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Biomineralogical Phenomenon of Mineralization (Calcification) of Arteries

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Abstract

The theory of biomineralization of human arteries was presented. The causes of formation of crystallization centers in the arteries and their types were discussed. Selected types of arterial mineralization were described.

Keywords: Arteries; Biomineralization

Introduction

Calcification of arteries is a phenomenon commonly known and widely studied because of its importance to human health and life. Extensive literature that deals with this topic can be divided into three parts: The most extensive portion of the publications concerns the description of the phenomenon of atherosclerosis in its various aspects [1, -30]. A significant number of scientists are also involved in searching for the causes of atherosclerosis, often represented by so-called "atherosclerotic plaque" [31-50]. On the other hand, the number of publications on research into the prevention and elimination of deposits in blood vessels is noticeably smaller [51-61]. The importance of atherosclerosis for the functioning of the whole organism is difficult to overestimate.

Biomineralisation is a phenomenon of mineralization (often crystallization) on biological substrates and in the biological environment. In this article, this term is used to refer to the arteries. It may, however, include other tissues and organs. It occurs in other species, including the world of both animals and plants. [11-22].

Therefore, it's crucial to learn about the phenomenon of biomineralization of arteries and its causes, and especially to find a way to prevent arterial calcification and remove (dissolve) it in cases of advanced calcification. In many cases, it may save lives.

Prevention and treatment of atherosclerosis are not very effective without a thorough study of the phenomenon, which is of mineralogical and chemical nature. It results in crystallization of various substances, which are known by the medical name of "atherosclerotic plaque". Those phenomena, related to medical problems, clearly have a mineralogical character. They should therefore be subject to structural mineralogical tests.

Biomineralization covers both the inner surface of the artery and its wall. Research indicates that it concentrates almost exclusively on the arteries and not veins. That is due to the chemical composition of arterial blood, which, unlike venous blood, is oxidized, slightly alkaline, and which carries nutrients. (Venous blood has a lower pH, and contains CO_2 and metabolism products, which prevents the crystallization of most substances that mineralize blood vessels [11,13,19,35,38].

Biomineralization of arteries is carried out with both inorganic (phosphates) and organic substances (cholesterol, fats, etc.). It can be represented only by inorganic compounds, exclusively by organic substances, or both at the same time.

Crystallization of these substances in the arteries requires the presence of crystallization centers [22] as well as crystallizing substances, i.e. substances that build the "atherosclerotic plaque". Presence of only one of those factors is insufficient for biomineralization of the arteries to occur.

Taking the above into consideration, we need to analyze the causes of concentration of components that build the atherosclerotic plaque, and the causes of the formation of crystallization centers, i.e. places where arterial biomineralization is formed.

There are many medical theories concerning the reasons for the increased content of cholesterol, calcium, phosphorus and other elements causing "mineralization" of arteries (atherosclerosis). The causes of the creation of biomineralization centers, i.e. sites of atherosclerotic plaque formation, are discussed below.

Biomineralization of arteries develops both on their internal surface (intima) and in the wall itself [15,18,19]. The causes and ways of development of crystallization centers in arteries (i.e. their biomineralization) will be presented in such order.

As studies show [8,31,35,37,39,50], biomineralization of arteries and other organs develops at sites of tissue damage. Such damaged sites are places where the atomic structure of organic substances was disturbed by destruction of interatomic bonds in tissue components. It's in those sites that we can find an electric field that acts as a magnet toward electrically charged particles flowing by. As a result of those interactions, local mineralization starts e.g. in the arteries. Initially, such mineralization does not manifest in the form of deposits, grains or concentrations. It is hidden mineralization involving the insertion of individual molecules of various compounds into the crystallization centers.

Biomineralization of arteries may stop at this stage or continue to evolve into overt biomineralization, visible e.g. as so-called atherosclerotic plaque. An important element of the discussion of the formation of crystallization centers are details of the causes of their formation. The causes of the formation of biomineralization centers, including the formation of calcifications, can be divided into primary (genetic) and secondary.

Genetic centers are defects of biological structures that are transmitted from generation to generation. Their presence in specific places leads to the formation of biomineralization in the same place, e.g. in a specific spot in the coronary artery.

Secondary centers are formed in the body throughout life. They can be caused by various factors, including mechanical or chemical effects of various substances on tissues - including arteries.

