Review Article

Update on the Cardiovascular Risk in Obesity: Endocrine and Paracrine Role of the Adipose Tissue

Katrin Schäfer[1], Stavros V. Konstantinides[2]

[1]*Department of Cardiology and Pulmonary Medicine, Georg August University, Göttingen, Germany;* [2]*Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece*

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Address:
Katrin Schäfer

Department of Cardiology and Pulmonary Medicine University of Göttingen Robert Koch Strasse 40 D-37099 Göttingen, Germany
e-mail: katrin.schaefer@med.uni-goettingen.de

The prevalence and incidence of obesity, an important cardiovascular risk factor, are increasing dramatically in Greece and worldwide. This article highlights recent insights into the role of adipose tissue-derived factors in mediating the vascular complications of obesity, particularly atherosclerosis.

The prevalence of obesity in Greece and worldwide

The mean body weight and prevalence of obesity in the population have increased alarmingly over the past two to three decades. According to the World Health Organization (WHO), 200 million adults worldwide were obese (defined as body mass index [BMI] >30 kg/m^2) in 1995, whereas in 2005 approximately 1.6 billion people were overweight (BMI 25-29.9 kg/m^2) and at least 400 million obese (www.who.int/mediacentre/factsheets/fs311/en). Projected estimates for 2015 indicate that 2.3 billion individuals will be overweight and more than 700 million obese.

A recently conducted cross-sectional nationwide survey in Greece included 17,341 men and women aged from 20 to 70 years and indicated (based on self-reported data) that the overall prevalence of overweight and obesity amounts to 35.2% and 22.5%, respectively.[1] Abdominal obesity (defined as waist circumference >102 cm in males and >88 cm in females) was present in 41.1% of men and 29.9% of women. Even higher percentages were reported in earlier, smaller studies. For example, the cross-sectional analysis of 4153 adult participants (older than 18 years) of the MetS-Greece Multicentre Study (data collected during 2003) revealed a high prevalence (56.8%) of abdominal obesity,[2] while the European Prospective Investigation into Cancer and Nutrition (EPIC) study (data collected between 1992-2000) found that abdominal obesity in Greece was present in 38.8% of men and 54.5% of women aged 50 to 64 years.[3] Furthermore, evaluation of more than 3000 persons (age 20-89 years) living in the Attica region between 2001 and 2002 revealed that 53% of men were overweight and 20% obese; for women, the rates were 31% and 15%, respectively.[4]

Overall, these numbers demonstrate the magnitude of the health problem associated with obesity. They also show that deeper insights into the molecular pathways and cardiovascular consequences of increased body weight are urgently needed to prevent and combat the impact of increased body fat mass on cardiovascular morbidity and mortality in the near future.

Obesity as cardiovascular risk factor

Obesity is a major risk factor for coronary heart disease[5] and clinical studies have shown that it increases the risk of suffering or dying from atherothrombotic complications such as myocardial infarction or stroke.[6] Obese persons have a higher incidence of arterial hypertension and left ventricular hypertrophy, both important risk factors for the development of heart failure.[7] Based on these facts, statistical forecasts have estimated that obesity-associated cardiovascular mortality will soon neutralize the increase in life expectancy achieved over the past decades as a consequence of improvements in living conditions and medical care.[8]

Important insights into potential pathomechanisms underlying the increased cardiovascular risk in obesity have been obtained over the past years; however, the molecular pathways are far from being completely understood. An increase in visceral adipose tissue mass is frequently accompanied by metabolic alterations such as hyperinsulinemia, glucose intolerance and diabetes, as well as hyper- or dyslipidemia, all of which may promote the development of atherosclerosis. In addition, factors produced and released from the adipose tissue may directly modulate the function of vascular cells and contribute to the formation of atherosclerotic lesions in obesity. The effects of some of these so-called adipokines on vascular cells and vascular lesion formation are discussed in more detail below.

