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DIABETES + INSULIN RESISTANCE (J ROBINSON, SECTION EDITOR)

Perivascular Fat and its Role in Vascular Disease, Insulin Resistance and Diabetes

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Abstract Perivascular adipose tissue is a visceral fat depot with an anatomical and functional contiguity to the vasculature system. Recent evidence suggests that perivascular adipose tissue could mechanically and functionally affect the vasculature, thereby possibly playing a role in adiposity-related atherosclerosis. Experimental and clinical observations suggest both favorable and unfavorable effects of perivascular fat. This review focuses on the emerging physiological and pathophysiological aspects of the perivascular fat and its role in vascular disease, insulin resistance and diabetes.

Keywords Perivascular fat · Epicardial fat · Diabetes · Insulin resistance

Introduction

A growing body of evidence suggests that regional fat distribution plays an important part in the development of an unfavorable metabolic and cardiovascular risk profile. Thus, the increased accumulation of visceral fat is now widely seen as a defining characteristic of the so-called metabolic syndrome [1, 2]. The recognition that adipose tissue is a highly complex endocrine organ that generates various molecules with profound local and systemic effects has spawned a remarkable interest in adipose-tissue research [3, 4]. Despite their similar qualitative properties, different types of adipose tissue, particularly subcutaneous and visceral adipose depots, are now recognized as having distinct quantitative characteristics [5, 6]. While much of the interest has focused on the importance of intra-abdominal visceral fat, some extra-abdominal visceral fat depots, including epicardial [7–9] and perivascular fat, have also been studied [10]. In this review paper we focus on the biomolecular properties of perivascular adipose tissue (PAT), and its role as cardiovascular risk factor.

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Anatomy of Perivascular Fat

All vascular vessels are surrounded by a perivascular sheath of adipose tissue called perivascular fat. Histologically, the perivascular fat differs according to which type of vessel they are surrounding: white adipose tissue in resistance vessels, whereas white and brown adipose tissue (BAT) in larger vessels like aorta [11]. At first it was suggested that this depot would offer mechanical support for the vasculature system, but as it has been discovered this is also an active endocrine organ which is thoroughly related to muscle tone control.

Physiology of Perivascular Fat

PAT plays a fundamental role in the "brain-vessel axis" control of vascular muscle tone [12]. The control of vascular function is dual, and depends on the stimuli around the vessel [13]. Vascular tone control by PAT is a complicated network of vasoactive substances, pathways and cellular subtypes that have recently begun to be described [14, 15, 16•, 17, 18]. Adipose-derived substances can modulate vascular tone. Insulin can also exert a dual role in modulating the vascular tone, by controlling endothelin-1 secretion via ERK1/2 (extracellular signal regulated kinases) and endothelial derived nitric oxide (eNOS) activation with subsequent production of NO via phosphatidylinositol-3-kinase and protein kinase B (PI3K/Akt)

[14]. Vascular tone also depends on adipose-derived relaxing factors (ADRFs) which are capable of activating inward rectifying K^+ channels to inhibit vasoconstriction [19]. Leptin and adiponectin have been considered to function as ADRFs. Sahin et al. [20] reported that leptin was capable of inducing vessel relaxation via endothelium derived nitric oxide (AMPK and Akt phosphorylation of eNOS), hydrogen peroxide, and also by inducing endothelium-derived hyperpolarizing factor [21], mechanisms which are exacerbated during the initial adapting period during over-nutrition and obesity to preserve vascular tone [22]. On the other hand, adiponectin is known to open K channels through its receptors adiponectin receptor 1 (AdipoR1) and AdipoR2 inducing relaxation in aortic and mesenteric rings [23]. Other relaxing factors include Angiotensin, which induces vasodilation by antagonizing angiotensin 1 (AT1) receptors in a bradykinin-NO pathway [24], and H_2O_2 through activation of several types of K^+ channels (calcium-dependent [25••], ATP-dependent [26], and voltage-dependent [27]). In summary, PAT has been recognized as a very active metabolic organ responsible for mechanical and functional tasks. PAT offers mechanical support during the arterial wave pulse and it can even maintain the integrity of the vascular wall during the pathological expansion during the formation of an atheromatous plaque.

Pathophysiology of Perivascular Fat

PAT & Atherosclerosis

Atherosclerosis and its consequent coronary artery disease (CAD) are the leading cause of death worldwide [28]. Current evidence has suggested that the basic pathogenesis includes lipid metabolism abnormalities and an awry immune response characterized by increased leukocyte trafficking, enhanced inflammatory microenvironment and progressive plaque formation [29]. Given the close anatomical proximity and its importance in vessel embryology, PAT has been placed in a very compromising place, with evidence that points to a local source of adipokines that seems to be the culprit of the very initial vascular dysfunction that ends in atherosclerosis.

