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PERIVASCULAR ADIPOSE TISSUE – ORCHESTRATOR OF CARDIOVASCULAR DISTURBANCES SEQUEL

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Abstract

Perivascular adipose tissue is a biologically active morphofunctional unit that is an active regulator of endovascular homeostasis, endothelial functioning, and the phenotypic state of smooth muscle. Under physiological conditions, perivascular adipose tissue maintains normal vascular function by releasing anti-atherogenic, anti-inflammatory, and vasodilating biologically active substances. Until recently, adipose tissue was considered a morphological unit with only a thermoregulatory and shock-absorbing function; however, with the development and improvement of modern medical science, we can confidently assert that adipose tissue is a factory for the production of biologically active substances with a broad spectrum of action. The released biologically active substances have both autocrine and paracrine effects, thus playing a pivotal role in maintaining the morphophysiological balance of the whole organism.

Various theories are put forward about the possible key role of perivascular adipose tissue in the pathogenesis of various diseases. It has been shown that perivascular tissue is an independent cardiovascular risk factor, even without visceral obesity. When exposed to specific pathogens, the regulation of adipocytes is disrupted, and a subsequent rearrangement of the adipocyte production profile occurs. The secretion of damaged adipocytes exhibits the following properties: anti-atherogenic, anti-inflammatory, and vasodilating, with subsequent initiation or progression of cardiovascular disease.

Within the framework of this review article, the following are raised and comprehensively discussed: the function of perivascular adipose tissue in health and disease and its contribution to the pathogenesis of cardiovascular disease. This review aims to analyze the data of modern literature, reflecting the photomorphogenesis of changes in the secretory activity of perivascular adipose tissue, along with the molecular mechanisms of cardiovascular system alteration.

Keywords: *low-grade inflammation, endothelium, adventitia, cytoctins, metabolism, adipose tissue*

Obesity is one of the most significant public health challenges of the 21st century [*Chang L et al., 2020*]. Obesity is a complex, multifactorial, polygenic disorder closely related to the psychosocial and cultural characteristics. According to modern statistical data, obesity is one of the leading causes of morbidity and mortality in developed countries [*Pronk M et al., 2022*].

At the same time, it is intriguing that data from large-scale epidemiological analyses have revealed a non-linear U-shaped relationship between body mass index and all-cause mortality among patients

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with a well-established cardiovascular diagnosis. Having widespread use, body mass index has several disadvantages, for instance, when calculating this index, variations in the qualitative and quantitative parameters of adipose tissue, which are currently of great importance for cardiovascular prognosis, are not considered. This fact is called the "obesity paradox", and confirms the complexity and polymorphism of the biochemical cascade of processes developed in the adipose tissue [*Shan B et al., 2020*]. In the context of studying the relationship between obesity and cardiovascular disease, the perivascular adipose tissue must be considered as a separate conglomerate. Perivascular adipose tissue directly modulates key signaling pathways in the vascular wall and myocardium through paracrine and vasocrine activity [*Rafeh R et al., 2020*].

The purpose of this review was to analyze the pathophysiological, pathomorphological and pathobiochemical mechanisms of the perivascular adipose tissue impact on cardiovascular homeostasis since understanding the continuum of pathways of the perivascular adipocytes influence will become the basis for creating new concepts for the cardiovascular disease treatment.

Adipose tissue is a type of connective tissue formed from the mesenchyme and made of adipocytes. It is established that perivascular adipose tissue adipocytes differ from other adipocytes by their origin from the precursors of vascular smooth muscle cells [*Balakumar P et al., 2021*]. Differential expression of the En-1, Emx-2, and Hox-A10 ontogenetic genes suggests that perivascular coronary adipocytes are smaller and more polymorphic with less lipid accumulation and a lower state of differentiation compared to subcutaneous and perirenal adipocytes [*Stanek A et al., 2021*]. Moreover, thoracic periaortic adipose tissue is dominated by brown adipocytes containing small lipid droplets and many mitochondria expressing the specific thermogenin uncoupling protein 1 [*Ye T et al., 2021*]. The adipose tissue surrounding the abdominal aorta and mesenteric vessels has more white adipocytes with one large lipid droplet, and infiltrated by macrophages, as well as has a secretome profile characteristic of white adipose tissue [*Turaihi A et al, 2020*]. In addition, bright adipocytes were found in perivascular adipose tissue, which can turn into brown or white adipocytes depending on environmental conditions. Adipose tissue also contains an interadipocyte stromal fraction with multipotent stem cells, endotheliocytes and myocytes, fibroblasts, and a full range of immune cells (macrophages, lymphocyte subpopulations, dendritic cells, etc.) [*Victorio J et al., 2020*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Perivascular adipose tissue did not drive attention for a long time and was usually separated from the blood vessel during the pathomorphological examination. It has long been thought that perivascular adipose tissue simply provides structural support for blood vessels. However, over the past two decades, it has been recognized as a physiologically and metabolically active morphological unit that plays an integral role in vascular homeostasis maintenance.

