More than a simple storage organ: Adipose tissue as a source of adipokines involved in cardiovascular disease

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Summary
Overweight and obesity in many countries have developed into a serious health problem by themselves and by their impact on other pathologies such as insulin resistance, type 2 diabetes, hypertension, heart disease and cancer. The modulation of these diseases by adipose tissue-derived biomolecules, so-called adipokines, could be the key to differentiate between metabolically healthy and unhealthy obesity. This review will discuss the pathophysiological role of selected adipokines, primarily focusing on cardiovascular diseases. Furthermore, we will highlight possible therapeutic approaches, which target these biomolecules.

Keywords
Obesity, atherosclerosis, thrombosis

Introduction
The global epidemic of overweight and obesity is rapidly becoming a major public health problem in most countries by enhancing the risk for chronic diseases such as insulin resistance, type 2 diabetes, hypertension, coronary heart disease and some forms of cancer (1, 2). In 2008, an estimated 1.46 billion adults globally were overweight and 502 million adults were obese (3). Forecasts suggest that by 2030 51% of the population of the United States of America will be obese, including 11% severe obese, an increase of 33% for obesity and 130% for severe obesity (4). Cardiovascular disease (CVD) is still the leading cause of death in men and women despite longer life expectancy and a decrease in cardiovascular mortality over the last years (5). Obesity was associated with 13% of CVD deaths in 2004. Above a body mass index (BMI) of 25 kg/m² each 5-kg/m²-higher BMI is associated with approximately 30% higher all-cause mortality (5). Calculations based on National Health and Nutrition Examination Survey (NHANES) data suggest that the gained life expectancy by smoking cessation is abrogated by the loss of life expectancy related to obesity (5). Furthermore, long-term follow-ups after gastric bypass surgery revealed a 40% reduction of death from any cause in the surgery group compared to obese control subjects and a decrease of cause-specific mortality by 59% for coronary artery disease, 92% for diabetes and 60% for cancer (6).

Interestingly, in a large study of 22,203 adults initially free of CVD, metabolically healthy obese individuals were not at an increased risk of CVD and all-cause mortality, followed up more than seven years (7). Up to 30% of obese subjects, so-called "healthy obese", seem to be protected against metabolic and cardiovascular complications of obesity (8).

The key question is how to discriminate between metabolically healthy obese subjects and obese patients with a considerable risk for cardiovascular disease. What is the missing link?

Visceral adipose tissue is considered an independent risk factor for cardiovascular disease and diabetes mellitus. For a long time white adipose tissue was believed to be just a fuel-storage organ, but it is now recognised as an endocrine organ that expresses and secretes a variety of cytokines and chemokines, also known as adipokines (9). Adipose tissue comprises mainly adipocytes, preadipocytes, fibroblasts, blood vessels with endothelial cells, and immune cells such as macrophages and lymphocytes. There is a shift toward a proinflammatory, atherogenic, and diabetogenic pattern in adipokine secretion supporting a low-grade systemic inflammation in obesity. Why adipose tissue becomes inflamed is not fully understood, but a dysfunction of adipose tissue - especially in increased visceral fat depots - seems to play a major role in the development of a metabolically unhealthy obese state accompanied by an increased risk for cardiovascular complications.

In this review article we present emerging and conflicting data concerning adipose tissue dysfunction and its possible impact on CVD. We describe some of the adipokines more in detail, namely leptin, adiponectin, omentin, osteopontin, pigment epithelium-derived factor (PEDF) and plasminogen activator inhibitor 1 (PAI-1), which are in our opinion prominent key-players in the network of adipose tissue dysfunction and its consequences such as insulin resistance, diabetes and cardiovascular disease. Furthermore, we highlight therapeutic approaches in this field.
Dysfunction of adipose tissue

Adipose tissue dysfunction is characterised by ectopic - predominantly visceral, perivascular and liver - fat accumulation, enlarged adipocytes, changes in cellular compounds of adipose tissue including an increased number of immune cells and a disturbed secretion of adipokines toward a proinflammatory, atherogenic and diabetogenic pattern (10).

