinosis are complex common but not fully understood mechanisms. These processes can have common risk factors when endothelial cells in different organs have been modified to osteoblasts–like bone cells and become intensive capture calcium crystals. In order to solve the problem prevention of the "calcium paradox" it is necessary to access whole multiple mechanisms: calcium and vitamin D, K_2 deficiency, reasons for secondary hyperparathyroidism, immuno-aging as senescence of stem cells, and influence microRNA and exosomes. A new understanding of the problem opens up opportunities for influencing all the known links and new perspectives of treatment.

References

1. Montero-Odasso MM, Kamkar N, Pieruccini-Faria F, et al. Evaluation of Clinical Practice Guidelines on Fall Prevention and Management for Older Adults: A Systematic Review. JAMA Netw Open. 2021;4(12):e2138911. doi: 10.1001/jamanetworkopen.2021.38911.

2. Reid IR. A broader strategy for osteoporosis interventions. Nat Rev Endocrinol. 2020 Jun;16(6):333-339. doi: 10.1038/s41574-020-0339-7.

3. Adami G, Rahn EJ, Saag KG. Glucocorticoid-induced osteoporosis: from clinical trials to clinical practice. Ther Adv Musculoskelet Dis. 2019 Sep 20;11:1759720X19876468. doi: 10.1177/1759720X19876468.

4. Ling Y, Xu F, Xia X, et al. Vitamin D supplementation reduces the risk of fall in the vitamin D deficient elderly: An updated meta-analysis. Clin Nutr. 2021 Nov;40(11):5531-5537. doi: 10.1016/j.clnu.2021.09.031.

5. Zanoli L, Lentini P, Briet M, et al. Arterial Stiffness in the Heart Disease of CKD. J Am Soc Nephrol. 2019 Jun;30(6):918-928. doi: 10.1681/ASN.2019020117.

6. Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: A Perspective From Developing Countries. Can J Cardiol. 2021 May;37(5):733-743. doi: 10.1016/j.cjca.2021.02.009.

7. García-Gómez MC, Vilahur G. Osteoporosis and vascular calcification: A shared scenario. Clin Investig Arterioscler. 2020 Jan-Feb;32(1):33-42. English, Spanish. doi: 10.1016/j.arteri.2019.03.008.

8. Wang ZX, Luo ZW, Li FX, et al. Aged bone matrix-derived extracellular vesicles as a messenger for calcification paradox. Nat Commun. 2022 Mar 18;13(1):1453. doi: 10.1038/s41467-022-29191-x.

9. Sutton NR, Malhotra R, St Hilaire C, et al. Molecular Mechanisms of Vascular Health: Insights From Vascular Aging and Calcification. Arterioscler Thromb Vasc Biol. 2023 Jan;43(1):15-29. doi: 10.1161/ATVBAHA.122.317332.

10. Komori T. Regulation of skeletal development by the Runx family of transcription factors. J Cell Biochem. 2005 Jun 1;95(3):445-53. doi: 10.1002/jcb.20420.

11. Latic N, Erben RG. Vitamin D and Cardiovascular Disease, with Emphasis on Hypertension, Atherosclerosis, and Heart Failure. Int J Mol Sci. 2020 Sep 4;21(18):6483. doi: 10.3390/ijms21186483.

12. de la Gu a-Galipienso F, Mart nez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D and cardiovascular health. Clin Nutr. 2021 May;40(5):2946-2957. doi: 10.1016/j.clnu.2020.12.025.

13. Biffi A, Fernando F, Palermi S, et al. Cardiovascular disease prevention in the worksite: Where are we? Int J Cardiol. 2022 Dec 1;368:104-107. doi: 10.1016/j.ijcard.2022.08.026.

14. Guzon-Illescas O, Perez Fernandez E, Cresp Villarias N, et al. Mortality after osteoporotic hip fracture: incidence, trends, and associated factors. J Orthop Surg Res. 2019 Jul 4;14(1):203. doi: 10.1186/s13018-019-1226-6.