Accumulations of fat cells around vessels of various sizes and fatty tissue of the vascular networks of the heart, kidneys, mesentery, and muscles represent perivascular adipose tissue. The relationship between the vascular wall and perivascular adipose tissue is bidirectional. Under physiological conditions, perivascular adipose tissue secretes vasoprotective agents that promote vasodilation and have anti-inflammatory, anti-adhesion and antioxidant properties to meet the hemodynamic and metabolic needs of organs [*Avagimyan A et al., 2022a*]. Immune cells actively interact with adipocytes to maintain the balance of cytokines and regulate inflammatory responses to external stimuli. In chronic caloric excess, a change in the phenotype of perivascular adipose tissue occurs: adipocytes hypertrophy and hypoxia with subsequent necrosis [*Sowka A, Dobrzyn P, 2021*]. The above-mentioned is accompanied by the secretome transformation towards pro-oxidant, pro-inflammatory and vasoconstrictor effects, which underlie the structural and functional changes of the heart and vessels [*Barp C et al, 2020*]. The dysfunctional phenotype of perivascular adipose tissue plays an essential role in atherosclerosis and

hypertension development by partially increasing insulin resistance [*Victorio J et al., 2020*].

Scientific evidence increasingly suggests that perivascular adipose tissue is an accepted biomarker for cardiometabolic risk and a probable target for cardiovascular disease treatment. perivascular adipose tissue volume measured by computer tomography correlated with higher levels of triglycerides, lipoproteins, blood glucose, blood pressure, and levels of pro-inflammatory cytokines: TNF-α, IL-1, IL-6, IL-8, MCP-1, etc. [*Pulgar V, 2020*]. Perivascular adipose tissue may reflect potential cardiometabolic risks, but a more meaningful indicator would be to evaluate its qualitative characteristics. The perivascular fat attenuation index is based on the change in signal during computed tomography in an inflammatory process in adipose tissue. The perivascular fat attenuation index method has shown high predictive value as an early marker of inflammation and atherosclerosis, even without visible coronary lesions [*Hillock-Watling C, Gotlieb A, 2022*]. Non-invasive detection of coronary inflammation with perivascular fat attenuation index in low- and intermediate-risk individuals may help for early detection of coronary artery disease, especially among high-risk individuals who do not have visible coronary lesions [*Tuttolomondo D et al., 2021*].

Assessment of inflammation using positron emission tomography revealed an association between high uptake of 18F-fluorodeoxyglucose by perivascular adipose tissue and the level of coronary artery stenosis [*Shi H et al., 2021*]. However, low spatial resolution, high background noise from myocardial 18F-fluorodeoxyglucose uptake, increased radiation exposure, and insufficient clinical availability limit positron emission tomography imaging in patients at low risk of cardiovascular disease. Interestingly, weight loss induced by 45% dietary caloric restriction in obese rats resulted in improved perivascular adipose tissue function, restoration of hypertrophied adipocyte size, increased eNOS and other vasodilatory factors, and normalized plasma levels of adipokines and TNF-α [*DeVallance E et al., 2021*].

Atherosclerosis is a chronic, undulating, progressive, low-grade inflammatory, a dysmetabolic disease characterized by the elastic and muscular-elastic type arteries' wall damage in the form of progressive focal deposition of cholesterol deposits in the subintima and hyperactivation of fibrocytes, followed by the formation of atheroma and subsequent stenosis of vascular lumen [*Avagimyan A et al., 2022b*].

