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The role of biomolecules in the development and progression of vascular calcification in cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVD) remain the most pressing problem in the healthcare system. Complex interactions between changes in the intima – media thickness of arteries and blood components (accumulation of lipids, complex carbohydrates, fibrous tissue, calcification, etc.) are involved in the pathogenesis of CVD. Various biomolecules play a crucial role in the development and progression of coronary artery calcification, the most common calcification inhibitors being osteopontin, osteoprotegerin, sclerostin, fetuin-A, inorganic pyrophosphate, matrix Gla protein, fibroblast growth factor 23 (FGF-23), Klotho, bone morphogenetic proteins (BMP), in particular BMP-7, and the most common activators being leptin, BMP-2, BMP-4, parathyroid hormone, calcitriol, etc. Currently, the most studied biomolecules associated with calcium metabolism are osteoprotegerin, osteopontin, osteonectin, osteocalcin, and Klotho protein.

The paper describes in detail the poorly studied effects of calcification inhibitors (sclerostin, fetuin-A, matrix Gla protein, FGF-23, inorganic pyrophosphate, BMP-7) and some calcification activators (leptin, BMP-2 and BMP-4, parathyroid hormone, and calcitriol).

The aim of this study was to analyze and systematize data on the role of biomolecules in the development and progression of vascular calcification in cardiovascular diseases.

Keywords: cardiovascular diseases, atherosclerosis, biomolecules, vascular calcification, blood

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Роль биомолекул в развитии и прогрессировании кальцификации сосудов при сердечно-сосудистых заболеваниях

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РЕЗЮМЕ

Сердечно-сосудистые заболевания (ССЗ) остаются наиболее актуальной проблемой в системе здравоохранения. В патогенез ССЗ вовлечены сложные взаимодействия между изменениями интима-медиа артерий и компонентами крови (накопление липидов, сложных углеводов, фиброзной ткани, кальцификация и др.). В развитии и прогрессировании кальцификации коронарных артерий огромную роль играют различные биомолекулы, где в качестве ингибиторов кальцификации чаще всего выступают остеопонтин, остеопротегерин, склеростин, фетуин-А, неорганический пирофосфат, матриксный Gla-протеин, фактор роста фибробластов 23 (FGF-23), Клото, белки морфогенеза костей (BMP), в частности BMP-7; а активаторов – лептин, BMP-2, BMP-4, паратиреоидный гормон, кальцитриол и др. В настоящее время наиболее изученными биомолекулами, ассоциированными с кальциевым обменом, считаются остеопротегерин, остеопонтин, остеонектин, остеокальцин и белок Клото.

В работе описаны малоизученные эффекты ингибиторов кальцификации (склеростин, фетуин А, матриксный Gla-протеин, FGF-23, неорганический пирофосфат, BMP-7), а также некоторых активаторов кальцификации (лептин, BMP-2 и BMP-4, паратиреоидный гормон и кальцитриол).

Цель данного исследования заключается в анализе и систематизации данных о роли биомолекул в развитии и прогрессировании кальцификации сосудов при ССЗ.

Ключевые слова: сердечно-сосудистые заболевания, атеросклероз, биомолекулы, кальцификация сосудов, кровь

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Cardiovascular diseases (CVD) remain the most pressing problem in healthcare, despite the significant progress in the diagnosis and treatment of cardiovascular pathology in last decades [1, 2]. The pathogenesis of atherosclerotic CVD involves complex interactions between changes in arterial intima – media thickness and blood components (accumulation of lipids, complex carbohydrates, fibrous tissue, calcification, etc.) [3]. For a long time, atherosclerosis can be asymptomatic due to a latent stage of the disease, which is already accompanied by morphologic changes in the coronary arteries. However, following atherosclerotic plaque (AP) progression, there is gradual stenosis of coronary and other arteries, which results in such complications as angina pectoris, cerebrovascular insufficiency, myocardial infarction (MI), sudden cardiacdeath, etc. [4].

Currently, at least three histologic types of unstable APs are distinguished:

1) lipid – fibroatheroma with a thin fibrous cap;

2) inflammatory – erosive – with increased proteoglycan or inflammation leading to erosion or thrombosis;

3) dystrophic – necrotic – with necrosis and / or calcification [3].

Vascular calcification is a part of atherosclerotic process; at the same time, the degree of mineralization can reflect the severity of AP [5]. Calcium deposition in coronary arteries reduces vasodilatory effects and changes the stability of AP [6]. Several authors have demonstrated that a fairly common mechanism of AP instability is the formation of a calcified nodule consisting of calcified plates similar to bone spicules that surround the area of fibrosis [7]. Nevertheless, the relationship between arterial calcification and the risk of plaque rupture is still controversial.

Various biomolecules play an essential role in the development and progression of coronary artery calcification (CAC), the most common inhibitors of calcification being osteopontin [8], osteoprotegerin [9], sclerostin [9], fetuin-A [10], inorganic

pyrophosphate [11, 12], matrix Gla protein [13], fibroblast growth factor 23 (FGF-23) [14, 15], Klotho [16], bone morphogenetic proteins (BMP), in particular BMP-7 [17], and the most common activators being leptin [18], BMP-2 and BMP-4 [19, 20], parathyroid hormone [21], calcitriol [22], and others.

Currently, the most studied molecules associated with vascular calcification are considered to be osteoprotegerin, osteopontin, osteonectin, osteocalcin, and Klotho protein. Therefore, this review will consider the less studied ones.

MATERIALS AND METHODS

References for this article were searched in PubMed and eLIBRARY.RU databases using the following keyword combinations: “sclerostin and CVD”, “fetuin-A and CVD”, “matrix Gla protein and CVD”, “fibroblast growth factor 23 and CVD”, “inorganic pyrophosphate and CVD”, “bone morphogenetic protein 2 and CVD”, “bone morphogenetic protein 4 and CVD”, “bone morphogenetic protein 7 and CVD”, “leptin and CVD”, “parathyroid hormone and CVD”, “calcitriol and CVD” in Russian and English. A total of 563 full-text articles for the period 2013–2025 were retrieved. Eighty-one articles were selected for review, containing information on the association of the above biomolecules with CVD, in particular, with coronary heart disease and coronary atherosclerosis.