Mechanical factors that destroy tissues, including arteries, are associated with their work, both natural and forced (e.g. sport). Long-lasting work, especially connected with prolonged physical effort, leads to damage in the biological structures that build tissues. In the places where such damage occurs, centers of crystallization (biomineralization) are created.

Among factors that damage our tissues mechanically there can be solid substances penetrating our body with air, food and liquids. Those are both mineral particles (quartz, carbon, asbestos, etc.) and various products of industrial origin (slag, enamel, etc.). These particles mechanically damage tissues, creating crystallization centers in places of such damage.

Chemical factors are many different types of substances penetrating into our body, but also substances produced by the body itself. One of the **external factors** destroying tissues are toxins produced by microorganisms that infect us (bacteria, viruses, etc.). Those are often dangerous, aggressive toxins (organic compounds) that destroy biological structures. Such damaged places become centers of crystallization.

Those toxins damage lungs, arteries, and other organs, and the magnitude of damage, and thus the extent of the crystallization centers being formed, is proportional to the time the toxins affected the body, i.e. the time and intensity of the infection. The longer and more dangerous the infection, the greater the chance of calcification (e.g. in the lungs). Hence quick elimination of infection (e.g. using antibiotics) appears crucial. Other **external factors** that damage tissues are chemicals contained in beverages, and also - as research has shown - some preservatives. Those substances, chemically affecting the tissues, destroy them, thus leading to the formation of biomineralization centers.

Each of the above factors may lead to destruction of biological tissue structures and formation of biomineralization centers. These factors can combine and co-exist in different configurations, significantly increasing the number of crystallization centers, calcifications etc., including atherosclerosis. In other words, a person with genetic defects of biological structures, subjecting themselves to excessive physical exertion, using stimulants, and living in a polluted environment has a much bigger chance of biomineralization than a person who does not meet these conditions.

Biomineralization on Intima of Arteries

One of the places of biomineralization in the arteries may be their inner wall, i.e. the surface of the intima. The intima cell membrane is composed of phospholipids with a polar structure (Figure. 1.1), i.e. phospholipids with electric charges at the ends of the molecules. The mineralization process is described.

