

The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease

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Abstract

Obesity, insulin resistance and the metabolic syndrome, are characterized by expansion and inflammation of adipose tissue, including the depots surrounding the heart and the blood vessels. Epicardial adipose tissue (EAT) is a visceral thoracic fat depot located along the large coronary arteries and on the surface of the ventricles and the apex of the heart, whereas perivascular adipose tissue (PVAT) surrounds the arteries. Both fat depots are not separated by a fascia from the underlying tissue. Therefore, factors secreted from epicardial and PVAT, like free fatty acids and adipokines, can directly affect the function of the heart and blood vessels. In this review, we describe the alterations found in EAT and PVAT in pathological states like obesity, type 2 diabetes, the metabolic syndrome and coronary artery disease. Furthermore, we discuss how changes in adipokine expression and secretion associated with these pathological states could contribute to the pathogenesis of cardiac contractile and vascular dysfunction.

Keywords: epicardial adipose tissue • perivascular adipose tissue • obesity • type 2 diabetes • cardiovascular dysfunction • atherosclerosis • adipokines • insulin resistance

Introduction

Cardiovascular disease (CVD) is highly associated with obesity, type 2 diabetes (T2DM) and the metabolic syndrome [1]. Risk factors for CVD, including hypertension, dyslipidaemia, increased visceral adipose tissue mass, obesity, increased plasma glucose, insulin resistance, coronary artery disease (CAD) and atherosclerosis, also associate with expansion of the fat depot surrounding the heart and coronary vessels [2–4]. Despite accumulating clinical

and epidemiological evidence, it is still unclear how this expanded adipose tissue depot contributes to the pathogenesis of CVD. Adipose tissue from patients with obesity, T2DM and CVD, is characterized by alterations in adipokine expression that are suggestive of low-grade inflammation [5, 6]. This review aims to discuss how the expanded and inflamed AT may contribute to the pathogenesis of diabetes-related CVD with focus on the interaction

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between epicardial adipose tissue (EAT) and the heart, and between perivascular adipose tissue (PVAT) and the vasculature.

Fat depots around the heart and vasculature

Definitions

Nearly all arteries as well as the heart are surrounded by fat depots. In the case of the human heart, two anatomically distinct fat depots cover approximately 80% of the heart, but the terminology used to describe these depots has been confusing. In this review, we will use the term EAT when referring to the adipose tissue located between the myocardium and the visceral pericardium, and pericardial fat when referring to the depot situated outside the visceral pericardium [3]. Others use the term paracardial fat for the adipose tissue located superficial to the pericardium and define pericardial fat as EAT plus paracardial adipose tissue [2]. PVAT refers to fat surrounding the blood vessels [7].

Epicardial adipose tissue

Epicardial fat cells have the same embryologic origin as mesenteric and omental fat cells, and are derived from the splanchnopleuric mesoderm associated with the gut [3, 8, 9]. Epicardial fat cells have the same embryologic origin as mesenteric and omental fat cells, and are derived from the splanchnopleuric mesoderm associated with the gut [3, 8, 9]. EAT is commonly found at both ventricles in the atrioventricular and interventricular grooves extending to the apex, and along the coronary arteries [2, 4, 10, 11]. Post-mortem studies on individuals without clinical signs of CVD or diabetes mellitus and a body mass index in the upper normal range (25.2 ± 3.6) showed that EAT constitutes approximately 20% of the total ventricular weight in the human heart [10]. The absolute amount of EAT is similar between the left and right ventricle [10]. However, when expressed per gram muscle tissue, the amount of fat covering the right ventricle is three times higher than for the left ventricle [10]. At the right ventricle, the adipose tissue is located over the lateral right ventricular wall followed by the right ventricular wall, with little present over the posterior wall [2, 4, 10, 11]. EAT and underlying myocardium share the same coronary blood supply and no fascia-like structure separates the two tissues [3, 11]. Based on these characteristics, EAT is considered to represent the true visceral fat depot of the heart.

Compared to other fat depots, the number of adipocytes per gram of EAT is higher, and their size is smaller [8, 12, 13]. Furthermore, differences in protein content and fatty acid composition have been described for epicardial fat as compared to other fat depots in animal models. In human EAT, the levels of saturated fatty acids were higher and unsaturated fatty acids were lower

when compared to subcutaneous adipose tissue [14]. Finally, the relative expression levels of various adipokines in EAT, like brain-derived neurotrophic factor, bone morphogenic protein 4, interleukin (IL)-1 β , IL-6, IL-17, monocyte chemoattractant protein-1 (MCP-1), omentin and tumour necrosis factor (TNF)- α , differ from that of other fat depots [15–17].