Adipose tissue as source of inflammatory cytokines

Obesity is accompanied by an increased expression of adhesion receptors on adipocytes, followed by an enhanced infiltration of the adipose tissue with inflammatory cells, primarily macrophages.[9] Adipose tissue macrophages, which may constitute up to 40% of all cells within the adipose tissue, are an important source of proinflammatory cytokines, such as tumor necrosis factor (TNF)α, interleukin (IL)1, IL6 or monocyte chemoattractant protein 1/CC-chemokine ligand 2 (MCP1/CCL2) (Figure 1); these not only contribute to the systemic proinflammatory condition frequently associated with obesity, but may also act locally and adversely affect adipocyte function, e.g. promote the development of insulin resistance. For instance, experimental studies in obese mice have shown that lack of the receptor for MCP1/CCL2 not only reduced adipose tissue inflammation, but also improved insulin resistance.[10] Furthermore, macrophage-secreted chemokines (e.g. MCP1/CCL2 and IL8/CXC ligand 8 [CXCL8]) as well as adipokines (e.g. leptin) are potent angiogenic growth factors, and an enhanced vascularization of the adipose tissue could further promote obesity and its metabolic complications by facilitating inflammatory cell recruitment. In agreement with these data, inhibition of angiogenesis was shown to reduce adipose tissue expansion and the development of obesity.[11] Reciprocally, binding of products released from adipocytes (e.g. free fatty

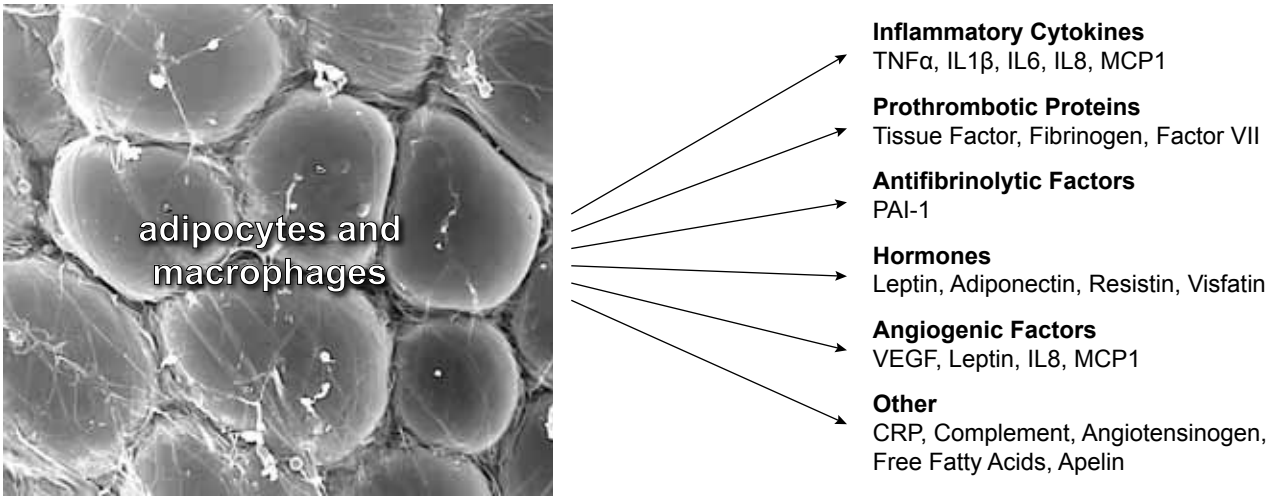

Figure 1. Obesity is associated with local and systemic inflammation. List of factors produced in and secreted from adipose tissue (adipocytes or adipose tissue-resident macrophages), grouped according to their major function. CRP – C-reactive protein; IL – interleukin; MCP-1 – monocyte chemoattractant protein-1; PAI-1 – plasminogen activator inhibitor-1; TNFα – tumor necrosis factor-alpha; VEGF - vascular endothelial growth factor.

acids) to receptors expressed on macrophages (e.g. Toll-like receptors) may lead to the subsequent activation of the latter cell type, ultimately resulting in a self-perpetuating vicious circle of macrophage and adipocyte stimulation.