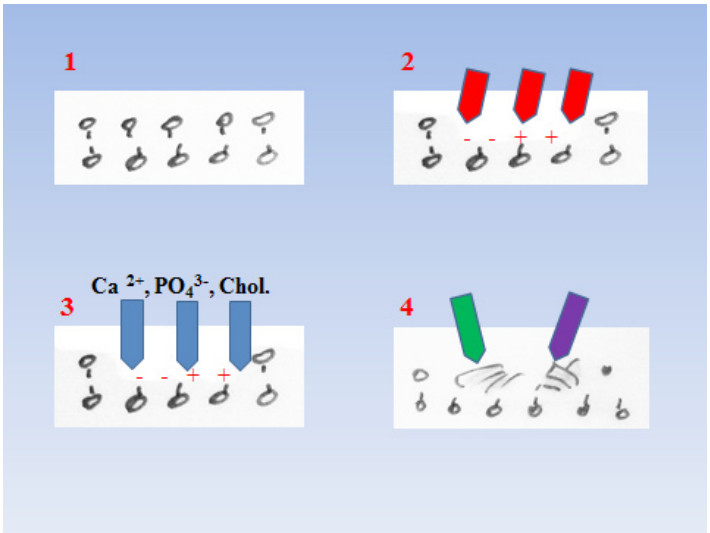
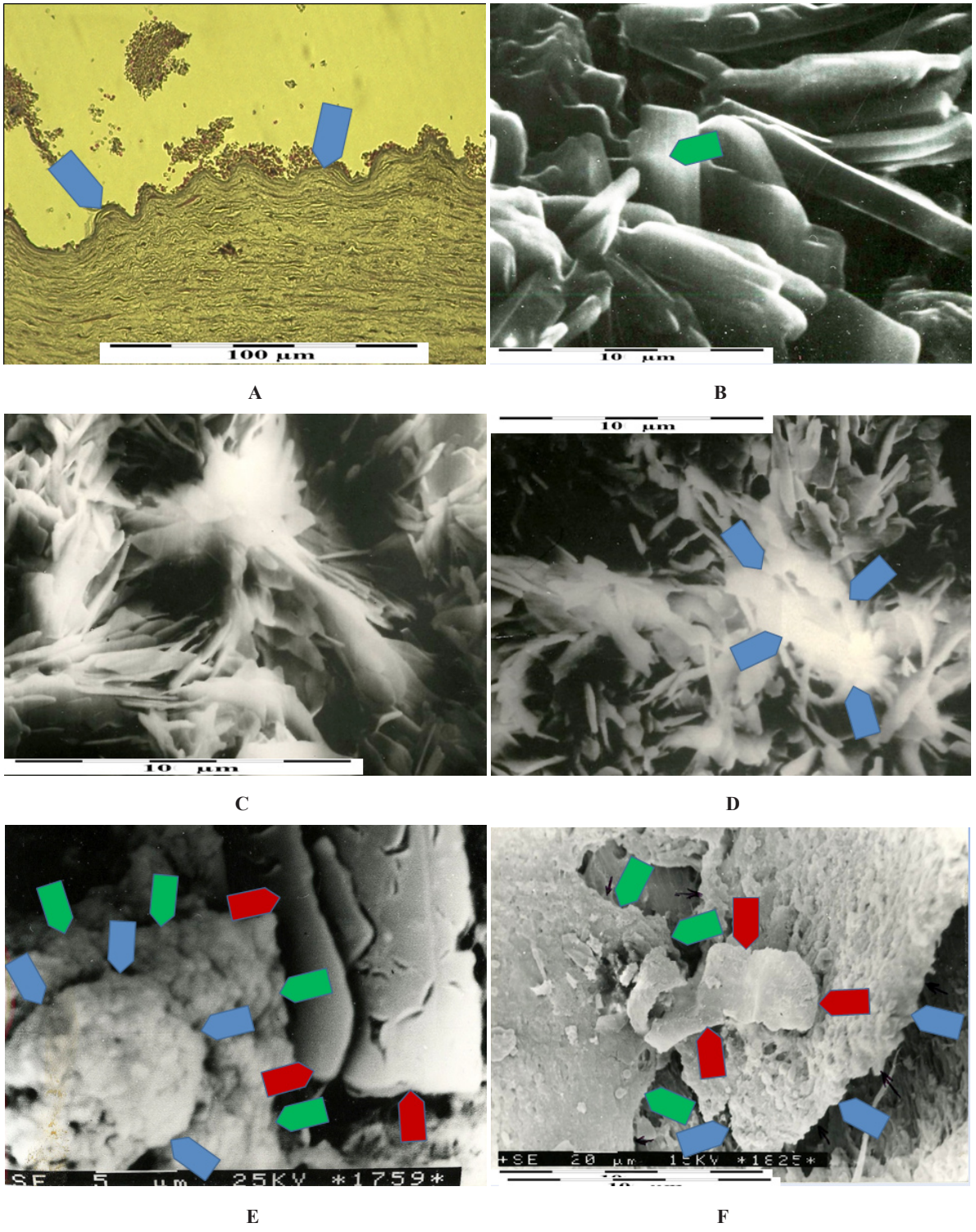


Figure. 1. 1: -diagram of the phospholipid system in the intima cell membrane. **2 -** diagram of cell membrane destruction caused by chemical substances (toxins associated with infection, chemical compounds penetrating the body from the outside, etc.). The consequence of such destruction is disintegration of interatomic bonds and development of electric charges, i.e. formation of a biomineralization center. **3 -** molecules with electric charges get connected in the crystallization center. Formation of the first stage of biomineralization - hidden mineralization. **4 -** further evolution of mineralization in the crystallization center, leading to the formation of visible mineralization (crystals, aggregates, concernments, atherosclerotic plaque, etc.). The substances that crystallize may be inorganic (phosphates, green arrow) and/or organic e.g. cholesterol (purple arrow).

In its first stage, the development of the intima destruction process is often imperceptible in histological studies (Photo 1A). Only high magnifications reveal the damage to the intima.



A **B**

C **D**

E **F**

Photo 1. A: – Section of the artery with visible intima. Arrows mark the places of deformation and damage to the intima. Histological preparation. **B** - inorganic mineralization. Crystals of phosphates crystallizing on the surface of the intima. Arrow shows the location of the chemical analysis using EDS

method. Scanning microscope. **C** - organic mineralization. Cholesterol crystal aggregates crystallized on the surface of the intima. Scanning microscope. **D** - mixed mineralization, organic-inorganic. Cholesterol crystals, in places covered with phosphates (arrow). Scanning microscope. **E** - multi-stage mineralization (fragment of atherosclerotic plaque). Red arrows - cholesterol crystals. Green arrows - older "layer" of phosphate mineralization. Blue arrows - newer "layer" of phosphate mineralization (phosphate aggregate). Scanning microscope. **F-** multi-stage mineralization (fragment of atherosclerotic plaque). Visible successive layers of cholesterol mineralization. **The oldest** mineralization (green arrows), **newer** (blue arrows), the **newest** (red arrows). Scanning microscope.