15. Katsanos S, Sioutis S, Reppas L, et al. What do hip fracture patients die from? Eur J Orthop Surg Traumatol. 2023 May;33(4):751-757. doi: 10.1007/s00590-022-03250-x.

16. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019 Jun 29;393(10191):2636-2646. doi: 10.1016/S0140-6736(19)31138-9.

17. Migliorini F, Giorgino R, Hildebrand F, et al. Fragility Fractures: Risk Factors and Management in the Elderly. Medicina (Kaunas). 2021 Oct 17;57(10):1119. doi: 10.3390/medicina57101119.

18. Shoji T, Nakatani S, Kabata D, et al. Comparative Effects of Etelcalcetide and Maxacalcitol on Serum Calcification Propensity in Secondary Hyperparathyroidism: A Randomized Clinical Trial. Clin J Am Soc Nephrol. 2021 Apr 7;16(4):599-612. doi: 10.2215/CJN.16601020.

19. Trajanoska K, Rivadeneira F. The genetic architecture of osteoporosis and fracture risk. Bone. 2019 Sep;126:2-10. doi: 10.1016/j.bone.2019.04.005.

20. Tada H, Fujino N, Hayashi K, Kawashiri MA, Takamura M. Human genetics and its impact on cardiovascular disease. J Cardiol. 2022 Feb;79(2):233-239. doi: 10.1016/j.jjcc.2021.09.005.

21. Cosentino N, Campodonico J, Milazzo V, et al. Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. Nutrients. 2021 Oct 14;13(10):3603. doi: 10.3390/nu13103603.

22. Reiss AB, Miyawaki N, Moon J, et al. CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. Atherosclerosis. 2018 Nov;278:49-59. doi: 10.1016/j.atherosclerosis.2018.08.046.

23. Gracia-Marco L. Calcium, Vitamin D, and Health. Nutrients. 2020 Feb 6;12(2):416. doi: 10.3390/nu12020416.

24. Michos ED, Cainzos-Achirica M, Heravi AS, Appel LJ. Vitamin D, Calcium Supplements, and Implications for Cardiovascular Health: JACC Focus Seminar. J Am Coll Cardiol. 2021 Feb 2;77(4):437-449. doi: 10.1016/j.jacc.2020.09.617.

25. Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010 Jul 29;341:c3691. doi: 10.1136/bmj.c3691.

26. Cheng CH, Chen LR, Chen KH. Osteoporosis Due to Hormone Imbalance: An Overview of the Effects of Estrogen Deficiency and Glucocorticoid Overuse on Bone Turnover. Int J Mol Sci. 2022 Jan 25;23(3):1376. doi: 10.3390/ijms23031376.

27. Cherukuri L, Kinninger A, Birudaraju D, et al. Coronary artery calcium and bone mineral density by serial CTA: Does menopausal hormone therapy modify the association? Clin Imaging. 2022 Oct;90:26-31. doi: 10.1016/j.clinimag.2022.06.023.

28. Burte C, Lejeune H, Faix A, et al. Practical recommendations for the management of testosterone deficiency. Prog Urol. 2021 Jun-Jul;31(8-9):458-476. French. doi: 10.1016/j.purol.2020.09.026.

29. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016 Apr;19(2):109-50. doi: 10.3109/13697137.2015.1129166.

30. Hodis HN, Mack WJ. Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing. Cancer J. 2022 May-Jun 01;28(3):208-223. doi: 10.1097/PPO.0000000000000591.

31. Banjabi AA, Kurunthachalam K, Kumosani TA, Abulnaja KO, Al-Malki AL, Moselhy SS. Serum heavy metals of passive smoker females and its correlation to bone biomarkers and risk of osteoporosis. Environ Sci Pollut Res Int. 2022 Jan;29(5):6943-6948. doi: 10.1007/s11356-021-16186-2.