The chronic, low-grade inflammation associated with obesity is reflected by elevated levels of the acute phase reactant C-reactive protein (CRP),[12] produced in the liver as a result of chronic stimulation with IL6 released from the adipose tissue. In addition, there is evidence that CRP is produced in the adipose tissue itself,[13] and plasma CRP levels correlate with body fat mass and indices of visceral adiposity,[14] whereas surgically or diet-induced weight loss are associated with reduced CRP levels.[15] Interestingly, serum CRP is not only a potential biomarker of increased cardiovascular risk,[16] but also appears to possess direct effects within the cardiovascular system. For example, experimental evidence suggests that CRP promotes angiogenesis[17] or thrombosis,[18] and CRP transgenic apolipoprotein E knockout mice exhibited accelerated atherosclerosis lesion formation.[19] However, opposite findings have also been reported.[20,21] Thus, the role of CRP as an active player within the cardiovascular system remains undetermined.

Cardiovascular risk associated with different adipose tissue depots

Clinical studies have found visceral adiposity, rather than the enlargement of subcutaneous fat depots, to be associated with an increased cardiovascular risk. Possible mechanisms include the direct drainage of adipokines and other metabolites from intra-abdominal fat depots into the portal circulation (followed by stimulation of the hepatic production of CRP, plasminogen activator inhibitor-1, or fibrinogen),[22] but also the higher expression of proinflammatory mediators[23] and stronger infiltration with macrophages[9] compared to subcutaneous adipose tissue. In addition, recent studies point to a role for other fat depots, e.g. those surrounding blood vessels or within the pericardium, in the pathogenesis of atherosclerosis in obesity (Figure 2). For example, the amount of intrathoracic or pericardial fat was found to correlate with the severity of coronary artery calcification,[24] or the incidence of coronary heart disease and myocardial infarction.[25] Interestingly, perivascular fat volumes >300 cm^3 were associated with a higher relative risk for coronary atherosclerosis than traditional systemic cardiovascular risk

