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Review

Potential beneficial effect of some adipokines positively correlated with the adipose tissue content on the cardiovascular system

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ABSTRACT

Obesity is a risk factor of cardiovascular diseases. However, in the case of heart failure, obese and overweight patients have a more favourable prognosis compared to patients who have a normal body weight. This phenomenon is referred to as the "obesity paradox," and it is explained by, among others, a positive effect of adipokines produced by adipose tissue, particularly by the tissue located in the direct vicinity of the heart and blood vessels. The favourable effect on the cardiovascular system is mostly associated with adiponectin and omentin, but the levels of these substances are reduced in obese patients. Among the adipokines which levels are positively correlated with the adipose tissue content, favourable activity is demonstrated by apelin, progranulin, chemerin, TNF-α (tumour necrosis factor-)α, CTRP-3 (C1q/tumour necrosis factor (TNF) related protein), leptin, visfatin and vaspin. This activity is associated with the promotion of regeneration processes in the damaged myocardium, formation of new blood vessels, reduction of the afterload, improvement of metabolic processes in cardiomyocytes and myocardial contractile function, inhibition of apoptosis and fibrosis of the myocardium, as well as anti-inflammatory and anti-atheromatous effects. The potential use of these properties in the treatment of heart failure and ischaemic heart disease, as well as in pulmonary hypertension, arterial hypertension and the limitation of the loss of cardiomyocytes during cardioplegia-requiring cardiosurgical procedures, is studied. The most advanced studies focus on analogues of apelin and progranulin.

1. Introduction

Heart failure is a consequence of many processes which are results of metabolic, morphologic and regulatory disturbances [1]. These disturbances are related not only to the cardiovascular system, but also to other systems which participate in modulation of its function, such as the immune system [2], the endocrine system [3], and the autonomic nervous system. [4] Heart failure contributes to the development of compensatory mechanisms which aim to preserve the function of other organs; however they finally contribute to improper regulation of their function and progression of heart failure. [1] One of these mechanisms is hyperactivation of the sympathetic nervous system and vasoconstriction –an example may constitute organs exhibiting high oxygen demand, such as skeletal muscles; oxygen supply during exertion in state of heart failure is an effect of hyperactivation of the sympathetic nervous system and vasoconstriction, without normal increase of cardiac output, what results in reduction of stroke volume. [4] One of the important risk factors in the development of heart failure is obesity [5] and associated with it disorders of lipid and carbohydrates metabolism, chronic low-grade inflammation [6], increased activity of rennin – angiotensin - aldosterone system [7] and the sympathetic nervous system. [8] These disturbances contribute, among others, to the dysfunction of endothelium, vasoconstriction, hypertension, tendency to thrombosis and accelerated development of atherosclerosis. [9] They are responsible for unfavourable remodelling of the left ventricle, fibrosis and steatosis of the myocardium [10], which also constitutes a basis for arrhythmia, QT extension [11] and sudden cardiac death [12]. However, it was demonstrated that the prognosis of patients with heart failure and overweight to grade 1 obesity was more favourable compared to patients who had a normal body weight [13], what is referred to as the "obesity paradox". One of conceptions explaining that phenomenon are favourable properties of adipokines produced by adipose tissue. [14] Besides adiponectin and omentin, which concentrations decrease as adipose tissue accumulate [15–18], adipokines are considered as factors participating in the development of cardiovascular disorders associated with obesity [19], however, some of them demonstrate potentially

Abbreviations: EAT, epicardial adipose tissue; PVAT, perivascular adipose tissue.

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cardioprotective activities. They improve the metabolism of cardiomyocytes and systolic function of the heart, inhibit apoptosis and fibrosis of the myocardium, as well they have vasodilatory, anti-inflammatory and anti-atherosclerotic properties. One of the adipokines' activities is a positive impact on the synthesis of proangiogenic factors and their receptors and the enhancement of endothelial progenitor cells' migration to ischemic areas. Taking into account that one of the causes, as well as results, of complex mechanism of heart failure is hypoxia, these activities of adipokines may result in the development of new blood vessels, better oxygen supplementation and improvement of metabolism and systolic function of the heart. Presence and efficiency of these processes and their real meaning for the heart's function in the context of complexity and number of mechanisms which contribute to the development of heart failure require further studies, all the more so, because proangiogenic effect is interpreted in various ways – as a favourable effect resulting in the reduced rate of heart failure [20] or as a factor favouring the formation of well vascularised, unstable atherosclerotic plaques, which are associated with a high risk of acute coronary syndrome [21]. Mixedinterpretation concerns also systemic concentrations of factors directly regulating creation of new blood vessels such as VEGF and angiopoietins. High levels of these factors are considered as a manifestation of high-grade ischaemia, requiring the intensification of angiogenesis and vasculogenesis [22,23], or as a manifestation of an efficient organism's reaction to hypoxia, possibly enabling the minimisation of its complications and longer survival [24] Nevertheless, possibility of proangiogenic activities of adipokines requires consideration, especially in the context of attempts during treatment of heart failure caused by ischemia by induction of angiogenesis within myocardium and studies concerning potential use of adipokines in treatment of other cardiovascular diseases. As most of the literature data concerns the adipokines with levels positively correlated with the adipose tissue content and negative impact on the cardiovascular system, this paper is aimed to present these from them, which, during studies, demonstrate a favourable effect. It is all the more important, because the adipokines, due to their positive properties, become subject of studies in new medicines used in therapy of cardiovascular diseases and in cardio surgery. Furthermore, due to the controversial aspect of the ‚obesity paradox", attempts to explain it by adipokines' activity and studies concerning treatment of heart failure caused by ischemia by induction of new blood vessels' formation within myocardium, this paper indicates positive mechanisms of adipokines' activities, independently of negative impacts of obesity on heart failure development. In this paper, we review the literature, both clinical and experimental, from PubMed base. The aim of review was to determine the mechanisms explaining potential favourable effects of adipokines. The review involves 1987–2016 years. (See Tables 1 and 2.)