CALCIFICATION INHIBITORS

Sclerostin

Sclerostin is a secreted glycoprotein that is expressed predominantly in osteocytes, but also in other tissues and organs, such as vascular smooth muscle cells (VSMCs) [23], and contains three distinct domains. It was found that sclerostin inhibits bone formation via the Wnt/β-catenin signaling pathway [24, 25].

A number of studies have shown an association between serum sclerostin levels and the incidence of CVD and / or cardiovascular mortality. In particular, W. He et al. found that higher serum sclerostin levels were associated with a better 3-year prognosis after percutaneous coronary intervention in elderly patients with stable coronary heart disease (CHD) [26]. Moreover, serum sclerostin is an independent prognostic parameter for predicting adverse cardiovascular and cerebrovascular events, MI, and all-cause mortality. In a prospective study, C.Y. Yang et al. [27] found an inverse relationship between serum sclerostin levels and aortic calcification in patients on long-term hemodialysis. The authors suggested that higher sclerostin levels led to fewer cardiovascular events (hazard ratio 0.982 for every 1 pmol / l of sclerostin increase). In a study on mice [28], it was shown that sclerostin can play a protective role, contributing to the maintenance of structural and functional integrity of the aorta by suppressing inflammation and degradation of extracellular matrix, which in turn prevents the development of aortic aneurysm and atherosclerosis. At the same time, a prospective population-based study by G. Klingenschmid et al. [29] revealed no association between serum sclerostin levels and cardiovascular events, such as stroke. Similarly, in the meta-analysis by M. Kanbay et al. [30], serum sclerostin levels were not associated with cardiovascular and all-cause mortality.

Fetuin-A

Fetuin-A is a serum protein with a molecular mass of 48 kDa synthesized by liver cells. Fetuin-A is thought to be involved in the regulation of bone and vascular calcification through the formation of stable colloidal mineral – protein complexes called calciprotein particles. Removal of these particles and, consequently, excess minerals from the circulation prevents local accumulation of minerals and calcification of soft tissues [31, 32].

In a study by L.E. Laugsand et al. [33], an increase in serum fetuin-A concentration was associated with a lower risk of CVD among participants without type 2 diabetes, while a reverse trend was observed among participants with type 2 diabetes. In a prospective cohort study, N. Kubota et al. concluded that despite the ability of fetuin-A to inhibit ectopic calcium deposition, its low serum level probably had no significant effect on the progression of aortic stenosis [34].

Another prospective study by M. Krajnc et al. found that serum fetuin-A may be inversely associated with the progression of CAC in patients

with type 2 diabetes [10]. In a one-stage cohort study by A.T. Makhieva et al., involving 84 patients with stage 5 chronic kidney disease (CKD), decreased blood levels of fetuin-A contributed to an increased risk of heart valve and aortic wall calcification both alone and in combination with decreased Klotho protein levels [35].

In addition, the work by L.B. Drygina et al. presented data on the relationship of fetuin-A levels with markers of endothelial dysfunction and the presence of atherosclerosis with vascular calcification [32]. Moreover, it was found that in individuals with very high calcium score (more than 400 Agatston units), the level of fetuin-A in serum was significantly lower than in patients with high calcium score (100–400 units) [36].

Matrix Gla Protein

Matrix gamma-carboxyglutamic acid protein (Gla protein, MGP) is a vitamin K-dependent mineral-binding protein with a molecular weight of 15 kDa, present in bone, cartilage, and vascular smooth muscles [37]. The biological activity of MGP depends on vitamin K, a cofactor for the enzyme gamma-glutamyl carboxylase, which converts inactive uncarboxylated MGP to active carboxylated MGP [38]. MGP also serves as an inhibitor of BMPs, in particular BMP-2. It is proposed that decreased MGP activity leads to unimpeded expression of BMP-2, which leads to osteochondrogenic differentiation of vascular smooth muscle cells and, subsequently, to vascular calcification. [39].

There are conflicting data on the role of MGP in patients with atherosclerosis. It is suggested that only the functional form of MGP (post-translationally modified, including carboxylated Gla residues and phosphorylated serine hydroxyl groups) has the ability to inhibit vascular calcification. However, low levels of this functional MGP are associated with increased vascular calcification in certain patient groups. At the same time, various non-functional fractions of MGP may serve as potential markers of CVD risk, correlating with cardiovascular mortality and the severity of vascular calcification.

Biologically inactive dephospho-uncarboxylated MGP (dp-ucMGP) in the study by O. Mayer Jr. et al. was described as a potential biomarker for predicting mortality in patients with heart failure and aortic stenosis. Over a mean follow-up period of 2,050 days (5.6 years), patients with plasma dp-ucMGP ≥ 977 pmol / l had a higher risk of five-year all-cause and cardiovascular mortality [40]. The study by R. Capoulade et al. showed that the total dpMGP level was associated with a faster rate of aortic stenosis progression ($r = 0.24$; $p = 0.008$) in patients under 57 years [41].

In a multicenter study by A. A. Berlot et al., a positive association was found between the inactive form of matrix Gla protein, dp-ucMGP, and the progression of coronary artery calcification, ascending (ATAC), and descending thoracic aorta (DTAC) calcification. For each standard deviation (SD, 178 pmol / l) in the increase in plasma dp-ucMGP, CAC increased by 3.44 Agatston units per year (AU / year) (95% confidence interval (CI): 1.68–5.21), $p < 0.001$), ATAC increased by 0.63 AU / year (95% CI: 0.27–0.98), $p = 0.001$), and DTAC increased by 8.61 AU / year (95% CI: 4.55–12.67), $p < 0.001$) [42].

In addition, there is increasing evidence suggesting that multiple single nucleotide polymorphisms in the *MGP* gene may significantly influence susceptibility to vascular calcification and atherosclerosis. A meta-analysis by K. Sheng et al., including 23 case-control studies, demonstrated a significant association between the rs1800801 polymorphism in the *MGP* gene and vascular calcification, especially in the Caucasian population [43].