Chronically nutritional overload results in storage of triglycerides in preexisting adipocytes leading to adipocytes hypertrophy. Increased adipocyte volume is associated with a higher secretion of cytokines, mainly proinflammatory cytokines (11). After correction for cell surface significant difference between the very large adipocyte fraction and the small cells remained for leptin, interleukin (IL)-6, IL-8, monocyte chemotactic protein-1 (MCP-1) and granulocyte-colony stimulating factor (G-CSF) (11). Despite an increased secretion of the anti-inflammatory cytokine adiponectin by enlarged adipocytes in vitro, obesity is well known to be associated with hypoadiponectinaemia (12). This could be explained by paracrine effects of other cytokines, e.g. tumour necrosis factor-α (TNF-α), IL-6 and IL-8, which are released from surrounding cells (13). During differentiation from preadipocytes to adipocytes a different pattern of genes is expressed (14, 15). Leptin and adiponectin are primarily released by mature adipocytes, but comparing adipocytes, stromal-vascular cells and undigested tissue matrix of adipose tissue the release of adipokines is mainly attributed to the latter fraction (16).

Macrophages accumulate in adipose tissue of obese individuals, thereby forming so-called crown-like structures, apparently acting as scavengers of apoptotic adipocytes (17) (Figure 1). Macrophages occur as M1 macrophages, which are "classically" activated by interferon-γ (IFN-γ) and produce inflammatory cytokines, e.g. IL-6, IL-1 and TNF-α and as M2 macrophages, which are "alternatively" stimulated by IL-4 and IL-13 and play predominantly an anti-inflammatory role. Human resident adipose tissue macrophages resemble an M2 phenotype, but in the obese state the cytokine pattern is shifted toward an inflammatory M1 profile (18, 19).

Recent data suggests that macrophages might adapt their profile to the prevalent environment in a graduated manner (20). The functional role of T-cells in adipose tissue has been recently recognised, involving different populations of T-cells such as CD3+, CD8+ and regulatory T-cells, termed Treg cells, derived from CD4+ helper cells (21). Changes in composition of lymphocytes in adipose tissue of obese individuals promote accumulation and activation of macrophages (21).

In the case of excessive intake of calories free fatty acids (FFA) and glucose can raise intracellular oxidative stress by increased production of mitochondrial reactive oxygen species (ROS) (22, 23). Resultant endothelial injury might attract inflammatory cells such as macrophages. Furthermore, FFA stimulate macrophage toll like receptor-4 (TLR-4), which increases expression and production of chemokines via JNK/IKKβ signalling pathways thereby enhancing inflammation (24). Hypoxia induced by adipocyte hypoxia and expanding fat mass could be another potential cause of adipose tissue inflammation in obesity by stimulating expression of MCP-α, IL-1, IL-6, transforming growth factor-β (TGF-β) and matrix metalloproteinase-9 (MMP-9), paralleled by a reduction of adiponectin (25).

Leptin

Leptin, which was the first adipocyte hormone discovered in 1994 by Zhang et al., is a 16kDa polypeptide encoded by the obese (ob) gene, the murine homologue of the human gene LEP (29).

By its central actions, predominantly on hypothalamic targets, leptin is a major regulator of energy balance by modulating food intake, and energy expenditure. Mice lacking leptin showed premature obesity with hyperphagia, hyperinsulinaemia and hypo-
gonadism that could be treated with recombinant leptin (30). However, in obese humans treatable congenital deficiency of leptin by mutations of LEP as well as loss-of-function mutations of the LEP receptor (LEPR) are rare (31, 32). In contrast, clinical trials have shown that the majority of obese patients have high levels of leptin accompanied by leptin resistance, and in these patients leptin treatment is not effective (33-36).

Leptin is predominantly produced by adipocytes, and circulating leptin levels show a positive correlation with adipose tissue depot, reaching higher secreted levels in the subcutaneous than in the visceral depot (37). Leptin expression and release depend on adipocytes’ size in rodents and humans. Furthermore, weight loss results in a hypercellular state with reduced adipocyte size and lower secretion of leptin while preadipocytes secrete leptin only in certain circumstances, i.e. under hypoxic conditions (38-41).