PAT & Adipokines

PAT secretes adipokines that modulate and affect vascular function. Inflammatory cell infiltration is markedly increased in PAT surrounding atherosclerotic human aorta as compared with a non-diseased aorta, and the inflammatory gene expression is upregulated in this location [30]. PAT is able to promote constriction via induction of NADPH and synthesis of superoxide anion, which enhances mitogen activated protein kinase/extracellular signal regulated kinases (MAPK/ERK) pathway [31], suggesting a never ending battle of control of vascular tone; only when one is truly defective will the other be able to sustain its corresponding effect. Additionally, superoxide anion is capable of uncoupling the eNOS activity, maintaining only the enzymes production of superoxide, which is an actual intermediary in the synthesis of NO [32]. The overproduction of superoxide anion and oxygen singlet (ROS) enhances the levels of nitrogen species such as peroxynitrite, which is a potent vasoconstrictor and inductor of apoptosis in cardiomyocytes, endothelium and vascular smooth muscle [33]. Additionally, PAT can secrete a number of constrictors like angiotensin-II (Ang-II), resistin and visfatin.

Ang-II is not only a potent vasoconstrictor via AT1 [34], but also an inductor of nictotinamides adenine dinucleotide (NADPH) activity and superoxide production [35]. Moreover, this hormone is capable of inducing CD44 and C chemokine receptor 5 (CCR5) in T cells and production of regulated upon activation normal T cell expressed and secreted (RANTES) in vascular endothelium, creating a migration gradient for $CD4^+$ and in a lesser extent to $CD8^+$, although 30 % of T cells present in perivascular fat are $CD4^-CD8^-$ [36], capable of secreting IL-17 - a proinflammatory cytokine [37]. These $CCR5^+CD44^{hi}$ cells are in fact effector T cells with a lower threshold for activation, releasing TNF-alpha and IFN-gamma which contribute to endothelial dysfunction and hypertension [36]. Ang-II has also been related to the formation of "neoantigens", such as heat shock protein (HSP) 70 and HSP25 [38], responsible for the production of autoantibodies in an endothelial-injury manner and enhanced atherogenesis in animal models [39, 40].

Resistin, another adipokine fairly recently added to the adipocyte secretome, has been linked to type 2 diabetes and insulin resistance [41]. Several pro-atherogenic properties have been described, including inducing oxidative stress via uncoupling of eNOS and activation of Jun N-terminal protein kinase (JNK) [42], vascular smooth muscle cell hyperplasia promotion with subsequent thickening of the intima [43], increased expression of IL-1beta, IL-6, TNF-alpha, alpha4beta1 integrin (VLA-4) and vascular cell adhesion molecule 1 (VCAM-1) [44•], becoming a useful marker for vascular inflammation [45•] and acute coronary syndrome [46]. Another adipokine involved in this scenario is visfatin (pre–B cell colony enhancing factor or nicotinamide phosphoribosyltransferase [Nampt]), a controversial protein with catalytic activity, capable of improving insulin sensitivity [47], inducing B cell differentiation [48], and mediating vessel relaxation through NO synthetized by endothelial cells [49]. Even though these properties seem beneficial, during type 2 diabetes and obesity visfatin has been related to impairment of vasodilation due to stimulation of NADPH via its Nampt activity [50] and synthesis of proinflammatory cytokines (IL-6 and C-reactive Protein) from VAT during obesity [51], using as main source incoming and circulating leukocytes [52].

Leptin also has a principal role in PAT physiology. As previously reported, leptin induces vasodilation, yet there is a concept – the "*leptin paradox*" – where this cytokine is associated with inhibition of NO-dependent relaxation [53]. Tune and Considine [53] reported that the vasodilating effects of leptin are dose-dependent, where leptin at 10–90 ng/ml impairs acetylcholine-mediated relaxation, yet at levels higher than 160 ng/ml induces vasodilation. These authors conclude that leptin induced vasodilation might just be a pharmacological phenomenon, nevertheless, other studies advocate for a physiological role [54–56]. There are other novel adipokines [57] that have vascular tone modulating functions like omentin (described previously), chemerin, vaspin, and nesfatin. Chemerin is a protein which has been described as a potent chemoattractant for macrophages and immature dendritic cells [58]. This adipokine has been related to degree of coronary atherosclerosis and epicardial fat [59], arterial stiffness [60], severity of coronary arterial disease in patients with metabolic syndrome [61], and insulin resistance and glucose intolerance [62, 63]. Its ability to attract immunocytes to the subendothelium, contributes to the progression of atherosclerosis plaque and the vicious circle of localized insulin resistance (see the following section). Vaspin (SERPIN12) is an adipocyte-derived serine protease inhibitor with insulin sensitizing properties [64] and capable of protecting endothelial cells from apoptosis via PI3K/Akt pathway [65] protecting them from lipid toxicity. Hypovaspinemia has been related to ischemic cardiovascular events [66] and severity of CAD [67], while normal secretion inhibits TNF-alpha-induced expression of ICAM-1 preventing the subsequent activation of NF-kB and PKC protecting the vascular smooth muscle cells from an inflammatory profile [68]. Finally, nesfatin is an anorexigenic hormone with influence in the energy expenditure control circuit [69], and capable of inducing glucagon secretion [70]. It has been recently published that it can also inhibit soluble guanylate cyclase, which reduces NO-dependent vasodilation, contributing to vascular dysfunction [71].