Fibroblast Growth Factor 23 (FGF-23)

Fibroblast growth factor 23 (FGF-23) is a 30-kDa hormone secreted by osteocytes and osteoblasts. It affects fibroblast growth factor receptors type 1–4 (FGFR1–4) and acts with the Klotho protein as a co-receptor in the kidneys, heart, intestines, and parathyroid gland [14, 15]. The role of FGF-23 in the development of CVD and calcification of atherosclerotic plaques is not completely clear.

In a prospective study by P. L. Lutsey et al., involving 15,792 men and women (aged 45–64 years), high serum FGF-23 levels were associated with an increased risk of CHD, heart failure, and cardiovascular mortality. However, at FGF-23 levels < 40 pg / ml, no association between FGF-23 and cardiovascular risk was noted, and at > 40 pg / ml, a positive association was observed. After

demographic adjustments, individuals in the group with the highest FGF-23 (≥ 58.8 pg / ml) had a higher risk of CHD (adjusted hazard ratio, 95% CI: 1.40–1.94, $p = 0.02$) compared to those with FGF-23 < 40 pg / ml [44].

The Multinational Study of Atherosclerosis (MESA) was conducted to evaluate the association of serum FGF-23 with major subclinical and clinical CVD events in 6,546 individuals aged 45–85 years. Exclusion criteria for this study were MI, angina, stroke, transient ischemic attack, heart failure, atrial fibrillation, nitroglycerin consumption, angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator placement, and any cardiac or arterial surgery. Participants with serum FGF-23 concentrations in the upper quartile (46.4–223 pg / ml) were found to have CAC (as determined by computed tomography (CT)) more often than those with FGF-23 levels in the lower quartile (< 30.5 pg / ml) (95% CI: 1.09–1.46) [45].

In a cross-sectional study by M.N. Turan et al., high plasma intact FGF-23 levels were an independent predictor of severe CAC, after adjustment for age, gender, diabetes, time on dialysis, and intima – media thickness [46]. A prospective cohort study of 204 outpatients found a positive association between plasma FGF-23 levels and plaque calcification. In men, FGF-23 was associated with an increase in the proportion of fat in plaques, while in women, it was associated with increased calcium content in these formations [47]. However, not all studies showed that the level of FGF-23 was reliably associated with arterial calcification. Thus, in the study by Y. Takashi Y., the simple regression analysis showed that the serum level of FGF23 was not associated with the aortic calcification index [48].

Pyrophosphates

Inorganic pyrophosphate (PPi) is one of the strongest inhibitors of hydroxyapatite formation, which leads to its ectopic deposition in the vascular wall, and, consequently, to the development of vascular calcification in soft tissues. Normally, PPi is expressed in the walls of blood vessels. Vascular calcification is associated with a decrease in PPi concentration and an increase in phosphate (Pi) levels. Mutations in the *ABCC6* gene (*ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 6*), encoding the ABCC6 transporter protein, which regulates the release of ATP from the liver into the blood, lead to a decrease in PPi levels. In addition to ABC proteins, PPi levels are regulated primarily by two enzymes: tissue-nonspecific alkaline phosphatase (TNAP), which converts PPi into two molecules of inorganic phosphate (Pi), and ectonucleotide pyrophosphatase / phosphodiesterase 1 (ENPP-1), which breaks down circulating adenosine triphosphate (ATP) into adenosine monophosphate (AMP) and PPi [49–51].

PPi deficiency can lead to vascular and soft tissue calcification, while excessive PPi elevation can cause premature loss of deciduous teeth, osteomalacia, stress fractures, etc. [52]. A study by D. Dedinszki et al. showed that orally administered PPi can suppress connective tissue calcification in mice modeling pseudoxanthoma elasticum and generalized arterial calcification [11].

The study by W. Gu et al. aimed to investigate the effects of adenosine disodium triphosphate (ADTP) and sodium alendronate (AL) as exogenous sources of PPi on atheromatous calcification in mice. The results showed that ADTP and AL, when administered intraperitoneally daily at a dose of 0.6 and 1.2 mg / kg / day for 2 months, reduced atheromatous calcification in mice by increasing serum PPi levels [53]. In a study by K.A. Lomashvili et al., it was shown that mice lacking the ENPP1 enzyme (Enpp1−/-) had reduced plasma PPi levels, which could subsequently cause spontaneous aortic calcification [12]. A number of studies on aortic valve calcification models showed that PPi significantly reduced calcium accumulation in aortic cusps and rings [54–56].

Bone Morphogenetic Proteins

BMPs belong to the transforming growth factor β (TGFβ) superfamily and regulate cellular differentiation and tissue mineralization [17]. Currently, at least 33 ligands have been identified in the TGFβ protein family, of which more than 20 belong to the BMP superfamily [57].

BMP-7 is expressed in the collecting ducts of the kidneys, lungs, and heart. BMP-7 is a pleiotropic growth factor and plays a critical role in the development of various tissues and organs. It supports many physiological processes, such as bone development, fracture healing, and brown adipose

tissue differentiation in the body. Decreased BMP-7 expression is associated with various diseases, including osteoporosis, CVD, and diabetes [58].

In the context of CVD, BMP-7 has attracted the attention of researchers due to its ability to participate in processes associated with atherosclerosis. It can modulate inflammatory responses and promote vascular wall remodeling, which potentially reduces the progression of atherosclerosis. [59]. A study by D. Merino et al. showed an inverse correlation between blood BMP-7 levels and cardiac hypertrophy, as well as diastolic dysfunction [60]. In a study by X. Yu et al., it was found that serum BMP-7 concentrations were significantly reduced in patients with CHD [61]. A study in mice showed that intravenous administration of BMP-7 at a dose of 200 μg / kg inhibited the formation of atherosclerotic plaques [62]. In a study by P. Urbina et al., it was shown that in laboratory mice with prediabetic cardiomyopathy, administration of BMP-7 at a dose of 200 μg / kg for 3 days significantly improved cardiac function, as evidenced by an increase in the shortening fraction and ejection fraction compared to the control group that did not receive BMP-7 ($p < 0.05$) [63].