The number of studies on the metabolic properties of EAT is limited. Mitochondrial copy numbers did not differ among various fat depots studied in guinea pigs, suggesting that the oxidative capacity of EAT is similar to other depots [8]. EAT from guinea pigs also showed enhanced rates of basal fatty acid uptake, lipogenesis and lipolysis when compared to the other fat depots studied [8, 18]. These findings were substantiated in human EAT by higher mRNA expression levels of the lipoprotein lipase and hormone sensitive lipase as compared to subcutaneous adipose tissue [16]. Glucose utilization was only studied in autopsy material from Macaque monkeys. Here, the activities of hexokinase and phosphofructokinase were lower in epicardial adipose fat than in intra-abdominal fat [8]. However, carbohydrate metabolism in human EAT and specifically its regulation by insulin has not been studied so far.

Perivascular adipose tissue

PVAT is surrounding the blood vessels in a way that no fascial layer separates this fat depot from the vascular wall. It should also be noted that infiltrations of adipocytes into the outer region of the adventitia have been observed [19]. PVAT is also pervaded by the so-called vasa vasorum, a network of small blood vessels that supply conduit vessels. Adipocytes in PVAT have been compared to subcutaneous and visceral adipocytes in human beings and rodents in various studies and found to be very inhomogeneous and different from the latter. Perivascular adipocytes are irregularly shaped and smaller in size when compared to subcutaneous and visceral adipocytes in human beings and rodents [19]. There is still controversy as for the classification of PVAT as a depot for white or brown adipose tissue. Although the expression of some markers for brown adipocytes, like positive-regulatory-domain-containing 16 and peroxisome proliferator activated receptor γ co-activator 1 α , and uncoupling protein 1 (UCP-1) is higher in perivascular adipocytes as compared to subcutaneous and perirenal adipocytes [19, 20], the levels of UCP-1 are approximately 1000-fold lower in perivascular adipocytes as compared to brown adipocytes [19]. Other studies support the white adipocytes-like phenotype being predominant in PVAT [21]. Thus it might be possible that PVAT of different blood vessels might be multifaceted as for its physiology and also function.

Pericardial adipose tissue

Pericardial adipose tissue covers approximately 80% of the heart and constitutes 20–50% of the heart weight in human beings [2, 10]. In addition to its location outside the pericardium on the

external surface of the parietal pericardium, it also differs from the epicardial fat in its embryologic origin and blood supply [3, 11]. Pericardial adipocytes are derived from the primitive thoracic mesenchyme, which splits to form the parietal pericardium and the outer thoracic wall [2, 3, 11]. The blood supply to the pericardial adipose tissue is by non-coronary sources, such as the pericardiacophrenic branch of the internal mammary artery [2, 3, 11].

This review will focus on the interaction between EAT and PVAT and the underlying myocardium and vasculature, respectively.

Physiological function of epicardial adipose tissue

Physicians in the 18th and 19th century attributed cases of sudden death in corpulent patients to the fatty heart, a condition where the heart is completely embedded in adipose tissue [22–24]. These early observations are suggestive of an involvement of expanded EAT in the pathogenesis of CVD. Under normal conditions, several functions have been proposed for EAT [4]. Fatty acids represent the major energy source for the healthy heart to maintain contractile function [25]. Therefore, the high rates of lipolysis observed in guinea pigs suggest that EAT could serve as local energy source for the heart [8]. In pathological states like obesity, diabetes and ischemia, an enhanced incorporation and oxidation of fatty acids by the myocardium, contributes to the development of cardiac lipotoxicity [26]. Based on the high rates of fatty acid uptake and synthesis by EAT observed in guinea pigs, it has been proposed that EAT might serve a protective role against elevated levels for free fatty acids in the coronary circulation [8]. In human beings, mRNA levels of UCP-1, and transcriptional regulators PR-domain-missing 16 and peroxisome proliferator activated receptor γ co-activator 1 α are higher in EAT than in other (thoracic) fat depots [27]. This suggests that EAT could act like brown fat to protect the myocardium and coronary vessels against hypothermia. Finally, adipokines secreted from EAT, like adiponectin, adrenomedullin and omentin, may have protective effects on the myocardium and vasculature by regulating energy substrate and Ca²⁺ metabolism [28, 29]. It should be noted that experimental evidence supporting these functions is limited. Most likely, this is due to the minute amounts of EAT present in small laboratory rodents like mice and rats, compared to larger mammals and human beings.