32. Bernabe-Ortiz A, Carrillo-Larco RM. Second-hand smoking, hypertension and cardiovascular risk: findings from Peru. BMC Cardiovasc Disord. 2021 Dec 3;21(1):576. doi: 10.1186/s12872-021-02410-x.

33. Craig WJ, Mangels AR, Fresán U, et al. The Safe and Effective Use of Plant-Based Diets with Guidelines for Health Professionals. Nutrients. 2021 Nov 19;13(11):4144. doi: 10.3390/nu13114144.

34. Le Daré B, Lagente V, Gicquel T. Ethanol and its metabolites: update on toxicity, benefits, and focus on immunomodulatory effects. Drug Metab Rev. 2019 Nov;51(4):545-561. doi: 10.1080/03602532.2019.1679169.

35. He FJ, Tan M, Ma Y, MacGregor GA. Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Feb 18;75(6):632-647. doi: 10.1016/j.jacc.2019.11.055.

36. Al-Hariri M, Aldhafery B. Association of Hypertension and Lipid Profile with Osteoporosis. Scientifica (Cairo). 2020 Jul 12;2020:7075815. doi: 10.1155/2020/7075815.

37. Chen Y, Zhao X, Wu H. Arterial Stiffness: A Focus on Vascular Calcification and Its Link to Bone Mineralization. Arterioscler Thromb Vasc Biol. 2020 May;40(5):1078-1093. doi: 10.1161/ATVBAHA.120.313131.

38. Kanis JA, Norton N, Harvey NC, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos. 2021 Jun 2;16(1):82. doi: 10.1007/s11657-020-00871-9.

39. Shevroja E, Cafarelli FP, Guglielmi G, Hans D. DXA parameters, Trabecular Bone Score (TBS) and Bone Mineral Density (BMD), in fracture risk prediction in endocrine-mediated secondary osteoporosis. Endocrine. 2021 Oct;74(1):20-28. doi: 10.1007/s12020-021-02806-x.

40. Jiang Y, Zhang P, Zhang X, Lv L, Zhou Y. Advances in mesenchymal stem cell transplantation for the treatment of osteoporosis. Cell Prolif. 2021 Jan;54(1):e12956. doi: 10.1111/cpr.12956.

41. McDonald MM, Khoo WH, Ng PY, et al. Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption. Cell. 2021 Mar 4;184(5):1330-1347.e13. doi: 10.1016/j.cell.2021.02.002.

42. Yasuda H. Discovery of the RANKL/RANK/OPG system. J Bone Miner Metab. 2021 Jan;39(1):2-11. doi: 10.1007/s00774-020-01175-1.

43. Carrillo-López N, Martínez-Arias L, Fernández-Villabrille S, et al; European Renal Osteodystrophy (EUROD) Workgroup. Role of the RANK/RANKL/OPG and Wnt/β-Catenin Systems in CKD Bone and Cardiovascular Disorders. Calcif Tissue Int. 2021 Apr;108(4):439-451. doi: 10.1007/s00223-020-00803-2.

44. Dalle Carbonare L, Valenti MT, Zanatta M, Donatelli L, Lo Cascio V. Circulating mesenchymal stem cells with abnormal osteogenic differentiation in patients with osteoporosis. Arthritis Rheum. 2009 Nov;60(11):3356-65. doi: 10.1002/art.24884.

45. Woodward HJ, Zhu D, Hadoke PWF, MacRae VE. Regulatory Role of Sex Hormones in Cardiovascular Calcification. Int J Mol Sci. 2021;22(9):4620. doi: 10.3390/ijms22094620.

46. Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial Stiffness and Cardiovascular Risk in Hypertension. Circ Res. 2021 Apr 2;128(7):864-886. doi: 10.1161/CIRCRESAHA.121.318061.

47. Farah BQ, Cucato GG, Andrade-Lima A, et al. Impact of hypertension on arterial stiffness and cardiac autonomic modulation in patients with peripheral artery disease: a cross-sectional study. Einstein (Sao Paulo). 2021 Dec 10;19:eA06100. doi: 10.31744/einstein_journal/2021AO6100.

