European Journal of Pharmacology 766 (2015) 16–24

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Review

Human perivascular adipose tissue dysfunction as a cause of vascular disease: Focus on vascular tone and wall remodeling

Gulsev Ozen [a,b], Armond Daci [a], Xavier Norel [b,c,*], Gokce Topal [a]

[a] Istanbul University, Faculty of Pharmacy, Department of Pharmacology, 34116 Beyazit, Istanbul, Turkey
[b] INSERM U1148, CHU X. Bichat, 46 rue H. Huchard, 75018 Paris, France
[c] Paris Nord University, Sorbonne Paris Cité, UMR-S1148, 75018 Paris, France

ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form
18 August 2015
Accepted 9 September 2015
Available online 28 September 2015

Keywords:
Perivascular adipose tissue
Vascular tone
Vascular remodeling
Human
Obesity
Atherosclerosis

ABSTRACT

Obesity is one of the major risk factors for the development of cardiovascular diseases. It is characterized by excessive or abnormal accumulation of adipose tissue, including depots which surround the blood vessels named perivascular adipose tissue (PVAT). PVAT plays endocrine and paracrine roles by producing large numbers of metabolically vasoactive adipokines. The present review outlines our current understanding of the beneficial roles of PVAT in vascular tone and remodeling in healthy subjects supported by clinical studies, highlighting different factors or mechanisms that could mediate protective effects of PVAT on vascular function. Most studies in humans show that adiponectin is the best candidate for the advantageous effect of PVAT. However, in pathological conditions especially obesity-related cardiovascular diseases, the beneficial effects of PVAT on vascular functions are impaired and transform into detrimental roles. This change is defined as PVAT dysfunction. In the current review, the contribution of PVAT dysfunction to obesity-related cardiovascular diseases has been discussed with a focus on possible mechanisms including an imbalance between beneficial and detrimental adipokines (commonly described as decreased levels of adiponectin and increased levels of leptin or tumor necrosis factor-alpha (TNFα)), increased quantity of adipose tissue, inflammation, cell proliferation and endothelial dysfunction. Finally, novel pharmacotherapeutic targets for the treatment of cardiovascular and metabolic disorders are addressed.

Contents

* Correspondence to: INSERM U1148, LVTS, Laboratory on Eicosanoids & Vascular Pharmacology, CHU X. Bichat, 46 rue Huchard, 75018 Paris, France. Fax: 33 01 40 25 86 02.
E-mail address: xavier.norel@inserm.fr (X. Norel).

http://dx.doi.org/10.1016/j.ejphar.2015.09.012
0014-2999/

1. Introduction

Obesity is one of the biggest epidemic health problems in the world and has been considered as a major risk factor for cardiovascular diseases. However, mechanisms of metabolic syndrome, diabetes mellitus and coronary artery disease in obese individuals are still under discussion. Obesity is characterized by excessive or abnormal accumulation of adipose tissue which is an active endocrine organ, secreting and producing many bioactive substances called adipokines (Boydens et al. 2012). It is well known that obesity-related cardiovascular diseases are accompanied by endothelial dysfunction which is characterized by a decrease in endothelium-dependent vasodilatatory factors such as nitric oxide (NO), prostacyclin (PGI_2) and an augmentation of endothelium-derived contractile factors (Hadi et al., 2005). Recent studies have proposed that not only endothelial dysfunction but also adipose tissue dysfunction has a potent role in the pathogenesis of obesity-related cardiovascular diseases. Maintenance of healthy adipose tissue function might become as important as preservation of endothelial integrity for prevention of vascular diseases (Gollasch, 2012; Gu and Xu, 2013).

Almost every blood vessel apart from cerebral artery and pulmonary vessels are surrounded by various quantities of perivascular adipose tissue (PVAT) (Szasz et al., 2013). It is now well established that PVAT not only provides mechanical protection for blood vessels, but also secretes vasoactive adipokines such as adiponectin, leptin, resistin, visfatin or other bioactive mediators (Oriowo, 2015). These mediators secreted from PVAT could easily reach the adjacent blood vessel wall since there is no anatomical barrier between PVAT and adventitia. They play important roles in regulation of the vascular tone and wall remodeling via their paracrine or endocrine effects. In this review, we aim to discuss these roles of PVAT on vascular functions in both physiologic and pathological conditions.

2. Release of adipokines from PVAT

Adipokines released from PVAT have been shown to have a more inflammatory, proliferative and angiogenic profile compared to other adipose depots such as subcutaneous or visceral adipose tissues in humans (Mazurek et al., 2003; Chatterjee et al., 2009; Rittig et al., 2012; Schlich et al., 2013).

Recent studies have focused on modulation of adipokines release depending on pathological conditions. In humans, most studies for determinating the role of adipose tissue in cardiovascular diseases have been performed in epicardial adipose tissue (EAT). EAT is the adipose tissue around the heart reaching from the myocardium to the pericardium. PVAT around coronary artery is a part of EAT. There is no obvious anatomical separation between coronary PVAT and EAT; however, PVAT releases greater levels of monocyte chemotactic protein-1 (MCP-1) than EAT (Chatterjee et al., 2009; Verhagen and Visseren, 2011). In coronary artery disease, inflammatory and proliferative adipokine expression or release such as interleukin-6 (IL-6), resistin, interleukin-1 beta (IL-1ß), MCP-1, chemerin, plasminogen activator inhibitor 1, tumor necrosis factor-alpha (TNFα), visfatin and leptin are increased, whereas adipokines with anti-inflammatory, anti-proliferative and vasodilatator properties (Terata et al., 2000; Xi et al., 2005) such as adiponectin or adrenomedullin are decreased in human EAT or PVAT surrounding coronary artery (Table 1). This imbalance between beneficial and detrimental adipokines may play a major role in cardiovascular diseases such as atherosclerosis, restenosis and hypertension by increasing vascular tone, inflammatory processes and vascular smooth muscle cell (VSMC) proliferation or migration.

3. Role of PVAT quantity in vascular disease

Recent studies have indicated a potential role of PVAT quantity in the development of coronary artery diseases. EAT thickness (Ahn et al., 2008; Demircelik et al., 2014; Eroglu et al., 2009) and also EAT volume (Mihl et al., 2014; Kaya et al., 2014; Mohar et al., 2014; Groves et al., 2014; Kim et al., 2014) were found to be higher in patients with coronary artery diseases. Total quantity of PVAT around coronary artery is strongly related to atherosclerotic plaque (Mahabadi et al., 2010; Maurovich-Horvat et al., 2011). More recently, extra media thickness has been suggested as a novel index of PVAT and associated with an increasing number of cardiovascular risk factors (Haberka and Gasior, 2015). A larger adipocyte size and increased density of differentiating preadipocyte are found in EAT obtained from coronary artery disease patients compared to healthy subjects (Silaghi et al., 2007).

It has been demonstrated that adipose tissue quantity is negatively correlated with microvascular coronary vasodilatation response and also coronary flow hyperemia in humans (Shen et al., 2013). EAT thickness is also negatively correlated with flow-mediated dilatation which has been established as a parameter of endothelial dysfunction (Temiz et al., 2015). Endothelial dysfunction has been indicated to be one of the critical initiating step in the development of atherosclerosis. Consistent with these studies, when there is no PVAT such as the intramyocardial portions of coronary arteries, less atherosclerosis has been observed (Ishikawa et al., 2006; Verhagen and Visseren, 2011).

PVAT surrounding human brachial artery is associated with insulin sensitivity; however, it is not correlated with local endothelial dysfunction (Rittig et al., 2008). Moreover, quantity of PVAT surrounding renal sinus is related to the number of prescribed antihypertensive medications and stage II hypertension (Chughtai et al., 2010). Framingham Heart study has indicated that higher thoracic and abdominal aortic dimensions are associated with PVAT quantity. This result has suggested that PVAT could induce aortic remodeling especially observed in aortic aneurysm (Thanassoulis et al., 2012).

4. Role of PVAT in vascular tone control *in vitro*

Firstly, Soltis and Cassis have shown that PVAT decreases the vascular contractile response to norepinephrine in rat aorta (Soltis and Cassis, 1991). Subsequently, it was confirmed that PVAT reduces vascular reactivity in response to not only norepinephrine but also serotonin, phenylephrine and angiotensin II (Lohn et al., 2002). This vasorelaxant effect of PVAT is mostly observed in animal tissues such as mesenteric arteries of rats/mice (Galvez et al., 2006; Takemori et al., 2007), venous rings of rats (Lu et al., 2011) and coronary arteries of pigs (Bunker and Laughlin, 2010).