Visualization of epicardial adipose tissue

Visceral obesity is a risk factor for the development of the metabolic syndrome, T2DM and insulin resistance [1]. Cardiovascular dysfunction is a common complication in these syndromes [1]. Accurate quantification of visceral adipose tissue mass using

magnetic resonance imaging or computed tomography is highly costly. Furthermore, application of magnetic resonance imaging is limited in obese patients, whereas computed tomography requires radiation exposure. Therefore, determination of epicardial fat thickness using transthoracic echocardiography was evaluated as predictor for visceral adiposity [30]. In 60 healthy individuals with varying range of body mass indices, EAT thickness as measured by echocardiography closely correlated with visceral adipose tissue as determined by magnetic resonance imaging [30].

Although echocardiography provides a simple and accurate determination of EAT thickness, several limitations exist. First, difficulties may occur in differentiating between epicardial and pericardial adipose tissue. Second, there is debate at when during the cardiac cycle EAT thickness should be measured, because the largest epicardial thickness observed during the cardiac cycle may fail to correspond to the values obtained at end-systole. Finally, anatomical studies have shown that EAT is not uniformly distributed around the heart and also interindividual differences in fat distribution have been observed. Because echocardiographic epicardial fat thickness is a linear measurement at a single location, it may not provide an accurate estimate of the absolute amount of EAT. More accurate assessment of EAT volume therefore requires the use of cardiac magnetic resonance imaging or multi-detector computed tomography [31–36].

Epicardial fat thickness as diagnostic marker

EAT thickness has been evaluated as a diagnostic marker for multiple pathological states, including risk factors for visceral obesity, T2DM, the metabolic syndrome and CAD [37]. As listed in Table 1, autopsy and imaging studies indicate an epicardial fat thickness of ~4.1 mm for the normal heart in Caucasians [30, 31, 38, 39]. EAT thickness tended to be lower in females, but none of the studies reported significance. However, EAT mass and volume was significantly lower in females [31, 40]. In addition to gender-related differences, correlations of EAT with age, waist circumference and heart weight have been reported [10, 40, 41]. Furthermore, EAT volume is higher in Caucasians, when compared to Asians, Blacks and Hispanics [40].

Association of epicardial fat with insulin resistance and T2DM

Visceral obesity, insulin resistance, and impaired glucose tolerance are important risk factors for the development of T2DM. EAT thickness and mass are increased in obesity [42, 43], although epicardial fat thickness was higher in patients with impaired glucose tolerance as compared to normal glucose tolerant patients [44]. In Chinese patients EAT volume in patients with T2DM was

Table 1. EAT in normal hearts and healthy controls

Parameter	Method	Both genders	Men	Women	References
EAT thickness (mm)	Autopsy	4.12 ± 1.4			[38]
	Echo		4.12 ± 1.67	3.13 ± 1.87	[30]
	Echo		4.5 (range 3–5.5)	3.5 (range 2–4.5)	[39]
	MRI	4.1 ± 1.1	4.2 ± 1.1	3.7 ± 1.0	[31]
EAT mass (g)	Autopsy	54 ± 23			[10]
	MRI		69.2 ± 21.6	47.5 ± 5.2*	[31]
EAT volume (ml)	MDCT	96 ± 44	92 ± 46	66 ± 34 [†]	[40]

MDCT, multidetector-computed-tomography.

* $P = 0.023$.

[†] $P < 0.001$ (men *versus* women).

higher than in patients without diabetes [45]. Correlations have been found between markers of visceral obesity, like waist circumference, body mass index and visceral adipose tissue mass, and EAT thickness and volume in Caucasian and Asian patients [30, 34, 35, 40–42, 45–49]. Furthermore, EAT thickness was related to fasting plasma insulin [42, 46, 47, 50], fasting plasma glucose [44, 45, 47] and insulin sensitivity as assessed by euglycaemic hyperinsulinemic clamps [47] or surrogate markers like HOMA- and QUICKI-indices [42]. For Europeans, a threshold value of 9.5 mm EAT thickness was found to predict insulin resistance [39]. Finally, hepatic steatosis, an important risk factor for insulin resistance, and serum levels of two indicators of hepatic steatosis, the alanine and aspartate aminotransferases were found to associate with EAT thickness [42, 50].

