

# Role of adipokines in cardiovascular disease

Harman S Mattu\* and Harpal S Randeva\*

Division of Metabolic and Vascular Health, University of Warwick Medical School, Gibbet Hill Road, Coventry CV4 7AL, UK

\*H S Mattu and H S Randeva equally contributed to this review article in terms of design, writing and editing)

Correspondence should be addressed to H S Randeva  
**Email**  
harpal.randeva@warwick.ac.uk

## Abstract

The discovery of leptin in 1994 sparked dramatic new interest in the study of white adipose tissue. It is now recognised to be a metabolically active endocrine organ, producing important chemical messengers – adipokines and cytokines (adipocytokines). The search for new adipocytokines or adipokines gained added fervour with the prospect of the reconciliation between cardiovascular diseases (CVDs), obesity and metabolic syndrome. The role these new chemical messengers play in inflammation, satiety, metabolism and cardiac function has paved the way for new research and theories examining the effects they have on (in this case) CVD. Adipokines are involved in a ‘good–bad’, yin–yang homeostatic balance whereby there are substantial benefits: cardioprotection, promoting endothelial function, angiogenesis and reducing hypertension, atherosclerosis and inflammation. The flip side may show contrasting, detrimental effects in aggravating these cardiac parameters.

## Key Words

- ▶ adipokines
- ▶ inflammation
- ▶ angiogenesis
- ▶ CVD
- ▶ vascular
- ▶ cardiac
- ▶ adiponectin
- ▶ leptin
- ▶ resistin
- ▶ visfatin
- ▶ apelin
- ▶ omentin
- ▶ chemerin
- ▶ perivascular adipose tissue

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## Introduction

Cardiovascular disease (CVD) remains the biggest cause of death worldwide. As the global population becomes increasingly sedentary, CVD and related diseases such as diabetes and obesity will increase. Mortality is not the only concern; the associated morbidity is placing an ever greater strain on healthcare providers and economies around the world, let alone the societal consequences of an unhealthy population. Risk factors according to the World Heart Federation include hypertension, smoking, type 2 diabetes mellitus, being overweight, hyperlipidaemia, lifestyle (poor nutrition and lack

of exercise), family history and having suffered a previous cardiovascular event.

The underlying cardiovascular pathology varies from defective contractility to inflammation and damage to blood vessels. The resulting conditions include (but are not limited to) hypertension, atherosclerosis, and endothelial and myocardial dysfunction. Diabetes, obesity and exogenous factors (exercise, lifestyle and nutrition) have been shown to interact (including through metabolic syndrome, MetS) and contribute to CVD. White adipose tissue (WAT) has been identified as a metabolically active

endocrine organ that affects a plethora of body functions including energy and feeding regulation, glucose and lipid metabolism, thermogenesis, neuroendocrine function, reproduction, immunity and most relevantly cardiovascular function (Trujillo & Scherer 2006).

Adipose tissue achieves these effects via the release of important chemical mediators, termed adipocytokines or adipokines. The discovery of leptin in 1994 heralded a new era in the study of WAT and the discovery of a number of adipocytokines, such as adiponectin, leptin, resistin, visfatin, apelin, omentin, chemerin, nesfatin and other cytokines, e.g. interleukin-6 (IL6), plasminogen activator inhibitor (PAI-1), monocyte chemoattractant protein 1 (MCP-1) and tumour necrosis factor- $\alpha$  (TNF $\alpha$ ). Many others have now been identified and the list is growing. Cytokines, under current terminology, refer to immunomodulating agents. However, conflicting data exist regarding what is termed a cytokine and what is termed a hormone, and more research is needed in this area of defining cytokines and hormones. According to Harrison's Principles of Internal Medicine, adiponectin, leptin and resistin are not appropriately considered adipokines (cytokines) as they do not act on the immune system. However, these peptides are referred to as adipokines but they can be more accurately described as adipose-derived hormones.

Adipose tissue comprises adipocytes (30–50%), pre-adipocytes and fibroblasts, collagen fibre matrix, blood vessels and immune cells (monocytes/macrophages and lymphocytes). Adipokines are peptides secreted by adipocytes (adiponectin, leptin, visfatin, etc.) whereas cytokines refer to the peptides secreted from the stromal vascular fraction of cells (MCP-1, macrophage inflammatory protein, TNF $\alpha$  and ILs 1B, 6, 8, 10, etc.). There is an overlap, however, because an adipokine may be secreted from both (e.g. apelin and resistin).

Obesity is characterised by a chronic, low-grade pro-inflammatory state causing hyperplasia and hypertrophy of fat cells leading to an imbalance in the release of adipokines. This in turn reduces insulin sensitivity and increases contractility and inflammation (Skurk *et al.* 2007). This leads to vascular diseases such as hypertension, atherosclerosis and vascular dysfunction. Endothelial dysfunction is characterised by impaired nitric oxide (NO) release from endothelium and decreased blood flow to insulin target tissues, contributing to insulin resistance (Kim *et al.* 2006). Systemic inflammation and abnormal production of adipose tissue-derived factors play a pivotal role in the genesis and progression of atherosclerosis (Lau *et al.* 2005), accompanied by endothelial cell (EC) dysfunction

and altered expression of pro-angiogenic/pro-atherogenic factors like matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) resulting in structural and functional changes of the endothelium (Rutkowski *et al.* 2009).

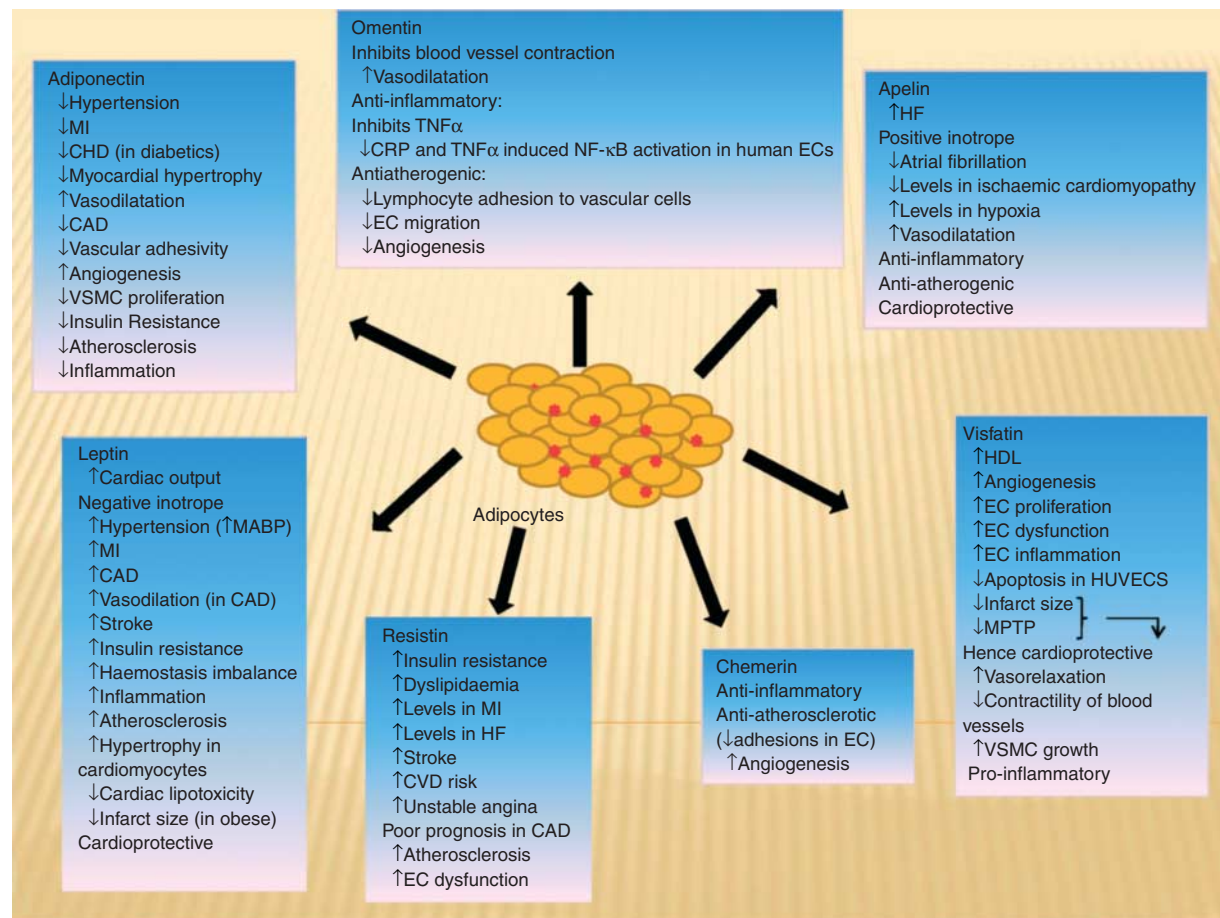
Adipokines fulfil their actions via different signalling pathways and chemical mediators. Their effects are achieved through the regulation of these mediators and through crosstalk with other adipokines and compounds, details of which will be covered. The adipokines have effects that may be beneficial and/or detrimental to cardiovascular physiology. Indeed, over the last decade, some adipose tissue-derived molecules have been shown to be cardioprotective against myocardial ischaemia/reperfusion (I/R) injury and may also play a role in cardiac remodelling in pathology by limiting the extent of myocardial hypertrophy (Ouchi *et al.* 2006).