CALCIFICATION ACTIVATORS

Leptin

Leptin is a hormone secreted mainly by adipose tissue. It regulates energy balance and body weight through a negative feedback mechanism [64, 65]. Leptin affects vascular calcification through activation of smooth muscle cell proliferation and production of proinflammatory cytokines [18].

Many studies have shown that hyperleptinemia is closely associated with CVD. Thus, a meta-analysis by V. A. Myasoedova et al., including 10 studies involving 2,360 patients, indicated a potential link between elevated blood leptin levels and severe aortic stenosis [66].

In a study by P. Szulc et al., involving 548 men aged 50–85 years, high serum leptin levels (> 8.93 ng / ml) were associated with greater severity and rapid progression of abdominal aortic calcification, resulting in higher cardiovascular risk [18] and also increased the risk of developing CHD [67].

In a study by Y. Liu et al., the median serum leptin level was higher in 200 patients with aortic valve calcification than in 197 controls (20.07 vs. 9.03 ng / ml; $p < 0.01$). In the same study, patients with aortic valve calcification had a higher proportion of advanced CHD (88.50 vs. 68.00%) ($p < 0.01$) than patients without calcification [68].

N. Roy et al. found that higher leptin levels were associated with progression of coronary atherosclerosis in patients on hemodialysis. However, lower leptin levels were associated with all-cause mortality [69]. A meta-analysis including 13 epidemiological studies involving 4,257 patients with CVD showed that high blood leptin levels were not independently associated with CHD [70].

BMP-2 and BMP-4

BMP-2 and BMP-4 affect VSMCs through transcription proteins (Msx2, Cbfa1), as a result of which muscle cells lose their contractile function and, like osteoblasts, synthesize alkaline phosphatase, bone sialoprotein, type I collagen, and osteocalcin [71]. Thus, BMP-2 and BMP-4 stimulate osteogenic differentiation of VSMCs, thereby promoting calcification and the development of atherosclerosis [19].

In the study by M. Scimeca et al., the multivariate analysis showed significant associations between increased BMP-2 expression and the presence of unstable plaques, as well as a significant positive relationship between hypertriglyceridemia and BMP-4 expression [20].

In the study by M. Zhang et al., involving 124 patients with type 2 diabetes, it was found that plaque volume index and plaque calcium density were positively correlated with BMP-2 in blood plasma ($p = 0.035$ and $p = 0.0025$, respectively) [72].

N. Wang et al., examining 204 patients with hypertension, found that plasma BMP-4 levels were significantly higher in the group with high cardio-ankle vascular index (CAVI) than in the group with low CAVI [38.51 (31.79–50.83) pg / ml vs. 31.15 (29.38–32.37) pg / ml; $p < 0.001$]. CAVI was used to determine the state of arterial stiffness [73].

Parathyroid Hormone

Parathyroid hormone (PTH) is a hormone synthesized by the parathyroid glands that increases the concentration of calcium in the blood due to its

release from bone tissue. In addition, PTH activates the renin – angiotensin – aldosterone system, which results in an increase in renin levels and, ultimately, in an increase in blood pressure [74].

There are studies on the relationship between PTH and vascular calcification [21]. A group of authors [75] showed that an increase in PTH levels in blood plasma was associated with an increase in the prevalence of atherosclerosis, assessed by magnetic resonance angiography, and mortality from atherosclerotic lesions of peripheral and large vessels in two independent cohorts with a total of 1,304 patients.

It was also found that PTH had a synergistic effect on calcification in combination with phosphate. In a study conducted by S. Fernández-Villabrille et al. on rats, it was found that the highest calcium content in the aorta was observed in animals with elevated serum phosphate levels, which was accompanied by a significant increase in PTH concentrations [76].

Calcitriol

Calcitriol [1,25(OH)2D] is an active form of vitamin D3 (cholecalciferol), which plays an important role in the regulation of calcium and phosphorus metabolism. Calcitriol precursors include calcidiol (25-hydroxyvitamin D [25(OH) D]), low circulating concentrations of which are commonly used to define vitamin D deficiency [77].

There are conflicting data on the role of calcidiol (25-hydroxyvitamin D [25(OH)D]) in vascular calcification and its association with CVD incidence and mortality. In the study by C. Robinson-Cohen et al., lower serum 25(OH)D concentrations were associated with an increased risk of CHD among participants who were Caucasian or Chinese, but not African American or Hispanic [78].

In a study of 11,022 patients (mean age 54.3 ± 17.2 years), Caucasians with 25(OH)D values < 20 ng / ml had higher all-cause mortality than those whose 25(OH)D was 20–50 ng / ml [79].

Other studies suggest an inverse J-shaped relationship between serum 25(OH)D and all-cause mortality [80]. In a study by C.T. Sempos et al., involving 15,099 individuals aged ≥ 20 years, women were found to have an increased risk of death when blood 25(OH)D concentrations ranged from 100 to 119 nmol / l, whereas for men, the increased risk occurred at values ≥ 120 nmol / l [81].

CONCLUSION

Understanding and more detailed study of biomolecules involved in the development and progression of vascular calcification in patients with CVD is a promising area of research. Data on the relationships of various molecules associated with calcium metabolism with lipid and lipoprotein indices and / or inflammatory biomarkers of CVD may be of interest for obtaining new data clarifying and complementing the mechanisms of development of CVD and its complications.