Association of epicardial fat with cardiovascular dysfunction

Visceral obesity is associated with an increased risk of CAD [51]. Interestingly, two population-based studies, the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart study, identified the fat depots around the heart as independent risk predictors for CVD [52–54]. In these studies, the sum of epicardial and pericardial adipose tissue was determined. Because of its anatomic proximity to the adventitia and the major epicardial coronary arteries, it is highly likely that in particular alterations in EAT play an important role in the pathogenesis of CAD. Indeed, EAT thickness and volume was increased in patients with CAD compared to patients with normal arteries, and in patients with unstable angina as compared to patients with stable angina or atypical chest pain [33, 41, 55, 56]. Importantly, EAT thickness was found to associate with subclinical markers of atherosclerosis. Patients with an EAT thickness >7 mm had increased carotid intima media thickness and carotid artery stiffness [57]. Also in HIV-positive patients on highly active anti-retroviral therapy, who are at increased risk for subclinical atherosclerosis, EAT thickness was found to associate with carotid intima media thickness [58, 59]. Finally, a study per-

formed in women, showed that a relation between epicardial fat thickness and low coronary reserve [60]. This suggests that EAT thickness may be a predictor of coronary reserve in women with angiographically normal arteries.

In patients with CAD, EAT thickness was related to the severity of CAD, as determined by the Gensini score [55, 61]. In contrast, in one study no correlation between EAT thickness and the presence or severity of CAD was found [62]. It is unclear whether differences in assessing EAT thickness or ethnicity underlie this discrepancy. EAT volume was also found to be larger in patients with increased coronary artery calcium and obstructive CAD [33, 36, 41, 45, 56, 63]. However, despite the correlation between EAT volume and CAD, further studies seem required to assess whether EAT volume is an indicator for the severity of CAD. Three reports demonstrate such relationship in patients with CAD [41, 45], but others could not confirm this [56, 63]. However, in lean patients, increased epicardial fat was related to more severe CAD and coronary artery calcium [63].

Cardiac hypertrophy is an independent risk factor for the development of CVD. Autopsy studies showed that EAT weight is related to myocardial mass in normal and hypertrophied hearts [10]. In obese patients, EAT thickness associated with left ventricular mass and right ventricular cavity size [64–66]. A study performed on morbidly obese patients, reported a relation between EAT thickness and enlargement of the atria [67]. At the functional level, epicardial fat volume was inversely correlated with cardiac index [43]. In obese patients, an association between EAT thickness and iso-volumetric relaxation time and myocardial performance index was reported [66]. Furthermore, in patients with an EAT thickness >7 mm, and morbidly obese patients, EAT thickness associated with diastolic dysfunction [57, 67].

Association of epicardial fat with the metabolic syndrome

The metabolic syndrome is a cluster of interrelated risk factors for CVD and T2DM [1]. Clinical markers for the metabolic syndrome

include visceral obesity, elevated triglyceride levels, low high-density lipoprotein levels, hypertension and elevated fasting glucose levels with insulin resistance as proposed link between these factors [1]. Epicardial fat thickness is significantly higher in patients with the metabolic syndrome [39, 46, 55]. Also increases in epicardial fat mass as determined by multidetector computed tomography were found to correlate with the metabolic syndrome [33–35, 45]. Based on echocardiographic observations in Europeans, cut-off values of 9.5 and 7.5 mm epicardial fat thickness have been proposed as predictors for the metabolic syndrome in man and women, respectively [39]. In addition to the earlier-mentioned associations between EAT and visceral obesity, fasting plasma glucose levels and insulin resistance, relations with the other diagnostic markers for the metabolic syndrome have been found. Hypertension, elevated triglyceride levels and reduced HDL-cholesterol levels have been reported in patients with an epicardial fat thickness >5.2 mm [55]. EAT thickness and volume have been found to correlate with triglyceride levels in obese patients and Chinese patients [42, 45, 55], but other studies did not find such correlation [46, 57]. HDL-cholesterol levels were inversely related to EAT [45, 46, 55], but association was not found in another study [57]. Finally, EAT was related to hypertension, systolic- and diastolic blood pressure [32, 46, 56, 57], but this was not found in Chinese patients [45]. It seems likely that differences in the composition of the study cohorts related to ethnic background and disease states may have contributed to the observed variations. Further studies in well-controlled cohorts seem required to clarify these issues.