To date, the polyetiology of atherosclerosis is beyond doubt. Many theories explain the development of morpho-functional shifts in the vascular wall. One of the most innovative theories is inflammatory; therefore, the role of perivascular adipose tissue in the pathogenesis of atherosclerosis is paramount [*Mu W et al., 2021*]. The current "inside out" theory states that damage to the vascular endothelium is the initial stage of atherosclerosis. Endothelial dysfunction leads to the low-density lipoprotein accumulation in the intima and monocytes adhesion from the bloodstream, their subsequent transformation into macrophages and the formation of foam cells [*AlZaim I et al., 2020*]. In the intima, macrophages cause local inflammation by secreting inflammatory cytokines (TNF-α, IL-1 and IL-6, etc.), which further attract immune cells to the lesion [*Queiroz M et al., 2020*]. Further, the inflammation of the intima spreads to the middle and adventitial membranes and only then to the perivascular adipose tissue.

As per another hypothesis, the initial manifestations of coronary atherosclerosis are an increase in the thickness of the intima with age, impaired oxygen diffusion, cell hypoxia, and compensatory neovascularization of the intima due to the vasa vasorum [*Kobalava Z et al, 2019*]. The "outside-in" hypothesis plays a valuable role in vascular dysfunction development and progression since perivascular adipose tissue is in direct contact with vascular adventitia [*Pogosova N et al., 2017*]. Adipocytes of perivascular adipose tissue, cells of the immune system and fibroblasts release vasoactive substances such as nitric oxide, angiotensin, leptin and adiponectin, which have a vasodilating effect [*Pogosova N et al., 2022*]. Perivascular adipose tissue also releases an adipocyte-derived relaxing factor that counteracts vasoconstriction and thereby regulates vascular tone [*Avagimyan A et al., 2022b*]. Because of obesity, hypoxia processes are triggered in the perivascular adipose tissue, tissue infiltrated by immune cells (monocytes, lymphocytes, and granulocytes) and produce pro-inflammatory cytokines. Inflammation spreads to

the vessel wall, causing local endothelial dysfunction, ultimately contributing to atherosclerosis development [*Chen Y et al., 2021*].

The importance of the perivascular adipose tissue action on the adjacent vascular wall is confirmed by the connection between the regional amount of perivascular adipose tissue and atherosclerotic plaques in the underlying coronary artery [*Kim H et al, 2020*]. Coronary arteries surrounded by large amounts of perivascular adipose tissue are most prone to developing atherosclerosis, while mouse coronary arteries lack perivascular adipose tissue and are resistant to atherosclerosis [*Saxton S et al., 2020a*]. Studies on experimental animals have revealed a predominant accumulation of perivascular adipose tissue with hypertrophied adipocytes in vascular regions more prone to atherosclerosis [*Nosalski R et al., 2020*].

It is also worth dwelling on the effect of the perivascular adipose tissue secretome on the vascular smooth muscle cells. Inflammatory phenotype of perivascular adipose tissue - significantly increased the matrix metalloproteinase-2 expression, leading to a TGF-β1 increase in vascular smooth muscle cells, and, therefore, to a switch in the phenotype of the latter [*Man A et al., 2022*]. It is also worth noting that with the help of resistin, homocysteine enhances vascular smooth muscle cell migration by overexpressing PKCε-dependent expression of matrix metalloproteinases [*Pogosova N et al., 2015, Ahmadieh S et al., 2020*].

Visfatin, a growth and migration factor for vascular smooth muscle cells, has also been identified in perivascular adipose tissue. This adipokine is the enzyme nicotinamide phosphoribosyltransferase, which synthesizes nicotinamide mononucleotide and stimulates the growth and proliferation of vascular smooth muscle cells [*Zorena K et al., 2020*]. Visfatin acts through protein kinase regulated by the extracellular signal ERK-1/-2 and mitogen-activated protein kinase p38. Visfatin has pro-inflammatory activity mediated through nuclear factor B and endothelial nitric oxide synthase [*Saxton S et al., 2020b*]. In atherosclerosis of the coronary arteries and aorta, the local production of visfatin in the perivascular adipose tissue increases [*Balakumar P et al., 2021*].

The contractile response of vascular smooth muscle in response to various stimuli enhances chemerin, another adipokine produced by perivascular adipose tissue. In atherosclerosis, the content of chemerin in the perivascular adipose tissue is increased. A protein kinase regulated by the MEK-ERK-1/-2 extracellular signal which involved in the contraction process.