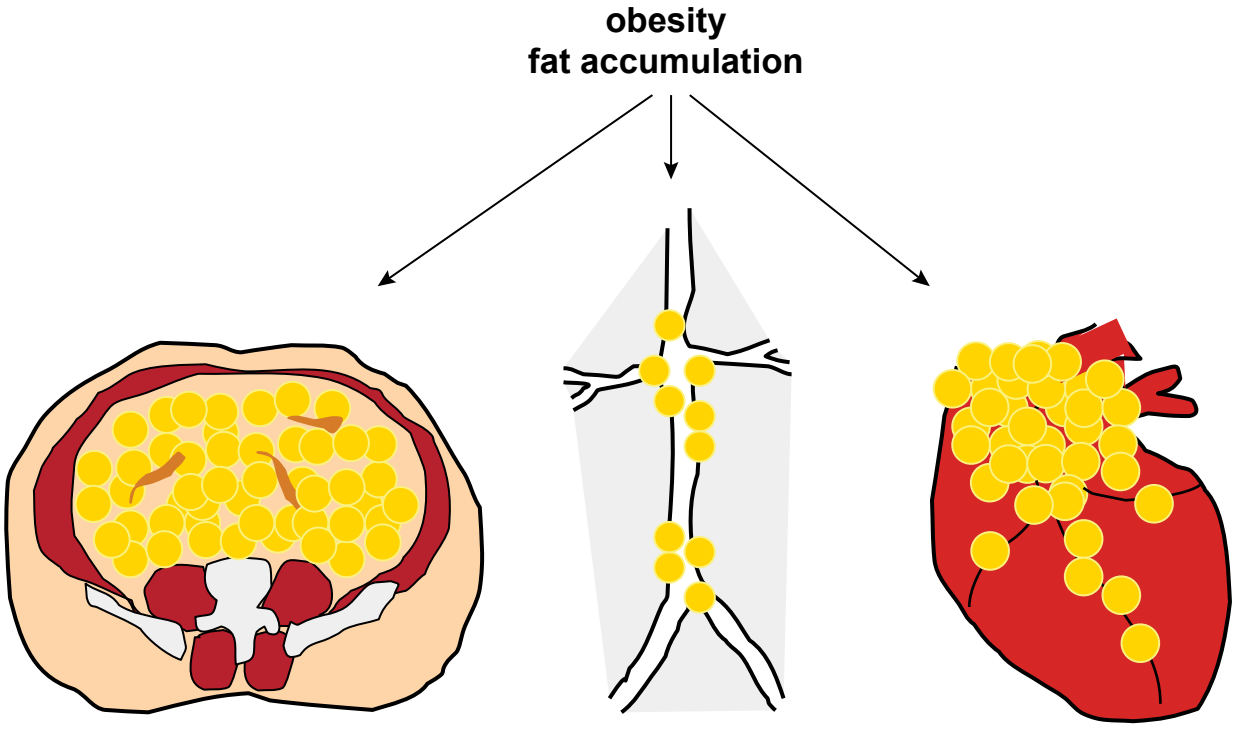

Figure 2. Fat deposition in obesity. Obesity is associated with increased fat deposition within the abdominal cavity, but also around blood vessels or within the pericardium.

Table 1. Short summary of some major effects of adipokines potentially relevant to vascular lesion formation in obesity.

	Findings in mouse models or vascular cells	References
Adiponectin	– increases insulin sensitivity	47
	– inhibits platelet activation and thrombosis	48
	– reduces neointima formation	49
	– overexpression protects against atherosclerosis	50
	– anti-inflammatory and anti-adhesive	51, 52
	– inhibits transformation of monocytes into macrophage foam cells	53
	– reduces SMC proliferation and migration	54
Apelin	– promotes SMC contraction and is involved in blood pressure regulation	82-84
	– prevents neointima and aneurysm formation by antagonizing angiotensin II	79
	– induces SMC proliferation	80
	– apelin or apelin receptor deficiency reduces atherosclerotic lesion formation	79, 80
	– increases endothelial NO bioavailability	79
	– stimulates hypoxia-induced EC proliferation and promotes angiogenesis	85
CRP	– promotes EC proliferation, migration and angiogenesis	17
	– promotes arterial thrombosis	18
	– accelerates the progression of atherosclerosis, but lack of proatherogenic effects has also been reported	19, 21
	– reduced neointima formation was observed in CRP transgenic mice	20
Leptin	– promotes platelet activation and thrombosis	41, 42
	– enhances neointima formation	37
	– promotes atherosclerosis	38
	– increases the angiogenic properties of EPC	33, 43
	– stimulates SMC proliferation and migration	40
MCP-1	– may mediate adipose tissue inflammation and insulin resistance in obesity	10
PAI-1	– inhibits plasminogen activation and fibrinolysis	60
	– promotes thrombus formation, neointima formation and atherosclerosis in mouse models	63, 64
	– modulates angiogenesis and cell migration	61
	– involved in the development of obesity and insulin resistance	65-71
Resistin	– interferes with the insulin-mediated cellular glucose uptake and is involved in the development of insulin resistance in obesity	72
	– inhibits adipocyte differentiation	73

CRP – C-reactive protein; EC – endothelial cells; EPC – endothelial progenitor cells; MCP-1 – monocyte chemoattractant protein-1; PAI-1 – plasminogen activator inhibitor-1; SMC – smooth muscle cells; TNFα – tumor necrosis factor-α.

factors,[26] suggesting that proinflammatory or vasoactive mediators from perivascular adipose depots may affect cardiovascular disease in a paracrine manner. In this regard, human aortic atherosclerosis was found to correlate with leptin, visfatin and chemerin expression in the peri-aortic adipose tissue,[27] and elevated perivascular expression of proinflammatory cytokines has also been reported in hypercholesterolemic or diet-induced obese mice.[28,29] However, a direct, causal link between perivascular fat accumulation and vascular wall dysfunction is still lacking. Clearly, further studies are needed to clarify the exact role of perivascular adipose tissue and the paracrine action of adipokines or other mediators in the pathogenesis of atherosclerosis.