Association of epicardial fat with adipokines

Obesity and CVD are associated with a state of low-grade inflammation [5]. Plasma levels of the inflammatory markers MCP-1, soluble IL-6 receptor/IL-6 complex, plasminogen activator inhibitor-1 (PAI-1) and visfatin associated with epicardial fat thickness in obesity. Epicardial fat thickness showed an inverse correlation with plasma adiponectin levels [46, 50].

Effect of weight loss on epicardial adipose tissue

Weight loss in obese patients following bariatric surgery, low calorie diets or exercise is accompanied by a reduction in EAT thickness [37, 68–71]. The relative reduction in epicardial fat as compared to visceral fat varied among the studies [71]. It seems plausible to ascribe this to variations in the ethnic background of the study cohorts as well as the methods used to achieve weight loss. Importantly, a reduction in epicardial fat thickness, rather than a decrease in waist circumference, was found to be a better predictor for improved left ventricular mass and diastolic function following weight loss by a very low calorie diet in morbidly obese Caucasians [68]. Furthermore, a reduction in epicardial fat thickness associated with improved systolic blood pressure and

increased insulin sensitivity following exercise-induced weight loss in obese Koreans [70].

Visualization of perivascular adipose tissue

A pilot study measuring peri-aortic adipose tissue by computer tomography showed that determination of the amount of PVAT in very specific areas is practicable with a reasonable reproducibility [72]. The amount of PVAT was highly associated with visceral obesity and moderately correlated with subcutaneous adipose tissue and body mass index [72]. So far, only a few studies measured the amount of PVAT in relation to insulin sensitivity. PVAT thickness at the brachial artery is significantly correlated with insulin resistance as assessed by OGTT, and inflammation as reflected by circulating CRP [73]. In the Framingham Heart Study, measurement of adipose tissue surrounding the thoracic aorta revealed a significant correlation of this depot with body mass index, visceral obesity, hypertension and diabetes [74]. Furthermore, it became evident that PVAT is associated with coronary and abdominal aortic calcification [74, 75].

Expression and secretion of fatty acids and adipokines from epicardial and perivascular fat depots

Like other fat depots, EAT and PVAT are a source of fatty acids and adipokines [28, 76]. It should be noted in this respect that adipokines are not only secreted by adipocytes, but also by other cell types present in adipose tissue, like stromal vascular cells and infiltrated immune cells [15, 77]. Because of the lack of a fascia separating EAT and PVAT from the myocardium and vasculature, respectively, factors secreted from these fat depots may directly affect these adjacent tissues [76].

Fatty acids

An overload of fatty acids, due to alterations in lipolysis and lipogenesis rates and mitochondrial dysfunction, has been linked to lipotoxicity-induced dysfunction of the cardiovascular system [78, 79]. In human beings, expression and secretion of secretory type II phospholipase A2 (sPLA2-IIA) was higher in EAT from patients with CAD as compared to patients without CAD. sPLA2-IIA catalyses the hydrolysis of the sn-2-ester bond of phospholipids to produce free fatty acids and lysophospholipids. However, it is unknown whether these changes are paralleled by an enhanced release of FFA from EAT. Therefore, further studies are needed to

assess whether alterations in lipid metabolism in EAT and PVAT contribute to the pathogenesis of cardiovascular dysfunction.

Adipokines

Adipokine expression in EAT has been profiled using microarrays analysis and real-time PCR in human beings and antibody arrays in guinea pigs [15–17, 80, 81]. In PVAT, antibody arrays and real-time PCR have been used for adipokine profiling [19, 82]. All studies show changes in adipokine expression levels among the various fat depots examined. Only a few studies have determined adipokine secretion from EAT and PVAT. EAT explants were found to secrete IL-1 β , IL-6, IL-6 sR, MCP-1 and TNF- α , PVAT was found to secrete adiponectin, IL-1/IL-1Ra, IL-6, IL-8, IP-10, leptin, MCP-1, RANTES and TNF- α , as well as an yet unidentified protein, termed adventitia-derived relaxation factor (ADRF) [15, 19, 76, 83, 84].