REFERENCES

1. Boytsov S.A., Pogosova S.A., Ansheles A.A., Badtieva V.A., Balakhonova T.V., Barbarash O.L. et al. Cardiovascular Prevention 2022. Russian National Guidelines. *Russian Journal of Cardiology*. 2023;28(5):5452. (In Russ.). DOI: 10.15829/1560-4071-2023-5452.
2. Begun D.N., Morozova T.A., Surikova A.V. Circulatory Disorders as a Medical and Social Problem. *Young Scientist.* 2019;8(246):25–28. (In Russ.).
3. Ragino Yu. I. Unstable Atherosclerotic Plaque and Its Laboratory Biochemical Markers. Novosibirsk: Nauka, 2019:120. (In Russ.).
4. Sergienko I.V., Ansheles A.A. Pathogenesis, Diagnosis, and Treatment of Atherosclerosis: Practical Aspects. *Russian Cardiology Bulletin.* 2021;16(1):64–72. (In Russ.). DOI: 10.17116/Cardiobulletin20211601164.
5. Kashtanova E.V., Polonskaya Ya.V., Ragino Yu.I. Calcification of Coronary Arteries and Its Role in Atherosclerosis Development. *Terapevticheskii Arkhiv.* 2021;93(1):84–86. (In Russ.). DOI: 10.26442/00403660.2021.01.200598.
6. Barbarash O.L., Kashtalap V.V., Shibanova I.A., Kokov A.N. Fundamental and Applied Aspects of Coronary Artery Calcification. *Russian Journal of Cardiology*. 2020;25(3S):40–49. (In Russ.). DOI: 10.15829/1560-4071-2020-4005.
7. Torii S., Sato Y., Otsuka F., Kolodgie F.D., Jinnouchi H., Sakamoto A., et al. Eruptive calcified nodules as a potential mechanism of acute coronary thrombosis and sudden death. *J. Am. Coll. Cardiol*. 2021;77(13):1599–1611. DOI: 10.1016/j.jacc.2021.02.016.
8. Abdalrhim A.D., Marroush T.S., Austin E.E., Gersh B.J., Solak N., Rizvi S.A. et al. Plasma Osteopontin Levels and Adverse Cardiovascular Outcomes in the PEACE Trial. *PLoS One.* 2016;11(6):e0156965. DOI: 10.1371/journal.pone.0156965.
9. Morena M., Jaussent I., Dupuy A.M., Bargnoux A.S., Kuster N., Chenine L. et al. Osteoprotegerin and sclerostin in chronic kidney disease prior to dialysis: potential partners in vascular calcifications. *Nephrol. Dial Transplant*. 2015;30(8):1345–1356. DOI: 10.1093/ndt/gfv081.
10. Krajnc M., Pečovnik Balon B., Krajnc I. Non-traditional risk factors for coronary calcification and its progression in patients with type 2 diabetes: The impact of postprandial

glycemia and fetuin-A. *J. Int. Med. Res*. 2019;47(2):846–858. DOI: 10.1177/0300060518814080.
11. Dedinszki D., Szeri F., Kozák E., Pomozi V., Tőkési N., Mezei T.R. et al. Oral administration of pyrophosphate inhibits connective tissue calcification. *EMBO Mol. Med*. 2017;9(11):1463–1470. DOI: 10.15252/emmm.201707532.
12. Lomashvili K.A., Narisawa S., Millán J.L., O'Neill W.C. Vascular calcification is dependent on plasma levels of pyrophosphate. *Kidney Int*. 2014;85(6):1351–1356. DOI: 10.1038/ki.2013.521.
13. Marulanda J., Eimar H., McKee M.D., Berkvens M., Nelea V., Roman H. et al. Matrix Gla protein deficiency impairs nasal septum growth, causing midface hypoplasia. *J. Biol. Chem*. 2017;292(27):11400–11412. DOI: 10.1074/jbc.M116.76980224.
14. Alehagen U., Aaseth J., Larsson A., Alexander J. Decreased Concentration of Fibroblast Growth Factor 23 (FGF-23) as a Result of Supplementation with Seleniumand Coenzyme Q10 in an Elderly Swedish Population: ASub-Analysis. *Cells.* 2022;11(3):509. DOI: 10.3390/cells11030509.
15. Xiao Y., Peng C., Huang W., Zhang J., Xia M., Zhang Y. et al. Circulating fibroblast growth factor 23 is associated with angiographic severity and extent of coronary artery disease. *PLoS One*. 2013;8(8):e72545. DOI: 10.1371/journal.pone.0072545.
16. Bergmark B.A., Udell J.A., Morrow D.A., Jarolim P., Kuder J.F., Solomon S.D. et al. Klotho, fibroblast growth factor-23, and the renin-angiotensin system - an analysis from the PEACE trial. *Eur. J. Heart Fail.* 2019;21(4):462–470. DOI: 10.1002/ejhf.1424.
17. Morrell N.W., Bloch D.B., ten Dijke P., Goumans M.J., Hata A., Smith J. et al. Targeting BMP signalling in cardiovascular disease and anaemia. *Nat. Rev. Cardiol*. 2016;13(2):106–120. DOI: 10.1038/nrcardio.2015.156.