48. Miyoshi T, Ito H. Arterial stiffness in health and disease: The role of cardio-ankle vascular index. J Cardiol. 2021 Dec;78(6):493-501. doi: 10.1016/j.jjcc.2021.07.011.

49. Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial Stiffness and Cardiovascular Risk in Hypertension. Circ Res. 2021 Apr 2;128(7):864-886. doi: 10.1161/CIRCRESAHA.121.318061.

50. Cannata-Andía JB, Carrillo-López N, Messina OD, et al. Pathophysiology of Vascular Calcification and Bone Loss: Linked Disorders of Ageing? Nutrients. 2021 Oct 27;13(11):3835. doi: 10.3390/nu13113835.

51. Tóth A, Balogh E, Jeney V. Regulation of Vascular Calcification by Reactive Oxygen Species. Antioxidants (Basel). 2020 Oct 8;9(10):963. doi: 10.3390/antiox9100963.

52. Alesutan I, Henze LA, Boehme B, et al. Periostin Augments Vascular Smooth Muscle Cell Calcification via β-Catenin Signaling. Biomolecules. 2022 Aug 21;12(8):1157. doi: 10.3390/biom12081157.

53. Chellan B, Sutton NR, Hofmann Bowman MA. S100/RAGE-Mediated Inflammation and Modified Cholesterol Lipoproteins as Mediators of Osteoblastic Differentiation of Vascular Smooth Muscle Cells. Front Cardiovasc Med. 2018 Nov 8;5:163. doi: 10.3389/fcvm.2018.00163.

54. Torzewski M. Enzymatically modified LDL, atherosclerosis and beyond: paving the way to acceptance. Front Biosci (Landmark Ed). 2018 Jan 1;23(7):1257-1271. doi: 10.2741/4642.

55. Rashdan NA, Sim AM, Cui L, et al. Osteocalcin Regulates Arterial Calcification Via Altered Wnt Signaling and Glucose Metabolism. J Bone Miner Res. 2020 Feb;35(2):357-367. doi: 10.1002/jbmr.3888.

56. Luzin VI, Ivanova LN, Nishkumaj OI, Goroshko SA. Features of bone strength in white rats of senile age treated with a high cholesterol diet. Problemi osteologii. 2003;7(3-4):23-25.

57. Luo J, Yang Z, Ma Y, et al. LGR4 is a receptor for RANKL and negatively regulates osteoclast differentiation and bone resorption. Nat Med. 2016 May;22(5):539-46. doi: 10.1038/nm.4076.

58. Carrillo-López N, Martínez-Arias L, Alonso-Montes C, et al. The receptor activator of nuclear factor κB ligand receptor leucine-rich repeat-containing G-protein-coupled receptor 4 contributes to parathyroid hormone-induced vascular calcification. Nephrol Dial Transplant. 2021 Mar 29;36(4):618-631. doi: 10.1093/ndt/gfaa290.

59. Almquist M, Isaksson E, Clyne N. The treatment of renal hyperparathyroidism. Endocr Relat Cancer. 2020 Jan;27(1):R21-R34. doi: 10.1530/ERC-19-0284.

60. Carrillo-López N, Panizo S, Alonso-Montes C, et al. Direct inhibition of osteoblastic Wnt pathway by fibroblast growth factor 23 contributes to bone loss in chronic kidney disease. Kidney Int. 2016 Jul;90(1):77-89. doi: 10.1016/j.kint.2016.01.024.

61. Carrillo-López N, Panizo S, Alonso-Montes C, et al. High-serum phosphate and parathyroid hormone distinctly regulate bone loss and vascular calcification in experimental chronic kidney disease. Nephrol Dial Transplant. 2019 Jun 1;34(6):934-941. doi: 10.1093/ndt/gfy287.