This article is intended to provide an overview of the role of prominent adipokines in CVD with an additional focus on key novel adipokines (Fig. 1 and Table 1). Their role in obesity and insulin sensitivity with their attendant effects on CVD will also be examined.

## Adiponectin

This adipokine is synthesised predominantly not only by adipocytes but also by skeletal muscle, ECs and cardiomyocytes. It is abundant in the plasma representing 0.01% of plasma proteins (3–30  $\mu$ g/ml; Ouchi *et al.* 2003). It is a 244 amino acid protein belonging to the collagen superfamily (Kadowaki & Yamauchi 2005, Pineiro *et al.* 2005). It exists as a 30 kDa molecule (high-molecular weight form, HMW) or as smaller globular fragments. The HMW version predominates in plasma (Scherer *et al.* 1995, Hu *et al.* 1996, Maeda *et al.* 1996, Nakano *et al.* 1996). Plasma adiponectin levels increase with weight loss and with insulin-sensitising drugs, thus appearing to be inversely proportional to insulin resistance and obesity (Kadowaki & Yamauchi 2005). Pro-inflammatory cytokines have also been found to inhibit adiponectin secretion in cultured adipocytes, contributing to evidence linking inflammation with insulin resistance and obesity (Lago *et al.* 2007).

Adiponectin mediates its actions via three receptors: AdipoR1 (expressed ubiquitously, but especially in skeletal muscle), AdipoR2 (predominantly in liver) (Yamauchi *et al.* 2003) and T-cadherin (Hug *et al.* 2004). All three receptors are expressed in cardiac tissue (Doyle *et al.* 1998, Fujioka *et al.* 2006). Adiponectin, via AMPK phosphorylation, increases insulin sensitivity, fatty acid oxidation

**Figure 1**

Adipocytokine influences on the cardiovascular system, inflammation and insulin resistance.

and reduces the synthesis of glucose in the liver and other tissues (Tomas *et al.* 2002, Yamauchi *et al.* 2002). Stimulation of the receptors modulates AMPK but also PI3K, p44/42 MAP kinase, p38 MAP kinase and cyclooxygenase-2 (COX-2; Shibata *et al.* 2004, Kadowaki & Yamauchi 2005, Karmazyn *et al.* 2008). Adiponectin may be intrinsically anti-atherogenic by regulating the main signalling pathways involved in the genesis of atherosclerosis: PI3K–Akt, endothelial NO synthase (eNOS) and AMPK (Shimada *et al.* 2004). Adiponectin appears to suppress monocyte adhesion to the vascular endothelium and promotes angiogenesis by stimulating crosstalk between Akt and AMPK in ECs (Ouchi *et al.* 1999). Akt is a serine/threonine protein kinase that plays an important role as a second messenger in many cellular functions such as cell proliferation, apoptosis and glucose metabolism.

Adiponectin also has anti-inflammatory properties, which may regulate steps in the atherogenic process

combined with prevention of apoptosis in ECs as well as angiogenic promoting actions (Hopkins *et al.* 2007). The anti-inflammatory properties are achieved via the suppression of nuclear factor kappa-light-chain enhancer of activated B cells (NF- $\kappa$ B) in macrophages and monocytes. Similarly, the suppression of NF- $\kappa$ B in ECs slows the development of atherosclerosis. Moreover, adiponectin inhibits macrophage conversion to foam cells and reduces oxidation of LDL. In both cases, suppression of NF- $\kappa$ B halts TNF $\alpha$  induced processes (inflammation/monocyte adhesion). Adiponectin signals via the AMPK pathway to reduce EC apoptosis and to promote NO synthesis (Ouchi *et al.* 2001).

The vascular endothelium is an important paracrine organ in regulating vascular tone, smooth muscle cell proliferation and inflammation. NO is critical in vasoconstriction/dilation, leukocyte transmigration, growth of smooth muscle cells and adhesion molecule expression