The factors mediating the vasorelaxant effect of PVAT are not fully understood. This mediator named adipocyte-derived relaxing factor (ADRF) is abolished in the presence of ATP-dependent K channel blocker, whereas it is not modified by nitric oxide synthase (NOS) or cyclooxygenase (COX) inhibitors in rat aorta preparations (Lohn et al., 2002). However, in rat mesenteric arteries, voltage-dependent K channel blocker inhibits the vasorelaxant effect of PVAT (Galvez et al., 2006). It is suggested that regulation of vascular tone by PVAT is mediated by release of different adipokines from PVAT, depending on anatomic location of the adipose tissue depots and also the species: Hydrogen peroxide (Gao et al., 2007), hydrogen sulfide (H_2S) (Fang et al., 2009), adiponectin (Lynch et al., 2013), leptin (Galvez-Prieto et al., 2012) and methyl palmitate (Lee et al., 2011) have been considered as candidates for the vasorelaxant effect of PVAT in animal tissues. However, this vasorelaxant effect is abolished in several models of pathologies

Table1
Increased (A) or decreased (B) level of adipokines (release/protein/mRNA) from human perivascular adipose tissue (PVAT) or epicardial adipose tissue (EAT) in coronary artery diseases comparing to healthy situation.

A. Increased level of adipokines

Adipokine	Protein/mRNA/ Release	Adipose tissue	References
IL-1β	mRNA	EAT	(Shimabukuro et al., 2013; Shibasaki et al., 2010)
TNFα	Release, mRNA	EAT	(Cheng et al., 2008; Gormez et al., 2011; Hirata et al., 2011)
Leptin	Release, mRNA	EAT	(Cheng et al., 2008; Shibasaki et al., 2010; Langheim et al., 2010)
Visfatin	Release, Protein	EAT, PVAT	(Cheng et al., 2008; Spiroglou et al., 2010)
IL-6	mRNA, Release	EAT	(Hirata et al., 2011; Langheim et al., 2010; Cheng et al., 2008; Shibasaki et al., 2010)
Resistin	mRNA, Release	EAT	(Langheim et al., 2010; Rachwalik et al., 2014)
PAI	mRNA	EAT	(Langheim et al., 2010)
MCP-1	mRNA	EAT	(Langheim et al., 2010; Shibasaki et al., 2010; Hirata et al., 2011)
ADM	mRNA	EAT	(Silaghi et al., 2007; Shibasaki et al., 2010)
lL-10	mRNA	EAT	(Eiras et al., 2010; Hirata et al., 2011)
Chemerin	Protein, mRNA	PVAT	(Eiras et al., 2010; Gao et al., 2011)

B. Decreased level of adipokines

Adipokine	Protein/mRNA/ Release	Adipose Tissue	References
Adiponectin	mRNA, Protein, Release	EAT, PVAT	(Gao et al., 2011; Zhou et al., 2011; Langheim, et al. 2010; Gormez et al., 2011; Iacobellis et al., 2005; Spiroglou et al., 2010; Cheng et al., 2008)
MIF	mRNA	EAT	(Langheim et al., 2010)
ADM	mRNA, Protein	EAT	(Iacobellis et al., 2009)

IL-1β, interleukin-1 beta; TNF-α, tumour necrosis factor-alpha; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemotactic protein-1; IL-10, interleukin-10; MIF, macrophage migration inhibitory factor; ADM, adrenomedullin. Release indicates ELISA measurement. Protein indicates Western blot measurement.

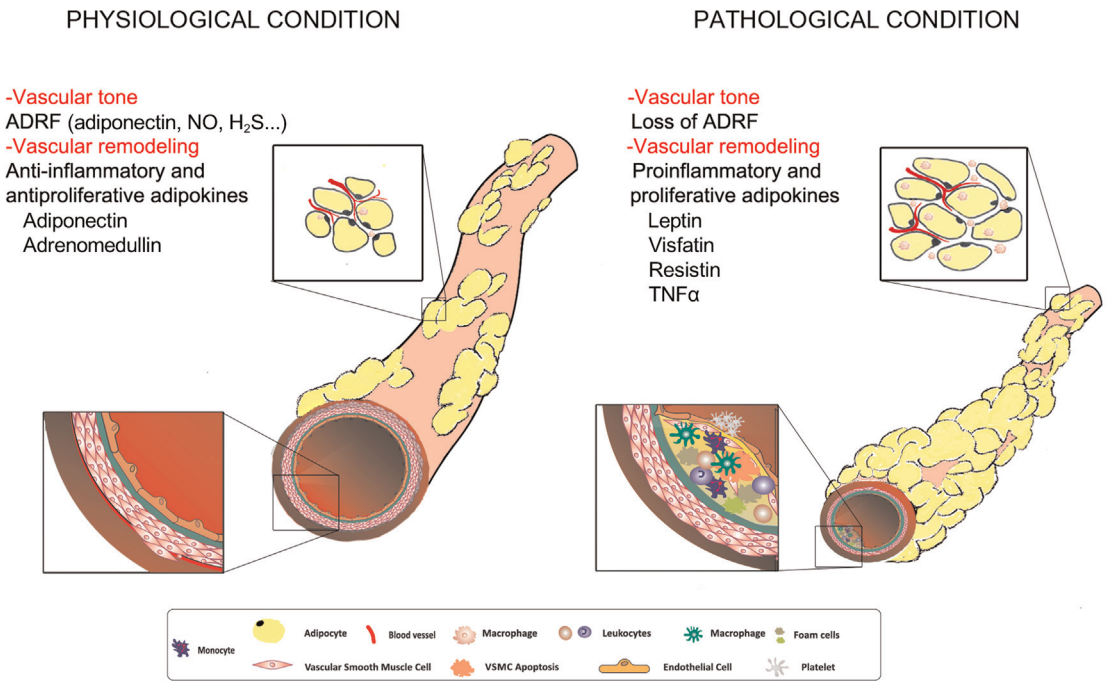

Fig. 1. Effects of perivascular adipose tissue (PVAT) in vascular functions under physiological and pathological conditions. PVAT releases vasodilator (Adipocyte Derived Relaxing Factor, ADFR such as adiponectin, nitric oxide (NO), hydrogen sulfide (H_2S)), anti-inflammatory and antiproliferative adipokines (adiponectin, adrenomedullin) in physiological condition and play important protective role in vascular tone and remodeling. However, in pathological conditions loss of ADRF and also increased release of proinflammatory and proliferative adipokines (leptin, visfatin, resistin, TNFα, IL-1β, chemerin) lead to development of obesity related cardiovascular diseases.

such as spontaneously hypertensive rats (Lu et al., 2011), mice with diet-induced obesity (Meijer et al., 2013), leptin receptor deficient diabetic and insulin-resistant mice (Ketonen et al., 2010) and mice with metabolic syndrome (Marchesi et al., 2009). In pathological conditions such as obesity or metabolic syndrome, PVAT has been shown to cause endothelial dysfunction by increased NADPH oxidase-derived oxidative stress and/or increased production of pro-inflammatory adipokines such as leptin (Ketonen et al., 2010; Gil-Ortega et al., 2014; Payne et al., 2010). Based on this, a dual role of PVAT has been suggested, a beneficial and protective role in physiological conditions which could disappear or transform into a deleterious role in pathological situations due to proinflammatory and procontractile environment (Fernandez-Alfonso et al., 2013) (Fig. 1).

4.1. Role of PVAT in human vascular tone control in vitro

In human vessels, there are only few studies which have evaluated the role of PVAT on the regulation of vascular tone. These *in vitro* studies are mostly performed in small arteries from gluteal/visseral fat biopsy samples or human coronary bypass graft materials such as internal mammary artery (IMA) or saphenous vein (SV).

It has been shown that PVAT of small arteries isolated from subcutaneous gluteal fat biopsy samples from healthy subjects, reduces contractile response to norepinephrine of these vessels placed in a myograph system. Incubation with an adiponectin blocking peptide or inhibition of NOS abolished the vasodilator effect of PVAT from healthy subjects. However, this vasorelaxant effect disappears in obese patients with metabolic syndrome (Greenstein et al., 2009). Weight loss procedures (bariatric surgery, gastric bypass or diet) have been shown to improve vascular response by restoration of the vasorelaxant effect of PVAT and also reversal of endothelial dysfunction (Brethauer et al., 2011; Aghamohammadzadeh et al., 2013).

More recently, the role of TNFα on the endothelin-1/NO imbalance in PVAT has been investigated in small arteries of visceral abdominal fat from obese patients. These results have suggested that PVAT could have role in the endothelial dysfunction observed in obesity (Virdis et al., 2015). Increased TNFα gene expression in obese-PVAT is associated with an increased vascular expression of endothelin-1 and endothelin receptors. In addition, this increased TNFα gene expression could be responsible for NOS uncoupling and decreased NO release due to NAD(P)H oxidase activation and increased reactive oxygen species (ROS) generation (Virdis et al., 2015). Finally, PVAT surrounding small abdominal arteries from obese subjects releases less NO compared to PVAT from non-obese subjects. This study highlights the vasorelaxant effect of PVAT in physiological conditions which transforms into an inflammatory pro-contractile phenotype in obesity (Virdis et al., 2015). This study highlights the vasorelaxant effect of PVAT in physiological conditions which transforms into an inflammatory pro-contractile phenotype in obesity (Virdis et al., 2015).

