Role of adipokines in cardiovascular disease

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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

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...
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-α (TNFα). 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 stromavascular fraction of cells (MCP-1, macrophage inflammatory protein, TNFα 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. 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, Fujikawa et al. 2006). Adiponectin, via AMPK phosphorylation, increases insulin sensitivity, fatty acid oxidation 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.
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-κB) in macrophages and monocytes. Similarly, the suppression of NF-κB 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-κB halts TNFα 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.

**Figure 1**
Adipocytokine influences on the cardiovascular system, inflammation and insulin resistance.
Table 1  Adipocytokine effects on cardiovascular pathophysiology

<table>
<thead>
<tr>
<th>Adipocytokine</th>
<th>Action</th>
<th>Experimental models</th>
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<tr>
<td></td>
<td>↓ EC monocyte adhesion</td>
<td>Human in vitro</td>
<td>Ouchi et al. (1999)</td>
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<td></td>
<td>↓ Apoptosis</td>
<td>Mouse/rabbit in vivo</td>
<td>Kobayashi et al. (2004)</td>
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<td></td>
<td>↓ VSMC proliferation</td>
<td>Human in vitro (EC)</td>
<td>Arita et al. (2002)</td>
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<td></td>
<td>↓ Systolic BP</td>
<td>Mouse in vivo</td>
<td>Ohashi et al. (2006)</td>
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<td></td>
<td>↓ Pressure overload induced cardiac hypertrophy</td>
<td>Mouse in vivo/rat ventricular myocytes</td>
<td>Shibata et al. (2004)</td>
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<td></td>
<td>↓ ET-1 induced hypertrophy</td>
<td>Rat cardiomyocytes</td>
<td>Fujioka et al. (2006)</td>
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<td></td>
<td>↓ Post-MI systolic dysfunction</td>
<td>Mouse in vivo knockout</td>
<td>Shibata et al. (2007)</td>
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<td></td>
<td>↓ Myocardial damage</td>
<td>Human cardiomyocytes</td>
<td>Takahashi et al. (2005)</td>
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<td>Leptin</td>
<td>↑ Vascular inflammation/EC dysfunction</td>
<td>Human in vitro (EC)</td>
<td>Bouloumnie et al. (1999)</td>
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<td></td>
<td>↑ VSMC migration and proliferation</td>
<td>Human in vitro (SMC)</td>
<td>Li et al. (2005)</td>
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<td></td>
<td>Hypertrophy</td>
<td>Rat cardiomyocytes</td>
<td>Tajmir et al. (2004)</td>
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<td>↑ Apoptosis</td>
<td>Mouse in vivo</td>
<td>Rajapurohitam et al. (2003)</td>
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<td></td>
<td>↑ Cardiac output</td>
<td>Rat cardiomyocytes</td>
<td>McGaffin et al. (2008)</td>
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<td>↑ MABP, HR</td>
<td>Rat cardiomyocytes</td>
<td>Eguchi et al. (2008)</td>
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<td>Resistin</td>
<td>↓ Lipotoxicity</td>
<td>Rat in vivo (i.v.)</td>
<td>Nickola et al. (2000)</td>
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<td>↑ Adhesion molecules</td>
<td>Rat in vivo (i.c.v.)</td>
<td>Shek et al. (1998)</td>
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<td></td>
<td>↑ Proatherogenic inflammatory markers</td>
<td>Rat/rabbit in vivo (i.v., i.c.v.)</td>
<td>Satoh et al. (1999)</td>
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<td></td>
<td>↑ CAD</td>
<td>Rat cardiomyocytes</td>
<td>Shirasaka et al. (2003)</td>
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<td>↑ Aortic SMC proliferation</td>
<td>Rat in vitro (SMC)</td>
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<td>↑ Bradykinin induced dilation of coronary arteries</td>
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<td>↑ Cardiac injury</td>
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<td>↑ Plaque destabilisation</td>
<td>Human plasma</td>
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<td>↑ VSMC growth</td>
<td>Human in vitro (SMC)</td>
<td>Dick et al. (2006)</td>
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<td></td>
<td>↑ Apoptosis in VSMCs and ECs</td>
<td>Human in vitro (EC)</td>
<td>Shimada et al. (2004)</td>
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<td></td>
<td>↑ EC proliferation</td>
<td>Human in vitro (EC)</td>
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<td>Apelin</td>
<td>Anti-atherogenic</td>
<td>Rat in vivo (i.v.)</td>
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<td></td>
<td>Prevent AAA formation</td>
<td>Rat in vivo (i.c.v.)</td>
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<td>↓ BP</td>
<td>Rat in vivo (SMC)</td>
<td>Dai et al. (2006)</td>
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<td></td>
<td>↑ HR and cardiac contractility</td>