**Table 1** Adipocytokine effects on cardiovascular pathophysiology

Adipocytokine	Action	Experimental models	References
Adiponectin	Anti-atherogenic	Mouse/rat/human <i>in vitro/in vivo</i>	Shimada <i>et al.</i> (2004)
	↓EC monocyte adhesion	Human <i>in vitro</i>	Ouchi <i>et al.</i> (1999)
	↑Angiogenesis	Human <i>in vitro</i> (EC)	Ouchi <i>et al.</i> (2004)
	↓Apoptosis	Mouse/rabbit <i>in vivo</i>	Kobayashi <i>et al.</i> (2004)
	↓VSMC proliferation	Human <i>in vitro</i> (EC)	Arita <i>et al.</i> (2002)
	↓Systolic BP	Human <i>in vitro</i> (SMC)	Ohashi <i>et al.</i> (2006)
	↓Pressure overload induced cardiac hypertrophy	Mouse <i>in vivo</i>	Shibata <i>et al.</i> (2004)
	↓ET-1 induced hypertrophy	Mouse <i>in vivo</i> /rat ventricular myocytes	Fujioka <i>et al.</i> (2006)
	↓Post-MI systolic dysfunction	Rat cardiomyocytes	Shibata <i>et al.</i> (2007)
	↓Myocardial damage	Mouse <i>in vivo</i> knockout	Takahashi <i>et al.</i> (2005)
Leptin	Proatherogenic:	Human cardiomyocytes	
	↑Vascular inflammation/EC dysfunction	Human <i>in vitro</i> (EC)	Bouloumie <i>et al.</i> (1999)
	↑VSMC migration and proliferation	Human <i>in vitro</i> (SMC)	Li <i>et al.</i> (2005)
		Rat <i>in vitro</i> (SMC)	Oda <i>et al.</i> (2001)
	Hypertrophy	Mouse/human cardiomyocytes	Tajmir <i>et al.</i> (2004)
		Rat cardiomyocytes	Rajapurohitam <i>et al.</i> (2003)
	↓Apoptosis	Mouse <i>in vivo</i>	McGaffin <i>et al.</i> (2008)
		Rat cardiomyocytes	Eguchi <i>et al.</i> (2008)
	↓Cardiac output	Rat cardiomyocytes	Nickola <i>et al.</i> (2000)
	↑MABP, HR	Rat <i>in vivo</i> (i.v.)	Shek <i>et al.</i> (1998)
Resistin	↓Lipotoxicity	Rat <i>in vivo</i> (i.c.v.)	Satoh <i>et al.</i> (1999)
	↑Adhesion molecules	Rat/rabbit <i>in vivo</i> (i.v., i.c.v.)	Shirasaka <i>et al.</i> (2003)
	↑Proatherogenic inflammatory markers	Rat cardiomyocytes	Rajapurohitam <i>et al.</i> (2003)
	↑CAD	Rat <i>in vitro/in vivo</i>	Lee <i>et al.</i> (2004)
	↑Aortic SMC proliferation	Human <i>in vitro</i> (aortic EC)	Kawanami <i>et al.</i> (2004)
	↓Bradykinin induced dilation of coronary arteries	Human plasma	Kunnari <i>et al.</i> (2006)
	↑Coronary EC proliferation	Human plasma	Lubos <i>et al.</i> (2007)
	↑Cardiac injury	Human <i>in vitro</i> (SMC)	Calabro <i>et al.</i> (2004)
	↑Plaque destabilisation	Dog <i>in vitro/in vivo</i>	Dick <i>et al.</i> (2006)
	↑Inflammatory response	Human cultures	Mu <i>et al.</i> (2006)
Visfatin	↑VSMC growth	Rat Langendorff	Rothwell <i>et al.</i> (2006)
	↓Apoptosis in VSMCs and ECs	Human <i>in vitro</i>	Dahl <i>et al.</i> (2007)
		Mouse <i>in vivo</i> /human cultures	Moschen <i>et al.</i> (2007)
	↑EC proliferation	Rat <i>in vitro</i> (SMC)	Wang <i>et al.</i> (2009)
	↑Endothelium-dependent vasodilation	Human <i>in vitro</i> (SMC)	van der veer <i>et al.</i> (2005)
	↑Cardioprotection	Human <i>in vitro</i> (EC)	Adya <i>et al.</i> (2008)
	Anti-atherogenic	Human <i>in vitro</i> (EC)	Adya <i>et al.</i> (2008)
	Prevent AAA formation	Rat <i>ex vivo</i>	Yamawaki <i>et al.</i> (2009)
		Mouse <i>in vitro/in vivo</i>	Lim <i>et al.</i> (2008)
		Mouse <i>in vivo/in vitro</i> (cell cultures)	Chun <i>et al.</i> (2008)
Apelin	↓BP	Mouse <i>in vivo</i>	Leeper <i>et al.</i> (2009)
	↑HR and cardiac contractility	Rat <i>in vivo</i> (i.v.)	Tatemoto <i>et al.</i> (2001)
		Rat Langendorff	Szokodi <i>et al.</i> (2002)
		Rat <i>in vivo</i> (trabeculae)	Dai <i>et al.</i> (2006)
		Rat <i>in vivo</i> (coronary ligation)	Berry <i>et al.</i> (2004)
	Regulates cardiomyocyte specification and cardiac development	Zebra fish <i>in vivo</i> (gene studies)	Scott <i>et al.</i> (2007)
	↓Heart failure	Human <i>in vivo</i> (i.v.)	Japp <i>et al.</i> (2010)
	↓Ischaemic cardiomyopathy	Rat <i>in vivo</i> (i.v., coronary ligation)	Atluri <i>et al.</i> (2007)
	↑Cardioprotection	Rat <i>in vivo</i> (i.v.)	Jia <i>et al.</i> (2006)
		Rat/mouse <i>in vivo/vitro</i>	Simpkin <i>et al.</i> (2007)
Omentin	Maintain cardiac function in pressure overload and aging	Mouse <i>in vivo</i>	Kuba <i>et al.</i> (2007)
	↑Endothelium-dependent vasodilation	Rat <i>ex vivo</i>	Yamawaki <i>et al.</i> (2010)
	↓Vascular inflammation	Human <i>in vitro</i> (EC)	Yamawaki <i>et al.</i> (2011)
	↓EC migration and angiogenesis	Human <i>in vitro</i> (EC)	Tan <i>et al.</i> (2010)

Table 1 Continued

Adipocytokine	Action	Experimental models	References
Chemerin	↑ EC angiogenesis and cell survival pathways Associated with arterial stiffness ↑ ET-1- and PE-induced contractility ↓ Vascular inflammation	Human <i>in vitro</i> (EC) Human plasma Rat <i>ex vivo</i> Human <i>in vitro</i> (EC)	Kaur <i>et al.</i> (2010) Yoo <i>et al.</i> (2012) Lobato <i>et al.</i> (2012) Yamawaki <i>et al.</i> (2012)

AAA, abdominal aortic aneurysm; BP, blood pressure; EC, endothelial cell; ET-1, endothelin-1; HR, heart rate; MABP, mean arterial blood pressure; PE, phenylephrine; SMC, smooth muscle cell; VSMC, vascular smooth muscle cell.

in normal physiological conditions. Adiponectin regulates the enzyme crucial for the production of NO-eNOS, and does so via the PI3K and AMPK pathways (Chen *et al.* 2003, 2006), and reduces vascular smooth muscle cell (VSMC) proliferation (Arita *et al.* 2002). Adiponectin-deficient mice produce less NO whereas adiponectin administration increases NO production in human aortic ECs (Ouchi *et al.* 2003, Ouedraogo *et al.* 2007). It is not only the decrease in adiponectin that may regulate NO production; knock-down of AdipoR1 or AdipoR2 results in reduced NO production and eNOS phosphorylation after adiponectin treatment in human umbilical vein ECs (Cheng *et al.* 2007). Hence, the dysregulation in adiponectin production may be an important factor in endothelial dysfunction, NO decrease and CVD.

It has also been reported that decreased levels of adiponectin are associated with hypertension through various mechanisms including the renin angiotensin system and sympathetic nervous system hyperactivity, endothelial dysfunction and renal pressure natriuresis impairment (Hall 2003). Hypoadiponectinaemia appears to exacerbate aortic stiffness in primary hypertension subjects (Tsioufis *et al.* 2007). Therefore, one would expect hypoadiponectinaemia may be an important link to obesity-related hypertension; however, it appears that hypoadiponectinaemia results in hypertension in lean subjects, independent of risk factors (Chow *et al.* 2007). Animal studies have suggested that adiponectin deficiency is linked to myocardial damage, heart failure and cardiac hypertrophy (Shibata *et al.* 2004, Kadowaki & Yamauchi 2005, Karmazyn *et al.* 2008).

Adiponectin may also play a role in cardiac remodeling in pathology by limiting the extent of myocardial hypertrophy (Ouchi *et al.* 2006). The adipokine also protects against myocardial I/R injury via activation of COX-2 and AMPK (Ouchi *et al.* 2006) and TNF $\alpha$  suppression (Shibata *et al.* 2005). Studies have also shown that adiponectin controlled eNOS and cytokine-inducible nitric oxide synthase (iNOS) regulation of NO

production in adiponectin knockout mice subjected to I/R: phosphorylation of eNOS was decreased and iNOS increased compared with wild-type mice (Tao *et al.* 2007). This would possibly lead one to conclude that in normal physiology, eNOS increases NO production due to adiponectin acting protectively. However, in pathology, iNOS activation is inhibited by adiponectin resulting in decreased overproduction of NO, possibly resulting in increased cardiac injury. Post-myocardial infarction (MI) protection by adiponectin against the development of systolic dysfunction has been demonstrated in mice (Shibata *et al.* 2007). In humans, plasma adiponectin levels appear to be inversely related to insulin resistance and the severity of coronary artery disease (Cesari *et al.* 2006). Interestingly, increased plasma adiponectin correlates with a reduced risk of MI in men (Pischon *et al.* 2004) and a lower risk of coronary heart disease in diabetics (Schulze *et al.* 2005). Oddly, adiponectin levels appear to decrease post-MI (Kojima *et al.* 2003). This would appear counterintuitive given that this could possibly spark a vicious cycle increasing inflammation, cardiovascular damage and reducing any cardioprotective effects of the low levels of adiponectin.