Several studies have evaluated alterations in adipokine expression in EAT in pathological states, like CAD and the metabolic syndrome, or following cardiac surgery (Table 2). In EAT from patients with CAD, the expression of protective factors, like adiponectin and adrenomedullin, was lower when compared to EAT from non-CAD patients [85–88]. Also intracoronary levels of adiponectin and adrenomedullin were lower in patients with CAD, and in the case of adiponectin, intracoronary levels were found to correlate with protein expression in EAT [88, 89]. Conversely, in CAD patients, EAT was found to express and secrete higher levels of the pro-inflammatory markers IL-1 β , IL-6, MCP-1 and TNF- α , as compared to subcutaneous adipose tissue [15]. When CAD patients were compared with non-CAD patients, elevated expression of IL-6, leptin, sPLA2-IIA, resistin, TNF- α and visfatin have been reported [80, 86, 87, 90]. For sPLA2-IIA and resistin, also increases in secretion were found in patients with CAD [81, 90]. Elective cardiac surgery, which represents a major risk factor for post-operative development of insulin resistance, also induced the expression of pro-inflammatory mediators, like angiotensinogen, IL-6, MCP-1 and resistin [91, 92]. Expression of adiponectin, hepcidin, leptin and TNF- α in EAT was not significantly affected by cardiac surgery [92, 93]. Studies towards alterations in adipokine expression in EAT in relation to diabetes are limited. One study reports an increased expression of fatty acid binding protein 4 (FABP-4) in patients with the metabolic syndrome [94]. Furthermore, in a rat model of type 1 diabetes, secretion of adiponectin, leptin and visfatin from EAT was decreased, and secretion of IL-6 was slightly increased as compared to control rats [95].

To our knowledge, there are no reports describing alterations in adipokine expression in PVAT in pathological states in human beings. In mice, the effects of high-fat and high-fat high sucrose feeding, which may contribute to the induction of insulin resistance, were examined [19, 96]. Compared to mice fed a control diet, PVAT expression of adiponectin and FABP-4 was lower, and expression of leptin, MCP-1 and MIP-1 α was higher in high-fat diet fed mice [19, 21]. Furthermore, high-fat diet feeding of mice led to increased release of MCP-1 from PVAT [21]. Also high-fat

high-sucrose feeding in mice was found to lower adiponectin expression, whereas expression of MCP-1, TNF- α and PAI-1 was elevated in PVAT of these animals [96].

Cross-talk between secretory products from EAT and the myocardium

Myocardial triglyceride accumulation, which is associated with EAT mass [43], has been implicated in the pathogenesis of diabetes-related heart disease, a common cause of death in these patients. To our knowledge, there are no reports describing direct effects of secretory products from EAT on cardiac function. However, detrimental effects of secretory products from other fat depots on cardiac function have been reported. Conditioned medium from epididymal adipose tissue from rats with chemically induced diabetes, was found to inhibit fatty acid oxidation and insulin-stimulated glucose uptake in primary rat cardiomyocytes [95]. Conditioned medium from subcutaneous human adipose tissue was found to inhibit contractile function in primary rat cardiomyocytes *in vitro* [97]. This cardio-depressant activity could be ascribed to FABP-4 [98]. Interestingly, FABP-4 expression is increased in EAT from patients with the metabolic syndrome [94]. It would be interesting to learn whether this increased expression is paralleled by enhanced secretion of FABP-4 from EAT.

One study describes an enhanced secretion of resistin from EAT in patients with CAD [90]. In the Framingham Offspring study, increased circulating levels of resistin were associated with incident heart failure [99]. Resistin may directly interfere with cardiac function. Overexpression of resistin was found to impair contractile function in rat cardiomyocytes [100], and in primary mouse cardiomyocytes, resistin was found to reduce insulin-stimulated glucose uptake [101].

Direct effects on cardiac function have also been reported for other adipokines, which include a cardioprotective action for adiponectin, and both cardioprotective and detrimental effects for leptin [102–105]. Importantly, however, it has to be determined whether the changes in adipokine expression in EAT listed in Table 2 are paralleled by changes in secretion in pathological states.