Vascular actions of specific adipokines

This section will briefly highlight important findings concerning the role of typical (e.g. leptin, adiponectin) and novel (e.g. apelin) adipokines on vascular cells and their effects in mouse models of atherosclerosis or intimal hyperplasia. Please also see Table 1.

Leptin

Under physiological conditions, a complex network of neuronal messenger proteins keeps our body weight relatively constant over time, within the range of a few kilograms. The adipocyte-derived hormone leptin plays an important role in this regulatory network by

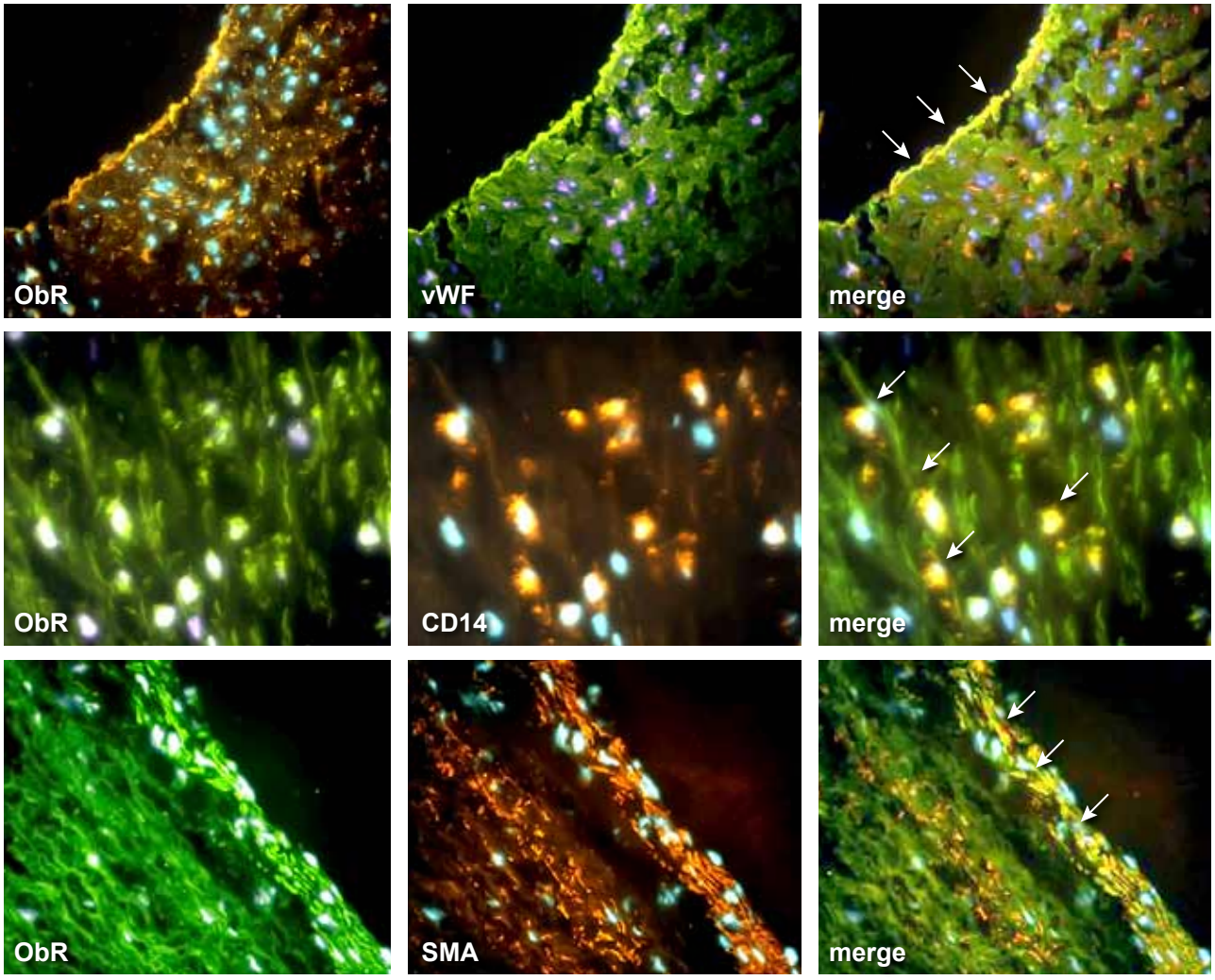

Figure 3. Expression of the leptin receptor in human atherosclerotic lesions. Double immunostaining of frozen sections through human atherosclerotic lesions for the leptin receptor (ObR) and von Willebrand factor (vWF), the LPS receptor (CD14) or smooth muscle cell α-actin (SMA), respectively, revealed its expression on endothelial cells (upper row), monocytes/macrophages (middle row) and vascular smooth muscle cells (lower row). Arrows point to double-positive cells. Magnification, 400 × (upper and lower rows) and 630 × (middle row).

functioning as mediator between the adipose tissue and hypothalamic neurons, controlling food intake, appetite and energy consumption.[30] The increase in adipose tissue mass in obesity is associated with increased circulating leptin levels;[31] however, obese subjects are unable to respond to the weight-reducing actions of the hormone. The exact molecular mechanisms of this so-called 'leptin resistance' are not fully understood, but failure of the adipokine to cross the blood-brain barrier, impairment of leptin-mediated signal transduction on the receptor and post-receptor level, or reduction of the free, biologically active form of leptin due to binding to plasma proteins, including CRP, are being discussed.