Biomineralization in The Wall of Arteries

In artery walls, concentrations of cholesterol are the most common, sometimes "Overgrown" with phosphates. Inorganic or phosphate grains are rarer. Studies show that the biomineralization of arterial walls easily develops at the sites of muscle deformity and damage. It may be related to intense physical activity (work, sport, etc.), which can lead to mechanical damage to muscle fibers. It cannot be ruled out that it is the result of aging of muscles or their long-term functioning. Explaining this phenomenon requires further research. Regardless of the causes, muscle fibers damage manifests in biological structures as breaking of interatomic bonds. That results in development of free bonds and electric charges at the damage sites, i.e. the formation of biomineralization centers (Figure. 2, 1, 2). The consequence of this phenomenon is connecting electrically charged particles in the immediate vicinity to the crystallization center (Figure. 2, 3). When the connected molecules saturate the crystallization center electrically, i.e. there are no more free bonds or electric charges at the crystallization site, biomineralization stops and remains in the arterial wall as hidden mineralization, only recognizable by sensitive chemical methods. As it continues to develop, it forms various kinds of concentrations and grains (Figures 2, 4).

The diagram presented above, showing the sequence of phenomena, is the result of studies of arteries from various parts of the body and of various ages. Cholesterol concentrations in various stages of development are easy to observe in stained histological preparations, because cholesterol stains poorly and is easily recognizable in stained arteries (Photo 2 A, B).