In IMA, the presence of PVAT reduces the contractile responses to both phenylephrine/norepinephrine and also U46619 (thromboxane mimetic) (Gao et al., 2005; Ozen et al., 2013). Another study also confirmed that PVAT of IMA attenuates the contractile response to serotonin and angiotensin II (Malinowski et al., 2013). In contrast to gluteal PVAT, the vasorelaxant effect of PVAT in IMA is not abolished in the presence of NOS inhibitor or COX inhibitor (indomethacin), which inhibits the production of PGI_2 (Malinowski et al., 2008; Ozen et al., 2013). However, incubation with a calcium-dependent potassium channel blocker abolishes the relaxing effect of PVAT in IMA preparations (Gao et al., 2005; Malinowski et al., 2008; Malinowski et al., 2013). These studies have shown that transferring PVAT of IMA or incubation of solution from PVAT-intact vessels to PVAT-removed vessels also causes vasodilatation. These results have suggested that this vasorelaxant effect of PVAT is independent of physical presence of PVAT (Gao et al., 2005; Malinowski et al., 2013).

In SV, it has also been demonstrated that PVAT reduces the contractile response or sensitivity to norepinephrine/serotonin

(Ford et al. 2006; Ozen et al., 2013). Contrary to IMA, incubation with indomethacin decreases vasorelaxant effect of PVAT in SV. PVAT of SV has been found as a source of prostaglandin E2 (PGE_2) and PGI_2 that induce SV vasorelaxation via EP4 and IP receptor, respectively (Foudi et al., 2011; Ozen et al., 2013). Other research groups have shown the presence of endothelial nitric oxide synthase (eNOS) activity (Dashwood et al., 2007), the release or expression of leptin (Dashwood et al., 2011) and adiponectin (Margaritis et al., 2013) in the PVAT of human SV.

Several adipokines such as leptin, adiponectin, adrenomedullin, apelin induce dose-dependent vasodilatation in human vessels (Fesus et al., 2007; Greenstein et al., 2009; Momin et al., 2006; Salcedo et al., 2007; Terata et al., 2000; Xi et al., 2005) whereas TNFα, IL-6, IL-10 induce contraction in human vessels (Iversen et al., 1999). Chemerin causes a contraction in human mesenteric artery from obese patients where the endothelium is dysfunctional (Watts et al. 2013). In addition, IL-1β and resistin reduce endothelium-dependent vasodilatation in human vessels (Bhagat and Vallance, 1997; Dick et al., 2006). However, there are few pharmacological studies showing that one of these substances could modify vasorelaxant effect of PVAT in human grafts.

4.2. Role of PVAT on human vascular tone control in vivo

Paradoxically, graft materials are mostly used as PVAT-removed in coronary artery bypass operation. However, intimal hyperplasia and vasospasm with a reduction of patency rate are common problems that occur after bypass surgery which may cause graft occlusion. (Mitra et al., 2006). Since PVAT of IMA/SV release vasorelaxant substances, retaining PVAT might be helpful in preventing these problems in the post-operative period. In this aspect, Souza and co-workers have investigated a no-touch technique to use the SV with surrounding PVAT. This new technique provides better endothelial cells preservation, reduced injury, increased eNOS expression, less VSMC differentiation, less atherosclerotic process and consequently better short and long-term patency rate have been observed (Souza et al., 2001; Verma et al., 2014). Although, no-touch studies were performed with only SV preparation, Malinowski et al. has suggested that preserving PVAT of IMA might also be beneficial by providing less surgical trauma and spasm to the artery (Malinowski et al., 2008).

5. Role of PVAT in remodeling of the vascular wall

PVAT may play a beneficial role in the physiological condition by not only reducing vascular tone, but also playing a protective role of vascular remodeling *via* the release of anti-inflammatory, antiproliferative and vasodilatator adipokines such as adiponectin. Hypoadiponectinemia is associated with the complexity of atherosclerotic lesions in the coronary and acute coronary syndromes (Otsuka et al., 2006; Barseghian et al., 2011).

Atherosclerosis is one of the major complications of type II diabetes. In patients with type II diabetes, serum adiponectin levels are decreased while in the vascular wall of their IMA NADPH-oxidase activity is increased (Antonopoulos et al., 2015). In contrast, adiponectin levels produced by these PVAT of IMA are correlated with the level of NADPH-oxidase activity in IMA. This paracrine compensatory mechanism depends on oxidation products released by vascular NADPH-oxidase, which could up-regulate adiponectin gene expression via peroxisome proliferator-activated receptor-γ (PPARγ) activation in PVAT of IMA (Antonopoulos et al., 2015). This crosstalk could be deficient in patients with atherosclerosis associated with type 2 diabetes and could be a new therapeutic target. A similar protective role of PVAT was described when exacerbated atherosclerosis was obtained in a mouse model lacking PVAT after deletion of PPARγ (Chang et al., 2012).

Consistent with the previous studies, Takaoka et al. suggested that PVAT (via adiponectin release) could have a protective role against neointimal formation after angioplasty under physiological conditions in healthy mice (Takaoka et al., 2009). However, under pathological conditions, PVAT expands, becomes dysfunctional, inflamed and shows proliferative characteristics (Takaoka et al., 2010).

5.1. Role of PVAT in cell proliferation and migration

Recently, Lamers et al. showed that adipocyte-conditioned media derived from human pathologic epicardial fat biopsies induces proliferation and migration of VSMC (Lamers et al., 2011). It is well known that migration and proliferation of VSMC plays a major role in vascular remodeling which is observed during pathogenesis of atherosclerosis, restenosis and hypertension.

Identification of PVAT-derived proliferative factors and their *in vivo* roles have been mostly shown in animal models. The PVAT-derived visfatin (Wang et al., 2009) resistin (Shyu et al., 2011) and TNFα (Takaoka et al., 2010) were found to be VSMC growth factors. In addition to animal studies, direct effects of several adipokines on human cells have been demonstrated. Resistin, leptin and MCP-1 induce human aortic smooth muscle cell proliferation through ERK 1/2 or/and NF-kappa B (NFκB) pathways (Mitchell et al., 2002; Li et al., 2005; Calabro et al., 2004). In contrast, adiponectin and adrenomedullin inhibit VSMC proliferation and/or migration (Kohno et al., 1997; Zhang et al., 2015; Horio et al., 1995).

Adipokines play a role not only in VSMC proliferation but also endothelial cell proliferation. *In vitro* studies have demonstrated that chemerin and leptin could promote endothelial cell proliferation, migration and mediate the formation of blood vessels to a similar extent as vascular endothelial growth factor in human endothelial cells. (Bozaoglu et al., 2010; Ferla et al., 2011; Kaur et al., 2010; Shen et al., 2013). Increased levels of mitochondrial reactive oxygen species, activation of PI3K/Akt and mitogen-activated protein kinases (MAPK) pathways and/or increased matrix metalloproteinase activity in response to chemerin has been suggested to play a role in these effect (Bozaoglu et al., 2010; Kaur et al., 2010; Shen et al., 2013). Similarly visfatin and resistin have induced angiogenesis by promoting vascular endothelial growth factor via matrix metalloproteinase and PI3K/Akt (Adya et al., 2008; Xiao et al., 2009) and increase endothelial cell proliferation, migration and the expression of cell adhesion molecules in human endothelial cells, partly via NFκB (Lee et al., 2009; Kim et al., 2008) and p38 MAPK-dependentpathway (Hsu et al., 2011; Mu et al., 2006). On the other hand, adiponectin and adrenomedullin suppresses human endothelial cell migration and proliferation (Mahadev et al., 2008; Chen et al., 2014). Altered release of proliferative and antiproliferative adipokines observed in obesity could lead to the development of vascular diseases.

5.2. Role of PVAT in fibroblast and inflammatory cells migration

In vessels, migration of vascular cells could be under the control of PVAT. Data have shown that adiponectin induces AMP-activated protein kinase (AMPK) phosphorylation and inhibits both the migration of cultured mouse adventitial fibroblasts and the expression of inducible nitric oxide synthase in response to lipopolysaccharide treatment (Cai et al., 2010). These authors suggested a protective role of adiponectin against development of coronary artery diseases. On the other hand, visfatin promotes proliferation of cardiac fibroblasts (Yu et al., 2010) and also upregulate endothelial fibroblast growth factor-2 in human endothelial cells (Bae et al., 2009).