62. Tanaka S, Matsumoto T. Sclerostin: from bench to bedside. J Bone Miner Metab. 2021 May;39(3):332-340. doi: 10.1007/s00774-020-01176-0.

63. Schunk SJ, Floege J, Fliser D, Speer T. WNT-β-catenin signalling - a versatile player in kidney injury and repair. Nat Rev Nephrol. 2021 Mar;17(3):172-184. doi: 10.1038/s41581-020-00343-w.

64. Golledge J, Thanigaimani S. Role of Sclerostin in Cardiovascular Disease. Arterioscler Thromb Vasc Biol. 2022 Jul;42(7):e187-e202. doi: 10.1161/ATVBAHA.122.317635.

65. Liu KH, Fu J, Zhou N, et al. 1,25-Dihydroxyvitamin D3 Prevents Epithelial-Mesenchymal Transition of HMrSV5 Human Peritoneal Mesothelial Cells by Inhibiting Histone Deacetylase 3 (HDAC3) and Increasing Vitamin D Receptor (VDR) Expression Through the Wnt/β-Catenin Signaling Pathway. Med Sci Monit. 2019 Aug 8;25:5892-5902. doi: 10.12659/MSM.916313.

66. Melguizo-Rodríguez L, Costela-Ruiz VJ, García-Recio E, De Luna-Bertos E, Ruiz C, Illescas-Montes R. Role of Vitamin D in the Metabolic Syndrome. Nutrients. 2021 Mar 3;13(3):830. doi: 10.3390/nu13030830.

67. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA. 2019 Oct 1;322(13):1294-1304. doi: 10.1001/jama.2019.14745.

68. Islam AK, Holt S, Reisch J, Nwariaku F, Antonelli J, Maalouf NM. What Predicts Recurrent Kidney Stone after Parathyroidectomy in Patients with Primary Hyperparathyroidism? J Am Coll Surg. 2020 Jul;231(1):74-82. doi: 10.1016/j.jamcollsurg.2020.04.015.

69. Jia Q, Huang Z, Wang G, et al. Osteopontin: An important protein in the formation of kidney stones. Front Pharmacol. 2022 Nov 9;13:1036423. doi: 10.3389/fphar.2022.1036423.

70. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H. Recent advances on the mechanisms of kidney stone formation (Review). Int J Mol Med. 2021 Aug;48(2):149. doi: 10.3892/ijmm.2021.4982.

71. Yang Y, Hong S, Wang Q, Wang S, Xun Y. Exosome-mediated crosstalk between epithelial cells amplifies the cell injury cascade in CaOx stone formation. J Biol Eng. 2023 Feb 28;17(1):16. doi: 10.1186/s13036-023-00324-0.

72. Lok ZSY, Lyle AN. Osteopontin in Vascular Disease. Arterioscler Thromb Vasc Biol. 2019 Apr;39(4):613-622. doi: 10.1161/ATVBAHA.118.311577.

73. Bailey S, Sroga GE, Hoac B, et al. The role of extracellular matrix phosphorylation on energy dissipation in bone. Elife. 2020 Dec 9;9:e58184. doi: 10.7554/eLife.58184.

74. Cao S, Li X, Feng T, et al. Hirudin promotes proliferation and osteogenic differentiation of HBMSCs via activation of cyclic guanosine monophosphate (cGMP)/protein kinase-G (PKG) signaling pathway. Bioengineered. 2022 Mar;13(3):6061-6069. doi: 10.1080/21655979.2021.2008697.

75. Stock M, Schett G. Vitamin K-Dependent Proteins in Skeletal Development and Disease. Int J Mol Sci. 2021 Aug 28;22(17):9328. doi: 10.3390/ijms22179328.

76. Halder M, Petsophonsakul P, Akbulut AC, et al. Vitamin K: Double Bonds beyond Coagulation Insights into Differences between Vitamin K1 and K2 in Health and Disease. Int J Mol Sci. 2019 Feb 19;20(4):896. doi: 10.3390/ijms20040896.