Cross-talk between secretory products from PVAT and the vasculature

Vascular relaxation factors, pro-atherogenic adipokines and growth factors secreted from PVAT were found to directly regulate vascular function through paracrine and endocrine effects on the vascular wall. Initial studies on the interaction between PVAT and the vessel wall concentrated on the regulation of vasoreactivity, and ascribed both vasorelaxation and vasoconstriction to secretory products from PVAT [83, 106, 107]. Furthermore, PVAT has

Table 2. Secretory products from human EAT in pathological states

Adipokine	Protein/mRNA	Pathological state	Expression	References
Adiponectin	Protein, mRNA	CAD	↓	[80, 85–87, 89]
	mRNA	Hypertension	↓	[124]
	mRNA	Cardiac surgery	=	[92]
Adrenomedullin	Protein, mRNA	CAD	↓	[88]
Angiotensinogen	mRNA	Cardiac surgery	↑	[91]
FABP-4	mRNA	Metabolic syndrome	↑	[94]
Hepcidin	mRNA	Cardiac surgery	=	[93]
IL-1β	Protein, mRNA	CAD	n.d.	[15]
	Secretion	CAD	n.d.	[15]
IL-6	Protein, mRNA	CAD	↑	[15, 80, 86, 87]
	Secretion	CAD	n.d.	
	mRNA	Cardiac surgery	↑	[15]
				[92]
Leptin	Protein, mRNA	CAD	↑	[80, 87]
	mRNA	Cardiac surgery	=	[92]
MCP-1	Protein, mRNA	CAD	n.d.	[15]
	Secretion	CAD	n.d.	[15]
	mRNA	Cardiac surgery	↑	[92]
Omentin	mRNA	CAD	n.d.	[29]
		Metabolic syndrome	n.d.	[29]
		T2DM	n.d.	[29]
PAI-1	mRNA	CAD	n.d.	[80]
sPLA2-IIA	Protein, mRNA	CAD	↑	[81]
	Secretion	CAD	↑	[81]
Resistin	mRNA	CAD	↑	[80, 90]
	Secretion	CAD	↑	[90]
		Cardiac surgery	↑	[92]
TNF-α	Protein, mRNA	CAD	↑	[15, 80, 87]
	Secretion	CAD	n.d.	[15]
	mRNA	Cardiac surgery	=	[92]
tPA	mRNA	CAD	n.d.	[80]
Visfatin	Protein	CAD	↑	[87]
	mRNA	CAD	n.d.	[29]
		Metabolic syndrome	n.d.	[29]
		T2DM	n.d.	[29]

n.d., not done.

been implicated in vascular remodelling [96]. Similar to other fat depots, obesity results in an expanded PVAT depot which is characterized by a state of low-grade inflammation [84]. Changes in adipokine expression and secretion associated with obesity may be directly related to the pathogenesis of vascular disease as will be discussed under 'Alterations in obesity and insulin resistance' in this review.

Vasorelaxation

An as yet unidentified factor, termed ADRF has been implicated in the induction of vasorelaxation in the aorta, as well as in smaller vessels in rats [83, 108]. It has been suggested that ADRF could be adiponectin. Indeed, adiponectin was found to act as a vasodilator, but studies on adiponectin-deficient mice showed that ADRF is not adiponectin [109]. Aortic rings from rats with and without PVAT and endothelium were used to study the mechanism of the anti-contractile action exerted by PVAT [110]. It was found that PVAT releases a transferable relaxing factor, which induces endothelium-dependent relaxation through nitric oxide release by endothelial cells and subsequent activation of Ca^{2+} -dependent K^+ channels in smooth muscle cells [110]. It needs to be determined whether this factor is similar to ADRF. In human beings subcutaneous PVAT collected from healthy individuals was found to induce vasodilation by increasing the bioavailability of nitric oxide [84]. This effect could be blunted by an adiponectin blocking peptide, which inhibits the adiponectin type 1 receptor [84], suggesting a role for adiponectin. Also endothelium-independent anti-contractile effects have been ascribed to PVAT, which involve the activation of soluble guanylyl cyclase by hydrogen peroxide [110].

Vasoconstriction

Factors from PVAT can stimulate both relaxation and constriction depending on the localization of the vessel and the pathophysiological condition. Perivascular nerve activation by electric stimulation in rat aortic rings induces vasoconstriction, dependent on the presence of intact PVAT [107]. This response involves the production of superoxide by NAD(P)H oxidase, and was prevented by inhibitors of tyrosine kinase and the extracellular-signal regulated kinase pathway [107]. In dogs, it could be demonstrated that PVAT releases a vasocontractile factor that impairs coronary endothelial NO production *via* a protein kinase C- β mediated inhibitory phosphorylation of endothelial nitric oxide synthase [111, 112].

