Atherosclerosis xxx (2017) 1–8

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Impact of the cardiovascular system-associated adipose tissue on atherosclerotic pathology

Dimitry A. Chistiakov [a], Andrey V. Grechko [b], Veronika A. Myasoedova [c], Alexandra A. Melnichenko [c], Alexander N. Orekhov [c, d, *]

[a] Department of Neurochemistry, Division of Basic and Applied Neurobiology, Serbsky Federal Medical Research Center of Psychiatry and Narcology, 119991 Moscow, Russia
[b] Federal Scientific Clinical Center for Resuscitation and Rehabilitation, 109240 Moscow, Russia
[c] Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow 125315, Russia
[d] Institute for Atherosclerosis Research, Skolkovo Innovative Center, Moscow 121609, Russia

ARTICLE INFO

Article history:
Received 20 March 2017
Received in revised form
29 May 2017
Accepted 7 June 2017
Available online xxx

Keywords:
Atherosclerosis
Adipose tissue
Inflammation
Imaging

ABSTRACT

Cardiac obesity makes an important contribution to the pathogenesis of cardiovascular disease. One of the important pathways of this contribution is the inflammatory process that takes place in the adipose tissue. In this review, we consider the role of the cardiovascular system-associated fat in atherosclerotic cardiovascular pathology and a non-atherosclerotic cause of coronary artery disease, such as atrial fibrillation.

Cardiovascular system-associated fat not only serves as the energy store, but also releases adipokines that control local and systemic metabolism, heart/vascular function and vessel tone, and a number of vasodilating and anti-inflammatory substances. Adipokine appears to play an important protective role in cardiovascular system. Under chronic inflammation conditions, the repertoire of signaling molecules secreted by cardiac fat can be altered, leading to a higher amount of pro-inflammatory messengers, vasoconstrictors, profibrotic modulators. This further aggravates cardiovascular inflammation and leads to hypertension, induction of the pathological tissue remodeling and cardiac fibrosis. Contemporary imaging techniques showed that epicardial fat thickness correlates with the visceral fat mass, which is an established risk factor and predictor of cardiovascular disease in obese subjects. However, this correlation is no longer present after adjustment for other covariates. Nevertheless, recent studies showed that pericardial fat volume and epicardial fat thickness can probably serve as a better indicator for atrial fibrillation.

1. Introduction

The well-known association of obesity with increased risk of deadly illnesses, such as cancer and cardiovascular disorders, makes this widespread condition one of the hot topics in modern medicine. The hypothesis that obesity is involved in chronic inflammation persisting in the visceral adipose tissue has been formulated in the mid-1990s. It was demonstrated that obesity was associated with increased level of tumor necrosis factor (TNF)-α, a well-known inflammatory molecule [1]. Furthermore, accumulation of macrophages was observed in the visceral adipose tissue (VAT) of obese humans and mice [2–4]. Decreased energy expenditure and chronically elevated caloric uptake lead to the enlargement of VAT mass due to adipocyte growth. This in turn leads to the increased production of inflammatory factors, such as chemokine (C-C motif) ligand 2 (CCL2), which induces infiltration of monocytes into the visceral fat, where they differentiate to macrophages [5]. In obesity, adipocyte progenitors undergo hyperplasia and produce high levels of CCL2 that attract monocytes to VAT and initiate differentiation to proinflammatory M1 macrophages [6]. Moreover, in obese patients, altered balance of peripheral blood monocytes leads to a skewed differentiation of classically-activated (M1) and alternatively-activated (M2) macrophages towards the pro-inflammatory phenotype [7].

Adipose inflammation leads to metabolic and structural changes

* Corresponding author. Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow 125315, Russia.
E-mail address: a.h.opexob@gmail.com (A.N. Orekhov).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.017
0021-9150/

in VAT, including activation of lipolysis, increased formation of free fatty acids (FFA), oxidative stress, hypoxia, and increased apoptosis of adipocytes [8]. Generation of M1 macrophages from infiltrated monocytes increases the total secretion of pro-inflammatory cytokines, such as TNF-α, interleukin (IL)-1β, and IL-6. TNF-α negatively regulates insulin-dependent signaling in adipocytes and glucose and FFA uptake, suppressing fat synthesis and increasing lipolysis [9]. Excessive VAT-associated lipolysis can lead to accumulation of toxic fatty acid species, such as ceramide and diacylglycerol in non-adipose tissue including liver, skeletal and heart muscle, and contribute to the development of insulin resistance (IR) [10].

According to the current understanding, cardiovascular risk in obese people is associated more with visceral than with subcutaneous adiposity [11,12]. Classical methods for assessment of obesity, such as waist circumference (WC) and body mass index (BMI) have limited sensitivity and specificity for measuring visceral fat. In particular, population of subjects known as normal weight metabolically obese people can have normal or only slightly increased BMI and WC, but share the increased risk of the metabolic syndrome to the same extent as 'classically' obese people [13]. These subjects often have increased visceral adipose tissue mass, as well as signs of adipose tissue inflammation and altered profiles of signaling molecules, such as adipokines and pro-inflammatory factors [14]. Moreover, metabolically obese subjects are often characterized by altered insulin sensitivity and lipid profile, which makes them susceptible for development of type 2 diabetes and atherosclerosis. Numerous studies were undertaken to define this at-risk phenotype and evaluate the prevalence (revised in Refs. [14,15]).