77. Jadhav N, Ajgaonkar S, Saha P, et al. Molecular Pathways and Roles for Vitamin K2-7 as a Health-Beneficial Nutraceutical: Challenges and Opportunities. Front Pharmacol. 2022 Jun 14;13:896920. doi: 10.3389/fphar.2022.896920.

78. Narvaez CJ, Bak MJ, Salman N, Welsh J. Vitamin K2 enhances the tumor suppressive effects of 1,25(OH)2D3 in triple negative breast cancer cells. J Steroid Biochem Mol Biol. 2023 Apr 6;231:106307. doi: 10.1016/j.jsbmb.2023.106307.

79. Nakagawa K. Diseases Due to the Deficiency in Vitamin K Conversion System and Its Prevention. Yakugaku Zasshi. 2021;141(5):669-674. Japanese. doi: 10.1248/yakushi.20-00243-1.

80. Akbulut AC, Pavlic A, Petsophonsakul P, et al. Vitamin K2 Needs an RDI Separate from Vitamin K1. Nutrients. 2020 Jun 21;12(6):1852. doi: 10.3390/nu12061852.

81. Mladěnka P, Macáková K, Kujovská Krčmová L, et al; OEMONOM researchers and collaborators. Vitamin K - sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. Nutr Rev. 2022 Mar 10;80(4):677-698. doi: 10.1093/nutrit/nuab061.

82. Fusaro M, Cianciolo G, Evenepoel P, Schurgers L, Plebani M. Vitamin K in CKD Bone Disorders. Calcif Tissue Int. 2021 Apr;108(4):476-485. doi: 10.1007/s00223-020-00792-2.

83. Ma H, Zhang BL, Liu BY, et al. Vitamin K2-Dependent GGCX and MGP Are Required for Homeostatic Calcium Regulation of Sperm Maturation. iScience. 2019 Apr 26;14:210-225. doi: 10.1016/j.isci.2019.03.030.

84. Liang X, Ding Y, Zhang Y, Tse HF, Lian Q. Paracrine mechanisms of mesenchymal stem cell-based therapy: current status and perspectives. Cell Transplant. 2014;23(9):1045-59. doi: 10.3727/096368913X667709.

85. Yang Z, Zhang W, Ren X, Tu C, Li Z. Exosomes: A Friend or Foe for Osteoporotic Fracture? Front Endocrinol (Lausanne). 2021 Jun 21;12:679914. doi: 10.3389/fendo.2021.679914.

86. Yu H, Wang Z. Cardiomyocyte-Derived Exosomes: Biological Functions and Potential Therapeutic Implications. Front Physiol. 2019 Aug 20;10:1049. doi: 10.3389/fphys.2019.01049.

87. Qin Z, Liao R, Xiong Y, et al. A narrative review of exosomes in vascular calcification. Ann Transl Med. 2021 Apr;9(7):579. doi: 10.21037/atm-20-7355.

88. Huang G, Zhao Q, Li W, et al. Exosomes: A new option for osteoporosis treatment. Medicine (Baltimore). 2022 Dec 30;101(52):e32402. doi: 10.1097/MD.0000000000032402.

89. Jiang W, Zhang Z, Li Y, et al. The Cell Origin and Role of Osteoclastogenesis and Osteoblastogenesis in Vascular Calcification. Front Cardiovasc Med. 2021 Apr 23;8:639740. doi: 10.3389/fcvm.2021.639740.

90. Huang J, Xu Y, Wang Y, et al Advances in the Study of Exosomes as Drug Delivery Systems for Bone-Related Diseases. Pharmaceutics. 2023 Jan 9;15(1):220. doi: 10.3390/pharmaceutics15010220.

91. Pavlic A, Bahram Sangani N, Kerins J, Nicolaes G, Schurgers L, Reutelingsperger C. Vascular Smooth Muscle Cell Neutral Sphingomyelinase 2 in the Release of Exosomes and Vascular Calcification. Int J Mol Sci. 2022 Aug 16;23(16):9178. doi: 10.3390/ijms23169178.