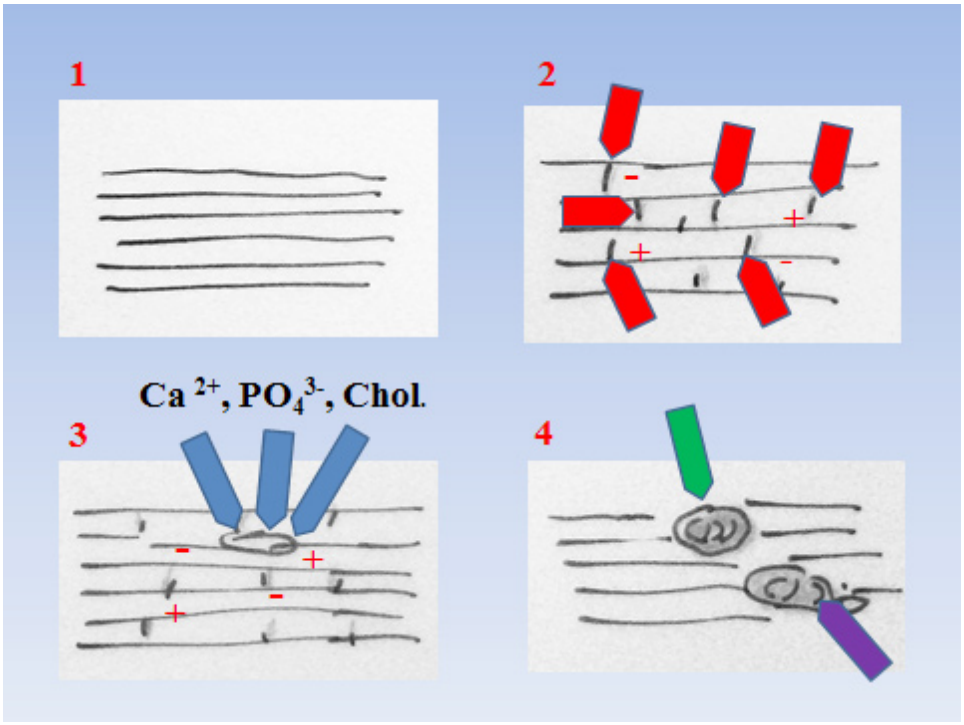
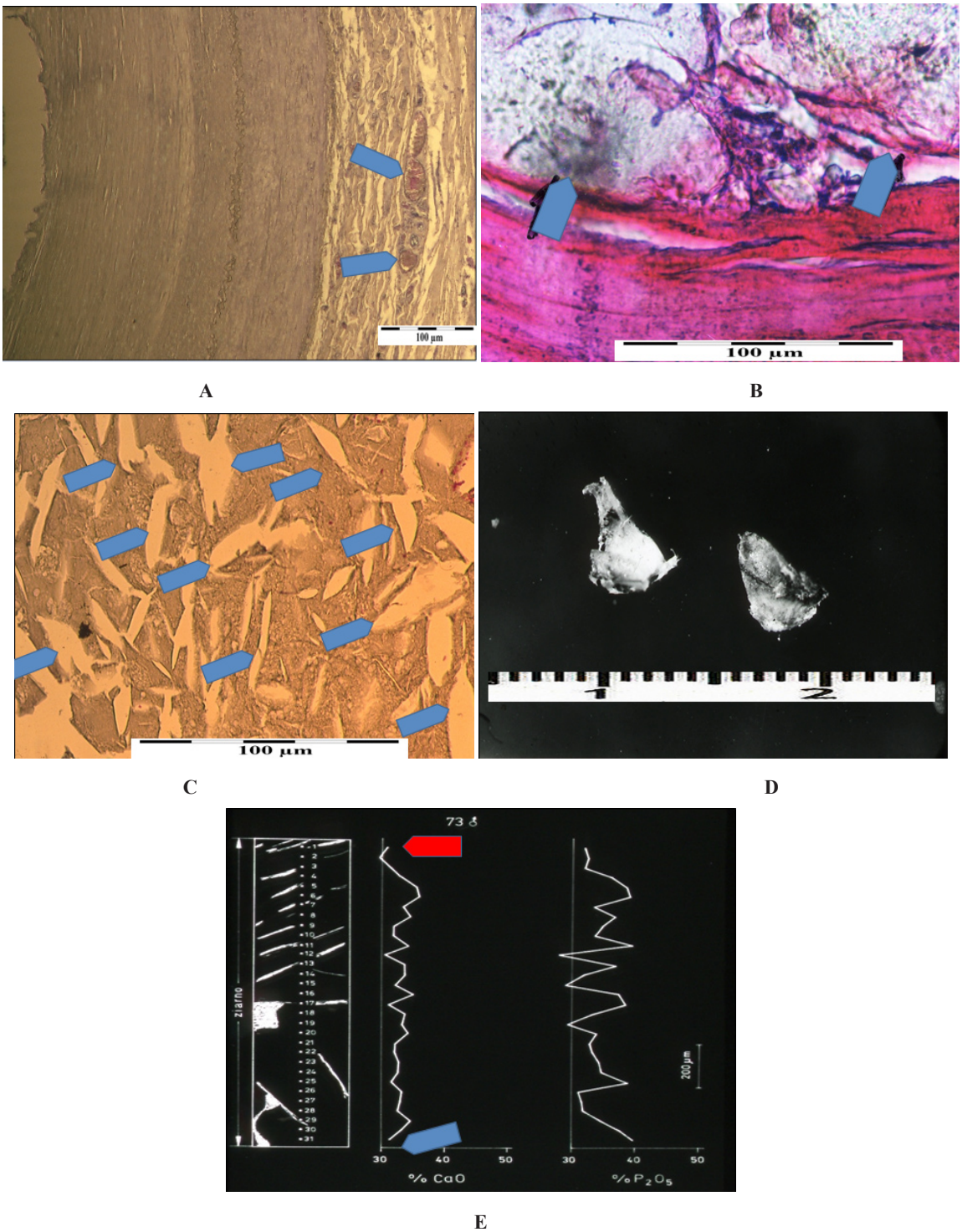


Figure. 2: Diagram of biomineralization development in the arterial wall (muscle lining). **1** - muscle fibers without crystallization centers. **2**-muscle damage sites with electric charges (crystallization centers). **3** - early stage of biomineralization of artery wall (hidden biomineralization). Connecting ions to the crystallization center. **4** - late stage of biomineralization of the arterial wall (overt biomineralization). The formation of organic, inorganic and mixed aggregates in the artery wall.

It was discovered that in some cholesterol concentrations, in their central part, i.e. the early phase of crystallization, there are elevated amounts of calcium (Photo 2, B). On the other hand, fine grain cholesterol may undergo recrystallization to pure, spindle-shaped crystals. In such case, it creates easily recognizable, histologically colorless concentrations (Photo 2, C).

Sometimes artery walls contain exceptionally hard phosphate grains (Photo 2, D). Their clean separation from the muscle is not easy. In detailed studies, they reveal heterogeneous structure and variable chemical composition (Photo 2, E). They are dominated, especially in the case of the older and larger grains, by hydroxyapatite with crystallographic features that are very similar to bone apatite.