18. Szulc P., Amri E.Z., Varennes A., Panaia-Ferrari P., Fontas E., Goudable J. et al. Positive Association of High Leptin Level and Abdominal Aortic Calcification in Men - The Prospective MINOS Study. *Circ. J.* 2018; 82(12):2954–2961. DOI: 10.1253/circj.CJ-18-0517.
19. Yang P., Troncone L., Augur Z.M., Kim S.S.J., McNeil M.E., Yu P.B. The role of bone morphogenetic protein signaling in vascular calcification. *Bone*. 2020; 141:115542. DOI: 10.1016/j.bone.2020.115542.
20. Scimeca M., Anemona L., Granaglia A., Bonfiglio R., Urbano N., Toschi N.et al. Plaque calcification is driven by different mechanisms of mineralization associated with specific cardiovascular risk factors. *Nutr. Metab. Cardiovasc. Dis.* 2019; 29(12):1330–1336. DOI: 10.1016/j.numecd.2019.08.009.
21. Carrillo-López N., Panizo S., Alonso-Montes C., Martínez-Arias L., Avello N., Sosa P. et al. High-serum phosphate and parathyroid hormone distinctly regulate bone loss and vascular calcification in experimental chronic kidney disease. *Nephrol. Dial Transplant*. 2019;34(6):934–941. DOI: 10.1093/ndt/gfy287.
22. Hahn D., Hodson E.M., Craig J.C. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database Syst. Rev*. 2015; 2015(11):CD008327. DOI: 10.1002/14651858.CD008327.pub2.
23. He F., Li L., Li P., Deng Y., Yang Y., Deng Y. et al. Cyclooxygenase-2/sclerostin mediates TGF-β1-induced calcification in vascular smooth muscle cells and rats undergoing renal failure. *Aging (Albany NY)*. 2020;12:21220–21235. DOI: 10.18632/aging.103827.
24. Yu S., Huang W., Zhang H., Guo Y., Zhang B., Zhang G., et al. Discovery of the small molecular inhibitors against sclerostin loop3 as potential anti-osteoporosis agents by structural based virtual screening and molecular design. *Eur. J. Med. Chem*. 2024;271:116414. DOI: 10.1016/j.ejmech.2024.116414.
25. Galea G.L., Lanyon L.E., Price J.S. Sclerostin's role in bone's adaptive response to mechanical loading. *Bone.* 2017;96:38–44. DOI: 10.1016/j.bone.2016.10.008.
26. He W., Li C., Chen Q., Xiang T., Wang P., Pang J. Serum sclerostin and adverse outcomes in elderly patients with stable coronary artery disease undergoing percutaneous coronary intervention. *Aging Clin. Exp. Res*. 2020;32(10):2065–2072. DOI: 10.1007/s40520-019-01393-2.
27. Yang C.Y., Chang Z.F., Chau Y.P., Chen A., Yang W.C., Yang A.H. et al. Circulating Wnt/β-catenin signalling inhibitors and uraemic vascular calcifications. *Nephrol. Dial Transplant.* 2015;30(8):1356–1363. DOI: 10.1093/ndt/gfv043.
28. Krishna S.M., Seto S.W., Jose R.J., Li J., Morton S. K., Biros E. et al. Wnt signaling pathway inhibitor sclerostin inhibits angiotensin ii-induced aortic aneurysmand atherosclerosis. *Arterioscler. Thromb. Vasc. Biol*. 2017;37(3):553–566. DOI: 10.1161/ATVBAHA.116.308723.
29. Klingenschmid G., Tschiderer L., Himmler G., Rungger G., Brugger S., Santer P. et al. Associations of Serum Dickkopf-1 and Sclerostin With Cardiovascular Events: Results From the Prospective Bruneck Study. *J. Am. Heart Assoc*. 2020;9(6):e014816. DOI: 10.1161/JAHA.119.014816.
30. Kanbay M., Solak Y., Siriopol D., Aslan G., Afsar B., Yazici D. et al. Sclerostin, cardiovascular disease and mortality: a systematic review and meta-analysis. *Int. Urol. Nephrol.* 2016;48(12):2029–2042. DOI: 10.1007/s11255-016-1387-8.
31. Brylka L., Jahnen-Dechent W. The role of fetuin-A in physiological and pathological mineralization. *Calcif Tissue Int.* 2013;93(4):355–364. DOI: 10.1007/s00223-012-9690-6.
32. Drygina L.B., Khirmanov V.N. Clinical and Laboratory Markers of Atherosclerotic Calcification. *Medical Alphabet*. 2021;1(30):43–47. (In Russ.). DOI: 10.33667/2078-5631-2021-30-43-47.
33. Laugsand L.E., Ix J.H., Bartz T.M., Djousse L., Kizer J.R., Tracy R.P. et al. Fetuin-A and risk of coronary heart disease: A Mendelian randomization analysis and a pooled analysis of AHSG genetic variants in 7 prospective studies. *Atherosclerosis*. 2015;243(1):44–52. DOI: 10.1016/j.atherosclerosis.2015.08.031.