EAT demonstrates higher macrophage infiltration compared with other adipose tissues (Baker et al., 2006; Eiras et al., 2008). This increased macrophage infiltration and inflammatory activity in adipose tissue surrounding vessels could contribute both to atherosclerosis and also abdominal aortic aneurysm pathogenesis (Henrichot et al., 2005; Police et al., 2009). Human PVAT induces CD14 expression and CD14 dependent chemotaxis, probably by IL-6, and promotes macrophage infiltration to induce aneurysmal development (Blomkalns et al., 2013). Another study has also indicated that human PVAT has strong chemotactic activity on monocytes, granulocytes, and T lymphocytes that is mainly mediated by MCP-1 and IL-8. These factors contribute to the infiltration of leukocytes at the interface between human PVAT and the adventitia of atherosclerotic aortas (Henrichot et al., 2005).

In coronary vessels of patients having bypass surgery, PVAT macrophages are associated with stenosis of the adjacent vessel. Either in coronary vessels with or without stenosis, anti-inflammatory M2 macrophages are more abundant than pro-inflammatory M1 macrophages in PVAT (Verhagen et al., 2014). This is in accordance with another study based on EAT in patients with or without coronary artery diseases, where M2 macrophage density is always greater than the M1 density (Hirata et al., 2011). In addition, in this last study the greatest increase of macrophage density in EAT was detected for M1 macrophage in patients with coronary artery diseases versus without coronary artery diseases.

6. Pharmacotherapeutic targets

Recent studies have focused on new therapeutic targets related to PVAT for the prevention and treatment of obesity-related cardiovascular disease. In this regard, different pharmacological treatments have been developed, targeting different PVAT intracellular pathways that are involved in the protection of vascular tone, the inhibition of VSMC proliferation and/or the inhibition of endothelial damage and proliferation. Activation of AMPK (metformin/thiazolidinediones; see review Almabrouk et el., 2014), mammalian target of rapamycin complex 2 (Lamers et al., 2011; Bhattacharya et al., 2013; Almabrouk et al., 2014) or NFκB/IKK/PPARγ (Antonopoulos et al., 2015) have been suggested as pharmacotherapeutic targets in relation with dysfunctional PVAT. Inactivation of the renin angiotensin system (captopril/telmisartan) (Kawahito et al., 2013; Rosei et al., 2015) and inhibition of HMG-CoA reductase (atorvastatin) (Zeng et al., 2009) have been shown to improve PVAT vasorelaxant effect. Atorvastatin could play important role by increasing net H_2S production in PVAT (Wojcicka et al., 2011; Beltowski and Jamroz-Wisniewska, 2012). Inhibition of P-Selectin Glycoprotein Ligand-1 binding is another novel target for vascular disease associated with obesity by reducing PVAT inflammation (Wang et al., 2012).

Other studies are focused on adipokines released from PVAT. Adiponectin has protective effects against endothelial dysfunction, atherosclerosis and hypertension via AMPK pathway and/or eNOS activation. By contrast, adipocyte fatty acid binding protein and leptin mediate obesity-related vascular dysfunctions by potentiating lipid-induced inflammation (Xu and Vanhoutte, 2012). Adiponectin receptor agonists and adipocyte fatty acid binding protein (Xu and Vanhoutte, 2012) or leptin receptor antagonists (Payne et al., 2014) are defined as promising therapeutic targets for treatment of obesity-related cardiovascular disease.

7. Conclusions and perspectives

The studies discussed in this review highlight the evidence that preservation of PVAT function is necessary for vascular biology and dysfunctional PVAT could be an important cause for vascular diseases.

More recently, meta analyses have indicated an obesity paradox, showing that low risk for cardiovascular mortality in overweight patients with heart failure (Sharma et al., 2015). Only overweight patients, not patients with severe obesity seem to be associated with an obesity paradox (Lavie et al., 2014). It could be due to protective effects of adipose tissue in overweight patient and this effect tends to disappear at more extreme levels of obesity.

In vitro studies have also indicated that beneficial effects of PVAT in the control of vascular functions in health is impaired and PVAT becomes dysfunctional in pathological conditions. Although there is a potential link between dysfunctional PVAT and vascular remodeling, mechanisms of action are still under discussion. We propose that the increased PVAT quantity observed in obesity could result in an imbalance of secretion between detrimental and beneficial adipokines released from PVAT (Fig. 1). This imbalance is commonly described as an increased level of leptin and decreased level of adiponectin (Payne et al., 2010). This could be a key pathway in the setting of obesity-related cardiovascular disease by accelerating inflammation, oxidative stress, VSMC proliferation and endothelial dysfunction.

Recently several therapeutic approaches related to PVAT were suggested; however, most of them were derived from animal studies. It is clear that the effects of PVAT on vascular function vary among species and vascular bed. More human studies are needed to determine accurate mechanisms by which PVAT-derived adipokines modulate vascular homeostasis in health or disease and consequently to discover new pharmacotherapeutic agents to preserve the beneficial function of healthy PVAT.

Acknowledgments

We would like to thank Scientific and Technological Research Council of Turkey (TUBITAK) for postgraduate fellowship (BIDEB-2214) of Gulsev Ozen. We would like to thank Dr. Richard Bayles for editing of the manuscript.

References

Adya, R., Tan, B.K., Punn, A., Chen, J., Randeva, H.S., 2008. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. Cardiovasc. Res. 78, 356–365.

Aghamohammadzadeh, R., Greenstein, A.S., Yadav, R., Jeziorska, M., Hama, S., Soltani, F., Pemberton, P.W., Ammori, B., Malik, R.A., Soran, H., Heagerty, A.M., 2013. Effects of bariatric surgery on human small artery function: evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. J. Am. Coll. Cardiol. 62, 128–135.

Ahn, S.G., Lim, H.S., Joe, D.Y., Kang, S.J., Choi, B.J., Choi, S.Y., Yoon, M.H., Hwang, G.S., Tahk, S.J., Shin, J.H., 2008. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart 94, e7.

Almabrouk, T.A., Ewart, M.A., Salt, I.P., Kennedy, S., 2014. Perivascular fat, AMP-activated protein kinase and vascular diseases. Br. J. Pharmacol. 171, 595–617.

Antonopoulos, A.S., Margaritis, M., Coutinho, P., Shirodaria, C., Psarros, C., Herdman, L., Sanna, F., De Silva, R., Petrou, M., Sayeed, R., Krasopoulos, G., Lee, R., Digby, J., Reilly, S., Bakogiannis, C., Tousoulis, D., Kessler, B., Casadei, B., Channon, K.M., Antoniades, C., 2015. Adiponectin as a link between type 2 diabetes and vascular NADPH oxidase activity in the human arterial wall: the regulatory role of perivascular adipose tissue. Diabetes 64, 2207–2219.

Bae, Y.H., Bae, M.K., Kim, S.R., Lee, J.H., Wee, H.J., Bae, S.K., 2009. Upregulation of fibroblast growth factor-2 by visfatin that promotes endothelial angiogenesis. Biochem. Biophys. Res. Commun. 379, 206–211.

Baker, A.R., Silva, N.F., Quinn, D.W., Harte, A.L., Pagano, D., Bonser, R.S., Kumar, S., McTernan, P.G., 2006. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc. Diabetol. 5, 1.