92. Bommanavar S, Hosmani J, Togoo RA, et al. Role of matrix vesicles and crystal ghosts in bio-mineralization. J Bone Miner Metab. 2020 Nov;38(6):759-764. doi: 10.1007/s00774-020-01125-x.

93. Pavlic A, Poelman H, Wasilewski G, et al. Inhibition of Neutral Sphingomyelinase 2 by Novel Small Molecule Inhibitors Results in Decreased Release of Extracellular Vesicles by Vascular Smooth Muscle Cells and Attenuated Calcification. Int J Mol Sci. 2023 Jan 19;24(3):2027. doi: 10.3390/ijms24032027.

94. Ciceri P, Falleni M, Tosi D, et al. Therapeutic Effect of Iron Citrate in Blocking Calcium Deposition in High Pi-Calcified VSMC: Role of Autophagy and Apoptosis. Int J Mol Sci. 2019 Nov 25;20(23):5925. doi: 10.3390/ijms20235925.

95. Gardin C, Ferroni L, Leo S, Tremoli E, Zavan B. Platelet-Derived Exosomes in Atherosclerosis. Int J Mol Sci. 2022 Oct 19;23(20):12546. doi: 10.3390/ijms232012546.

96. Tkach M, Théry C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. Cell. 2016 Mar 10;164(6):1226-1232. doi: 10.1016/j.cell.2016.01.043.

97. Dolz S, Górriz D, Tembl JI, et al. Circulating MicroRNAs as Novel Biomarkers of Stenosis Progression in Asymptomatic Carotid Stenosis. Stroke. 2017 Jan;48(1):10-16. doi: 10.1161/STROKEAHA.116.013650.

98. Qin Z, Li Y, Li J, et al. Exosomal STAT1 derived from high phosphorus-stimulated vascular endothelial cells induces vascular smooth muscle cell calcification via the Wnt/β-catenin signaling pathway. Int J Mol Med. 2022 Dec;50(6):139. doi: 10.3892/ijmm.2022.5195.

99. Djuric P, Dimkovic N, Schlieper G, et al. Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomized, placebo-controlled study. Nephrol Dial Transplant. 2020 Jan 1;35(1):162-169. doi: 10.1093/ndt/gfz204.

100. Raggi P, Bellasi A, Bushinsky D, et al. Slowing Progression of Cardiovascular Calcification With SNF472 in Patients on Hemodialysis: Results of a Randomized Phase 2b Study. Circulation. 2020 Mar 3;141(9):728-739. doi: 10.1161/CIRCULATIONAHA.119.044195.

101. Lee BC, Kang I, Yu KR. Therapeutic Features and Updated Clinical Trials of Mesenchymal Stem Cell (MSC)-Derived Exosomes. J Clin Med. 2021 Feb 11;10(4):711. doi: 10.3390/jcm10040711.

102. Tan SHS, Wong JRY, Sim SJY, et al. Mesenchymal stem cell exosomes in bone regenerative strategies-a systematic review of preclinical studies. Mater Today Bio. 2020 Jun 27;7:100067. doi: 10.1016/j.mtbio.2020.100067.

103. Liao YJ, Tang PC, Lin CH, Chen LR, Yang JR. Porcine-induced pluripotent stem cell-derived osteoblast-like cells ameliorate trabecular bone mass of osteoporotic rats. Regen Med. 2018 Sep;13(6):659-671. doi: 10.2217/rme-2018-0014.

104. Xu F, Zhong JY, Lin X, et al. Melatonin alleviates vascular calcification and ageing through exosomal miR-204/miR-211 cluster in a paracrine manner. J Pineal Res. 2020 Apr;68(3):e12631. doi: 10.1111/jpi.12631.