[32] Importantly, weight loss may restore the cellular response to leptin, as we were recently able to show for circulating angiogenic cells (also called early outgrowth endothelial progenitor cells), isolated from the blood of formerly obese individuals.[33] Notably, clinical studies suggested that elevated leptin levels may constitute an independent cardiovascular risk factor,[34] although prospective clinical trials on the importance of leptin as a mediator of the elevated cardiovascular risk in obesity have found only moderate associations.[35]

Interestingly, the leptin receptor is expressed on a variety of cell types outside the central nervous system; these include cells present within the normal vascular wall (endothelial and smooth muscle cells), and also monocytes and T lymphocytes involved in the pathogenesis of atherosclerosis (Figure 3).[36] In

mice, leptin has been shown to promote neointima formation in response to vascular injury[37] or to enhance atherosclerotic lesion formation.[38] The many effects of leptin within the cardiovascular system have been reviewed in detail elsewhere,[39] and include enhanced proliferation and migration of smooth muscle cells[40] and the potentiation of platelet aggregation and thrombosis.[41,42]

On the other hand, leptin may also exert potentially beneficial effects. Importantly, the hormone was found to promote the angiogenic properties of endothelial (progenitor) cells[33,43] and to enhance the re-endothelization of vascular lesions.[44] Thus, it remains to be shown whether the elevated cardiovascular risk in obesity is the consequence of elevated leptin levels or rather the result of resistance to leptin's potentially beneficial effects (Figure 4). In any case, the finding that an adipocyte-derived hormone, in addition to its primary mode of action (i.e. the central regulation of food intake) also exerts pleiotropic effects on vascular cells, has stimulated further research into the adipose tissue as an endocrine/paracrine organ and the vascular effects of adipokines.