A **B** **C** **D** **E**

Photo 2: Advanced (visible) biomineralization of arterial walls. **A** - the stage of formation of a cholesterol-phosphate lens in the arterial wall (arrows).

B - large bright cholesterol concentrations in delaminated arterial muscle. **C** - numerous, bright cholesterol crystals (arrows) embedded in the fine cholesterol mass removed from the artery wall. **D** - phosphate grains (hydroxyapatite) prepared from the walls of the artery. **E** - graphs of chemical analyzes of one of the grains shown in Figure. 2, D, carried out with the use of electron microprobe. Left side of the Figure.: diagrams of a grain cross-section with marked, numbered locations of chemical analyzes. Right side of Figure.: Variation charts of CaO and PO_4^{3-} from the beginning of grain formation (blue arrow) to the end of its crystallization (red arrow).

Cases where biomineralization develops simultaneously on the intima and in the arterial wall are quite common. They result in a significant narrowing of the active section of the artery, leading to increase in blood pressure.

Conclusion

Presented research helps in better understanding of the mechanisms of arterial biomineralization, becoming the basis for prevention of atherosclerosis, among other things. Understanding those processes is the foundation for undertaking experimental studies on dissolution of arterial biomineralization (Pawlikowski). Clearing the arteries and restoring normal functioning of the cardiovascular system is difficult to overestimate from the point of view of human health.

The heterogeneity of mineral and chemical composition of the discussed forms of artery biomineralization proves the oscillation of phenomena during their formation.

Different levels of calcium and phosphorus found in these concentrations, as well as variable amounts of cholesterol indicate that biomineralization of the arteries is a dynamic process. It is a reflection of certain "chemical states" of an organism affecting blood chemistry.

Although our knowledge in this area is rapidly expanding, it is still incomplete, obligating us to carry on further intensive research.

References

1. Bas A, Lopez I, Perez J, Rodriguez M, Aguilera-Tejero E (2006) Reversibility of calcitriol-induced medial artery calcification in rats with intact renal function. J Bone Miner Res 21: 484-490.
2. Callaway MP, Richards P, Goddard P, Rees M, (1997) The incidence of coronary artery calcification on standard thoracic CT scans. Br J Radiol 834: 572-574.
3. Huang H, Virmani R, Younis H, Burke AP, Kamm RD, et al. (2001) The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation 103: 1051-1056.
4. Iribarren C, Sidney S, Sternfeld B, Browner WS (2000) Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. JAMA 283: 2810-2815
5. Keelan PC, Bielak LF, Ashai K, Jamjoum LS, Denktas AE, et al. (2001) Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 104: 412-417.
6. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, et al. (1997) Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature 386: 78-81.
7. Matsushita M, Nishikimi N, Sakurai T, Nimura Y, (2000) Relationship between aortic calcification and atherosclerotic disease in patients with abdominal aortic aneurysm. Int Angiol 3: 276-279.
8. Nadra I, Mason JC, Philippidis P, Florey O, Smythe CD, et al. (2005) Proinflammatory activation of macrophages by basic calcium phosphate crystals via protein kinase C and MAP kinase pathways: a vicious cycle of inflammation and arterial calcification? Circ Res 96: 1248-1256.
9. Neves KR, Graciolli FG, dos Reis LM, Graciolli RG, Neves CL, et al. (2007) Vascular calcification: contribution of parathyroid hormone in renal failure. Kidney Int 71: 1262-1270.
10. Niskanen L, Siitonen O, Suhonen M, Uusitupa MI (1994) Medial artery calcification predicts cardiovascular mortality in patients with NIDDM. Diabetes Care 11: 1252.
11. Pawlikowski M (1987) Mineralizacja organizmu człowieka żyjącego, (Mineralization of human living organism). Prace Mineral 79: 121.
12. Pawlikowski M Ryskala Z (1991) Charakterystyka mineralogiczno-chemicznafosforanowej mineralizacji wybranych naczyń tętniczych człowieka. (Mineralogical-chemical characteristic of phosphate mineralization of human arteries). Roczniki Nauk Dyd, WSP w Krakowie Prace Fizjologiczne 81-104.
13. Pawlikowski M (1991) Mineralizacja nowotworowa (Mineralization of cancer) In: Biomineralizacja i biomateriały. PWN, Warszawa 84-92.
14. Pawlikowski M (1993) Kryształy w organizmie człowieka, (Crystals of humanorganism). Secesja 132.
15. Pawlikowski M Pfitzner R (1995) Zastosowanie metod mineralogicznychw badaniach tkanek człowieka. I. Sposoby badania mineralizacji. (Mineralogical methods useful for examination of human tissues). Przegl. Lekarski 52:119-123.
16. Pawlikowski M Pfitzner R (1995) Zastosowanie metod mineralogicznych w badaniach tkanek człowieka. II. Mineralizacja struktur serca. (Mineralogical methods useful for examination of human tissues. Mineralization of heart structures). Przegl. Lekarski 52:24-27.
17. Pawlikowski M Pfitzner K, Skinner C, (1995) Cholesterol-mineral concentrations of the aneurysmatic wall. Acta Angiologica 1-15.
18. Pawlikowski M, Pfitzner R, (1999) Mineralizacja serca i dużych naczyń, (Mineralization of heart and big blood vessels). Wyd IGSMiE PAN Kraków, :142
19. Pawlikowski M, Skinner HCW, Berger AW (2003) Geology and health. Oxford University Press 155-158.
20. Pawlikowski M (2014) Osteoporosis as a source of tissue mineralization. Research on osteoporosis therapy and dissolution of arterial mineralization. Jour. Life Science 8: 610-625.
21. Pawlikowski M (2017) a Centers of Human Tissue Biomineralization (Calcification). Cardiol. Cardiovasc. Med 1: 252-262.
22. Price PA, Faus SA, Williamson MK (2000) Warfarin-induced artery calcification is accelerated by growth and vitamin D. Arterioscler Thromb Vasc Biol 20: 317-327.