Inflammatory cytokines, including TNF-α, IL-1, and leukaemia inhibitory factor (LIF), induce leptin production while the anti-inflammatory factor IL-1 receptor antagonist can abolish the anorexigenic properties of leptin (42, 43).

Elevated levels of the chemoattractant leptin may promote atherosclerosis by stimulating monocyte migration, and leptin deficiency in obese mice (LepR<sup>db/db</sup>) results in less macrophages accumulated in the adipose tissue (44, 45). In vitro studies show time-dependent beneficial or detrimental effects of leptin on cells of the cardiovascular system, e.g. acute exposure increases angiogenesis and nitric oxide (NO) production in endothelial cells while prolonged exposure leads to accumulation of ROS, inflammation and thrombosis (46). Proliferation and migration of smooth muscle cells as well as hypertrophy of cardiomyocytes and myocardial extracellular matrix remodelling are further harmful effects linking elevated leptin levels to CVD (46).

Increased appetite and lower energy expenditure as a result of relative leptin deficiency after weight loss could explain the difficulties maintaining the weight. Administration of leptin to reach pre-weight loss levels might prevent weight gain (47).

Despite the disappointing results of leptin administration in obese patients, leptin resistance could be an interesting target to lose weight. In an experimental animal model Ozcan et al. showed that chemical chaperons that reduce endoplasmatic reticulum stress also improved leptin sensitivity (48). After surgical weight loss, especially after gastric bypass surgery, leptin levels were markedly reduced concomitant with an improvement in insulin resistance, pancreatic β-cell function and metabolic and inflammatory parameters such as haemoglobin A1c, triglycerides, high-density lipoprotein (HDL) and high-sensitivity CRP (49).

### Adiponectin

Adiponectin, also known as GBP-28, apM1, AdipoQ and Acrp30, is primarily expressed and secreted by mature adipocytes (50, 51). It exhibits structural homology to collagen VIII and X and complement factor C1q, binding to its receptors AdipoR1 and AdipoR2. The high molecular weight oligomer is thought to be the most active form of the three main configurations (low-, medium- and high-molecular-weight). Adiponectin stimulates fatty acid oxidation via AMP-activated protein kinase, reduces hepatic gluconeogenesis and glucose plasma levels and thus, supports indirectly and directly insulin sensitivity by different pathways (52, 53). Adiponectin is abundant in human plasma, constituting for approximately 0.01% of total plasma protein and significantly reduced levels are found in central obesity and insulin resistance (12). Expression of adiponectin receptors is not only decreased in obesity, but also in non-alcoholic steatohepatitis (NASH), a possible secondary complication of obesity and diabetes (54).

The molecular mechanisms leading to hypoadiponectinaemia are not completely understood, but co-culture of subcutaneous adipocytes with visceral adipose tissue resulted in decreased adiponectin expression in adipocytes, suggesting that inhibiting factors derived from adipose tissue such as TNF-α may be causative (55, 56).

Experimental and clinical data suggest that adiponectin may exert anti-inflammatory and anti-atherogenic properties. Mice lacking adiponectin have severe neointimal thickening in mechanically injured arteries, and adenovirus-mediated adiponectin restoration has been shown to attenuate this effect (57, 58). In the
case of endothelial injury adiponectin accumulates in the subendothelial space of vascular walls by binding to collagen; furthermore, adiponectin suppresses monocyte attachment to endothelial cells by inhibiting TNF-α induced expression of adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell AM-1 (VCAM-1) and endothelial-selectin (E-selectin) via nuclear factor-κB (NF-κB) inhibition (59, 60). In addition, adiponectin may be a plaque stabiliser by increasing the production of tissue inhibitor of metalloproteinase-1 (TIMP-1) in macrophages via IL-10 upregulation (61). Adiponectin polarises resident macrophages in adipose tissue and in many other tissues toward an anti-inflammatory M2 phenotype (62). In human monocyte-derived macrophages adiponectin decreased class A scavenger receptor expression and suppressed cholesterol ester accumulation leading to reduced foam cell formation (63). Clinical trials confirmed that low levels of adiponectin were associated with higher incidence of cardiovascular events and worse outcome after percutaneous coronary intervention (64-66). Contradictorily, Sattar et al. reported no significant relationship of plasma adiponectin levels with risk of coronary heart disease and another study showed high adiponectin levels as predictor of adverse outcome in patients suffering from acute coronary syndrome (67). Differences in the study population and in blood storage before adiponectin analysis are discussed (68). A recent study presented adiponectin only in combination with parameters of the metabolic syndrome as predictor for cardiovascular disease, suggesting a second vascular stress factor to be required (69). In cardiac myocytes and pancreatic β-cells adiponectin seems to have anti-apoptotic properties via its receptor AdipoR1 and AdipoR2-mediated activation of the sphingolipid pathways (70).

