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Cerebrovascular Diseases and Atherosclerosis

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Abstract In modern modern medicine, the rise of cerebrovascular disease causes various secondary diseases. Cerebral and cardiovascular pathology is associated with nitric oxide deficiency, the role of which is beyond doubt in the pathogenesis of these diseases, and in the development of osteoporosis is associated with a decrease in the synthesis and differentiation of osteoblasts. In recent years, quite numerous studies have been devoted to studying the relationship between the development of multifocal atherosclerosis accompanied and complicated by diseases of the cardiovascular system, cerebrovascular diseases in particular, and osteoporosis. The data and scientific findings presented in this literature review reveal the relationship between cerebrovascular disease and multifocal atherosclerosis.

Keywords Cerebrovascular disease, Multifocal atherosclerosis, Osteoporosis, Disability, Myocardial infarction, Vascular wall

In the last 40-50 years, according to the State Statistics Committee of the Republic of Uzbekistan, 2021 "Circulatory diseases", including cerebrovascular diseases (CVD), have been distinguished by their superiority and noticeable rejuvenation, mortality and disability compared to numerous other diseases characteristic of mankind (oncology, pulmonary and respiratory tract, traumatology and surgery, infectious diseases and diseases of the digestive system...) This is especially true for multifocal atherosclerosis with a predominant lesion of the coronary, carotid, iliac, and other arteries. The introduction of neuroimaging and ultrasound diagnostics into clinical practice has made it possible to identify hemodynamically significant embologenic and unstable atheromatous and atherocalcinous (ACP) plaques, which are the main cause in the development of cerebral strokes and myocardial infarctions. ACZ are considered the end stage of the general atherosclerotic process, refractory to drug therapy and requiring only surgical treatment by carotid endarteriectomy or coronary artery bypass grafting. It should be noted that in 2021 in the structure of total mortality, "Circulatory diseases" accounted for 61.7%, when 7.8% - oncology, 5.2% - poisoning, injuries, accidents, 4.1% - gastrointestinal, 3.1% - infectious and 18.1% all other diseases. Cancer diseases, ending in most cases with inevitable mortality, have a mortality rate of almost 8 times less than circulatory diseases. According to the WHO, if 10-20 years ago stroke was mainly considered a disease of the elderly, now it is more common on average (44-59 years), and worse at a young or flowering age (29-44 years) with a clear prevalence in men. In other words, that part of the population that is at the most able-bodied and intellectually developed age, having gained sufficient experience in a certain profession, faces disability or death. Not only in Uzbekistan, but also on our planet, the main cause of diseases of the circulatory system "atherosclerosis" is repeatedly called a pandemic of the 21st century. Chemically, their structure consists of salts, proteins and fats. Dissolution of the saline part of the ACZ, or at least a decrease in its size, the transformation of hemodynamically significant stenosis into non-pathological, i.e. Hemodynamically insignificant stenosis is extremely important, and it is certain that this number can prevent countless future strokes and myocardial infarctions. As a rule, in the pathogenesis of atherosclerosis (AS), lipid metabolism disorders are associated with microelements, and the target of the process is the vascular wall, which is affected by various pathological factors, metabolic disorders, chemical imbalance elements, and the placement of calcium in the ASP, i.e., in clogged cells, the main place is occupied by the formation of atherocalcinosis. In fact, in the early period of AS, protective mechanisms are activated that are aimed at regenerating and restoring oxygenation of the intima of the vascular wall. However, as a result of oxidative stress and inflammation in the vessel wall, the angiogenic response becomes persistent and pathological. As a result, the connections between the endothelium are disrupted, the integrity of the endothelial lining is disrupted, and due to the lack of pericytes, mechanical strength decreases, permeability increases, blood enters the ASP, inflammation starts, oxidative stress increases, and AS develops. Interestingly, in most cases, ASP is formed only in the bifurcated part of large and large-caliber great vessels, while the intima is clear in other parts of the vessel. For example, the common carotid artery extending directly from

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the aorta is divided into external and internal carotid arteries and it is in this region that atheromatous plaques form. In general, 4 periods are distinguished in the development of plaques: lipomatosis, fibromatosis, ulceration, and finally atherocalcinosis (AKZ), contributing to hemodynamically significant stenosis and the formation of thromboembolism with subsequent development of cerebral strokes. The question arises from where the body takes the salt part of the ABC, which consists mainly of calcium and phosphates, resembling bone tissue in chemical structure. At the same time, according to numerous Russian and foreign publications, in patients who have suffered a hip fracture that develops on the basis of osteoporosis, in 70% of cases there is a pathology of the cardiovascular system, formed against the background of severe multifocal atherosclerosis [11]. The significance of this problem lies in the fact that each of these conditions individually significantly reduces the quality of life, and their frequent combination in the older age group greatly enhances this effect. Moreover, these conditions are asymptomatic for a long time, and one of the first manifestations of clinically significant multifocal atherosclerosis may be a cerebral stroke or myocardial infarction, and one of the first manifestations of osteoporosis – various vertebrogenic diseases or fractures of the bones of the human skeleton [12,51,37].