Hence, adiponectin is termed a 'good' adipokine due to its anti-inflammatory, anti-atherogenic, anti-diabetic and cardioprotective effects and promotion of good endothelial function. It offers a reduced risk of coronary artery disease and post-MI protection. It promotes angiogenesis and reduces insulin resistance. There are also therapeutic implications with the up-regulation of adiponectin and/or its receptors to effectuate its positive actions.

## Leptin

This was the first adipokine to be characterised – a 16 kDa peptide hormone encoded by the *ob* gene and mainly produced by WAT (Zhang *et al.* 1994) regulated by energy level, food intake, several hormones and various inflammatory mediators. Leptin provides the functional



link between the immune system and energy homeostasis (Lago *et al.* 2007). *db/db* mice lack leptin receptors and suffer from thymus atrophy; *ob/ob* mice lack leptin and are immunodeficient (Kimura *et al.* 1998). Hence, leptin must play a role in immunity. This may explain why the murine immune system is depressed by reduced food intake and acute starvation, both of which result in low leptin levels, and why this depression is reverted by administration of exogenous leptin (Howard *et al.* 1999). Leptin acts centrally on the hypothalamus to reduce food intake and increase energy utilisation and its levels correlate directly with the mass of WAT (Beltowski 2006a). In the obese, there are high concentrations of leptin – directly due to increased adipose tissue mass. This paradox of raised levels of this satiety molecule in obesity may be explained in part by the resistance of leptin via an increase in levels of suppressor of cytokine signalling 3 (SOCS3) – an inhibitor of leptin signalling (Enriori *et al.* 2006).

Leptin acts on target cells through plasma membrane receptors that include at least six isoforms, Ob-Ra through Ob-Rf (Ob-Rb the predominant). The actions of leptin are mediated via Ob-R modulation of the JAK/STAT (Zabeau *et al.* 2003) and AMPK pathways (Minokoshi *et al.* 2002) and inhibited by cytokine signalling 3 receptors (SOCS3; Ren 2004, Sahu 2004, Fruhbeck 2006). In addition to these pathways, leptin also mediates its actions via PI3–Akt and MAPK pathways (Ren 2004, Fruhbeck 2006). These pathways are involved in the reperfusion injury salvation kinase (RISK) pathway, protecting the myocardium against I/R injury via mechanical and chemical pathways (Hausenloy & Yellon 2006, 2009, Yellon & Hausenloy 2007). Leptin and its receptors have been shown to be present in the cardiovascular system (Beltowski 2006a).

Hyperleptinaemia in the general population is associated with atherosclerosis, hypertension and MetS. Leptin plays an important role in the early stages of atherosclerosis development by initiating leukocyte and macrophage recruitment to the endothelial wall. This is achieved by the induction of mitochondrial superoxide production and expression of MCP-1 in ECs (Yamagishi *et al.* 2001). Interestingly, animal *in vivo* studies have shown that *db/db* (leptin resistant) and *ob/ob* are resistant to atherosclerosis (Beltowski 2006a), supporting a pathological role of leptin in atherosclerosis. Furthermore, increased leptin serum concentrations in humans are also associated with an increased risk of MI and stroke independent of obesity status and cardiovascular risk factors (Sierra-Johnson *et al.* 2007). This may be in part explained by the fact that increased leptin also leads to increased insulin resistance,

haemostasis imbalance and vascular inflammation (Wannamethee *et al.* 2007).

Leptin has been shown to up-regulate various mediators of vascular inflammation like TNF $\alpha$ , IL2, IL6, MCP-1, ROS, Th1-type cytokines from ECs and peripheral blood mononuclear cells (Bouloumie *et al.* 1999). Clinical studies have shown a positive correlation between leptin and PAI-1, von Willebrand factor, tissue plasminogen activator (tPA), plasma fibrinogen levels and an inverse relationship with protein C and tissue factor pathway inhibitor. These findings clearly demonstrate a strong link with circulating leptin and increased platelet activity observed in the MetS. With respect to CVD, leptin also appears to have a variety of pro-atherogenic functions. It stimulates the hypertrophy and proliferation of VSMCs and their production of metalloproteinase 2. In addition, leptin promotes the production of proliferative and pro-fibrinolytic cytokines, it increases platelet aggregation and enhances the secretion of pro-atherogenic lipoprotein lipase by cultured human and rodent macrophages (Beltowski 2006a) causing endothelial dysfunction by inducing oxidative stress (Beltowski 2006b). Another pro-atherogenic action of leptin is its ability to induce CRP expression in coronary artery ECs (Singh *et al.* 2007). Through its inflammatory and pro-atherogenic properties, leptin plays an important pro-inflammatory role in CVD.

Indeed, leptin provides a functional link between obesity and CVD. Leptin levels rise exponentially with increasing body fat. The widespread leptin increases oxidative stress in ECs, promotes smooth muscle cell proliferation and migration and vascular calcification. The link between fat mass and atherogenesis is confirmed by the findings in the obese, leptin-deficient *ob/ob* mouse as described earlier. A second proposition for the link between vascular dysfunction and obesity lies in the fact that CRP levels are elevated in the obese and correlate with increased risk of CVD via inflammation.

Many studies have shown a positive association between leptin concentration and blood pressure, possibly suggesting that leptin induces hypertension (Beltowski 2006b). Somewhat conversely, leptin appears to be a potent vasodilator in those with coronary artery disease (Momin *et al.* 2006). Moreover, in rodents, leptin has been demonstrated to phosphorylate eNOS leading to NO release (Rodriguez *et al.* 2007). Intra-arterial administration of leptin showed a similar vasoactive response independent of NO in humans (Matsuda *et al.* 2003), including a vasorelaxing effect of leptin on smooth muscle cells (Momin *et al.* 2006). Hence, acute hyperleptinaemia induces vasodilatory effects and seemingly contradicts the

coexisting hypertension and increased leptin levels in obesity. A plausible explanation could be attributed to the acute and chronic effects of leptin on the vasculature. Chronic i.v. infusion of leptin increases heart rate and mean arterial blood pressure (MABP). This is achieved by sympathetic nervous system activation and increased release of catecholamines (Shek *et al.* 1998, Satoh *et al.* 1999, Shirasaka *et al.* 2003). Importantly, hyperleptinaemia-induced endothelial dysfunction may play a crucial role in the differential actions of leptin. Leptin induces oxidative stress by increasing the formation of ROS, a key mediator of endothelial dysfunction (Bouloumie *et al.* 1999). The generated ROS reduces the bioavailability of NO in ECs and VSMCs by inactivating NO or eNOS potentially leading to endothelial dysfunction (Hare & Stamler 2005).

The heart produces leptin itself, suggesting that it may act locally to mediate physiological effects (Purdham *et al.* 2004, Karmazyn *et al.* 2008). The primary cardiac physiological response to leptin is a reduction in cardiac output. Leptin is a negative inotrope (mediated by NO) and its effects are primarily in cardiomyocytes (Nickola *et al.* 2000). Leptin regulates cardiac contractility (Dong *et al.* 2006), metabolism (Palanivel *et al.* 2006), cell size as well as production of extracellular matrix substances (Madani *et al.* 2006) in cardiomyocytes.