PAT & Vascular Smooth Muscle Cells

There is an undeniable relationship between vascular smooth muscle cells and the white adipose tissue sheath that surrounds them. These cells are the basic motor units of the vessels, but they are also capable of altering its structure and modifying the extracellular matrix composition. Their phenotypes vary according to different stimuli and are considered not terminally differentiated, being classified into 2 classes: the spindle-shaped and the epithelioid vascular smooth muscle cells. The crosstalk between PAT and vascular smooth muscle cells is very complex and fairly new in concept. PAT is capable of modulating neointimal hyperplasia by increased secretion of TNF-alpha with parallel decreased secretion of adiponectin [72•]. Free fatty acids are released which can induce inflammation, as was proven using oleic acid in an adipocyte-conditioned media, where NF-kB and mTOR pathways are activated inducing proliferation of the smooth muscle cells [73, 74]. Insulin-like growth factor-I is able to induce vascular muscle cells migration via ERK1/2, signaling which is inhibited by adiponectin implicating AMPK activation [75]. Interestingly, PAT can also modulate the local renin-angiotensin-aldosterone system by inducing JNK, p38MAPK, and ERK1/2 via mineralocorticoid receptor, glucocorticoid receptor and AT1 receptor [76, 77].

PAT & Localized Insulin Resistance

Obesity is a disease closely associated with an array of cardiovascular risk factors such as diabetes, hypertension, proinflammatory and prothrombotic states, and obstructive sleep apnea. Remarkably these five risk factors are also related to insulin resistance [78–82]. Obesity milieu induces inflammation of the PAT, with the subsequent release of adipocytokines and the start and amplification of several pathways that will conclude in the development of the atherosclerotic plaque and the risk of rupture [83]. In fact, Rittig et al. [84] reported that PAT is an independent player in insulin resistance and it correlates negatively with insulin sensitivity. Moreover, they also reported that PAT secrets higher amounts of angiogenic factors like MC-1, insulin-like growth factor-binding protein-3, thrombospondin-1, fibroblastic growth factor and hepatocyte growth factor [85•], contributing to plaque rupture risk [86]. Obesity has systemic effects which affect short and long axis loops during the development of the disease, but at the vascular level obesity has an ample role in its pathophysiology like enhanced vasoconstriction, functional hyperemia, sympathetic neural hyperactivity, microvascular rarefaction, vascular remodeling, and local inflammation [87]. Insulin is a Janus-type controller in tone control: it can induce vasodilation via PKB/Akt and eNOS induction [88], while it induces vasoconstriction via MAPK and ERK1/2 pathways culminating in endothelin-1 synthesis [88]; nevertheless, the overall result is vasodilation [89]. As insulin resistance develops hyperinsulinemia occurs, stimulating MAPK pathways while PI3K/Akt is blunted, inducing an increase production of endothelin-1 and enhanced arterial and terminal arterioles constriction. This phenomenon alters the uptake of glucose and perfusion of the vascular muscles, describing a vicious circle concerning local insulin resistance and vascular tone control [90].

Conclusions

The general hypothesis for atherosclerosis is an "inside-out" model which is focused on lipid accumulation and monocyte attraction toward vascular intima. However, accumulating evidence supports an outside-in hypothesis in which the vascular *adventitia* promotes vascular inflammation and tone

deregulation [91] which would suggest that PAT have a role in this signaling landscape. Results from *in vitro*, *ex vivo*, animal and clinical studies support the double role of PAT in the pathogenesis of atherosclerosis. It is possible that a mass-dependent mechanism could influence the equilibrium between harmful and protective effects of this fat depot; however, a causal effect of PAT on atherosclerosis remains to be demonstrated. Therefore, future studies in this direction are needed to confirm or refute the relationship between PAT and cardiovascular risk.

Compliance with Ethics Guidelines

Conflict of Interest Chengyu Xu and Gianluca Iacobellis declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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