Review

Ectopic fat depots: physiological role and impact on cardiovascular disease continuum

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Abstract: Obesity is a non-infectious pandemic. The visceral distribution of adipose tissue is a significant factor in the development of cardiovascular diseases and their complications. Along with the visceral abdominal depot in omentum and subcutaneous tissue, there are other ectopic adipose tissue depots: epicardial adipose tissue (EAT), perivascular adipose tissue (PVAT) and perirenal adipose tissue. This article presents a review of the physiological role and molecular basis of the PVAT and EAT function in healthy, as well as in pathological, conditions; the interaction of adipokines and cytokines, their contribution to the development and progression of cardiovascular diseases. The review discusses well-known facts and controversial issues in this field. Comprehensive investigation of the mechanisms of vascular and myocardial pathology in obese people, along with identification of biomarkers for early prediction of cardiovascular complications, would contribute to the development of targeted preventive measures and choice of therapeutic strategies, which is consistent with the contemporary concept of personalized medicine. We have analyzed domestic and foreign literature sources in eLIBRARY and PubMed scientific libraries for the period of 2001-2020.

Keywords: cardiovascular disease, epicardial adipose tissue, perivascular adipose tissue, adipokine.

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Introduction

Obesity is a global health issue [1]. The visceral type of adipose tissue deposition has the greatest impact on morbidity and mortality [2]. It is characterized by high hormonal activity with an increase in proinflammatory, oxidative, thrombogenic and fibrotic consequences [2]. According to the Epidemiology of Cardiovascular Diseases Study (ECDS-RF), the prevalence of abdominal obesity in Russia, measured by waist circumference, was 24.3% in men and 38.4% in women [3]. However, an increase in the waist circumference is not invariably associated with severe visceral obesity; it may be caused by the subcutaneous adipose tissue accumulation [4].

The emergence and widespread implementation of highly informative visualization methods elucidated both the types of adipose tissue distribution in the body and classification of ectopic adipose tissue (along with abdominal fat depot): epicardial, perivascular and perirenal [5,6].

Currently, ectopic adipose tissue is considered an independent marker of cardiovascular risk [5]. Its unique anatomical features, specific secretory activity, strong correlation between adipokine/cytokine imbalance, and structural and functional remodeling of the cardiovascular system determine the relevance of a comprehensive investigation of its function, and clarification of the diagnostic value of various methods of ectopic fat depot imaging [6].

Most recent reviews and meta-analyses in the field have been focused on the role of ectopic adipose tissue in the development of either certain diseases, such as atrial fibrillation and coronary heart disease, or their risk factors. The review by M. Zhou et al. described the role of the epicardial adipose tissue in development and progression of atrial fibrillation. Also, the potential ways of local epicardial obesity correction via intake of antidiabetic drugs and statins were discussed. The authors provided experimental data on the possibility of epicardial adipose tissue ablation for improving the prognosis for the surgical treatment of atrial fibrillation [7]. N. Katsiki et al. in another review raised the question of the relation between epicardial adipose tissue and coronary atherosclerosis/coronary heart disease. The main emphasis was made on possible approaches to reducing the volume of epicardial adipose tissue [8]. Meta-analysis by Y. Li et al. interpreted the results of 13 studies, combining data on 1,102 patients. Authors estimated epicardial adipose tissue thickness in patients with type 2 diabetes mellitus, which was on average 1.23 mm higher than in healthy participants (95% confidence interval: 0.98; 1.48, p=0.000) [9]. The correlation of epicardial adipose tissue with the development of chronic kidney disease via the activation of proinflammatory cytokines synthesis was presented in a review by N.R. Aeddula [10]. The available data on perivascular adipose tissue are quite limited. A review by K.A. Britton and C.S. Fox focused on methods of detecting adipose tissue deposition around blood vessels, as well as on the probable physiological role of perivascular fat [6]. The authors pointed out...
that data on the role of dysfunctional perivascular adipose tissue were extremely limited, thus requiring further studying.