Aside from the damaging effects leptin plays on the cardiovascular system, there also appear to be beneficial actions such as reducing cardiac lipotoxicity (Lee *et al.* 2004). Lipotoxicity features apoptosis induced by fatty acids and is associated with leptin resistance or deficiency (Unger 2002). Leptin also causes hypertrophy of rat cardiomyocytes via activation of p44/42 MAPK and p38 MAPK (Rajapurohitam *et al.* 2003). Cardiomyocyte proliferation is prevented by inhibitors of PI3K-Akt and p44/42 MAPK signalling (Tajmir *et al.* 2004). Factors that activate these pathways are growth promoting and protect against I/R injury. In a murine model, leptin (at levels normally found in obese patients) reduces infarct size via these signalling pathways and P38 MAPK (Smith *et al.* 2006a). Hence, leptin may act (cardioprotectively) in an autocrine manner to protect the heart against I/R injury feeding back on the myocardium to limit damage and regulate heart activity. Leptin delays mitochondrial permeability transition pore (MPTP) opening (possibly determining protection against I/R injury) (Halestrap *et al.* 2004). Leptin also protects cardiomyocytes from hypoxia-induced damage (Erkasap *et al.* 2006). JAK/STAT signalling as well as activation of the RISK pathway are responsible

for leptin-induced protection against I/R injury (Smith *et al.* 2010).

The cardioprotective effect of leptin against ischaemic injury lends weight to the clinical phenomenon of the 'obesity paradox'. This phenomenon manifests itself in the unexpected reduction of mortality and morbidity from CVD in those with elevated BMI (Karmazyn *et al.* 2008).

Leptin then does not have a particularly good cardiovascular profile. In fact, its beneficial effects are limited to reducing infarct size, protecting against I/R injury and decreasing hypoxia-induced damage in cardiomyocytes. With respect to CVD, it could be considered a 'bad' adipokine given that it promotes insulin resistance, high blood pressure, atherosclerosis, MI risk, vascular inflammation, VSMC hypertrophy and proliferation, oxidative stress and endothelial dysfunction.

## Resistin

Resistin, also known as found in inflammatory zone 3 (FIZZ3) and adipocyte-secreted factor (ADSF), is a 12.5 kDa peptide (Steppan *et al.* 2001, Adeghate 2004) that circulates in the plasma at concentrations of 2.5–21.5 ng/ml (Silha *et al.* 2003, Weikert *et al.* 2008); its receptors are yet to be identified. Resistin over-expression is associated with insulin resistance and dyslipidaemia (Silha *et al.* 2003, Rajala *et al.* 2004, Sato *et al.* 2005). Resistin levels are increased in obesity (Kusminski *et al.* 2005), and it inhibits cellular glucose uptake (Graveleau *et al.* 2005).

There is a degree of crosstalk between resistin and other adipokines. There appears to be a direct reciprocal effect between resistin and adiponectin with respect to the inflammation of vascular ECs. Resistin induces the expression of adhesion molecules vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1); adiponectin inhibits resistin's actions (Kawanami *et al.* 2004). There is a functional link between leptin and resistin: leptin administration suppresses resistin's mRNA expression and protein levels in *ob/ob* mice along with reductions in glucose and insulin (Rajala *et al.* 2004). Other studies confirm that certain actions of resistin are dependent on crosstalk with leptin (presence/absence of) with respect to glucose metabolism and energy regulation (Qi *et al.* 2006). High plasma levels of resistin correlate with pro-atherogenic inflammatory markers (Kunnari *et al.* 2006), increased cardiovascular risk, unstable angina, poor prognosis in coronary artery disease and MetS (Lubos *et al.* 2007, Norata *et al.* 2007).

The pro-inflammatory role of resistin in atherosclerosis is supported by its role in human vascular ECs.

It induces endothelin-1 (ET-1) release, MCP-1 and VCAM-1. This pro-inflammatory role is also supported by its presence in sclerotic lesions of animal models of atherosclerosis whereby resistin levels are proportional to the severity of the sclerotic lesion (Lago *et al.* 2007). In further support of its inflammatory profile, resistin has been shown to increase transcriptional events, leading to an increased expression of several pro-inflammatory cytokines including (but not limited to) IL1, IL6, IL12 and TNF $\alpha$  in an NF- $\kappa$ B-mediated fashion (Milan *et al.* 2002, Silswal *et al.* 2005). Accordingly, it is expected that if resistin does indeed serve as a functional link between obesity and type 2 diabetes mellitus while at the same time contributing to the inflammatory response, then proportional increases in chronic inflammation in association with obesity and insulin resistance should be observed. In fact, recent data have shown that this possibility is indeed the case by demonstrating positive correlations between obesity, insulin resistance and chronic inflammation, which is believed to be orchestrated in part by resistin signalling (Yokota *et al.* 2000, Wulster-Radcliffe *et al.* 2004).

Atheroma macrophage secretion of resistin has been linked to atherogenesis in humans (Jung *et al.* 2006). Of note, plasma resistin is associated with an elevated risk in the 5-year mortality of patients with atherothrombotic strokes (Efstathiou *et al.* 2007). Plasma resistin is elevated in female patients with coronary heart disease (Pischon *et al.* 2005) and has been proposed as a diagnostic marker of MI and future cardiovascular death (Lubos *et al.* 2007). However, despite the apparent predictive power of resistin, these studies do not demonstrate a cause and effect relationship.

Resistin promotes the proliferation of human aortic smooth muscle cells via PI3-Akt and p44/42 signalling (Calabro *et al.* 2004). In addition, resistin also increases the migration and proliferation of ECs derived from human coronary arteries via the stimulation of p38 and p44/42 signalling (Mu *et al.* 2006). Furthermore, in isolated coronary artery rings, resistin can induce endothelial dysfunction (Dick *et al.* 2006). Resistin has also been shown to negatively affect myocardial protection. It has also been demonstrated to have a detrimental effect on I/R injury in isolated perfused rat hearts (Rothwell *et al.* 2006) – although this effect is disputed by other studies (Gao *et al.* 2007). Resistin counteracts the beneficial effects of insulin, a cardioprotective agent (Hausenloy & Yellon 2009). Rothwell *et al.* (2006) found resistin to worsen cardiac I/R injury in rat hearts preconditioned with resistin. However, Gao *et al.* (2007) in a more detailed study using murine hearts (where resistin was

administered before ischaemia) revealed protection against I/R injury via PI3K and PKC activation. Resistin neither altered contractile function in a human atrial trabeculae model nor influenced MPTP operation in murine cardiomyocytes (Smith *et al.* 2011). Further investigation is required to clarify the cardioprotective effects of resistin with respect to I/R injury.

Resistin, like leptin, does not lend itself especially well to benefiting CVD. High levels are associated with insulin resistance, increased cardiovascular risk, unstable angina, endothelial dysfunction (via promotion of adhesion molecules, endothelial migration and proliferation), increased pro-atherogenic inflammatory marker, VSMC proliferation and poor prognosis in coronary artery disease.

## Visfatin

This 52 kDa adipokine, predominantly produced in the visceral fat of humans and mice, was discovered by Fukuhara *et al.* (2005) and circulating levels were reported to be higher in obesity. Interestingly, visfatin was found to be identical to the protein initially recognised as pre-B-cell colony-enhancing factor (PBEF; Samal *et al.* 1994); PBEF was first isolated from an activated peripheral blood lymphocyte cDNA library and is involved in the maturation of B-cell precursors. It was subsequently identified as one of the genes up-regulated by distending the human foetal membranes *in vitro* (Ognjanovic *et al.* 2001), and since then in bone marrow, skeletal muscle, liver and lymphocytes and was subsequently termed nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme in nicotinamide adenine dinucleotide (NAD) synthesis (Hausenloy 2009).

Visfatin was suggested to be the missing link between diabetes and intra-abdominal obesity (Sethi & Vidal-Puig 2005); however, data in another study disputed this (Kloting & Kloting 2005). Another team (Berndt *et al.* 2005) was not able to confirm the correlation between visfatin levels and BMI, fasting glucose, fasting insulin and visfatin mRNA levels in visceral adipose tissue of non-diabetics. On the contrary, other authors have found increased levels of visfatin in patients with type 2 diabetes (Chen *et al.* 2006) and type 1 diabetes mellitus (Haider *et al.* 2006). Also there appears to be a significant association between plasma insulin levels and two gene variants of visfatin (Bailey *et al.* 2006). More recently, our team has shown visfatin to increase insulin secretion and significantly insulin receptor phosphorylation and intracellular signalling in the pancreas, suggesting that



visfatin's actions may be insulin receptor mediated (Brown *et al.* 2010).