23. Reaven PD, Sacks J (2005) Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. Diabetologia 48: 379-385.

24. Rennenberg RJ, Schurgers LJ, Kroon AA, Stehouwer CD (2010) Arterial calcifications. J Cell Mol Med 14: 2203-2210.

25. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, et. al. (2004) Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol 15: 2857-2867.

26. Shanahan CM, Proudfoot D, Farzaneh-Far A, Weissberg PL (1998) The role of Gla proteins in vascular calcification. Crit Rev Eukaryot Gene Expr 8: 357-375.

27. Tse J, Martin-McNaulty B, Halks-Miller M, Kauser K, DelVecchio V, et al. (1999) Accelerated atherosclerosis and premature calcified cartilaginous metaplasia in the aorta of diabetic male Apo E knockout mice can be prevented by chronic treatment with 17 beta-estradiol. Atherosclerosis 144: 303-313.

28. Wada T, McKee MD, Steitz S, Giachelli CM (1999) Calcification of vascular smooth muscle cell cultures: inhibition by osteopontin. Circ Res 84: 166-178.

29. Weiss RM, Ohashi M, Miller JD, Young SG, Heistad DD (2006) Calcific aortic valve stenosis in old hypercholesterolemic mice. Circulation 114: 2065-2069.

30. Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijck W, et all. (2005) Coronary calcification improves cardiovascular risk prediction in the elderly. Circulation 112: 572-577.

31. Allison MA, Criqui MH, Wright CM (2004) Patterns and risk factors for systemic calcified atherosclerosis. Arterioscl Thromb Vasc Biol 24: 331-336.

32. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD (2005) Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: The St. Francis Heart Study. J Am Coll Cardiol 46: 158-65.

33. Bostrom K, Watson KE, Horn S, Wortham C, Herman IM, et al. (1993) Bone morphogenetic protein expression in human atherosclerotic lesions. J Clin Invest 91: 1800-1809.

34. Campbell GR, Campbell JH, (2000) Vascular smooth muscle and arterial calcification. Z Kardiol 89: 54-62.

35. Canfield AE, Sutton AB, Hoyland JA, Schor AM, (1996) Association of thrombospondin-1 with osteogenic differentiation of retinal pericytes in vitro J Cell Sci 109 : 343-353.

36. El-Abbadi M, Giachelli CM, (2007) Mechanisms of vascular calcification. Adv Chronic Kidney Dis 14: 54-66.

37. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, et al. (2000) Phosphate regulation of vascular smooth muscle cell calcification. Circ Res 87: E10-E17.

38. Lomashvili KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC (2004) Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. J Am. Soc Nephrol 15: 1392-1401.