<td>Rat in vivo (trabeculae)</td>
<td>Berry et al. (2004)</td>
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<td></td>
<td>Regulates cardiomyocyte specification and cardiac development</td>
<td>Rat in vivo (coronary ligation)</td>
<td>Scott et al. (2007)</td>
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<td></td>
<td>↓ Heart failure</td>
<td>Human in vivo (i.v.)</td>
<td>Japp et al. (2010)</td>
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<td></td>
<td>↓ Ischaemic cardiomyopathy</td>
<td>Human in vivo (i.v., coronary ligation)</td>
<td>Atluri et al. (2007)</td>
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<td></td>
<td>↑ Cardioprotection</td>
<td>Rat in vivo (i.v.)</td>
<td>Jia et al. (2006)</td>
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<td></td>
<td>Maintain cardiac function in pressure overload and aging</td>
<td>Rat/mouse in vivo/vitro</td>
<td>Simpkin et al. (2007)</td>
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<td>Omentin</td>
<td>↑ Endothelium-dependent vasodilation</td>
<td>Rat ex vivo</td>
<td>Yamawaki et al. (2010)</td>
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<td></td>
<td>↓ Vascular inflammation</td>
<td>Human in vitro (EC)</td>
<td>Yamawaki et al. (2011)</td>
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<td></td>
<td>↓ EC migration and angiogenesis</td>
<td>Human in vitro (EC)</td>
<td>Tan et al. (2010)</td>
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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; knockdown 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 (Tsiofis 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 TNFα 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
The link between the immune system and energy homoeostasis (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 (Eniori 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 salvage 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 TNFα, 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-fibrinotic 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 & Stampler 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 TNFα in an NF-kB-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 (Hauserlo & Yellon 2005). 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 trabecule 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 (Hauserlo 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 HDL 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-kB activation. Visfatin also seems to mediate inflammatory responses in monocytes by induction of pro-inflammatory cytokines IL1B, IL6 and TNFα. 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)-1α pathway. Indeed, Kido et al. (2005) suggest that HIF-1α (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-1α pathway. These findings could suggest that myocardial ischaemia (as well as HIF-1α 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 (AT1) receptor (Lee et al. 2006) and 3T3-L1 adipocytes (van der Veer 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. 2008).

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) \textit{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 cardiovascular 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, Kleinz & 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 myofilamental 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, Kleinz & Baxter 2008). Administration of pharmacological doses of apelin (1 μM) reduced infarct size in both \textit{in vitro} and \textit{in vivo} murine I/R models, the \textit{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 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. 2006). 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.

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 TNFα induced inflammatory responses in HUVECs were studied. The investigators observed that omentin could cause NO production via S'-AMPK-mediated eNOS phosphorylation and that omentin-derived NO could inhibit TNFα 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 (Sarem 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-κB activation in human ECs induced by human sera, CRP and TNFα. 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 peri-adventitial 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 knock-out 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 chemottractant 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, protein-coupled receptor whose expression is manifest 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 TNFα) 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 and cell survival cascades. We also found that chemerin activates PI3K/Akt and MAPK pathways – the main angiogenic expression. We also found that chemerin activates ERK1 and 2 (p44/42) of the MAPK pathway upon 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 TNFα mediated VCAM-1 induction and subsequent lymphocyte adhesion through suppression of the activation of NF-κB 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 vasoconstrictors (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 VMSCs) 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-contractility (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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