2. Obesity and heart failure

Obesity is a result of a long-term positive energy balance, leading to the specific excess of the volume of basic fat deposits constituted by subcutaneous fat, and adipose tissue accumulation in and around internal organs, resulting in their dysfunction. In the case of the heart, this state is enhanced by changes occurring in cardiomyocyte metabolism. In normal conditions, fatty acids constitute the main source of energy for the heart of adult people [25]. Their high levels stimulate the expression of peroxisome proliferator-activated receptors alpha (PPAR-α), which are responsible for their increased transport into cardiomyocytes and mitochondria and subsequent oxidation [26]. Oxidation of fatty acids requires a large amount of oxygen. In the case of heart failure, hypoxia results in the accumulation of lipids inside cells, development of lipotoxicity and conversion of cardiomyocyte metabolism to glycolysis [27]. However, hypoxia is associated with reduced ATP production, which is insufficient for the maintenance of effective contractile function of the myocardium, what leads to the aggravation of existing hypoxia. In addition, expression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC1α) is induced, promoting the activity of myocyte enhancement factor 2 (MEF-2), which is responsible for the enhanced expression of beta - myosin heavy chains (β-MHC), in obesity and heart failure, which have an inferior contractile activity compared to alpha – myosin heavy chains (α-MHC) synthesised under physiological conditions [28]. The activity of protein kinase C isoforms, which is associated with an abnormal response of myofilaments to variable calcium levels in cardiomyocytes [29] and the reduced response to adrenergic stimulation [30], is also increased. The development of heart failure in obese patients is also a result of apoptotic cardiomyocyte loss resulting from enhanced oxidative stress, activation of mitogen-activated protein kinases (MAPK) [31] and damage of the endoplasmic reticulum [32] by lipids accumulated in cardiomyocytes. As described above, obesity is associated with the accumulation of adipose tissue around internal organs. Indeed, it is not a process of formation of its ectopic deposits, but rather an enlargement of pre-existing deposits. Under physiological conditions, these deposits are small and exhibit specific functions depending on their localisation [33]. In the case of epicardial adipose tissue (EAT), post-mortem examinations have revealed that it is maintained even in the case of chronic diseases associated with significant body weight loss and depletion of adipose tissue in other areas of the organism [34], which suggests an important role of EAT in heart function. Moreover, patients with heart failure and a small thickness of EAT are characterised by a less favourable prognosis [35]. In physiological conditions, EAT is located in the interventricular sulcus, between the ventricles and atria, and on the posterior wall of the right ventricle and the anterior wall of the left ventricle (LV). Considering the vicinity of coronary vessels, it is a specific equivalent of perivascular adipose tissue (PVAT) [36]. Considering the high mRNA and protein characteristics of brown adipose tissue, one of the functions associated with EAT is the maintenance of stable thermal conditions for the prevention of cardiac rhythmic disorders [37]. The tissue is a constant source of fatty acids, the energy source for the operating heart [38], and provides a mechanical barrier preventing the deformation of arteries during contraction of the myocardium. Excess EAT results in disorders of the synchronisation of the heart, even in individuals with no injuries of the myocardium [39]. A thickness over 5 mm is associated with an increased weight of the LV, reduced ejection fraction, diastolic dysfunction and enlargement of the left atrium (LA), which may be a result of both an additional mechanical load of the LV by the surrounding adipose tissue and of the previously described toxic effect of lipids on the myocardium [40]. Moreover, a positive correlation between the amount of EAT and the level of narrowing [41] as well as the number of altered coronary vessels [42] was demonstrated. In that context, it is difficult to conclude any positive effect of excessive adipose tissue on the cardiovascular system. However, the obesity paradox and unfavourable prognosis of patients with a low EAT content indicate its existence. Considering hypoxia as the basis for circulatory failure and remodelling and cardiac rhythmic disorders, this effect may be a result of the neovascularisation promoting effect of adipokines produced by the adipose tissue.

Table 1
Distribution of adipokines by presence or lack of activities related to pathogenesis of the cardiovascular diseases.

Adipokines demonstrating no activity associated with the pathogenesis of cardiovascular diseases	Adipokines demonstrating the activity associated with the pathogenesis of cardiovascular diseases
Apelin	Progranulin
Vaspin	Chemerin
CTRP3	Visfatin/Nampt
	Leptin
	TNF-α