Regarding lipid metabolism and atherosclerosis, there appears to be a positive correlation between visfatin and HLD cholesterol – a potential beneficial effect of the adipokine (Smith *et al.* 2006b). Visfatin expression is increased by plaque macrophages in patients with unstable carotid and coronary atherosclerosis, and given the localisation of visfatin in regions of lipid laden macrophages, it has been suggested that visfatin plays a role in inflammation and plaque destabilisation (Dahl *et al.* 2007).

Visfatin appears to mediate vascular endothelial inflammation by inducing the expression of adhesion molecules (VCAM-1 and ICAM-1) via oxidative stress-dependent NF- $\kappa$ B activation. Visfatin also seems to mediate inflammatory responses in monocytes by induction of pro-inflammatory cytokines IL1B, IL6 and TNF $\alpha$ . However, higher concentrations of visfatin augment the expression of anti-inflammatory cytokines, e.g. IL10 (Moschen *et al.* 2007). Plasma levels of visfatin are negatively correlated with vascular endothelial function (Takebayashi *et al.* 2007). Moreover, visfatin has been demonstrated to stimulate endothelial proliferation and capillary tube formation in human ECs via increased VEGF and MMP-2/9 production via PI3–Akt, p44/42 and ERK 1/2 signalling (Adya *et al.* 2008). Visfatin also stimulates VSMC growth via activation of ERK1/2 and p38 signalling (Wang *et al.* 2009). Paradoxically, visfatin has been reported to reduce apoptosis in human VSMCs (van der Veer *et al.* 2005) and human umbilical vein endothelial cells (HUVECS; Adya *et al.* 2008). One study examined the role of visfatin on contractility of isolated rat blood vessels. They found that pre-treatment with visfatin inhibited noradrenaline-induced contractility in the rat aorta (Yamawaki *et al.* 2009). They also discovered that visfatin directly induces an endothelium-dependent vasorelaxation (mediated by endothelium-produced NO) in rat aorta and mesenteric arteries. NO production induced by visfatin was determined to be dependent on the activation of PI3K/Akt/eNOS pathways but not insulin receptors (Yamawaki *et al.* 2009).

Lim *et al.* (2008) have demonstrated direct cardioprotective effects of visfatin in an *in vivo* I/R model with a 50% reduction in the size of the infarct following a single i.v. bolus dose of visfatin. They found this myocardial protection to be dependent on PI3K and MEK1/2 activation, a finding reported by others (Hausenloy & Yellon 2006, 2009, Yellon & Hausenloy 2007). Hausenloy & Yellon reported that visfatin reduced cell death

substantially, when administered at reoxygenation to murine ventricular cardiomyocytes subjected to hypoxia reoxygenation. Following on, Lim *et al.* (2008) demonstrated that visfatin delays MPTP opening induced by oxidative stress. From this, it can be understood that visfatin has a direct cardioprotective effect via cellular mechanisms involving the activation of components of the RISK pathway, which terminates on MPTP. Alternatively, visfatin may also involve the hypoxia-inducible factor (HIF)-1 $\alpha$  pathway. Indeed, Kido *et al.* (2005) suggest that HIF-1 $\alpha$  (which regulates the transcription of hypoxia-activated genes) may play a crucial role in cardioprotection. Interestingly, it was discovered that hypoxia significantly increased visfatin expression in both MCF7 breast cancer cells (Bae *et al.* 2006) and 3T3-L1 adipocytes (Segawa *et al.* 2006) and that this involved activation of the HIF-1 $\alpha$  pathway. These findings could suggest that myocardial ischaemia (as well as HIF-1 $\alpha$  induction) could up-regulate visfatin expression.

Visfatin appears to be a mixed bag regarding its role in CVD. Its beneficial effects include reducing apoptosis in VSMCs, cardiac contractility and infarct size. It delays MPTP opening in I/R models and reduces hypoxia-induced damage. However, high visfatin levels are associated with endothelial inflammation and plaque destabilisation, increased oxidative stress and pro-inflammatory cytokine levels. Its levels negatively correlate with VSMC growth, EC function and proliferation. Overall, it appears to contribute to CVD more than alleviate it.

## Apelin

Apelin is a peptide produced and secreted by adipocytes, stromal vascular fraction and cardiovascular tissues (Lee *et al.* 2006). In serum, its levels range from 0.2 to 1.5 ng/ml (Heinonen *et al.* 2005, Soriguer *et al.* 2009). The gene encoding the apelin receptor (APJ) shares the greatest sequence identity with the angiotensin (AT<sub>1</sub>) receptor (Lee *et al.* 2006). The apelin G protein-coupled angiotensin receptor-like 1b, APJ, was discovered before its ligand (O'Dowd *et al.* 1993). In humans, apelin seems to function as a paracrine hormone (Lee *et al.* 2006) and its levels are significantly increased by insulin in obese patients. Apelin and APJ expression are found in many tissues where they play roles in satiety, immune function and fluid balance (Habata *et al.* 1999, Lee *et al.* 2000, Katugampola *et al.* 2001, Taheri *et al.* 2002).

Obesity linked with diabetes is a major contributor to CVD. There is a positive correlation between plasma apelin levels and BMI (Heinonen *et al.* 2005). Apelin

administration has been found to decrease body adiposity and serum levels of insulin and triglycerides in obese mice fed a high-fat diet. Apelin increases the serum adiponectin level and decreases that of leptin. Apelin plays a role regulating insulin resistance by influencing serum adiponectin levels, energy expenditure and expression of uncoupling proteins in brown adipose tissue in mice (Higuchi *et al.* 2007).

Plasma levels of apelin are reduced in subjects with dyslipidaemia (Tasci *et al.* 2009), and therapeutic reduction in the atherogenic LDL (via statins or lifestyle changes) in patients with isolated hypercholesterolaemia leads to a rise in circulating apelin (Tasci *et al.* 2009). In hyperlipidaemic animal models, apelin appears to antagonise angiotensin II-enhanced atherogenesis (Chun *et al.* 2008). It has also been reported that apelin prevents aortic aneurysm formation in a murine model by limiting macrophage inflammation – possibly via chemokine activation and inhibition of inflammatory cytokines (Leeper *et al.* 2009).

Apelin and APJ have been discovered in ECs of blood vessels (Katugampola *et al.* 2001). As such, apelin (apelin-12, -13 and -36) produces endothelium-dependent vasodilatation (reduction in mean arterial pressure, MAP) *in vivo* by increased NO production via eNOS phosphorylation in the femoral arteries of Wistar rats. Apelin-12 (preproapelin 66–77) is most effective in reducing MAP. Administration of apelin-12 causes no change in blood pressure if pre-treated with NO synthase inhibitor (L-NAME), hence supporting the role of NO in apelin's vascular actions (Tatemoto *et al.* 2001). Research using HUVECS and Chinese hamster ovary cells suggests that apelin activates various cell signalling pathways including PI3-K/Akt and p44/42 and p70S6 kinase. The phosphorylation of these three kinases is mediated via PKC (Masri *et al.* 2002, 2004). Additionally, the apelin system is expressed in the heart: apelin is found in endocardial EC whereas APJs are located in cardiomyocytes, suggesting that endothelial apelin acts on cardiomyocyte APJ to increase cardiac contractility and heart rate. Thus, apelin is a potent inotrope and chronotrope (Szokodi *et al.* 2002, Klein & Davenport 2004, 2005). Furthermore, it has been proposed that apelin may play an important role in heart development and cardiomyocyte specification (Scott *et al.* 2007).