In this regard, the goal of this review was to systematize actual information on the effects of epicardial and perivascular fat deposits in both physiological and dysfunctional states. It is of particular interest to consider the contribution of these structures to the global process of cardiovascular remodeling, starting with risk factors, through formation of myocardial and vascular wall injury, up to further development of clinically significant cardiovascular diseases.

**Perivascular adipose tissue**

Perivascular adipose tissue surrounds large vessels, arteries and veins of a smaller size, along with microcirculatory vessels. Large arteries are separated from the surrounding perivascular adipose tissue by anatomical barriers, which consist of collagen fibers, fibroblasts, autonomic nerve endings and vasa vasorum, while there are no prominent laminar structures in small-diameter and microcirculatory vessels [11]. These anatomical features differentiate perivascular adipose tissue from other ectopic depots and provide continuous paracrine interaction among fat deposits and vascular walls [11].

Perivascular adipose tissue includes both white and brown adipocytes, and their ratio is determined by the localization of the vessel [12]. Thus, the thoracic aorta and its branches are surrounded mainly by brown adipose tissue, which takes active part in the thermogenesis, is reach with sympathetic nerves and blood vessels. For example, the thoracic aorta and its branches are surrounded predominantly by brown adipose tissue, which participates actively in thermogenesis and is rich in sympathetic nerves and blood vessels.

Perivascular adipose tissue of mesenteric vessels and the abdominal aorta is represented by white adipose tissue. Along with its role in the thermoregulation and metabolism, it acts as an endocrine organ responsible for the synthesis of both adipokines and cytokines [12].

Under physiological conditions, perivascular adipose tissue actively secretes a wide range of adipokines and cytokines with anticontractile, antioxidant and anti-inflammatory activity [11]. The most significant perivascular relaxing factors are adiponectin, omentin-1, palmitic acid methyl ester, nitric oxide (NO) and hydrogen sulfide (H\textsubscript{2}S) [13-15].

Adiponectin is a vasodilator that acts directly on vascular smooth muscles via opening of calcium-dependent potassium channels, stimulating the nitric oxide (NO) release by surrounding adipocytes via a paracrine pathway [11]. This adipokine inhibits the proliferation and migration of endothelial cells [13], reduces vascular stiffness in arterial hypertension [14], and has a powerful antiatherogenic effect [16]. The results of recent studies indicated that low adiponectin level was associated with development of the endothelial dysfunction and arterial hypertension [17].

Along with anticontractile effects, omentin-1 helps reducing the expression of proinflammatory cytokines in affected vessels and prevents neointima thickening [18]. Experimental data [19] demonstrated that systemic administration of omentin-1 to mice significantly reduced the size of myocardial infarction. It was found that this adipokine reduced acute ischemic injury of myocardium by suppressing apoptosis of myocytes [19].

In addition, perivascular adipose tissue is in charge of secreting the palmitic acid methyl ester, which also possesses a prominent vasodilating potency. An experimental study revealed [20] reduced synthesis of this biologically active substance with arterial hypertension. This process is accompanied by an increased release of angiotensin II from the perivascular adipose tissue and an inhibition of vasodilation.

Some studies indicated that adipocytes and endothelial cells of vasa vasorum perivascular adipose tissue produced NO [21]. A study on mice [21] have shown that the level of NO increased at the early stages of vascular remodeling, which was probably associated with a compensatory reaction of the vascular wall. However, with a progress of pathological processes, the concentration of NO declined, implying endothelial dysfunction [21]. Furthermore, it was noted that NO, synthesized by perivascular adipose tissue, prevented platelet aggregation in the microcirculatory vessels [22].

Hydrogen sulfide (H\textsubscript{2}S), synthesized by perivascular adipose tissue, is a powerful vasodilating agent. It was noted that its synthesis declined during the proliferation of vascular smooth muscle cells. It has been shown that H\textsubscript{2}S was able to reduce the level of angiotensin II in conditions of hypertension – as a compensatory mechanism maintaining normal blood pressure [15].