34. Kubota N., Testuz A., Boutten A., Robert T., Codogno I., Duval X. et al. Impact of fetuin-A on progression of calcific aortic valve stenosis - The COFRASA - GENERAC study. *Int. J. Cardiol.* 2018;265:5257. DOI: 10.1016/j.ijcard.2018.03.070.
35. Makhieva A.T., Mambetova A.M. Fetuin-A as a Marker for Assessing the Risk of Mineral and Bone Disorders and Coronary Artery Calcification in Patients with Chronic Stage 5 Kidney Disease. *Nephrology*. 2022;26(4):105–109. (In Russ.). DOI: 10.36485/1561-6274-2022-26-4-105-109.
36. Drygina L.B., Khirmanov V.N. Coronary Artery Calcification and Metabolic Disorders in Chernobyl Disaster Liquidators. *Medico-Biological and Socio-Psychological Problems of Safety in Emergency*. 2021;(2):11–17. (In Russ.). DOI: 10.25016/2541-7487-2021-0-2-11-17.
37. Bjørklund G., Svanberg E., Dadar M., Card D.J., Chirumbolo S., Harrington D.J. et al. The role of matrix gla protein (MGP) in vascular calcification. *Curr. Med. Chem.* 2020;27(10):1647–1660. DOI: 10.2174/0929867325666180716104159.
38. Chin K.Y. The Relationship between Vitamin K and Osteoarthritis: A Review of Current Evidence. *Nutrients.* 2020;12(5):1208. DOI: 10.3390/nu12051208.
39. Durham A.L., Speer M.Y., Scatena M., Giachelli C.M., Shanahan C.M. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. *Cardiovasc. Res*. 2018;114(4):590–600. DOI: 10.1093/cvr/cvy010.
40. Mayer O. Jr., Seidlerová J., Bruthans J., Filipovský J., Timorácká K., Vaněk J. et al. Desphospho-uncarboxylated matrix Gla-protein is associated with mortality risk in patients with chronic stable vascular disease. *Atherosclerosis*. 2014;235(1):162–168. DOI: 10.1016/j.atherosclerosis.2014.04.027.
41. Capoulade R., Côté N., Mathieu P., Chan K.L., Clavel M.A., Dumesnil J.G. et al. Circulating levels of matrix gla protein and progression of aortic stenosis: a substudy of the Aortic Stenosis Progression Observation: Measuring Effects of rosuvastatin (ASTRONOMER) Trial. *Can. J. Cardiol.* 2014;30(9):1088–1095. DOI: 10.1016/j.cjca.2014.03.025.
42. Berlot A.A., Fu X., Shea M.K., Tracy R., Budoff M., Kim R.S. et al. Matrix Gla protein and the long-term incidence and progression of coronary artery and aortic calcification in the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2024;392:117505. DOI: 10.1016/j.atherosclerosis.2024.117505.
43. Sheng K., Zhang P., Lin W., Cheng J., Li J., Chen J. Association of Matrix Gla protein gene (rs1800801, rs1800802, rs4236) polymorphism with vascular calcification and atherosclerotic disease: a meta-analysis. *SciRep*. 2017;7(1):8713. DOI: 10.1038/s41598-017-09328-5.
44. Lutsey P.L., Alonso A., Selvin E., Pankow J.S., Michos E.D., Agarwal S.K. et al. Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and cardiovascular mortality: the Atherosclerosis Risk in Communities study. *J. Am. Heart Assoc*. 2014;3(3):e000936. DOI: 10.1161/JAHA.114.000936.
45. Kestenbaum B., Sachs M.C., Hoofnagle A.N., Siscovick D.S., Ix J.H., Robinson-Cohen C. et al. Fibroblast growth factor-23 and cardiovascular disease in the general population: the Multi-Ethnic Study of Atherosclerosis. *Circ. Heart Fail*. 2014;7(3):409–417. DOI: 10.1161/CIRCHEARTFAILURE.113.000952.
46. Turan M.N., Kircelli F., Yaprak M., Sisman A.R., Gungor O., Bayraktaroglu S. et al. FGF-23 levels are associated with vascular calcification, but not with atherosclerosis, in hemodialysis patients. *Int. Urol. Nephrol*. 2016;48(4):609–617. DOI: 10.1007/s11255-016-1231-1.
47. Holden R.M., Hétu M.F., Li T.Y., Ward E., Couture L.E., Herr J.E. et al. The heart and kidney: abnormal phosphate homeostasis is associated with atherosclerosis. *J. Endocr. Soc*. 2018;3(1):159–170. DOI: 10.1210/js.2018-00311.
48. Takashi Y., Wakino S., Minakuchi H., Ishizu M., Kuroda A., Shima H. et al. Circulating FGF23 is not associated with cardiac dysfunction, atherosclerosis, infection or inflammation in hemodialysis patients. *J. Bone Miner. Metab.* 2020;38(1):70–77. DOI: 10.1007/s00774-019-01027-7.
49. Murcia Casas B., Carrillo Linares J.L., Baquero Aranda I., Rioja Villodres J., Merino Bohórquez V., González Jiménez A. et al. Lansoprazole Increases Inorganic Pyrophosphate in Patients with Pseudoxanthoma Elasticum: A Double-Blind, Randomized, Placebo-Controlled Crossover Trial. *Int. J. Mol. Sci*. 2023;24(5):4899. DOI: 10.3390/ijms24054899.
50. Bartstra J.W., de Jong P.A., Kranenburg G., Wolterink J.M., Isgum I., Wijsman A. et al. Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum. *Atherosclerosis*. 2020;292:37–41. DOI: 10.1016/j.atherosclerosis.2019.10.004.
51. Jansen R.S., Duijst S., Mahakena S., Sommer D., Szeri F., Váradi A. et al. ABCC6-mediated ATP secretion by the liver is the main source of the mineralization inhibitor inorganic pyrophosphate in the systemic circulation-brief report. *Arterioscler. Thromb. Vasc. Biol.* 2014;34(9):1985–1989. DOI: 10.1161/ATVBAHA.114.304017.
52. Maruyama S., Visser H., Ito T., Limsakun T., Zahir H., Ford D. et. al. Phase I studies of the safety, tolerability, pharmacokinetics, and pharmacodynamics of DS-1211, a tissue-nonspecific alkaline phosphatase inhibitor. *Clin. Transl. Sci*. 2022;15(4):967–980. DOI: 10.1111/cts.13214.
53. Gu W., Wei Y., Tang Y., Zhang S., Li S., Shi Y. et al. Supplement of exogenous inorganic pyrophosphate inhibits atheromatous calcification in Apolipoprotein E knockout mice. *Heliyon.* 2023;9(8):e19214. DOI: 10.1016/j.heliyon.2023.e19214.
54. Rathan S., Yoganathan A.P., O'Neill C.W. The role of inorganic pyrophosphate in aortic valve calcification. *J. Heart Valve Dis*. 2014;23(4):387–394.
55. Villa-Bellosta R. Synthesis of extracellular pyrophosphate increases in vascular smooth muscle cells during phosphate-induced calcification. *Arterioscler. Thromb. Vasc. Biol*. 2018;38(9):2137–2147. DOI: 10.1161/ATVBAHA.118.311444. PMID: 30002059.