At the same time, many clinical researchers, such as cardiologists, neurologists, therapists, endocrinologists, orthopedic traumatologists, and other specialists, assume the presence of a common pathophysiological basis and common genetic risk factors [4,7,19].

Of course, on the one hand, there are such common risk factors as age, smoking, low level of physical activity or physical inactivity, alcohol abuse, dyshormonal conditions (pre-, menopausal and postmenopausal syndromes with the formation of menopause in women or erectile dysfunction in men...) and etc. By now, everyone knows that reduced physical activity in patients with cardiovascular disease will increase bone loss and the appearance of a clinic of osteoporosis. There is also a mechanical-rheological point of view, according to which atherosclerotic damage to the arteries, arterioles and capillaries extending from the iliac artery, using the example of aseptic necrosis of the femoral head, leads to a violation of intraosseous microcirculation, then bone metabolism, which, in turn, contributes to the development of regional and general osteoporosis [8,26,30]. On the other hand, it is possible that these states also connect other, more subtle regulatory mechanisms, which opens up new common points of application for the treatment of cardiovascular diseases and bone metabolism disorders.

At the same time, it is necessary to single out three directions of the pathogenetic relationship of vascular atherosclerosis with cerebro- and cardiovascular pathology and loss of bone mineral density (BMD): CVD and components of bone metabolism, CVD and calcium deficiency; CVD and vitamin D3 deficiency [9,43,56].

It should be emphasized that a number of authors classify the loss of BMD as a predictor of CVD, namely, lesions of the coronary arteries [7]. This is explained by a certain similarity in the pathogenesis of osteoporosis and atherosclerosis, in which damaged monocytic cells differentiate in the vascular wall into macrophage- like "foamy" cells in one case, and into osteoclasts in the other.

Vascular calcification is the final stage in the formation of an atherosclerotic plaque or ectopic mineralization of the vascular wall. Vascular wall calcification is not just a passive process of precipitation and deposition of phosphates and calcium, but a complexly organized active mechanism, largely similar to the system of regulation of bone tissue mineralization [18]. These common regulatory factors include [39]: BMP (bone morphogenesis protein), RANKL and osteoprotegerin, alkaline phosphatase, osteopontin, vitamin K and matrix Gla-protein, osteonectin, some cytokines (in particular, interleukin-1, interleukin-6, FN O - α), estrogens [10], androgens, parathyroid hormone and homocysteine.

In particular, BMP, RANK-L, and some inflammatory factors have a stimulating effect on the process of transformation of vascular smooth muscle cells into osteoblast -like cells [48].

Osteopontin is an acidic glycoprotein that controls biomineralization by mimicking bone calcification. This protein is involved not only in the reconstruction of bone tissue, but also in the production of cytokines regulating cell migration, adhesion and differentiation of various cells, and exhibits pro- and anti-inflammatory properties.

An association between osteopontin content, vascular wall stiffness and atheroma calcification has been established. This protein is absent in normal vessels, but is found in large quantities in calcified arteries. A direct relationship between the content of osteopontin and the severity of atheroma calcification and stability of the atherosclerotic plaque cap [57].

O. Uz et al. (2009) showed that plasma osteopontin concentration correlated with coronary calcium levels measured by multispiral computed tomography [54].

Data from Minoretti et al. (2006) indicate that the presence of osteopontin is associated with calcium deposition in monotonous atherosclerotic plaques. The authors found that osteopontin is an indicator of their stability [33]. Similar data are given in the work of R. Ohmori et al. (2003): the level of osteopontin was associated with the presence and severity of atherosclerotic lesions of the coronary arteries and the severity of coronary artery disease [44].

In the thesis of A.A. Novitskaya (2016) showed that osteopontin is a marker for the prognosis of the course of stable coronary artery disease: patients undergoing coronary bypass surgery with cardiovascular events that developed within three years before surgery have a higher level of osteopontin. Also in this work it was found that in men with stable coronary artery disease, violations of phosphorus-calcium metabolism correlated with the severity of atherosclerosis and calcification of the coronary arteries. The author found that in elderly patients with stable coronary artery disease, there is a relationship between the severity of coronary atherosclerosis, assessed by the Syntax school, and

the level of ionized calcium and osteopontin [53].