Interestingly, in contrast to states of low-grade inflammation mostly associated with central obesity, elevated adiponectin levels are seen in conditions with chronic inflammation and autoimmune diseases, e.g. type 1 diabetes mellitus and rheumatoid arthritis (71).

Higher levels of adiponectin are also found in patients with chronic heart failure, possibly as a compensatory cardiac protective effect (72). After treatment of acute decompensated heart failure, the degree of adiponectin reduction - in contrast to the well-established heart failure marker natriuretic peptide (BNP) - seems to be an important determinant of prognosis, e.g. cardiac death and hospitalisation due to heart failure (73).

The PPAR-γ agonists thiazolidindiones (TZDs), widely administered as oral anti-diabetic drugs, show anti-inflammatory and vasculoprotective effects. TZDs, e.g. pioglitazone and rosiglitazone have been demonstrated to enhance adiponectin expression and secretion (74-76). Pioglitazone retards the progression of carotid intima media thickness and induces regression and stabilisation of coronary atherosclerotic plaques, at least partly mediated by adiponectin increase (77, 78). The increase in adiponectin by pioglitazone treatment predicted improvement for triglyceride and HDL cholesterol levels and low-density lipoprotein (LDL) and HDL particle size (79). Furthermore, in an animal study pioglitazone prevented hyperglycaemia-induced decrease of AdipoR1 and AdipoR2 in coronary arteries and coronary vascular smooth muscle cells (80). Adverse events of TZDs have been reported, e.g. fluid retention, oedema and congestive heart failure (81). In 2007, a meta-analysis of 42 clinical trials revealed a significantly increased risk for myocardial infarction (MI) in patients treated with rosiglitazone (82). In contrast to heart failure this seems not to be a class effect since a large prospective, randomised study indicated no increased cardiovascular risk for pioglitazone (83). The secondary composite endpoint of this study including MI, stroke and death from any cause showed even a benefit for pioglitazone.

Other drugs such as pravastatin, angiotensin converting enzyme (ACE) inhibitors and the beta-blocker nebivolol also augment adiponectin plasma levels (84, 85).

Large reduction in adipose tissue mass by bariatric surgery leads to adiponectin elevation while there are conflicting results concerning the effect of weight reduction following life style changes such as diet and exercise training on pre-existing hypoadiponectinaemia (85-88).