Omentin, which has a direct vasodilatory effect, as well as adrenomedullin, vaspin, adipsin, and nesfatin, as mediators of perivascular adipose tissue, presumably participate in the implementation of its vasodilating effect [*Adachi Y et al., 2022*].

In addition to adipokines, perivascular adipose tissue produces tumor necrosis factor α, interleukins -1, -6, -8, macrophage chemotactic protein-1, plasminogen activator inhibitor-1, and complement factor C3. These molecules are associated with developing an inflammatory response and tissue changes under hypoxia. In addition, the plasminogen activator-1 inhibitor enhances the proliferation of smooth muscle cells, and the C3 component of complement promotes fibroblast migration. The content of pro-inflammatory cytokines in perivascular adipose tissue increases significantly in atherosclerosis, arterial hypertension, and obesity [*Chen J et al., 2020*].

Reactive oxygen species – superoxide and hydrogen peroxide, produced in the perivascular adipose tissue, are involved in vascular tone regulation, exerting multidirectional effects: the superoxide radical contributes to vasoconstriction, while hydrogen peroxide, together with hydrogen sulfide and nitrogen monoxide, provides vasodilation. In apolipoprotein E- deficient mice prone to hyperlipidemic atherosclerosis, the main site of accumulation of vascular inflammatory cells is the adventitia rather than the intima [*Man A et al., 2020*].

Moreover, secretome disturbances of perivascular adipose tissue are also associated with arterial hypertension development and progression [*Mikami T et al., 2021*]. The morphological determinant of arterial hypertension formation is the vessel wall's fibrosis. Arterial hypertension is associated with renin-angiotensin-aldosterone system activation and vascular oxidative stress increase. All components of the renin-angiotensin-aldosterone system, except for renin, are expressed in perivascular adipose tissue [*Katsiki N et al, 2022*]. It is known that arterial hypertension increases the production of angiotensin II, which is

involved in the contractile response of the vascular wall to impulses from the perivascular nerves. Angiotensin II also induces the production of pro-inflammatory cytokines IL-6, IFN-γ and TNF-α due to increased infiltration of immune cells into the surrounding tissues [*Saxton S et al., 2020b*].

A shift of the balance towards procontractile, proliferative, pro-inflammatory and fibrous-forming factors leads to narrowing and decrease in the elasticity of blood vessels, an increase in the speed of the pulse wave and an increase in the level of blood pressure. In discussing the pathogenetic relationship of perivascular adipose tissue with hypertension, it is also worth dwelling on the role of leptin. Leptin is one of the first known adipokines, isolated in 1995 from the adipose tissue of *ob/ob* mice. Normally, leptin has a direct vasodilation effect, increases permeability, and stimulates vascular smooth muscle cell proliferation and migration. In arterial hypertension, leptin production in the perivascular adipose tissue decreases, weakening its vasodilating effect [*Victorio J et al.,* 2020].

In pathological conditions, perivascular adipose tissue undergoes structural and functional changes. In the early period of obesity, an increase in adaptive nitric oxide production occurs in the perivascular adipose tissue, probably aimed at protecting vascular function. However, with established obesity, perivascular adipose tissue loses its anticontractile properties due to increased oxidative stress, which leads to endothelial dysfunction. In addition, with obesity, there is an increase in leptin, and the plasma concentration correlates with the number of adipocytes [*Lu C et al., 2020*]. The vascular effects of leptin appear to result from two distinct actions: indirect vasoconstriction through stimulation of sympathetic activity at the hypothalamus level and direct vasodilation, which altogether predetermine the functional state of the endothelium of various vessels. Perivascular adipose tissue dysfunction may play a role in refractory or difficult-to-treat arterial hypertension development.

Conclusion

Numerous studies indicate that perivascular adipose tissue significantly contributes to cardiovascular pathology development. Being a fragment of the vascular wall, perivascular adipose tissue has all the properties of adipose tissue of any other localization and, simultaneously, has special functions inherent only to it. Understanding the pathogenetic mechanisms and pathobiochemical aspects of the dysregulated phenotype of perivascular adipose tissue will allow us to put forward new concepts of cardiovascular prevention since the role of the adipocyte secretome in the development of cardiovascular pathology is colossal.

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IN MEMORY
of Professor Artashes V. Aznauryan,
Honored Worker of the Republic of Armenia

Artashes V. Aznauryan is an outstanding and distinguished professor with international authority and worldwide recognition. Professor Aznauryan devoted more than 50 years of his life to the Yerevan State Medical University after M. Heratsi. Justice, wisdom, masculinity, bravery, severity and kindness – these epithets embody the spirit and energy of the professor!