Secretory activity of perivascular adipose tissue changes with obesity and cardiovascular diseases [23]. These conditions contribute to the onset of oxidative stress, systemic inflammation, and the transformation of adipocyte protective phenotype into dysfunctional variety. The latter is characterized by the secretion of such proinflammatory and profibrotic adipokines and cytokines as leptin, visfatin, chemerin and resistin [11]. This results in development and progression of cardiovascular pathology, which has been demonstrated in the Framingham Heart Study on the subgroup of 1,067 patients [24]. In that study, the perivascular adipose tissue development correlated with metabolic risk factors and degree of aortic and coronary calcification.

Leptin is the adipokine expressed predominantly by white adipose tissue [25]. It affects the processes of inflammation in the vessel wall, stimulates the secretion of proinflammatory cytokines (TNF-\alpha and IL-6), proliferation, hypertrophy of vascular smooth muscle cells, and oxidative stress [25]. The results of clinical studies have demonstrated a significant correlation of the circulating leptin content with cardiovascular events, as well as with the severity of atherosclerotic vascular lesions [26]. Some authors stated that an enlarged secretion of leptin contributed to the neointima formation [27].

Visfatin is another growth factor with proinflammatory potency that affects vascular smooth muscle cells, stimulating their proliferation [28]. It is known that these processes are closely related to the development of atherosclerosis, which confirms the direct role of visfatin in its pathophysiology. In the study by G.S. Spiroglou et al., an increase of visfatin in perivascular adipose tissue with coronary atherosclerosis has been shown [29]. Similarly, in the group of patients with type 2 diabetes, a significantly higher level of visfatin was detected with atherosclerotic lesions of the carotid arteries, compared with the control subjects [30].

Another proinflammatory cytokine, chemerin, which is actively involved in smooth muscle contraction, has similar effects [31]. High expression of chemerin is related to an increase in vascular...
endothelial growth factor, which stimulates the proliferation of vascular endothelial cells and activates angiogenesis [32].

Resistin, which is synthesized predominantly by white adipose tissue, plays an important role in the development of insulin resistance and endothelial dysfunction, and activates potent vasoconstrictor endothelin-1 [33, 34]. In addition, resistin initiates proliferation of smooth muscle cells and endothelium and demonstrates proatherogenic effects [33].

The unique feature of perivascular adipose tissue that distinguishes it from other ectopic fat depots is the synthesis of hepatocyte growth factor, which is not produced by other adipose tissue varieties [35]. K. Rittig et al. [35] noted an increased level of hepatocyte growth factor in obese patients. It was found that this agent was directly involved in the development and progression of atherosclerosis by means of neovascularization of plaques, proliferation of endothelial cells, and activation of proinflammatory cytokine secretion, mainly IL-6 and IL-8 [35]. The latter promoted the adhesion of monocytes and macrophages, with further progression of atherosclerotic lesions [36].

Thus, the available data indicated that perivascular adipose tissue, under physiological conditions, acted as protective adaptive structure with numerous favorable metabolic effects. In contrast, dysfunctional perivascular adipose tissue exhibited proatherogenic, proinflammatory, and oxidative effects stimulating vascular remodeling and endothelial dysfunction, which reduced insulin-dependent glucose transport in muscles, thus contributing to peripheral insulin resistance [37], along with the development and progression of atherosclerosis and arterial hypertension (Figure 1).

**Epicardial adipose tissue**

Epicardial adipose tissue is located between the myocardium and the visceral pericardial sac. It surrounds mainly the areas of atrioventricular and interventricular grooves, coronary arteries, and the surface of the right ventricle [38]. Physiological functions of epicardial adipose tissue are mechanical, thermogenic, metabolic, and endocrine/paracrine [39]. This ectopic fat depot is a powerful source of various biologically active adipokines affecting the coronary arteries and myocardium via the paracrine pathway [40].

Increased volume of epicardial fat leads to the formation of a fatty shell around the heart, and dysfunction of adipose tissue. The essential marker of such dysfunctional fat is an imbalance of adipokines and cytokines with a predominance of substances with harmful cardiovascular effects [41]. In the absence of a fascial barrier between the epicardial adipose tissue and the myocardium, a general blood supply with a wide network of capillaries promotes the direct effect of adipokines on surrounding tissues with local inflammation, hypercoagulation, atherogenesis, and fibrosis [42].