Omentin

Another adipose tissue derived cytokine with assigned anti-inflammatory properties is omentin, initially described as intelectin in intestinal paneth cells and at a later date discovered in an omental fat cDNA library (89-91). Omentin-1 (further referred to as omentin in this review) is the major circulating form, a 313 amino acid molecule, preferentially expressed and secreted by visceral adipose tissue but poorly by subcutaneous fat. Omentin is present in the stromal-vascular fraction of fat, but not in mature adipocytes. It increases insulin-stimulated glucose uptake in both omental and subcutaneous fat cells, and enhances phosphorylation of Akt (91). Decreased expression of omentin in visceral adipose tissue and low blood levels of omentin are associated with obesity. Furthermore, not only BMI, waist circumference and insulin resistance are negatively correlated with omentin, but also the metabolic syndrome, a consequence often seen in obesity while adiponectin and HDL are positively correlated with omentin (92-94). The levels of omentin decreased further when metabolic syndrome was associated with enhanced carotid intima-media thickness and carotid plaques (95). Moreno-Navarrete et al. showed recently that circulating omentin is an independent predictor for endothelium-dependent vasodilatation in subjects with and without impaired glucose tolerance (96). These findings are supported by in vitro studies showing an activation of nitric oxide synthase 3 (NOS3) through phosphorylation at Ser1177 by omentin-stimulation of endothelial cells, which leads to vasorelaxation, tube formation and decreased apoptosis (46). Furthermore, omentin reduces the up-regulation of TNF-α induced adhesion molecules of human endothelial cells (97). Until now no specific cell surface receptor for omentin has been identified.

Thus, circulating omentin concentration could be an interesting marker of endothelial dysfunction. Low levels of omentin have been demonstrated to be associated with the presence and severity of coronary artery disease in patients with metabolic syndrome and also after adjustment for BMI and other cardiovascular risk.
factors (98, 99). Omentin exhibits anti-inflammatory properties, e.g. by preventing TNF-α induced cyclooxygenase-2 (COX-2) expression in vascular endothelial cells through activation of AMP activated kinase (AMPK)/NOS3/NO pathways (100).

Metformin was the first antidiabetic drug, which has been shown to increase omentin levels in overweight insulin-resistant women with polycystic ovary syndrome (PCOS) with concomitant decrease in carotid intima media thickness (101). After multiple regression analyses changes in omentin levels were only associated with changes in high-sensitivity CRP, possibly implicating that omentin is more likely to be linked to inflammatory parameters than metabolic parameters in PCOS women. In contrast to these findings, which were confirmed by Shaker et al., Esteghamati et al. found a reduction in omentin levels after three months of treatment with metformin or the insulin-sensitising drug pioglitazone in newly diagnosed type 2 diabetes patients (102, 103). In a recent smaller study the combined treatment of poorly controlled diabetes patients with metformin and iraglutide, a human glucagon like peptide-1 analog, resulted in increased omentin levels after six months (104).

After 12 weeks of aerobic training omentin levels increased concomitantly with improvement of insulin resistance parameters in overweight and obese subjects, moreover, diet-induced weight loss over four month was followed by an omentin increase (105, 106).

**Osteopontin**

Osteopontin (OPN), a matrix glycoprotein primarily secreted by activated macrophages and T-cells, is an important attachment and signalling molecule that has been demonstrated to be involved not only in bone metabolism but also in inflammatory processes, e.g. chemotaxis of monocytes, adhesion, migration, differentiation and phagocytosis (107). Hyperlipidaemic ApoE-deficient mice lacking OPN showed attenuated development of atherosclerosis (108). In a recent paper OPN was associated with arterial stiffness and the severity of cardiovascular disease (109). Furthermore, OPN is implicated in cardiac fibrosis and diabetic micro- and macrovascular long-term consequences (110-112). In adipose tissue of obese individuals OPN is highly expressed and upregulation of OPN in adipose tissue of obese patients and in obese mouse models was detected by different research groups (113-116). The incretin hormone GIP (glucose-dependent insulinotropic polypeptide) seems to be involved in adipose tissue formation leading to an obese state. Recently, GIP was discovered to be one of the stimulators of OPN expression in adipose tissue (117, 118). On the other hand OPN activates adipose tissue macrophages and impairs differentiation and insulin sensitivity of primary adipocytes (119). Apart from its accepted local role in adipose tissue, the origin and the relevance of altered blood levels of OPN in the obese state are controversially discussed. Modestly elevated OPN levels were found in obesity and weight reduction following hypocaloric diets resulted in a decrease of circulating concentrations of OPN (114). In contrast, weight loss after bariatric surgery was significantly associated with a strong increase of OPN levels exhibiting a relation to markers of bone turnover but not to insulin resistance and inflammation (120, 121). PPAR-α agonists, e.g. fibrates usually administered to reduce triglycerides, have been demonstrated to inhibit OPN expression at the transcriptional level in human macrophages. As a second finding of this study the authors provide evidence that PPAR-α agonists could reduce elevated OPN plasma levels in a cohort of diabetic patients (122).