Professor Aznauryan is one of the Armenian scientists who has achieved international recognition! Until the last day, Professor Aznauryan maintained close scientific contacts with academicians and professors from Russia, Georgia, Ukraine, Belarus, Kazakhstan, the USA, Italy, Spain, etc. Professor Aznauryan is an Honorary Professor of the Russian Academy of Sciences, an Academician of the Armenian Academy of Medical Sciences, an Honorary Member of the Russian Society of Pathologists, a Member of the Board of the International Association of Morphologists, and it's an extensive list of other recognition of his professionalism.

The morphological school of Professor Aznauryan is the locomotive of medical science in Armenia. Under the supervision of Professor Aznauryan, 30 candidates and 24 doctoral dissertations were defended, thereby raising several generations of doctors, lecturers and scientists who, in addition to Armenia, work in leading universities, clinics and scientific centers in more than 25 countries of the world.

Unfortunately, on November 18, 2022, the beloved and respected professor passed away! The memory of Professor Aznauryan is indestructible and eternal and will forever remain in the history of the Armenian people!

The memory of professor Artashes V. Aznauryan is indesttructible and eternal and will forever remain in the history of the Armenian peopal and our hearts.

Memory of a friend.

With deep sorrow and profound grief, I heard about the death of my colleague and friend, a man of great soul and charm, honored scientist of the RA, honorary doctor of the Russian Academy of Sciences, professor A.V. Aznauryan.

For the period of my residency at the department of Pathological Anatomy, prof. Aznauryan A.V. provided me with invaluable support in mastering the basics of the subject, teaching and scientific activity. Due to a wide knowledge and high practical skills, prof. Aznauryan was the first to introduce the newest immunomorphological research methods at that time, which were successfully used not only by the employees of the Department of Pathological Anatomy of YSMU, but also by scientists working in various fields of theoretical and practical medicine of our republic. As an employee of the Department of Pathological Anatomy, A.V. Aznauryan was involved in the implementation of the topic: "Pathogenesis and morphogenesis of acquired connective tissue diseases with immune disorders". Due to his researches, new pathogenesis mechanisms of these diseases were discovered.

Using the latest methods of immunomorphological analysis, Aznauryan A.V. revealed previously unknown shifts associated with DNA metabolism alteration (immunogenicity) in collagen diseases.As a successful result of this activity, he published a monograph, which was a reference book for many of us in the process of studying the nature of immunopathological disorders in collagen diseases. After the tragic earthquake in the cities of Spitak and Leninakan (Gyumri) of Armenia, when many residents were trapped under the rubble of destroyed buildings for a long time, prof. Aznauryan A.V. headed a new scientific direction devoted to aspects of the pathogenesis and morphogenesis of the crash syndrome. To this day, this direction seems to be the most relevant for those regions and countries where such natural disasters as earthquakes are quite common. In fact, prof. Aznauryan A.V. is the founder of studying the crush syndrome aspects in our republic. Together with his staff members he personally studied almost all the integrative systems of the macroorganism, under the conditions of experimental reproduction of the crush syndrome model. So, the cardiovascular, nervous, immune and endocrine systems were studied at a high scientific and methodological level, including the methods of morphometric, cytological, immunomorphological and electron microscopic analysis, with a contribution to the crash syndrome development of each of them.

This stage of prof. Aznauryan's scientific activity was highly appreciated by medical scientists of near- and far-abroad countries. In particular, this is evidenced by numerous reviews for his monograph, as well as the fact that he was awarded the high title – "Honorary Doctor" by the Russian Academy of Sciences. Back at the end of the twentieth century, the journal "Problems of Chronobiology" – the only scientific periodical of this profile in the territory of the former USSR functioned in Armenia. The journal was published under the auspices of the Ministry of Health of the Armenian SSR, and the Honored Worker of Science of the Republic of Armenia, Professor Aznauryan A.V.. A man "with a capital letter", a talented teacher and scientist, has passed away. This is a great, irreparable loss for all of us.

Prof. Arto Zilfyan,
Honored Worker of the Republic of Armenia,
Editor-in-Chief of "New Armenian Medical Journal",
Head of the Research Center of YSMU.

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