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**Figure 1. The role of dysfunctional perivascular adipose tissue in cardiovascular disease development.**

NO, nitric oxide; H2S, hydrogen sulfide; AH, arterial hypertension; SMC, smooth muscle cells; IL interleukin; TNF-α, tumor necrosis factor-α.
Current studies demonstrated that epicardial adipose tissue was a significant component of the cardiovascular disease continuum [43-46]. The role of epicardial adipose tissue in the development of atherosclerosis and the coronary heart disease progression has been demonstrated [42, 47, 48]. The publication of G.N. Bachar et al. showed the relationship between the thickness of epicardial adipose tissue and atherosclerosis of the coronary arteries in patients without clinical manifestations of coronary heart disease and with one or more risk factors for cardiovascular diseases [47]. The MESA (Multi-Ethnic Study of Atherosclerosis) study on a group of 1,119 patients demonstrated that epicardial adipose tissue volume was an independent predictor of coronary events [43]. Proinflammatory adipokines (leptin, IL-1, IL-1β, IL-6-8, TNF-α), synthesized by dysfunctional epicardial adipose tissue, activated inflammation in the wall of coronary arteries, leading to endothelial dysfunction, damaging vascular intima [42], thereby playing an important role in the pathogenesis of coronary atherosclerosis. The study results [48], where a relationship has been established between the signs of instability of atherosclerotic plaques in the coronary arteries and the volume of epicardial adipose tissue (according to computed tomography), also confirmed the direct impact of proinflammatory and proatherogenic adipokines of epicardial adipose tissue on the processes of atherogenesis.

The role of epicardial fat in the development and progression of atrial fibrillation was a subject of numerous studies [44, 45, 49]. The research by I. Abe et al. demonstrated that fibrosis of the left atrial myocardium correlated with adipocytokines, secreted by epicardial adipose tissue and possessing proinflammatory and profibrotic activity (IL-6, TNF-α, monocytic chemoattractant protein-1, vascular endothelial growth factor, matrix metalloproteinases – MMP-3 and MMP-9) [44]. The study by S. Tao et al. investigated the omentin-1 levels in 220 patients with atrial fibrillation and 115 healthy subjects. Patients with atrial fibrillation had a significantly lower content of serum omentin-1, compared with the control group [45]. The role of the profibrotic factor, galectin-3, in the development of atrial fibrillation is widely discussed [46]. This protein, being a stimulator of fibroblast proliferation and collagen synthesis, is actively expressed and secreted by macrophages derived from the epicardial adipose tissue [50]. Galectin-3 was a subject of the meta-analysis by M. Gong et al., which encompassed 28 studies and 10,830 patients. It has demonstrated significantly higher levels of galectin-3 in patients with permanent atrial fibrillation, compared with the
subjects with paroxysmal atrial fibrillation [46]. Hence, the results of current studies indicated that inflammation induced by adipocytokines of epicardial adipose tissue has contributed to the development of atrial fibrillation. It is worth noting that the latter is a morphological background for the onset and progression of atrial fibrillation.

The meta-analysis by M. Gaeta et al., which included the results of seven studies, exhibited the correlation between the volume of epicardial adipose tissue and atrial fibrillation. Patients with atrial fibrillation had higher volumes of epicardial adipose tissue, compared with the healthy people. The difference between patients with atrial fibrillation and healthy individuals was 32.0 mL (95% confidence interval: 21.5; 42.5). The analysis in the subgroups with atrial fibrillation demonstrated higher volumes of epicardial adipose tissue among those with permanent atrial fibrillation versus its persistent variety: the difference from the healthy subjects was 48.0 mL (95% confidence interval: 25.2; 70.8) and 15.7 mL (10.1; 21.4), respectively [51].

It has been noted that an enlargement of the epicardial adipose tissue thickness was associated with an increase in the mass of the left ventricle [52,53]. D. Corradi et al. demonstrated a positive correlation between the epicardial fat weight and the mass of both ventricles [52]. Similar results were obtained in the study by H. Park et al, confirming a significant relationship of the epicardial fat with left ventricle mass, and markers of left ventricular systolic and diastolic functions in patients with metabolic syndrome [53].