Revealing the abnormal adiposity in such 'normal weight obese' patients requires special imaging techniques, such as abdominal computed tomography (CT). Rapid progress in imaging approaches during the recent years facilitated visualization and evaluation of epicardial adipose tissue (EAT) and perivascular adipose tissue (PVAT) as proxy markers of visceral adiposity, making them more precise markers of the cardiometabolic risk [16]. EAT is located mostly in atrioventricular and interventricular grooves, and can be regarded as a unique fat depot, with a distinct metabolic profile and location allowing it to support the normal cardiac function [17]. EAT is characterized by a higher capacity to uptake and release FFA than other visceral fat stores, being an efficient source of fatty acids for the energy-demanding myocardial tissue. It is also a source of a number of adipokines and other signaling molecules that are important for cardiac development, but it can also play a role in inflammation and atherosclerosis. Characteristics of PVAT depend on its location: it was demonstrated that thoracic PVAT functions as brown adipose tissue, being responsible for heat production, while abdominal PVAT resembles white adipose tissue and serves mostly to store lipids [18]. PVAT is also an important source of adipokines that can have paracrine function on the vascular wall. PVAT has been considered as a potential therapeutic target for treatment of atherosclerosis. There is an intriguing possibility that cardiovascular system-associated fat stores may represent not only valuable indicators of visceral adiposity, but also the independent markers of the cardiovascular risk [19]. In this review, we will consider the potential role of EAT and PVAT in cardiovascular pathology in conjunction with adiposity.

2. Cardiovascular system-associated adipose tissue: structural and anatomical aspects

Both EAT and PVAT are typical in healthy mammals. In obese animals and humans, the volume of these local fat stores increases proportionately with the visceral fat. This increase, however, represents not an "ectopic fat" deposition, but rather an enlargement of normally existing anatomical formation. In the cardiovascular system, fat deposits are located at several major sites (Fig. 1). Identification of the types of cardiac deposits requires accuracy and adherence to the imaging investigation manuals, due to the possible confusion of the definitions of heart fat stores, such as paracardial and pericardial fat [20]. Paracardial (mediastinal, thoracic) fat is located on the outer surface of the parietal pericardium [21] and combines characteristics of both white and brown fat [22]. Pericardial adipose tissue (PAT) comprises both paracardial fat and EAT [23,24]. It follows the coronary artery course, where preferentially functions as PVAT. In ventricles, EAT lies on the lateral wall (right ventricle) and the anterior wall (left ventricle) [25] and adjoins directly to the myocardium. Structurally, EAT is identical to white fat [26]. Epicardial fat is a true cardiac VAT depot, which has the same origin as mesenteric and omental fat, i.e. originates from the splanchnopleuric mesoderm. Together with the parietal pericardium, paracardial fat arises from the thoracic mesenchyme [27].

PVAT includes EAT associated with coronary arteries and fat stores that surround aorta, medium-size, and small arteries. It is likely that PVAT has different functions in each of these locations. Thoracic periaortic fat surrounds the thoracic aorta and has a structure similar to the brown fat, at least in rodents [28,29]. Abdominal periaortic fat, which is present in both humans and rodents, is located in the abdominal aorta and is identical to white fat [30,31]. According to current understanding, these fat depots have distinct cellular composition and undergo different pathological changes associated with excessive adiposity (Fig. 2). Small artery fat, which is associated with medium and small caliber arteries, exhibits typical characteristics of white fat. Small artery fat may contribute to the regulation of vascular tone and nutritional supply [32].

3. Cardiovascular system-associated adipose tissue: functional aspects

In coronary arteries, EAT mostly functions as PVAT. This fat store is characterized by active lipid metabolism with increased rates of

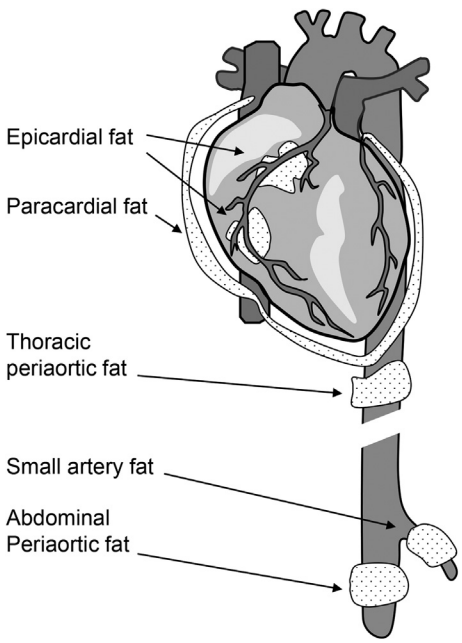

Fig. 1. Different types of fat deposits in the cardiovascular system.

Please cite this article in press as: D.A. Chistiakov, et al., Impact of the cardiovascular system-associated adipose tissue on atherosclerotic pathology, Atherosclerosis (2017), http://dx.doi.org/10.1016/j.atherosclerosis.2017.06.017