Collagenous bone tissue protein, osteonectin, is also involved in the process of atherosclerosis: it is over expressed by cells present in the vessel wall during the progression of atherosclerosis, namely, calcification of an atherosclerotic plaque.

A number of studies have noted the commonality of the pathogenesis of hypertension and osteoporosis. In particular, the activity of the renin-angiotensin-aldosterone system (RAAS), on the one hand, causes vasoconstriction of the microcirculatory bed due to the effect on local blood flow and blood supply to the bones, and on the other hand, has a direct effect on the production of angiotensin II. The latter is a growth factor that directly stimulates the proliferation of osteoclasts and increases the level of endothelin-1, the content of which, upon activation of the RAAS, increases not only in the endothelium, but also in osteoclasts [36]. These data are confirmed in the clinic by the osteoprotective effect of angiotensin -converting enzyme inhibitors [47]. These drugs, by inhibiting the activity of angiotensin II, contribute to less resorption of bone tissue osteoclasts, reducing its loss of BMD [19].

The role of calcium in a number of physiological processes is also known, including in the cardiovascular and endocrine systems. Therefore, calcium deficiency can play one of the key roles in the pathogenesis of cardiovascular pathology, primarily from the standpoint of a deficit in the electrical activity of the heart and an imbalance in vascular tone. At the same time, a decrease in insulin synthesis due to calcium deficiency may be an additional factor in the development of a more unfavorable course of insulin resistance. CVD and vitamin D3 deficiency Vitamin D3 and its active metabolites are structural units of the hormonal system that regulates phosphorus-calcium metabolism. In the body, through complex transformations in the liver and kidneys, cholecalciferol is converted into more active metabolites that can regulate the absorption of calcium and phosphorus salts in the small intestine, reabsorption in the kidneys and their deposition in the bones. It is known that the multicomponent regulation of phosphorus-calcium homeostasis is mainly carried out by parathyroid hormone, vitamin D3 and calcitonin. In violation of calcium and phosphorus homeostasis, the action of these substances on target cells of various organs (bone marrow, gastrointestinal tract, liver, kidneys) contributes to the rapid restoration of the optimal level of calcium outside and inside body cells. All components of vitamin D3 metabolism, as well as tissue nuclear receptors for 1α,25-dihydroxyvitamin D3 (D-hormone), called vitamin D receptors (RV D), are combined into the vitamin D3 endocrine system, the functions of which are the ability to generate biological reactions in more than 40 target tissues due to the regulation of gene transcription by PBDs (genomic mechanism) and rapid extra genomic reactions carried out when interacting with PBDs localized on the surface of a number of cells. Due to genomic and extra genomic mechanisms, the D-endocrine system carries out the reactions of maintaining mineral homeostasis (primarily within the framework of calcium-phosphorus metabolism), electrolyte concentration and energy exchange. In addition, it takes part in maintaining an adequate BMD, lipid metabolism, regulation of blood pressure (BP), hair growth, stimulation of cell differentiation, inhibition of cell proliferation, implementation of immunological reactions (immunosuppressive effect). A significant number of studies by foreign authors show the relationship between vitamin D3 deficiency and diseases not directly related to bone tissue. There is no doubt that vitamin D3 deficiency is associated with CVD and hypertension. Decreased vitamin D3 levels are associated with an increased risk of metabolic syndrome, including hypertension. Normalization of vitamin D3 levels can reduce systolic blood pressure (SBP) and thus reduce the risk of CVD. Studies have also shown that correction of vitamin D3 deficiency prevents further hypertrophy of cardiomyocytes in hypertensive patients. Since vitamin D3 deficiency affects cardiotonic properties and vascular remodeling, hypertension may increase the negative effects of vitamin D3 deficiency on the cardiovascular system. In addition, experimental and clinical data suggest that vitamin D3 deficiency directly causes the development of hypertension. Experimental studies indicate that vitamin D3 is involved in the regulation of rennin activation and angiotensin formation by directly inhibiting rennin over expression.

Modern clinical and experimental studies are aimed at actively studying possible common biochemical factors responsible for pathological bone resorption and extra skeletal calcification, which in the future may determine the likelihood of identifying molecular targets for subsequent drug effects on " osteocoronary " co morbidity [37].

Thus, to date, there are clear scientific prerequisites that the penetration of calcium and phosphate salts into an atheromatous plaque occurs on the basis of osteoporosis, accompanied by a decrease in BMD with the subsequent formation of various complications, both cerebral strokes and cardiovascular diseases.

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