**Pigment epithelium-derived factor**

Pigment epithelium-derived factor (PEDF), is a 50 kDa secreted glycoprotein belonging to the non-inhibitory serpin family and was originally described as an inhibitor of angiogenesis (123). In 2010 Famulla et al. identified PEDF as one of the most abundant adipokines in conditioned media of in vitro differentiated human adipocytes. During adipogenesis PEDF expression and secretion are significantly increased, showing mature adipocytes as major source of PEDF, while preadipocytes and adipose tissue-derived macrophages express significantly lower amounts of PEDF (124). In the same study TNF-α suppressed PEDF expression in human primary adipocytes without impact on PEDF secretion, whereas hypoxia reduced PEDF secretion by 15-20%. Previously, elevated levels of PEDF have been linked to visceral obesity and insulin resistance, and increased PEDF concentrations are found in subjects with metabolic syndrome, type 2 diabetes and in PCOS women (125-129). In contrast, a recently published paper could not confirm omental adipose tissue PEDF expression linked to elevated PEDF levels and insulin resistance, but rather linked liver PEDF secretion to circulating PEDF and insulin resistance (130). Furthermore, prolonged administration of PEDF promoted insulin resistance in lean C57Bl/6 mice while neutralising PEDF improved insulin sensitivity in obese mice (126). Exercise and weight loss following bariatric surgery have been demonstrated to reduce PEDF concentrations concomitant with decrease in insulin resistance (131, 132). Elevated levels of PEDF could be a compensatory response to microvascular injury seen in diabetes, particularly when proliferative retinopathy is present (133).

PEDF has been described also as a mediator of inflammation that activates macrophages to produce TNF-α and IL-1. PEDF mediates inflammatory signalling via activation of NF-κB, p38 MAPK and ERK1/2, and PEDF receptor adipose triglyceride lipase (ATGL) but not laminin receptor (LR) seems to be required for PEDF-mediated macrophage activation (124, 134). PEDF induced a slight proliferative effect in human smooth muscle cells in vitro, but did not stimulate migration of these cells (124). Furthermore, in a recent paper Tahara et al. showed that PEDF levels were positively correlated with human carotid intima media thickness and markers of inflammation (135).

In contrast to these findings, data obtained in animal models suggest a protective role of PEDF against vascular inflammation and atherosclerosis (136). PEDF has been reported to inhibit carotid artery thrombus formation, prevent vascular remodelling after balloon angioplasty and administration of PEDF suppressed tissue damage.
remodelling and improved cardiac function in a rat model of MI (136, 137). However, most of these investigations suggesting a protective role of PEDF in cardiovascular diseases were performed in animal models or in cell culture in vitro, whereas most of the evidence that PEDF might exert detrimental effects comes from clinical studies (127-130, 135, 138). Still, further studies are warranted to clarify if elevated levels of PEDF described in these clinical studies are cause or consequence of obesity, insulin resistance, vascular inflammation and atherosclerosis. Such studies would help to elucidate the exact role of PEDF in the modulation of inflammation and cardiovascular pathologies and to more closely characterise the adipokine PEDF as a possible therapeutic target.