56. Rattazzi M., Bertacco E., Iop L., D'Andrea S., Puato M., Buso G. et al. Extracellular pyrophosphate is reduced in aortic interstitial valve cells acquiring a calcifying profile: implications for aortic valve calcification. *Atherosclerosis.* 2014;237(2):568–576. DOI: 10.1016/j.atherosclerosis.2014.10.027.
57. Tang H., Zhang X., Xue G., Xu F., Wang Q., Yang P. et al. The biology of bone morphogenetic protein signaling pathway in cerebrovascular system. *Chin. Neurosurg. J.* 2021;7(1):36. DOI: 10.1186/s41016-021-00254-0.
58. Aluganti Narasimhulu C., Singla D.K. The role of bone morphogenetic protein 7 (BMP-7) in inflammation in heart diseases. *Cells.* 2020;9(2):280. DOI: 10.3390/cells9020280.
59. Elmadbouh I., Singla D.K. BMP-7 Attenuates inflammation-induced pyroptosis and improves cardiac repair in diabetic cardiomyopathy. *Cells.* 2021;10(10):2640. DOI: 10.3390/cells10102640.
60. Merino D., Villar A.V., García R., Tramullas M., Ruiz L., Ribas C. et al. BMP-7 attenuates left ventricular remodelling under pressure overload and facilitates reverse remodelling and functional recovery. *Cardiovasc. Res*. 2016;110(3):331–345. DOI: 10.1093/cvr/cvw076.
61. Yu X., Guan W., Zhang Y., Deng Q., Li J., Ye H. et al. Large-scale gene analysis of rabbit atherosclerosis to discover new biomarkers for coronary artery disease. *Open Biol*. 2019;9(1):180238. DOI: 10.1098/rsob.180238.
62. Singla D.K., Singla R., Wang J. BMP-7 Treatment increases m2 macrophage differentiation and reduces inflammation and plaque formation in Apo E-/-mice. *PLoS One*. 2016;11(1):e0147897. DOI: 10.1371/journal.pone.0147897.
63. Urbina P., Singla D.K. BMP-7 attenuates adverse cardiac remodeling mediated through M2 macrophages in prediabetic cardiomyopathy. *Am. J. Physiol. Heart Circ. Physiol.* 2014;307(5):H762–772. DOI: 10.1152/ajpheart.00367.2014.
64. Wang C., Chang L., Wang J., Xia L., Cao L., Wang W. et al. Leptin and risk factors for atherosclerosis: A review. *Medicine (Baltimore).* 2023;102(46):e36076. DOI: 10.1097/MD.0000000000036076.
65. Sweeney T., Ogunmoroti O., Ndumele C.E., Zhao D., Varma B., Allison M.A. et al. Associations of adipokine levels with the prevalence and extent of valvular and thoracic aortic calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* 2021;338:15–22. DOI: 10.1016/j.atherosclerosis.2021.11.002.
66. Myasoedova V.A., Bertolini F., Valerio V., Moschetta D., Massaiu I., Rusconi V. et al. The Role of Adiponectin and Leptin in Fibro-Calcific Aortic Valve Disease: A Systematic Review and Meta-Analysis. *Biomedicines.* 2024;12(9):1977. DOI: 10.3390/biomedicines12091977.
67. Criqui M.H., Denenberg J.O., McClelland R.L., Allison M.A., Ix J.H., Guerci A. et al. Abdominal aortic calcium, coronary artery calcium, and cardiovascular morbidity and mortality in the Multi-Ethnic Study of Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 2014;34(7):1574–1579.
68. Liu Y., Gu Y., Shen Y., Lin B., Li Y., He X. et al. association between serum leptin level and calcific aortic valve disease. *J. Am. Heart Assoc*. 2019;8(19):e012495. DOI: 10.1161/JAHA.119.012495.
69. Roy N., Haddad D., Yang W., Rosas S.E. Adipokines and coronary artery calcification in incident dialysis participants. *Endocrine*. 2022;77(2):272–280. DOI: 10.1007/s12020-022-03111-x.
70. Yang H., Guo W., Li J., Cao S., Zhang J., Pan J. et al. Leptin concentration and risk of coronary heart disease and stroke: A systematic review and meta-analysis. *PloS One*. 2017;12(3):e0166360. DOI: 10.1371/journal.pone.0166360.
71. Patidar A., Singh D.K., Winocour P., Farrington K., Baydoun A.R. Human uraemic serum displays calcific potential in vitro that increases with advancing chronic kidney disease. *Clin. Sci. (Lond.).* 2013;125:237–245. DOI: 10.1042/CS20120638.
72. Zhang M., Sara J.D., Wang F.L., Liu L.P., Su L.X., Zhe J. et al. Increased plasma BMP-2 levels are associated with atherosclerosis burden and coronary calcification in type 2 diabetic patients. *Cardiovasc Diabetol*. 2015;14:64. DOI: 10.1186/s12933-015-0214-3.
73. Wang N., Guo Y., Dong Y., Li X., Liu Q., Liu Q. et al. Association of plasma bone morphogenetic protein-4 levels with arterial stiffness in hypertensive patients. *J. Clin. Lab. Anal.* 2022;36(11):e24746. DOI: 10.1002/jcla.24746.
74. Feng M., Xu M., Wang Q., Xia S., Yu C., Li M. et al. Association of parathyroid hormone with risk of hypertension and type 2 diabetes: a dose-response meta-analysis. *BMC Cardiovasc. Disord.* 2024;24(1):13. DOI: 10.1186/s12872-023-03682-1.
75. Hagström E., Michaëlsson K., Melhus H., Hansen T., Ahlström H., Johansson L. et al. Plasma-parathyroid hormone is associated with subclinical and clinical atherosclerotic disease in 2 community-based cohorts. *Arterioscler. Thromb. Vasc. Biol.* 2014;34(7):1567–1573. DOI: 10.1161/ATVBAHA.113.303062.
76. Fernández-Villabrille S., Martín-Vírgala J., Martín-Carro B., Baena-Huerta F., González-García N., Gil-Peña H. et al. RANKL, but Not R-spondins, is involved in vascular smooth muscle cell calcification through LGR4 interaction. *Int. J. Mol. Sci*. 2024;25(11):5735. DOI: 10.3390/ijms25115735.
77. Hsu S., Prince D.K., Williams K., Allen N.B., Burke G.L., Hoofnagle A.N.et al. Clinical and biomarker modifiers of vitamin D treatment response: the Multi-Ethnic Study of Atherosclerosis. *Am. J. Clin. Nutr*. 2022;115(3):914–924. DOI: 10.1093/ajcn/nqab390.
78. Robinson-Cohen C., Hoofnagle A.N., Ix J.H., Sachs M.C., Tracy R.P., Siscovick D.S. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. *JAMA*. 2013;310(2):179–188. DOI: 10.1001/jama.2013.7228.
79. Dudenkov D.V., Mara K.C., Petterson T.M., Maxson J.A., Thacher T.D. Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study. *Mayo*

Clin. Proc. 2018;93(6):721–730. DOI: 10.1016/j.mayocp.2018.03.006.
80. Amrein K., Quraishi S.A., Litonjua A. ., Gibbons F.K., Pieber T.R., Camargo C.A. et al. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. *J. Clin. Endocrinol. Metab*. 2014;99(4):1461–1469. DOI: 10.1210/jc.2013-3481.
81. Sempos C.T., Durazo-Arvizu R.A., Dawson-Hughes B., Yetley E.A., Looker A.C., Schleicher R L. et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. *J. Clin. Endocrinol. Metab*. 2013;98(7):3001–3009. DOI: 10.1210/jc.2013-1333.

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