Impairment of diastolic function in epicardial obesity is associated with the fatty shell formation and the reactive fibrosis development; the latter, in some cases, precedes left ventricular hypertrophy [41]. Along with the above-mentioned profibrotic factors, myocardial fibrosis is promoted by the actions of epicardial adipose tissue-derived thrombospondin-2, activin A, leptin, and angiotensin II, stimulating the production of transforming growth factor-β responsible for the synthesis of collagen and other components of the extracellular matrix [54].

A specific role in the chronic heart failure progression with epicardial obesity is attributed to the imbalance in the system of matrix metalloproteinases (MMPs) and their tissue inhibitors, which affects the extracellular matrix structure, cell proliferation, migration, inflammation, and apoptosis [55]. It is known that leptin, IL-1, and TNF-α, secreted by epicardial adipose tissue, stimulate the production and activation of MMPs [56]. These processes cause the destruction of the myocardial extracellular matrix components, contributing to the disruption of the connective tissue structure and myocardial remodeling [55]. These were confirmed by a positive correlation of the epicardial adipose tissue thickness with MMP-3, collagen level, transforming growth factor-β, and leptin [57].

An important impact on the prevention of the cardiovascular remodeling is inherent in adipocytokines with anti-inflammatory, antiatherogenic, and cardioprotective effects. Their concentrations decrease with dysfunctional epicardial fat [58-61]. One of them, adiponectin, increases the insulin sensitivity, has favorable effects on lipids, and protects against ventricular hypertrophy [59]. Adrenomedullin has a vasodilating effect and helps maintaining the vascular integrity [59]. Omentin-1 is characterized by a prominent anti-inflammatory effect; the secretion of this protein contributes to the postischemic reflow [60], vasodilation, and insulin sensitivity [61].

At present, the gender-related characteristics of the epicardial adipose tissue thickness are actively studied. The available data are quite controversial. Some studies detected lower epicardial fat thickness in women, compared with men [62, 63]. In contrast, there is some evidence of a positive correlation between the epicardial fat thickness and female sex [64]. Along with this finding, some studies reported no relationship between gender and epicardial fat [65]. Such discrepancies could be caused by the concomitant pathology, heterogeneity of the studied sample, or lack of data on the hormonal status of women.

Hence, current data imply the relationship between epicardial adipose tissue and various cardiovascular structural and functional abnormalities. The pathophysiology of cardiovascular remodeling involves an imbalance of adipokines and cytokines with predominance of proinflammatory, proatherogenic, profibrotic and prothrombogenic agents. These changes trigger oxidative stress, inflammation, proliferation of endothelial and smooth muscle cells, activation of the sympathetic and renin-angiotensin systems, formation of atherosclerotic plaques, and fibrosis. All of these changes contribute to the onset and progression of cardiovascular diseases (Figure 2).

Conclusion

Obesity continues to be among the most important global health issues, both due to its high prevalence and because of its close relationship with majority of non-infectious diseases. Since discovery of the visceral adipose tissue endocrine function, many studies have demonstrated the ability of adipose cells to synthesize wide range of biologically active substances. A number of fundamental, experimental, clinical, and epidemiological studies evaluated ectopic forms of obesity: epicardial and perivascular adipose tissues. It has become apparent that ectopic depots affect the myocardium and vessels via the unique mechanism. However, available data in this field remain controversial. In this regard, further epidemiological studies are required to clarify the characteristics of ectopic fat distribution, dependent on blood vessel size and location, in healthy people vs. patients with cardiovascular diseases. It is necessary to combine the methods of ectopic obesity measurement in order to develop classification approaches to determining its severity. The accumulation of data on the biological role of ectopic adipose tissue in healthy state vs. in the course of the disease may lead to the emergence of at least additional, or possibly alternative, criteria for obesity. Such criteria would enable more accurate assessment of the degree of obesity. Further studies are needed on the effect of treatment on the volume and synthetic activity of ectopic fat depots. All these factors could improve the diagnosis and choice of treatment for obesity and associated conditions, taking into consideration the current concepts of personalized, preventive and predictive medicine.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

Ethical Approval

None
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