Barseghian, A., Gawande, D., Bajaj, M., 2011. Adiponectin and vulnerable

atherosclerotic plaques. J. Am. Coll. Cardiol. 57, 761–770.
Beltowski, J., Jamroz-Wisniewska, A., 2012. Modulation of h(2)s metabolism by statins: a new aspect of cardiovascular pharmacology. Antioxid. Redox Signal 17, 81–94.
Bhagat, K., Vallance, P., 1997. Inflammatory cytokines impair endothelium-dependent dilatation in human veins in vivo. Circulation 96, 3042–3047.
Bhattacharya, I., Dragert, K., Albert, V., Contassot, E., Damjanovic, M., Hagiwara, A., Zimmerli, L., Humar, R., Hall, M.N., Battegay, E.J., Haas, E., 2013. Rictor in perivascular adipose tissue controls vascular function by regulating inflammatory molecule expression. Arterioscler. Thromb. Vasc. Biol. 33, 2105–2111.
Blomkalns, A.L., Gavrila, D., Thomas, M., Neltner, B.S., Blanco, V.M., Benjamin, S.B., McCormick, M.L., Stoll, L.L., Denning, G.M., Collins, S.P., Qin, Z., Daugherty, A., Cassis, L.A., Thompson, R.W., Weiss, R.M., Lindower, P.D., Pinney, S.M., Chatterjee, T., Weintraub, N.L., 2013. CD14 directs adventitial macrophage precursor recruitment: role in early abdominal aortic aneurysm formation. J. Am. Heart Assoc. 2; p. e000065.
Brethauer, S.A., Heneghan, H.M., Eldar, S., Gatmaitan, P., Huang, H., Kashyap, S., Gornik, H.L., Kirwan, J.P., Schauer, P.R., 2011. Early effects of gastric bypass on endothelial function, inflammation, and cardiovascular risk in obese patients. Surg. Endosc. 25, 2650–2659.
Boydens, C., Maenhaut, N., Pauwels, B., Decaluwé, K., Van de Voorde, J., 2012. Adipose tissue as regulator of vascular tone. Curr. Hypertens. Rep. 14, 270–278.
Bozaoglu, K., Curran, J.E., Stocker, C.J., Zaibi, M.S., Segal, D., Konstantopoulos, N., Morrison, S., Carless, M., Dyer, T.D., Cole, S.A., Goring, H.H., Moses, E.K., Walder, K., Cawthorne, M.A., Blangero, J., Jowett, J.B., 2010. Chemerin, a novel adipokine in the regulation of angiogenesis. J. Clin. Endocrinol. Metab. 95, 2476–2485.
Bunker, A.K., Laughlin, M.H., 2010. Influence of exercise and perivascular adipose tissue on coronary artery vasomotor function in a familial hypercholesterolemic porcine atherosclerosis model. J. Appl. Physiol. 108 (1985), 490–497.
Cai, X.J., Chen, L., Li, L., Feng, M., Li, X., Zhang, K., Rong, Y.Y., Hu, X.B., Zhang, M.X., Zhang, Y., Zhang, M., 2010. Adiponectin inhibits lipopolysaccharide-induced adventitial fibroblast migration and transition to myofibroblasts via AdipoR1-AMPK-iNOS pathway. Mol. Endocrinol. 24, 218–228.
Calabro, P., Samudio, I., Willerson, J.T., Yeh, E.T., 2004. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation 110, 3335–3340.
Chang, L., Villacorta, L., Li, R., Hamblin, M., Xu, W., Dou, C., Zhang, J., Wu, J., Zeng, R., Chen, Y.E., 2012. Loss of perivascular adipose tissue on peroxisome proliferator-activated receptor-gamma deletion in smooth muscle cells impairs intravascular thermoregulation and enhances atherosclerosis. Circulation 126, 1067–1078.
Chatterjee, T.K., Stoll, L.L., Denning, G.M., Harrelson, A., Blomkalns, A.L., Idelman, G., Rothenberg, F.G., Neltner, B., Romig-Martin, S.A., Dickson, E.W., Rudich, S., Weintraub, N.L., 2009. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. Circ. Res. 104, 541–549.
Chen, Z., Liu, G., Xiao, Y., Lu, P., 2014. Adrenomedullin22-52 suppresses high-glucose-induced migration, proliferation, and tube formation of human retinal endothelial cells. Mol. Vis. 20, 259–269.
Cheng, K.H., Chu, C.S., Lee, K.T., Lin, T.H., Hsieh, C.C., Chiu, C.C., Voon, W.C., Sheu, S. H., Lai, W.T., 2008. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. Int. J. Obes. (Lond.) 32, 268–274.
Chughtai, H.L., Morgan, T.M., Rocco, M., Stacey, B., Brinkley, T.E., Ding, J., Nicklas, B., Hamilton, C., Hundle, W.G., 2010. Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. Hypertension 56, 901–906.
Dashwood, M.R., Dooley, A., Shi-Wen, X., Abraham, D.J., Dreifaldt, M., Souza, D.S., 2011. Perivascular fat-derived leptin: a potential role in improved vein graft performance in coronary artery bypass surgery. Interact. Cardiovasc. Thorac. Surg. 12, 170–173.
Dashwood, M.R., Dooley, A., Shi-Wen, X., Abraham, D.J., Souza, D.S., 2007. Does periadventitial fat-derived nitric oxide play a role in improved saphenous vein graft patency in patients undergoing coronary artery bypass surgery? J. Vasc. Res. 44, 175–181.
Demircelik, M.B., Yilmaz, O.C., Gurel, O.M., Selcoki, Y., Atar, I.A., Bozkurt, A., Akin, K., Eryonucu, B., 2014. Epicardial adipose tissue and pericoronary fat thickness measured with 64-multidetector computed tomography: potential predictors of the severity of coronary artery disease. Clinics (Sao Paulo) 69, 388–392.
Dick, G.M., Katz, P.S., Farias 3rd, M., Morris, M., James, J., Knudson, J.D., Tune, J.D., 2006. Resistin impairs endothelium-dependent dilation to bradykinin, but not acetylcholine, in the coronary circulation. Am. J. Physiol. Hear. Circ. Physiol. 291, 2997–3002.
Eiras, S., Teijeira-Fernandez, E., Salgado-Somoza, A., Couso, E., Garcia-Caballero, T., Sierra, J., Juanatey, J.R., 2010. Relationship between epicardial adipose tissue adipocyte size and MCP-1 expression. Cytokine 51, 207–212.
Eiras, S., Teijeira-Fernandez, E., Shamagian, L.G., Fernandez, A.L., Vazquez-Boquete, A., Gonzalez-Juanatey, J.R., 2008. Extension of coronary artery disease is associated with increased IL-6 and decreased adiponectin gene expression in epicardial adipose tissue. Cytokine 43, 174–180.
Eroglu, S., Sade, L.E., Yildirir, A., Bal, U., Ozbicer, S., Ozgul, A.S., Bozbas, H., Aydinalp, A., Muderrisoglu, H., 2009. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. Nutr. Metab. Cardiovasc. Dis. 19, 211–217.
Fang, L., Zhao, J., Chen, Y., Ma, T., Xu, G., Tang, C., Liu, X., Geng, B., 2009. Hydrogen sulfide derived from periadventitial adipose tissue is a vasodilator. J. Hypertens. 27, 2174–2185.