Decreased plasma levels of apelin have been observed in patients with lone atrial fibrillation (Ellinor *et al.* 2006) and chronic heart failure (Chong *et al.* 2006) in which cardiac resynchronisation therapy helps to improve them (Francia *et al.* 2007). Hypoxia up-regulates apelin synthesis

in cardiovascular tissues (Ronkainen *et al.* 2007) as does ischaemic cardiomyopathy in rats (Atluri *et al.* 2007). This may occur as a compensatory mechanism with the failing heart attempting to maintain normal function by increasing ventricular apelin. Physical exercise in spontaneously hypertensive rats also up-regulates apelin production in cardiovascular tissues (Zhang *et al.* 2006). Animal models of heart failure demonstrate cardiac apelin to be down-regulated by angiotensin II. This cardiac apelin is restored by treatment with angiotensin type 1 blocker (Iwanaga *et al.* 2006). However, myocardial expression of apelin is increased in ischaemic heart failure (Atluri *et al.* 2007). So myocardial expression of apelin may be decreased or increased but plasma levels of apelin are decreased in patients with chronic heart failure (Foldes *et al.* 2003, Chong *et al.* 2006). Contributing to the complexity of the picture, myocardial unloading in heart failure patients (using a left ventricular assist device) results in up-regulation of left ventricular apelin expression (Chen *et al.* 2003). Beyond these observations and hypotheses, the cardiovascular role of apelin is not entirely understood and further study is required to clarify this.

Apelin exerts positive inotropic effects in normal and failing rat hearts (Berry *et al.* 2004) and in isolated cardiomyocytes (Farkasfalvi *et al.* 2007). These effects are mediated via complex cell signalling mechanisms, involving multiple kinases including PKC and Na-H exchange activity (Szokodi *et al.* 2002). It was suggested that apelin increases myofilament sensitivity to calcium, affecting a positive inotropic response (Szokodi *et al.* 2002). However, a more recent study confirmed that apelin increases contractility in failing rat heart muscle and demonstrated that this was due to increased calcium ion transients rather than changes in myofilament calcium sensitivity (Dai *et al.* 2006).

Apelin has also been shown to exert cardioprotective effects, demonstrated against both I/R injury and isoproterenol-induced cardiotoxicity (Jia *et al.* 2006, Klein & Baxter 2008). Administration of pharmacological doses of apelin (1 µM) reduced infarct size in both *in vitro* and *in vivo* murine I/R models, the *in vitro* effects being mediated via the RISK pathway (Simpkin *et al.* 2007). It has been reported that apelin enhanced not only myocardial Akt (and p44/42) phosphorylation but also Akt activity (Smith *et al.* 2007) and crucially delayed MPTP opening (a factor that determines cardioprotection) in rat cardiomyocytes (Simpkin *et al.* 2007). The mechanisms for these cardioprotective effects of apelin are not completely understood. Pharmacological inhibition of PI3/Akt or P70S6 kinase was found to produce no effect on

apelin-mediated cardioprotection (Kleinz & Baxter 2008). Further evidence for apelin's role in myocardial injury was provided by a report whereby plasma apelin is reduced in humans following MI and remains depressed for 24 weeks (Weir *et al.* 2009). In animal studies, apelin knockout mice display increased cardiac dysfunction and increased myocardial remodelling in aging and in response to pressure overload, suggesting an important role for endogenous apelin in the regulation of cardiac function in response to insult (Kuba *et al.* 2007).

Apelin could be considered a 'good' adipokine when considering CVD. It reduces atherogenesis, macrophage inflammation, MAP, cardiomyocyte contractility, atrial fibrillation and heart failure. It is cardioprotective given that it reduces infarct size in I/R models, delaying MPTP opening. Knockout studies demonstrate that the absence of apelin increases cardiac dysfunction. However, its role in ischaemic heart disease and heart failure is not fully understood. Its myocardial expression may differ from plasma levels, the conclusions from which are as yet unclear. Further research is required in delineating its role in the myocardium in different pathologies.

## Omentin

Omentin/intelectin, discovered in 2005, is a novel adipokine, a secretory protein of 313 amino acids (Schaffler *et al.* 2005, Yang *et al.* 2006). It is codified by two genes (1 and 2) with omentin 1 predominating as the circulating form of the adipokine (de Souza Batista *et al.* 2007). It stimulates insulin-mediated glucose transport in human adipocytes and triggers Akt signalling (Yang *et al.* 2006). The expression of omentin is greater in visceral than subcutaneous adipose tissue (Yang *et al.* 2006). Omentin 1 adipose tissue gene expression and plasma levels are decreased in obesity and correlate negatively with BMI, waist circumference and insulin resistance and positively with HDL and plasma adiponectin (de Souza Batista *et al.* 2007). These are markers of MetS and so omentin has implications on CVD.

In one study, pre-treatment with omentin in isolated rat blood vessels inhibited noradrenaline-induced concentration-dependent contractions in rat aorta. It was also found that omentin directly induced endothelium-dependent vasodilation (in the aorta and mesenteric artery), mediated via endothelium-produced NO. This NO production induced by omentin was found to be dependent on eNOS activation but not on the activation of PI3K/Akt and tyrosine kinase (Yamawaki *et al.* 2010). In another study by the same team, the effects of omentin on

TNF $\alpha$  induced inflammatory responses in HUVECs were studied. The investigators observed that omentin could cause NO production via 5'-AMPK-mediated eNOS phosphorylation and that omentin-derived NO could inhibit TNF $\alpha$  mediated COX-2 induction via suppression of c-Jun N-terminal kinase (JNK) activation. Furthermore, AMPK activated by omentin could directly inhibit p38-mediated e-selectin induction and subsequent lymphocyte adhesion to vascular ECs (Yamawaki *et al.* 2011). Taken together, these results could partly explain the relationships between obesity and CVD such as hypertension and atherosclerosis respectively.

It has also been reported that 12 weeks of aerobic exercise reduced CVD risk in obese subjects with a corresponding elevation of plasma omentin (Saremi *et al.* 2010). Omentin could also reduce endothelial dysfunction (important in atherosclerosis development) by enhancing Akt signalling, thereby modulating EC eNOS (Montagnani *et al.* 2002, Sacks & Fain 2007). Our team found that omentin decreased *in vitro* migration and angiogenesis in human ECs induced by human sera, CRP and VEGF. This study also demonstrated that omentin decreased NF- $\kappa$ B activation in human ECs induced by human sera, CRP and TNF $\alpha$ . Furthermore, it was found that omentin decreased human sera-induced Akt activation in human ECs (Tan *et al.* 2010). Omentin mRNA is predominantly expressed in human epicardial and omental adipose tissue rather than subcutaneous and internal mammary artery periadventitial adipose tissue reserves. Epicardial adipose tissue shares a common embryological origin with omental and mesenteric adipose tissue (Fain *et al.* 2008). Omentin, like other periadventitial epicardial adipokines, could play an important role in CVD pathogenesis, particularly in coronary atherosclerosis, as the absence of a fibrous fascial layer allows for more diffusion of adipokines and free fatty acids between epicardial adipose tissue and the underlying vessel wall in addition to the myocardium.

Thus, omentin appears to be a 'protective adipokine' with respect to CVD, given that it induces vasodilatation and inhibits EC migration, vascular inflammation and angiogenesis. As well as reducing endothelial dysfunction, it is also anti-inflammatory. This is a relatively novel adipokine and so one may expect much more of its role in CVD to be illuminated in the near future.