Vascular remodelling

Removal of PVAT in mice markedly enhanced neointima formation following endovascular injury [96]. This response was blunted by transplantation of subcutaneous adipose tissue [96]. These transplantation experiments provide the first evidence for a protective role of PVAT against neointima formation by regulatory effects on

smooth muscle cell proliferation [96]. However, it should be noted that subcutaneous adipose tissue is phenotypically distinct from PVAT [19, 76]. Therefore, it would be interesting to evaluate the effects of PVAT transplantation or local administration of conditioned medium from PVAT explants following PVAT removal in this animal model.

Alterations in obesity and insulin resistance

Expansion and inflammation of PVAT have been implicated in the development of endothelial dysfunction, atherosclerosis, but also in the pathogenesis of insulin resistance.

Endothelial dysfunction, which is often considered to precede atherosclerotic disease, is associated with diabetes and CVD, and characterized by deregulation of vasoreactivity, increased inflammatory and oxidative stress, and impaired barrier function [113]. In human beings, the vasorelaxing effects of PVAT were lost in obesity, and the loss of this vasodilator effect was associated with expansion of PVAT [84]. Addition of TNF- α , IL-6 or inhibition of adiponectin using a blocking peptide reduced the vasodilator activity of PVAT around healthy blood vessels, thus mimicking the effects of obesity [84]. Finally, the effects of obesity could be reversed by TNF- α antibodies [84]. Collectively, this study suggests important roles for adiponectin and pro-inflammatory cytokines in the pathogenesis of endothelial dysfunction. Accordingly, hypo adiponectinaemia, and IL-6 have been linked to endothelial dysfunction [114–117]. It should be noted, however, that a study in human beings could not find a correlation between PVAT mass and local endothelial function [73]. Rather, PVAT was negatively correlated with insulin sensitivity and muscular blood flow [73], which supports the hypothesis that vascular effects on muscular blood flow could contribute to the pathogenesis of insulin resistance [7].

Critical steps in arterial wall thickening are the migration of vascular smooth muscle cells from the media to the intima and their concomitant proliferation in the synthetic state. Conditioned medium from PVAT explants from high-fat diet-fed rats markedly enhanced human smooth cell proliferation when compared to conditioned medium from PVAT explants of control-diet fed animals [118]. In mice, increased neointima formation in high-fat high-sucrose fed mice was paralleled by a decreased expression of adiponectin [96, 119], and induction of inflammatory markers like MCP-1, TNF- α , IL-6 and PAI-1 in PVAT. Importantly, adiponectin-deficient mice display increased neo-intima formation when compared wild-type mice, and this effect could be reversed by local administration of adiponectin to the periadventitial area [96]. In line with this, adiponectin has been found to abrogate growth-factor induced smooth muscle cell proliferation and migration [120]. It is currently unknown which factors secreted from PVAT contribute to vascular smooth muscle cell migration and proliferation. Potential candidates include leptin, resistin and visfatin, which have been found to directly affect vascular smooth muscle cell function [121–123].

Finally, conditioned media from PVAT strongly induced the chemotaxis of peripheral blood leukocytes. These chemotactic

effects have been ascribed to IL-8 and MCP-1, and have been proposed to underlie the accumulation of macrophages and T cells at the interface between PVAT and the adventitia in human atherosclerotic arteries [82].

the function of the EAT and PVAT are still hampered by the absence of appropriate healthy controls. Future studies may anticipate on these limitations.

Perspectives and conclusions

This review focused on the role of EAT and PVAT in the pathogenesis of CVD. We propose that alterations in the secretion of adipokines, and possibly fatty acids, from these depots could contribute to the development of cardiovascular dysfunction in T2DM and the metabolic syndrome. However, studies addressing secretion rather than expression of factors from the adipose tissue depots are limited. Characterization of the secretory profile of EAT and PVAT could identify factors that protect or contribute to the development of CVD, and in the case of PVAT reveal the identity of ADRF. Furthermore, the cellular composition of EAT and PVAT in health and disease, including disease-related changes in adipocyte size and differentiation, as well as infiltration of immune cells, is still unclear. Finally, it should be noted that most studies towards

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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