Adiponectin

Adiponectin is exclusively produced in adipocytes and regulates energy metabolism and insulin sensitivity. For example, mice deficient in adiponectin exhibit severe diabetic features,[45] whereas adiponectin over-

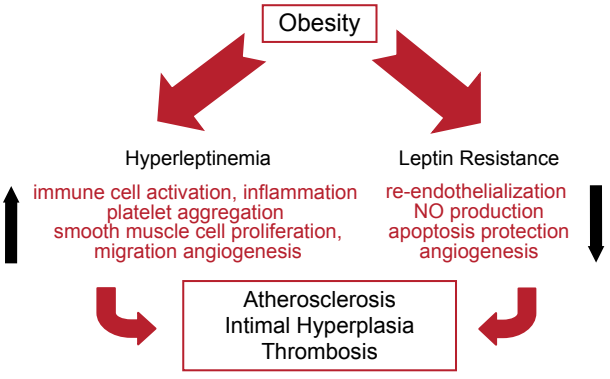

Figure 4. Hyperleptinemia and cardiovascular risk. It remains to be determined whether the increased cardiovascular risk associated with obesity occurs as consequence of a undisturbed response of vascular (e.g. endothelial and smooth muscle cells, macrophages) and hematological cells (i.e. platelets, monocytes, T-lymphocytes) to the increased circulating levels of the adipokine, and/or whether atherosclerosis initiation and progression are enhanced due to resistance to the beneficial effects of leptin.

expression[45] or replenishment[46] was found to ameliorate insulin resistance. Adiponectin receptors are expressed (among other organs) in the liver (adipoR2), skeletal muscle and heart (adipoR1), and binding of the hormone increases insulin sensitivity through inhibition of hepatic gluconeogenesis and stimulation of glucose uptake and fatty acid oxidation in muscle.[47] Thus, the reduction in circulating adiponectin levels in overweight individuals may contribute to the insulin resistance associated with obesity.

Apart from its metabolic and insulin-sensitizing activities, adiponectin also possesses direct vasculoprotective and anti-atherosclerotic properties. Studies in animal models have shown that a lack of adiponectin enhanced thrombus formation[48] and intimal hyperplasia,[49] whereas adiponectin overexpression was found to protect against atherosclerosis progression.[50] The latter observation might be related to the finding that adiponectin inhibits activation of the proinflammatory transcription factor NFκB[51] and reduces the adhesion of monocytes on activated endothelial cells,[52] a crucial step in the initiation of vascular lesion development. Furthermore, adiponectin inhibits the transformation of monocytes into macrophage-foam cells,[53] and reduces the growth factor-induced proliferation and migration of vascular smooth muscle cells.[54] In accordance with these findings, persons with increased cardiovascular risk,[55] angiographically confirmed coronary heart disease,[56] or acute coronary syndromes[57] were reported to have reduced circulating adiponectin levels. However, the potential usefulness of adiponectin as biomarker for cardiovascular disease is unclear so far, possibly because determination of plasma adiponectin levels is unreliable due to the presence of multiple isoforms (at least 3 different isoforms are known to date), multimerization or binding of adiponectin to other plasma proteins.

Plasminogen activator inhibitor type-1

Plasminogen activator inhibitor type-1 (PAI-1) is produced in the adipose tissue (primarily by cells residing within the stromal cell fraction of visceral fat).[58] Elevated plasma levels of PAI-1 are frequently observed in overweight and obese subjects and decrease after weight loss.[59] PAI-1 is the principal inhibitor of urokinase and tissue-type plasminogen activator and thus a key regulator of fibrinolysis,[60] but also of other plasmin-mediated processes including activation of matrix-metalloproteinases, cell migration and angiogenesis, i.e. processes which may be of potential relevance during the evolution of vascular lesions.[61]