## Chemerin

Chemerin, also known as tazarotene-induced gene 2 and retinoic acid receptor responder 2, is an 18 kDa protein that was originally identified as the protein produced by the

gene that was up-regulated by the RAR b/c-selective anti-psoriatic synthetic retinoid tazarotene (Nagpal *et al.* 1997). This is a relatively novel adipokine, 131–137 amino acids long whose human plasma levels are significantly positively associated with key factors of MetS including BMI, blood pressure and circulating triglycerides (Bozaoglu *et al.* 2007). Blood chemerin concentrations have been shown to be increased in morbidly obese patients (Sell *et al.* 2010). Mice fed a high-fat diet were demonstrated to have enhanced chemerin expression in adipocytes (Roh *et al.* 2007). Chemerin or knockout of its receptor has been found to impair differentiation of 3T3-L1 cells into adipocytes, alter metabolic functions in mature adipocytes and reduce expression of adipocyte genes involved in lipid and glucose regulation (Goralski *et al.* 2007). In addition, chemerin augments insulin-stimulated glucose uptake in fat cells (Takahashi *et al.* 2008).

Chemerin was initially known to be a chemo-attractant for immune cells such as dendritic cells and macrophages (Wittamer *et al.* 2003). Chemerin mediates its effects through a specific receptor: chemokine-like receptor 1 (CMKLR1). This is a  $G_i$  protein-coupled receptor whose expression is manifested in adipocytes, dendritic cells, macrophages and the cardiovascular system (Samson *et al.* 1998, Wittamer *et al.* 2003, Zabel *et al.* 2005, Bozaoglu *et al.* 2007, Roh *et al.* 2007, Takahashi *et al.* 2008). Chemerin also binds to two other orphan G protein-coupled receptors: GPR1 and CCRL2, though little is known about their detailed function (Zabel *et al.* 2006, Cash *et al.* 2008).

More recently, our laboratory has discovered that vascular ECs express CMKLR1 and that pro-inflammatory cytokines (such as IL6, IL1B and TNF $\alpha$ ) up-regulate its expression. We also found that chemerin activates PI3K/Akt and MAPK pathways – the main angiogenic and cell survival cascades. We produced the first evidence of chemerin inducing endothelial angiogenesis and MMP production and activity (Kaur *et al.* 2010). Chemerin activates ERK1 and 2 (p44/42) of the MAPK pathway upon which the angiogenic effects are dependant (Zabel *et al.* 2006, Bozaoglu *et al.* 2010).

Chemerin positively correlates with markers of inflammation but has been found to fail to predict coronary atherosclerosis (Lehrke *et al.* 2009). Another investigating team found chemerin plasma levels to be associated with arterial stiffness after adjusting for other cardiovascular risk factors (Yoo *et al.* 2012). It has also recently been ascertained that chemerin increases contractile responses to phenylephrine (PE) and ET-1 via ERK1/2 activation (Lobato *et al.* 2012).

Hence, it is likely that this adipokine plays a role in vascular EC inflammation. With respect to this, it has been observed that chemerin possibly has no effects on the basal inflammatory state in HUVECS. However, there is a possibility that it could induce NO synthesis through activation of PI3K/Akt/eNOS cellular pathways. This NO synthesised by chemerin appears to exert anti-inflammatory effects, given that it could inhibit TNF $\alpha$  mediated VCAM-1 induction and subsequent lymphocyte adhesion through suppression of the activation of NF- $\kappa$ B and p38 signalling (Yamawaki *et al.* 2012).

Like omentin, chemerin is a relatively novel adipokine and hence does not have the cardiovascular profile of others. It appears to reduce EC inflammation, promote angiogenesis and reduce adhesion to the endothelial wall. Chemerin potentiates the contractile response to PE in VSMCs and endothelium. Overall, with the information so far, it appears to be a protective adipokine.

### Perivascular adipose tissue

It is clear that adipocytes are present throughout the body. However, they also surround almost every vessel in the human body and this depot is referred to as perivascular adipose tissue (PVAT). This WAT depot provides mechanical support as well as sending chemical messengers and vasoactive mediators into the bloodstream, but importantly functioning as a paracrine organ. In brief, PVAT-derived adipokines play a role in inflammation, disrupting the normal balance of secretion and leading to vascular pathology (Yudkin *et al.* 2005). In healthy individuals, PVAT has been demonstrated to exert anti-contractile effects on neighbouring vessels, and this PVAT is less responsive to noradrenaline than naked vessels (Soltis & Cassis 1991). In addition, adventitium-derived relaxing factor (ADRF) experiments have demonstrated PVAT anti-contractility to be due to its function as a paracrine tissue rather than adipose merely obstructing vaso-constrictors (Lohn *et al.* 2002, Gao *et al.* 2005, Malinowski *et al.* 2008, Greenstein *et al.* 2009).

The adipocytes in response to vasoconstriction secrete adipokines that induce anti-contractility on the smooth muscle cells of neighbouring vessels. A number of different potassium channels appear to be involved in this process (Gao *et al.* 2005). Plasma ADRF employs these channels (found in endothelium, adipocytes and VSMCs) to induce anti-contractility – including NO release from WAT and ECs (Hughes *et al.* 2010). In hypoxia, macrophages and ROS also appear to attenuate anti-contractility in PVAT (Withers *et al.* 2011). Obesity increases PVAT and reduces



anti-contraction (Gao *et al.* 2005), although the interplay between the chronic inflammatory state of obesity and feedback to adipokines to influence contractility (amongst other things) has yet to be researched further.

PVAT inhibits VSMC contraction and stimulates VSMC proliferation by releasing protein factors (Lohn *et al.* 2002, Barandier *et al.* 2005). One study explored perivascular adipose secretion of visfatin and discovered that it is not involved in the regulation of vascular tone by PVAT. However, visfatin does play a role in PVAT-induced VSMC proliferation. Visfatin-induced VSMC proliferation is through ERK1/2 and p38 signalling pathways, rather than JNK and PI3K/Akt signalling pathways. This is achieved in part via nicotinamide mononucleotide being a key mediator for visfatin-induced VSMC proliferation (Wang *et al.* 2009). This demonstrates that PVAT has important implications in vascular biology with protective and harmful effects – dependent on the balance of adipokines. Naturally, in metabolic diseases such as diabetes and obesity, the imbalance will set off a chain of adipokine secretion producing contrasting effects on inflammation and vascular homeostasis.

Finally, as described earlier, there has been much interest in PVAT as a potential link between obesity and the development of MetS and diabetes, given the influence PVAT has on the vasculature. Although the mechanisms explaining these have not yet been elucidated, it is clear that they heavily and independently affect CVD.

## Conclusion

CVD is common in both obesity and diabetes. The metabolic interactions between these diseases have contributed to the discovery of adipokines. Inflamed adipose tissue has particular ramifications for CVD given the effects they have on cardiovascular pathophysiology as well as obesity and diabetes. Adipokines have contrasting actions on hypertension, endothelial function, cardiomyocyte actions, cardiac pathology, atherosclerosis and inflammation. Some adipokines such as adiponectin, apelin, omentin and chemerin may act to protect cardiac function and preserve normal physiology and counteract inflammation and endothelial dysfunction, but excluding adiponectin, this is not quite so clear-cut. Leptin, resistin and visfatin may contribute to atherosclerosis, inflammation and endothelial dysfunction. Again, there are exceptions whereby leptin and visfatin may act cardio-protectively in an I/R injury model for example. Apelin, for example, has both pro- and anti-inflammatory properties. Conflicting actions on insulin sensitivity and

metabolic pathways complicate the picture. Broadly speaking, adipokines may be understood to have important implications on the cardiovascular system predicting and improving the outcome following disease. Visceral fat has been recognised as an aggravating factor in diabetes, which correlates well with the role of PVAT in disease. Under normal circumstances, it is advantageous, but in pathology, the imbalance of adipokines released may wreak havoc with cardiovascular function disrupting contractility and endothelial function for example. More adipokines are being discovered and with further research, their role in CVD and their 'cause or effect' nature of certain parameters may be clarified.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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