Ferla, R., Bonomi, M., Otvos Jr., L., Surmacz, E., 2011. Glioblastoma-derived leptin induces tube formation and growth of endothelial cells: comparison with VEGF effects. BMC Cancer 11, 303.
Fernandez-Alfonso, M.S., Gil-Ortega, M., Garcia-Prieto, C.F., Aranguez, I., Ruiz-Gayo, M., Somoza, B., 2013. Mechanisms of perivascular adipose tissue dysfunction in obesity. Int. J. Endocrinol. 2013, 402053.
Fesus, G., Dubrovska, G., Gorzelniak, K., Kluge, R., Huang, Y., Luft, F.C., Gollasch, M., 2007. Adiponectin is a novel humoral vasodilator. Cardiovasc. Res. 75, 719–727.
Ford, C.A., Mong, K., Tabrizchi, R., 2006. Influence of tangential stress on mechanical responses to vasoactive agents in human saphenous vein with and without perivascular adipose tissue. Can. J. Cardiol. 22, 1209–1216.
Foudi, N., Kotelevets, L., Gomez, I., Louedec, L., Longrois, D., Chastre, E., Norel, X., 2011. Differential reactivity of human mammary artery and saphenous vein to prostaglandin E(2): implication for cardiovascular grafts. Br. J. Pharmacol. 163, 826–834.
Galvez-Prieto, B., Somoza, B., Gil-Ortega, M., Garcia-Prieto, C.F., de Las Heras, A.I., Gonzalez, M.C., Arribas, S., Aranguez, I., Bolbrinker, J., Kreutz, R., Ruiz-Gayo, M., Fernandez-Alfonso, M.S., 2012. Anticontractile effect of perivascular adipose tissue and leptin are reduced in hypertension. Front. Pharmacol. 3, 103.
Galvez, B., de Castro, J., Herold, D., Dubrovska, G., Arribas, S., Gonzalez, M.C., Aranguez, I., Luft, F.C., Ramos, M.P., Gollasch, M., Fernandez Alfonso, M.S., 2006. Perivascular adipose tissue and mesenteric vascular function in spontaneously hypertensive rats. Arterioscler. Thromb. Vasc. Biol. 26, 1297–1302.
Gao, X., Mi, S., Zhang, F., Gong, F., Lai, Y., Gao, F., Zhang, X., Wang, L., Tao, H., 2011. Association of chemerin mRNA expression in human epicardial adipose tissue with coronary atherosclerosis. Cardiovasc. Diabetol. 10, 87.
Gao, Y.J., Lu, C., Su, L.Y., Sharma, A.M., Lee, R.M., 2007. Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. Br. J. Pharmacol. 151, 323–331.
Gao, Y.J., Zeng, Z.H., Teoh, K., Sharma, A.M., Abouzahr, L., Cybulsky, I., Lamy, A., Semelhago, L., Lee, R.M., 2005. Perivascular adipose tissue modulates vascular function in the human internal thoracic artery. J. Thorac. Cardiovasc. Surg. 130, 1130–1136.
Gil-Ortega, M., Condezo-Hoyos, L., Garcia-Prieto, C.F., Arribas, S.M., Gonzalez, M.C., Aranguez, I., Ruiz-Gayo, M., Somoza, B., Fernandez-Alfonso, M.S., 2014. Imbalance between pro and anti-oxidant mechanisms in perivascular adipose tissue aggravates long-term high-fat diet-derived endothelial dysfunction. PLoS One 9, e95312.
Gollasch, M., 2012. Vasodilator signals from perivascular adipose tissue. Br. J. Pharmacol. 165, 633–642.
Gormez, S., Demirkan, A., Atalar, F., Caynak, B., Erdim, R., Sozer, V., Gunay, D., Akpinar, B., Ozbek, U., Buyukdevrim, A.S., 2011. Adipose tissue gene expression of adiponectin, tumor necrosis factor-alpha and leptin in metabolic syndrome patients with coronary artery disease. Intern. Med. 50, 805–810.
Greenstein, A.S., Khavandi, K., Withers, S.B., Sonoyama, K., Clancy, O., Jeziorska, M., Laing, I., Yates, A.P., Pemberton, P.W., Malik, R.A., Heagerty, A.M., 2009. Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation 119, 1661–1670.
Groves, E.M., Erande, A.S., Le, C., Salcedo, J., Hoang, K.C., Kumar, S., Mohar, D.S., Saremi, F., Im, J., Agrawal, Y., Nadeswaran, P., Naderi, N., Malik, S., 2014. Comparison of epicardial adipose tissue volume and coronary artery disease severity in asymptomatic adults with versus without diabetes mellitus. Am. J. Cardiol. 114, 686–691.
Gu, P., Xu, A., 2013. Interplay between adipose tissue and blood vessels in obesity and vascular dysfunction. Rev. Endocr. Metab. Disord. 14, 49–58.
Haberka, M., Gasior, Z., 2015. Carotid extra-media thickness in obesity and metabolic syndrome: a novel index of perivascular adipose tissue: extra-media thickness in obesity and metabolic syndrome. Atherosclerosis 239, 169–177.
Hadi, H.A., Carr, C.S., Al Suwaidi, J., 2005. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc. Heal. Risk Manag. 1, 183–198.
Henrichot, E., Juge-Aubry, C.E., Pernin, A., Pache, J.C., Velebit, V., Dayer, J.M., Meda, P., Chizzolini, C., Meier, C.A., 2005. Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? Arterioscler. Thromb. Vasc. Biol. 25, 2594–2599.
Hirata, Y., Tabata, M., Kurobe, H., Motoki, T., Akaike, M., Nishio, C., Higashida, M., Mikasa, H., Nakaya, Y., Takanashi, S., Igarashi, T., Kitagawa, T., Sata, M., 2011. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. J. Am. Coll. Cardiol. 58, 248–255.
Horio, T., Kohno, M., Kano, H., Ikeda, M., Yasunari, K., Yokokawa, K., Minami, M., Takeda, T., 1995. Adrenomedullin as a novel antimigration factor of vascular smooth muscle cells. Circ. Res. 77, 660–664.
Hsu, W.Y., Chao, Y.W., Tsai, Y.L., Lien, C.C., Chang, C.F., Deng, M.C., Ho, L.T., Kwok, C.F., Juan, C.C., 2011. Resistin induces monocyte-endothelial cell adhesion by increasing ICAM-1 and VCAM-1 expression in endothelial cells via p38MAPK-dependent pathway. J. Cell. Physiol. 226, 2181–2188.
Iacobellis, G., di Gioia, C.R., Di Vito, M., Petramala, L., Cotesta, D., De Santis, V., Vitale, D., Tritapepe, L., Letizia, C., 2009. Epicardial adipose tissue and intracoronary adrenomedullin levels in coronary artery disease. Horm. Metab. Res. 41, 855–860.
Iacobellis, G., Pistilli, D., Gucciardo, M., Leonetti, F., Miraldi, F., Brancaccio, G., Gallo, P., di Gioia, C.R., 2005. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. Cytokine 29, 251–255.
Ishikawa, Y., Akasaka, Y., Ito, K., Akishima, Y., Kimura, M., Kiguchi, H., Fujimoto, A., Ishii, T., 2006. Significance of anatomical properties of myocardial bridge on