39. Orita Y, Yamamoto H, Kohno N, Sugihara M, Honda H, et al. (2007) Role of osteoprotegerin in arterial calcification: development of new animal model. Arterioscler. Thromb Vasc Biol 27: 2058-2064.

40. Parhami F, Morrow AD, Balucan J, Leitinger N, Watson AD, et (1997) Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation: a possible explanation for the paradox of arterial calcification in osteoporotic patients. Arterioscler Thromb Vasc Biol 17: 680-687.

41. Parhami F, Basseri B, Hwang J, Tintut Y, Demer LL (2002) High-density lipoprotein regulates calcification of vascular cells. Circ Res 91: 570-576.

42. Pawlikowski M (1995) Sekrety mineralizacji tkanek (Secrets of tissue mineralization). PAN Kraków 97.

43. Pawlikowski M (2017) Biomineralogy of angiogenesis. Arch Clin Biomed Res 1: 161-167.

44. Price PA, June HH, Buckley JR, Williamson MK, (2001) Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol 21: 1610-1616.

45. Qiao JH, Xie PZ, Fishbein MC, Kreuzer J, Drake TA (1994) Pathology of atheromatous lesions in inbred and genetically engineered mice: genetic determination of arterial calcification. Arterioscler Thromb 14: 1480-1497.

46. Qiao JH, Fishbein MC, Demer LL, Lusis AJ (1995) Genetic determination of cartilaginous metaplasia in mouse aorta. Arterioscler. Thromb. Vasc. Biol 15: 2265-2272.

47. Qiao JH, Mertens RB, Fishbein MC, Geller SA (2003) Cartilaginous metaplasia in calcified diabetic peripheral vascular disease: morphologic evidence of enchondral ossification. Hum Pathol 34: 402-407.

48. Rajamannan NM, Subramaniam M, Stock SR, Stone NJ, Springett M, et al. (2005) Atorvastatin inhibits calcification and enhances nitric oxide synthase production in the hypercholesterolaemic aortic valve. Heart 91: 806-810.

49. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, et al. (1998) Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 31: 126-133.

50. Shao JS, Cheng SL, Charlton-Kachigian N, Loewy AP, Towler DA (2003) Teriparatide (human parathyroid hormone (1-34)) inhibits osteogenic vascular calcification in diabetic low density lipoprotein receptor-deficient mice. J Biol Chem 278: 50195-50202.

51. Abedin M, Lim J, Tang TB, Park D, Demer LL, et al. (2006) N-3 fatty acids inhibit vascular calcification via the p38-mitogen-activated protein kinase and peroxisome proliferator-activated receptor-gamma pathways. Circ Res 98: 727-729.

52. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, et al. (2005) A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 352: 2389-2397.

53. Nicholls SJ, Tuzcu EM, Wolski K, Sipahi I, Schoenhagen P, et al. (2007) Coronary artery calcification and changes in atheroma burden in response to established medical therapies. J Am Coll Cardiol 49: 263-270.

54. Pawlikowski M (1999) Preliminary results of dissolution of substances mineralizing human arteries. Arch Mineralog 52: 195.

55. Pawlikowski M (2011) Biomineralization of cancer tissues. 20th Int. Symp. Molecular and Physiological Aspects of Regulatory Processes of the Organism. Cracow, H Lach editors. Wyd Abaton Kraków 190-191.

56. Price PA, Faus SA, Williamson MK (2001) Bisphosphonates alendronate and ibandronate inhibit artery calcificationnn at doses comparable to those that inhibit bone resorption. Arterioscler Thromb Vasc Biol 21: 817-824.

57. Proudfoot D, Skepper JN, Shanahan CM, Weissberg PL (1998) Calcification of human vascular cells in vitro is correlated with high levels of matrix Gla protein and low levels of osteopontin expression. Arterioscler Thromb Vasc Biol 18: 379-388.

58. Steitz SA, Speer MY, McKee MD, Liaw L, Almeida M, et al. (2002) Osteopontin inhibits mineral deposition and promotes regression of ectopic calcification. Am J Pathol 161: 2035-2046.

59. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Forster A, et al. (2006) Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation 113: 427-437.

60. Tanimura A, McGregor DH, Anderson HC (1983) Matrix vesicles in atherosclerotic calcification. Proc Soc Exp Biol Med 172: 173-177.

61. Wang L, Jerosch-Herold M, Jacobs DR Jr, Shahar E, Detrano R, (2006) Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 48: 1018-1026.