Clinical studies have revealed an association between elevated plasma PAI-1 levels and the incidence of thrombosis and atherosclerosis,[62] while experimental studies in mice confirmed the importance of PAI-1 in the pathogenesis of the vascular complications in obesity.[63,64] Experimental studies have also suggested a direct, causal role of PAI-1 in obesity and insulin resistance. For example, PAI-1 deficiency was found to reduce adiposity and improve the metabolic profile in both genetically and diet-induced obese mice,[65] while bone marrow transplantation studies revealed that PAI-1 expressed by macrophages within the visceral adipose tissue contributes to the development of obesity.[66] Also, pharmacological inhibition of PAI-1 dose-dependently ameliorated the development of obesity in mice that were fed a high-fat diet,[67] and prevented the development of obesity in mice,[68] whereas injection of pre-adipocytes overexpressing murine PAI-1 increased the size of *de novo* fat pads in response to a high-fat diet.[69] It should be noted that opposite findings also have been reported, namely that transgenic overexpression of PAI-1 in fat ameliorates the development of obesity in mice,[70] and that PAI-1 deficiency reduces weight gain in response to a high-fat diet.[71]

Resistin

Resistin (for "resistance to insulin") was described for the first time in 2001 and was found to circulate at elevated concentrations in the plasma of obese and diabetic mice.[72] Injection of resistin into mice produces insulin resistance, whereas administration of neutralizing antibodies improves the insulin sensitivity of obese animals.[73] Similarly, adipocytes in culture respond to resistin with a reduction of insulin-mediated glucose uptake.[72] Thus, resistin could represent an important link between obesity and insulin resistance or diabetes mellitus. However, not all clinical studies were able to demonstrate elevated resistin levels in overweight persons.[74] Moreover, and in contrast to mice, human resistin is produced primarily in inflammatory cells, such as macrophages, but not in adipocytes.[75] For these reasons, findings in mice cannot be directly extrapolated to the human situation and the role of resistin in the increased cardiovascular risk associated with obesity is still not clear.

Apelin

In 1998, a small peptide was isolated from bovine stomach extracts and identified as endogenous ligand for the orphan G-protein-coupled receptor APJ.[76] Further studies revealed that apelin is widely expressed, including within the adipose tissue. Interestingly, its expression in adipocytes was found to increase in response to insulin or TNFα, and elevated apelin plasma levels have been described in obesity.[77] However, weight loss did not alter plasma apelin levels in obese individuals, in contrast to those of leptin and adiponectin, suggesting a weak correlation between fat mass and apelin secretion.[78] Interestingly, the receptor for apelin possesses close homologies with the angiotensin II receptor, and apelin was shown to inhibit native atherosclerosis or to prevent aneurysm and neointima formation accelerated by angiotensin II.[79] Similarly, atherosclerosis-prone mice lacking apelin receptors exhibited smaller lesions.[80] Apelin receptors are expressed on the main cellular components of the normal vascular wall,[81] and apelin was shown to promote the proliferation[80] and contraction of smooth muscle cells[82] or to regulate blood pressure.[83,84] Also, apelin was found to promote endothelial nitric monoxide production, while hypoxia-induced apelin expression stimulated endothelial cell proliferation and angiogenesis.[85] Thus, the true or net effect of apelin on the cardiovascular system, including those in the context of increased body fat, is not fully understood at the moment.

Other adipokines

Finally, recently described adipokines include visfatin (for "visceral adipose tissue-derived serpin"), omentin and chemerin; however, their effects on vascular cells and the arterial wall in obesity are largely unknown, leaving space for future exciting discoveries in the rapidly evolving field of clinical and experimental obesity research.

Summary and future perspectives

The high prevalence of obesity, an important cardiovascular risk factor, underlines the necessity to better understand the causal relationship and interactions between the adipose tissue and the vascular wall. Adipokines, their receptors on vascular cells, and downstream intracellular signal transduction events may constitute important therapeutic target structures to modulate the effects of adipokines within the cardiovascular system, in addition to the modulation of adipose tissue inflammation or neovascularization. Along with the growing knowledge about the cellu-

lar and molecular mediators of obesity and its consequences within the cardiovascular system, our efforts should focus on the primary prevention of obesity, especially in the young, as well as the implementation of lifestyle modification strategies aiming at weight loss and increased physical activity.

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