atherosclerosis evolution in the left anterior descending coronary artery. Atherosclerosis 186, 380–389.
Iversen, P.O., Nicolaysen, A., Kvernebo, K., Benestad, H.B., Nicolaysen, G., 1999. Human cytokines modulate arterial vascular tone via endothelial receptors. Pflugers Arch. 439, 93–100.
Kaur, J., Adya, R., Tan, B.K., Chen, J., Randeva, H.S., 2010. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem. Biophys. Res. Commun. 391, 1762–1768.
Kawahito, H., Yamada, H., Irie, D., Kato, T., Akakabe, Y., Kishida, S., Takata, H., Wakana, N., Ogata, T., Ikeda, K., Ueyama, T., Matoba, S., Mori, Y., Matsubara, H., 2013. Periaortic adipose tissue-specific activation of the renin–angiotensin system contributes to atherosclerosis development in uninephrectomized apoE-/- mice. Am. J. Physiol. Hear. Circ. Physiol. 305, H667–H675.
Kaya, M., Yeniterzi, M., Yazici, P., Diker, M., Celik, O., Erturk, M., Bakir, I., 2014. Epicardial adipose tissue is associated with extensive coronary artery lesions in patients undergoing coronary artery bypass grafting: an observational study. Maedica (Buchar) 9, 135–143.
Ketonen, J., Shi, J., Martonen, E., Mervaala, E., 2010. Periadventitial adipose tissue promotes endothelial dysfunction via oxidative stress in diet-induced obese C57Bl/6 mice. Circ. J. 74, 1479–1487.
Kim, S.H., Chung, J.H., Kwon, B.J., Song, S.W., Choi, W.S., 2014. The associations of epicardial adipose tissue with coronary artery disease and coronary atherosclerosis. Int. Hear. J. 55, 197–203.
Kim, S.R., Bae, Y.H., Bae, S.K., Choi, K.S., Yoon, K.H., Koo, T.H., Jang, H.O., Yun, I., Kim, K.W., Kwon, Y.G., Yoo, M.A., Bae, M.K., 2008. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-kappaB activation in endothelial cells. Biochim. Biophys. Acta 1783, 886–895.
Kohno, M., Yokokawa, K., Kano, H., Yasunari, K., Minami, M., Hanehira, T., Yoshikawa, J., 1997. Adrenomedullin is a potent inhibitor of angiotensin II-induced migration of human coronary artery smooth muscle cells. Hypertension 29, 1309–1313.
Lamers, D., Schlich, R., Greulich, S., Sasson, S., Sell, H., Eckel, J., 2011. Oleic acid and adipokines synergize in inducing proliferation and inflammatory signalling in human vascular smooth muscle cells. J. Cell. Mol. Med. 15, 1177–1188.
Langheim, S., Dreas, L., Veschini, L., Maisano, F., Foglieni, C., Ferrarello, S., Sinagra, G., Zingone, B., Alfieri, O., Ferrero, E., Maseri, A., Ruotolo, G., 2010. Increased expression and secretion of resistin in epicardial adipose tissue of patients with acute coronary syndrome. Am. J. Physiol. Hear. Circ. Physiol. 298, H746–H753.
Lavie, C.J., McAuley, P.A., Church, T.S., Milani, R.V., Blair, S.N., 2014. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J. Am. Coll. Cardiol. 63, 1345–1354.
Lee, W.J., Wu, C.S., Lin, H., Lee, I.T., Wu, C.M., Tseng, J.J., Chou, M.M., Sheu, W.H., 2009. Visfatin-induced expression of inflammatory mediators in human endothelial cells through the NF-kappaB pathway. Int. J. Obes. (Lond) 33, 465–472.
Lee, Y.C., Chang, H.H., Chiang, C.L., Liu, C.H., Yeh, J.I., Chen, M.F., Chen, P.Y., Kuo, J.S., Lee, T.J., 2011. Role of perivascular adipose tissue-derived methyl palmitate in vascular tone regulation and pathogenesis of hypertension. Circulation 124, 1160–1171.
Li, L., Mamputu, J.C., Wiernsperger, N., Renier, G., 2005. Signaling pathways involved in human vascular smooth muscle cell proliferation and matrix metalloproteinase-2 expression induced by leptin: inhibitory effect of metformin. Diabetes 54, 2227–2234.
Lohn, M., Dubrovska, G., Lauterbach, B., Luft, F.C., Gollasch, M., Sharma, A.M., 2002. Periadventitial fat releases a vascular relaxing factor. FASEB J. 16, 1057–1063.
Lu, C., Zhao, A.X., Gao, Y.J., Lee, R.M., 2011. Modulation of vein function by perivascular adipose tissue. Eur. J. Pharmacol. 657, 111–116.
Lynch, F.M., Withers, S.B., Yao, Z., Werner, M.E., Edwards, G., Weston, A.H., Heagerty, A.M., 2013. Perivascular adipose tissue-derived adiponectin activates BK(Ca) channels to induce anticontractile responses. Am. J. Physiol. Hear. Circ. Physiol. 304, H786–H795.
Mahabadi, A.A., Reinsch, N., Lehmann, N., Altenbernd, J., Kalsch, H., Seibel, R.M., Erbel, R., Mohlenkamp, S., 2010. Association of pericoronary fat volume with atherosclerotic plaque burden in the underlying coronary artery: a segment analysis. Atherosclerosis 211, 195–199.
Mahadev, K., Wu, X., Donnelly, S., Ouedraogo, R., Eckhart, A.D., Goldstein, B.J., 2008. Adiponectin inhibits vascular endothelial growth factor-induced migration of human coronary artery endothelial cells. Cardiovasc. Res. 78, 376–384.
Malinowski, M., Deja, M.A., Golba, K.S., Roleder, T., Biernat, J., Wos, S., 2008. Perivascular tissue of internal thoracic artery releases potent nitric oxide and prostacyclin-independent anticontractile factor. Eur. J. Cardiothorac. Surg. 33, 225–231.
Malinowski, M., Deja, M.A., Janusiewicz, P., Golba, K.S., Roleder, T., Wos, S., 2013. Mechanisms of vasodilatatory effect of perivascular tissue of human internal thoracic artery. J. Physiol. Pharmacol. 64, 309–316.
Marchesi, C., Ebrahimian, T., Angulo, O., Paradis, P., Schiffrin, E.L., 2009. Endothelial nitric oxide synthase uncoupling and perivascular adipose oxidative stress and inflammation contribute to vascular dysfunction in a rodent model of metabolic syndrome. Hypertension 54, 1384–1392.
Margaritis, M., Antonopoulos, A.S., Digby, J., Lee, R., Reilly, S., Coutinho, P., Shirodaria, C., Sayeed, R., Petrou, M., De Silva, R., Jalilzadeh, S., Demosthenous, M., Bakogiannis, C., Tousoulis, D., Stefanadis, C., Choudhury, R.P., Casadei, B., Channon, K.M., Antoniades, C., 2013. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. Circulation 127, 2209–2221.
Maurovich-Horvat, P., Kallianos, K., Engel, L.C., Szymonifka, J., Fox, C.S., Hoffmann, U., Truong, Q.A., 2011. Influence of pericoronary adipose tissue on local coronary atherosclerosis as assessed by a novel MDCT volumetric method. Atherosclerosis 219, 151–157.
Mazurek, T., Zhang, L., Zalewski, A., Mannion, J.D., Diehl, J.T., Arafat, H., Sarov-Blat, L., O'Brien, S., Keiper, E.A., Johnson, A.G., Martin, J., Goldstein, B.J., Shi, Y., 2003. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 108, 2460–2466.
Meijer, R.I., Bakker, W., Alta, C.L., Sipkema, P., Yudkin, J.S., Viollet, B., Richter, E.A., Smulders, Y.M., van Hinsbergh, V.W., Serne, E.H., Eringa, E.C., 2013. Perivascular adipose tissue control of insulin-induced vasoreactivity in muscle is impaired in db/db mice. Diabetes 62, 590–598.
Mihl, C., Loeffen, D., Versteylen, M.O., Takx, R.A., Nelemans, P.J., Nijssen, E.C., Vega-Higuera, F., Wildberger, J.E., Das, M., 2014. Automated quantification of epicardial adipose tissue (EAT) in coronary CT angiography; comparison with manual assessment and correlation with coronary artery disease. J. Cardiovasc. Comput. Tomogr. 8, 215–221.
Mitchell, D.G., Parker, L., Sunshine, J.H., Levin, D.C., 2002. Body MR imaging and CT volume: variations and trends based on an analysis of medicare and fee-for-service health insurance databases. AJR Am. J. Roentgenol. 179, 27–31.
Mitra, A.K., Gangahar, D.M., Agrawal, D.K., 2006. Cellular, molecular and immunological mechanisms in the pathophysiology of vein graft intimal hyperplasia. Immunol. Cell. Biol. 84, 115–124.
Mohar, D.S., Salcedo, J., Hoang, K.C., Kumar, S., Saremi, F., Erande, A.S., Naderi, N., Nadeswaran, P., Le, C., Malik, S., 2014. Epicardial adipose tissue volume as a marker of coronary artery disease severity in patients with diabetes independent of coronary artery calcium: findings from the CTRAD study. Diabetes Res. Clin. Pract. 106, 228–235.
Momin, A.U., Melikian, N., Shah, A.M., Grieve, D.J., Wheatcroft, S.B., John, L., El Gamel, A., Desai, J.B., Nelson, T., Driver, C., Sherwood, R.A., Kearney, M.T., 2006. Leptin is an endothelial-independent vasodilator in humans with coronary artery disease: evidence for tissue specificity of leptin resistance. Eur. Hear. J. 27, 2294–2299.
Mu, H., Ohashi, R., Yan, S., Chai, H., Yang, H., Lin, P., Yao, Q., Chen, C., 2006. Adipokine resistin promotes in vitro angiogenesis of human endothelial cells. Cardiovasc. Res. 70, 146–157.
Oriowo, M.A., 2015. Perivascular adipose tissue, vascular reactivity and hypertension. Med. Princ. Pract. 24 (Suppl. 1), S29–S37.
Otsuka, F., Sugiyama, S., Kojima, S., Maruyoshi, H., Funahashi, T., Matsui, K., Sakamoto, T., Yoshimura, M., Kimura, K., Umemura, S., Ogawa, H., 2006. Plasma adiponectin levels are associated with coronary lesion complexity in men with coronary artery disease. J. Am. Coll. Cardiol. 48, 1155–1162.
Ozen, G., Topal, G., Gomez, I., Ghorreshi, A., Boukais, K., Benyahia, C., Kanyinda, L., Longrois, D., Teskin, O., Uydes-Dogan, B.S., Norel, X., 2013. Control of human vascular tone by prostanoids derived from perivascular adipose tissue. Prostaglandins Other Lipid Mediat. 107, 13–17.
Payne, G.A., Borbouse, L., Kumar, S., Neeb, Z., Alloosh, M., Sturek, M., Tune, J.D., 2010. Epicardial perivascular adipose-derived leptin exacerbates coronary endothelial dysfunction in metabolic syndrome via a protein kinase C-beta pathway. Arterioscler. Thromb. Vasc. Biol. 30, 1711–1717.
Payne, G.A., Tune, J.D., Knudson, J.D., 2014. Leptin-induced endothelial dysfunction: a target for therapeutic interventions. Curr. Pharm. Des. 20, 603–608.
Police, S.B., Thatcher, S.E., Charnigo, R., Daugherty, A., Cassis, L.A., 2009. Obesity promotes inflammation in periaortic adipose tissue and angiotensin II-induced abdominal aortic aneurysm formation. Arterioscler. Thromb. Vasc. Biol. 29, 1458–1464.
Rachwalik, M., Zysko, D., Diakowska, D., Kustrzycki, W., 2014. Increased content of resistin in epicardial adipose tissue of patients with advanced coronary atherosclerosis and history of myocardial infarction. Thorac. Cardiovasc. Surg. 62, 554–560.
Rittig, K., Dolderer, J.H., Balletshofer, B., Machann, J., Schick, F., Meile, T., Kuper, M., Stock, U.A., Staiger, H., Machicao, F., Schaller, H.E., Konigsrainer, A., Haring, H.U., Siegel-Axel, D.I., 2012. The secretion pattern of perivascular fat cells is different from that of subcutaneous and visceral fat cells. Diabetologia 55, 1514–1525.
Rittig, K., Staib, K., Machann, J., Böttcher, M., Peter, A., Schick, F., Claussen, C., Stefan, N., Fritsche, A., Häring, H.U., Balletshofer, B., 2008. Perivascular fatty tissue at the brachial artery is linked to insulin resistance but not to local endothelial dysfunction. Diabetologia 51, 2093–2099.
Rosei, C.A., Withers, S.B., Belcaid, L., De Ciuceis, C., Rizzoni, D., Heagerty, A.M., 2015. Blockade of the renin-angiotensin system in small arteries and anticontractile function of perivascular adipose tissue. J. Hypertens. 33, 1039–1045.
Salcedo, A., Garijo, J., Monge, L., Fernandez, N., Luis Garcia-Villalon, A., Sanchez Turrion, V., Cuervas-Mons, V., Dieguez, G., 2007. Apelin effects in human splanchnic arteries. Role of nitric oxide and prostanoids. Regul. Pept. 144, 50–55.
Schlich, R., Willems, M., Greulich, S., Ruppe, F., Knoefel, W.T., Ouwens, D.M., Maxhera, B., Lichtenberg, A., Eckel, J., Sell, H., 2013. VEGF in the crosstalk between human adipocytes and smooth muscle cells: depot-specific release from visceral and perivascular adipose tissue. Mediators Inflamm. 2013, 982458.
Sharma, A., Lavie, C.J., Borer, J.S., Vallakati, A., Goel, S., Lopez-Jimenez, F., Arbab-Zadeh, A., Mukherjee, D., Lazar, J.M., 2015. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. Am. J. Cardiol.
Shen, W., Tian, C., Chen, H., Yang, Y., Zhu, D., Gao, P., Liu, J., 2013. Oxidative stress mediates chemerin-induced autophagy in endothelial cells. Free. Radic. Biol. Med. 55, 73–82.
Shibasaki, I., Nishikimi, T., Mochizuki, Y., Yamada, Y., Yoshitatsu, M., Inoue, Y.,