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Information about authors
Olga Nishkumay, MD, PhD, Professor at the Internal Medicine Department 2, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/0000-0001-9958-0858
Mike K.S. Chan, Co-Owner & Founder of the European Wellness Biomedical Group, Senior Technical Consultant, Professor, European Wellness Academy, Edenkoben, Germany; https://orcid.org/0000-0002-9046-3863
Yury Nalapko, PhD, Associate Professor, Head of the European Wellness Biomedical Group Medical Advisors Department, Edenkoben, Germany; https://orcid.org/0000-0001-7431-4545
Halyna Mostbauer, PhD, Head of the Internal Medicine Department 2, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/0000-0002-0142-0416
Oleksandra Alekseenko, Assistant at the Internal Medicine Department 2, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/0000-0002-9096-6460
Oleh Nikitin, MD, PhD, Professor, Head of the Department of Urology, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/000-0002-6563-7008
Ilya Kordubailo, Senior Laboratory Technician at the Department of Urology, Bogomolets National Medical University, Kyiv, Ukraine; https://orcid.org/0000-0001-7087-561X

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Нішкумай О.І.[1], Mike K.S. Chan[2], Налапко Ю.І.[2], Мостбауер Г.В.[1], Алексєєнко О.О.[1], Нікітін О.Д.[1], Кордубайло І.А.[1]
[1]Національний медичний університет імені О.О. Богомольця, м. Київ, Україна
[2]European Wellness Academy, Edenkoben, Germany

Остеопороз, артеріальна кальцифікація та сечокам'яна хвороба: сучасні методи боротьби зі старінням (огляд літератури)

Резюме. ***Актуальність.*** Проблема остеопорозу, як і серцево-судинних захворювань, залишається однією з головних у статистиці захворюваності та смертності через старіння населення в усьому світі. У сучасних публікаціях підкреслюють нову точку зору на зв'язок цієї статистики з механізмом «кальцієвого парадоксу». Ці процеси можуть мати загальні фактори ризику, що впливають на спільні механізми, коли ендотеліальні клітини різних органів перетворюються на бластоподібні та починають інтенсивно захоплювати кристали кальцію з відкладанням у судинній стінці та органах, наприклад нирках. Цей патологічний процес призводить до ламкості кісток і судин, нефрокальцинозу. Патогенез патологічної кальцифікації є складним, його механізм на сьогодні залишається не з'ясованим. ***Мета:*** проаналізувати поточні літературні дані про причини та молекулярні механізми ремоделювання кісток і кальцифікації судин відповідно до огляду літератури за останні 5 років. ***Матеріали та методи.*** Аналітичний огляд літературних даних (статті, резюме, метааналізи) було проведено з використанням інформаційного аналізу баз даних Medline (PubMed), Web of Science та Scopus, Google Scholar та Кокранівського центрального реєстру контрольованих досліджень (CENTRAL) за 2018–2023 рр. за ключовими словами «остеопороз», «атеросклероз», «кальцифікація судин», «стовбурові клітини», «екзосоми», «сечокам'яна хвороба». ***Результати.*** Аналіз літератури підкреслює численні патогенетичні механізми «кальцієвого парадоксу»: загальні фактори ризику (гіподинамія, дефіцит кальцію, вітаміну D та K_2, паління), остеосаркопенію, імунне старіння й старіння стовбурових клітин. ***Висновки.*** Для вирішення проблеми «кальцієвого парадоксу» необхідна корекція багатьох механізмів: нормалізація добового вживання кальцію, вітамінів D та K_2; профілактика причин, що викликають вторинний гіперпаратиреоз, падіння, остеосаркопенію, імунне старіння; вивчення можливостей застосування стовбурової терапії, мікроРНК та екзосом. Нове розуміння проблеми відкриває можливості для впливу на всі відомі ланки та впровадження нових методів лікування.

Ключові слова: артеріальна кальцифікація; остеопороз; остеопонтин; стовбурові клітини; екзосоми; сечокам'яна хвороба