**Table 1: Main functions and therapeutic potential of selected adipokines.**

<table>
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<tr>
<th>Adipokine</th>
<th>Main physiological and pathophysiological function</th>
<th>Therapeutic approach</th>
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<tbody>
<tr>
<td><strong>Leptin</strong></td>
<td>Modulator of food intake (43)</td>
<td>• Chemical chaperons improve leptin sensitivity (48)</td>
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<td></td>
<td>† Hyper trophy of cardiomyocytes and cardiac remodelling (46)</td>
<td>• Gastric bypass surgery reduces leptin levels (49)</td>
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<td></td>
<td>† Monocyte migration (44, 45)</td>
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<td></td>
<td>† Angiogenesis, NO, ROS, inflammation, thrombosis (46)</td>
<td></td>
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<tr>
<td><strong>Adiponectin</strong></td>
<td>† Fatty acid oxidation (52, 53)</td>
<td>• TZDs (pioglitazone, rosiglitazone) enhance adiponectin expression and secretion (74–76)</td>
</tr>
<tr>
<td></td>
<td>† Hepatic glucoseogenesis (52, 53)</td>
<td>• Increased by pravastatin, ACE inhibitor and nebivolol (84)</td>
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<td></td>
<td>† Neointimal thickening in injured arteries (57, 58)</td>
<td>• Bariatric surgery increases adiponectin levels (88)</td>
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<td></td>
<td>† TNF-α induced ICAM-1, VCAM-1, E-selectin expression (59, 60)</td>
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<td></td>
<td>† TIMP-1 (61)</td>
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<td></td>
<td>† Apoptosis of cardiac myocytes (70)</td>
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<tr>
<td><strong>Omentin</strong></td>
<td>† Insulin-stimulated glucose uptake in fat cells (91)</td>
<td>• Increased by metformin (101, 102)</td>
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<td></td>
<td>† Vasorelaxation, tube formation</td>
<td>• Reduced by pioglitazone (103)</td>
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<td></td>
<td>† Apoptosis via NO53 (46)</td>
<td>• Increased by liaglutide (104)</td>
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<td></td>
<td>† TNF-α induced adhesion molecules (97)</td>
<td>• Aerobic training and diet increase omentin levels (105, 106)</td>
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<td>† COX-2 (100)</td>
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<tr>
<td><strong>Osteopontin</strong></td>
<td>† Chemotaxis, adhesion, migration, differentiation of monocytes (107)</td>
<td>• PPAR-α agonists inhibit OPN expression (122)</td>
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<td></td>
<td>† Arterial stiffness (109)</td>
<td>• Hypocaloric diets decrease OPN levels (114)</td>
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<td></td>
<td>† Cardiac fibrosis (110)</td>
<td>• Weight loss by bariatric surgery increases OPN levels (120, 121)</td>
</tr>
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<td></td>
<td>† Diabetic micro- and macrovascular complications (111, 112)</td>
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<tr>
<td><strong>PEDF</strong></td>
<td>† Angiogenesis, thrombosis, proliferation, inflammation (123)</td>
<td>• Exercise reduces PEDF levels (131)</td>
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<td></td>
<td>† Neurotrophic (123)</td>
<td>• Weight loss by bariatric surgery decreases PEDF levels (131, 132)</td>
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<td></td>
<td>† Insulin resistance (126)</td>
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<td></td>
<td>† Suppression of tissue remodelling and improved cardiac function after MI (137)</td>
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<td>† Macrophage activation (134)</td>
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<tr>
<td><strong>PAI-1</strong></td>
<td>Primary physiological inhibitor of the plasminogen/plasmin system (140)</td>
<td>• Weight reduction by hypocaloric diet or bariatric surgery decreases PAI-1 activity (141, 142)</td>
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<tr>
<td></td>
<td>† Tissue remodelling, cell migration and degradation of extracellular matrix (146)</td>
<td>• Metformin and TZDs (troglitazone) reduce PAI-1 levels (144, 145)</td>
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<td></td>
<td>† Development of adipose tissue (?) (140, 147, 148)</td>
<td>• Direct pharmacologically PAI-1 inhibition shows limited success (140)</td>
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Conclusion and outlook

In this review we have described selected adipokines, their respective functions in pathologies such as insulin resistance, diabetes and cardiovascular disease and therapeutic approaches targeting these functions (Table 1). The global epidemic of overweight and obesity has driven intensive research that made considerable progress in characterising adipose tissue as an active player in pathologies described above. Within the last years this research has identified an ever increasing number of adipokines with various pathophysiological functions. Future investigations are warranted to more closely characterise these functions and to translate such findings into new therapies to combat obesity and diseases associated with this pathology.

Conflicts of interest

None declared.

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Obesity and vascular disease


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