Kuwata, X., Ogawa, H., Tsuchiya, G., Ishimitsu, T., Fukuda, H., 2010. Greater expression of inflammatory cytokines, adrenomedullin, and natriuretic peptide receptor-C in epicardial adipose tissue in coronary artery disease. Regul. Pept. 165, 210–217.
Shimabukuro, M., Hirata, Y., Tabata, M., Dagvasumberel, M., Sato, H., Kurobe, H., Fukuda, D., Soeki, T., Kitagawa, T., Takanashi, S., Sata, M., 2013. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 33, 1077–1084.
Shyu, K.G., Lien, L.M., Wang, B.W., Kuan, P., Chang, H., 2011. Resistin contributes to neointimal formation via oxidative stress after vascular injury. Clin. Sci. (Lond.) 120, 121–129.
Silaghi, A., Achard, V., Paulmyer-Lacroix, O., Scridon, T., Tassistro, V., Duncea, I., Clement, K., Dutour, A., Grino, M., 2007. Expression of adrenomedullin in human epicardial adipose tissue: role of coronary status. Am. J. Physiol. Endocrinol. Metab. 293, E1443–E1450.
Soltis, E.E., Cassis, L.A., 1991. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin. Exp. Hypertens. A 13, 277–296.
Souza, D.S., Bomfim, V., Skoglund, H., Dashwood, M.R., Borowiec, J.W., Bodin, L., Filbey, D., 2001. High early patency of saphenous vein graft for coronary artery bypass harvested with surrounding tissue. Ann. Thorac. Surg. 71, 797–800.
Spiroglou, S.G., Kostopoulos, C.G., Varakis, J.N., Papadaki, H.H., 2010. Adipokines in periaortic and epicardial adipose tissue: differential expression and relation to atherosclerosis. J. Atheroscler. Thromb. 17, 115–130.
Szasz, T., Bomfim, G.F., Webb, R.C., 2013. The influence of perivascular adipose tissue on vascular homeostasis. Vasc. Heal. Risk Manag. 9, 105–116.
Takaoka, M., Nagata, D., Kihara, S., Shimomura, I., Kimura, Y., Tabata, Y., Saito, Y., Nagai, R., Sata, M., 2009. Periadventitial adipose tissue plays a critical role in vascular remodeling. Circ. Res. 105, 906–911.
Takaoka, M., Suzuki, H., Shioda, S., Sekikawa, K., Saito, Y., Nagai, R., Sata, M., 2010. Endovascular injury induces rapid phenotypic changes in perivascular adipose tissue. Arterioscler. Thromb. Vasc. Biol. 30, 1576–1582.
Takemori, K., Gao, Y.J., Ding, L., Lu, C., Su, L.Y., An, W.S., Vinson, C., Lee, R.M., 2007. Elevated blood pressure in transgenic lipoatrophic mice and altered vascular function. Hypertension 49, 365–372.
Temiz, A., Gokmen, F., Gazi, E., Akbal, A., Barutcu, A., Bekler, A., Altun, B., Tan, Y.Z., Gunes, F., Sen, H., 2015. Epicardial adipose tissue thickness, flow-mediated dilatation of the brachial artery, and carotid intima-media thickness: associations in rheumatoid arthritis patients. Herz 40, 217–224.
Terata, K., Miura, H., Liu, Y., Loberiza, F., Gutterman, D.D., 2000. Human coronary arteriolar dilation to adrenomedullin: role of nitric oxide and K(+) channels. Am. J. Physiol. Hear. Circ. Physiol. 279, H2620–H2626.
Thanassoulis, G., Massaro, J.M., Corsini, E., Rogers, I., Schlett, C.L., Meigs, J.B., Hoffmann, U., O'Donnell, C.J., Fox, C.S., 2012. Periaortic adipose tissue and aortic dimensions in the Framingham Heart Study. J. Am. Hear. Assoc. 1, e000885.
Verhagen, S.N., Buijsrogge, M.P., Vink, A., van Herwerden, L.A., van der Graaf, Y., Visseren, F.L., 2014. Secretion of adipocytokines by perivascular adipose tissue near stenotic and non-stenotic coronary artery segments in patients undergoing CABG. Atherosclerosis 233, 242–247.
Verhagen, S.N., Visseren, F.L., 2011. Perivascular adipose tissue as a cause of atherosclerosis. Atherosclerosis 214, 3–10.
Verma, S., Lovren, F., Pan, Y., Yanagawa, B., Deb, S., Karkhanis, R., Quan, A., Teoh, H., Feder-Elituv, R., Moussa, F., Souza, D.S., Fremes, S.E., 2014. Pedicled no-touch saphenous vein graft harvest limits vascular smooth muscle cell activation: the PATENT saphenous vein graft study. Eur. J. Cardiothorac. Surg. 45, 717–725.
Virdis, A., Duranti, E., Rossi, C., Dell'Agnello, U., Santini, E., Anselmino, M., Chiarugi, M., Taddei, S., Solini, A., 2015. Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue. Eur. Hear. J. 36, 784–794.
Wang, H., Luo, W., Wang, J., Guo, C., Wang, X., Wolffe, S.L., Bodary, P.F., Eitzman, D.T., 2012. Obesity-induced endothelial dysfunction is prevented by deficiency of P-selectin glycoprotein ligand-1. Diabetes 61, 3219–3227.
Wang, P., Xu, T.Y., Guan, Y.F., Su, D.F., Fan, G.R., Miao, C.Y., 2009. Perivascular adipose tissue-derived visfatin is a vascular smooth muscle cell growth factor: role of nicotinamide mononucleotide. Cardiovasc. Res. 81, 370–380.
Watts, S.W., Dorrance, A.M., Penfold, M.E., Rourke, J.L., Sinal, C.J., Seitz, B., Sullivan, T. J., Charvat, T.T., Thompson, J.M., Burnett, R., Fink, G.D., 2013. Chemerin connects fat to arterial contraction. Arterioscler. Thromb. Vasc. Biol. 33, 1320–1328.
Wojcicka, G., Jamroz-Wisniewska, A., Atanasova, P., Chaldakov, G.N., Chylinska-Kula, B., Beltowski, J., 2011. Differential effects of statins on endogenous H2S formation in perivascular adipose tissue. Pharmacol. Res. 63, 68–76.
Xi, W., Satoh, H., Kase, H., Suzuki, K., Hattori, Y., 2005. Stimulated HSP90 binding to eNOS and activation of the PI3-Akt pathway contribute to globular adiponectin-induced NO production: vasorelaxation in response to globular adiponectin. Biochem. Biophys. Res. Commun. 332, 200–205.
Xiao, J., Xiao, Z.J., Liu, Z.G., Gong, H.Y., Yuan, Q., Wang, S., Li, Y.J., Jiang, D.J., 2009. Involvement of dimethylarginine dimethylaminohydrolase-2 in visfatin-enhanced angiogenic function of endothelial cells. Diabetes Metab. Res. Rev. 25, 242–249.
Xu, A., Vanhoutte, P.M., 2012. Adiponectin and adipocyte fatty acid binding protein in the pathogenesis of cardiovascular disease. Am. J. Physiol. Hear. Circ. Physiol. 302, H1231–H1240.
Yu, X.Y., Qiao, S.B., Guan, H.S., Liu, S.W., Meng, X.M., 2010. Effects of visfatin on proliferation and collagen synthesis in rat cardiac fibroblasts. Horm. Metab. Res. 42, 507–513.
Zeng, Z.H., Zhang, Z.H., Luo, B.H., He, W.K., Liang, L.Y., He, C.C., Su, C.J., 2009. The functional changes of the perivascular adipose tissue in spontaneously hypertensive rats and the effects of atorvastatin therapy. Clin. Exp. Hypertens. 31, 355–363.
Zhang, W., Shu, C., Li, Q., Li, M., Li, X., 2015. Adiponectin affects vascular smooth muscle cell proliferation and apoptosis through modulation of the mitofusin-2-mediated Ras-Raf-Erk1/2 signaling pathway. Mol. Med. Rep.
Zhou, Y., Wei, Y., Wang, L., Wang, X., Du, X., Sun, Z., Dong, N., Chen, X., 2011. Decreased adiponectin and increased inflammation expression in epicardial adipose tissue in coronary artery disease. Cardiovasc. Diabetol. 10, 2.