Adipokines at the crossroad between obesity and cardiovascular disease

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Summary

Obesity, and especially excessive visceral adipose tissue accumulation, is considered as a low-grade inflammatory state that is responsible for adipocyte dysfunction and associated metabolic disorders. Adipose tissue displays endocrine functions by releasing pro- or anti-inflammatory bioactive molecules named adipokines. An altered expression of these molecules, provoked by obesity or adipocyte dysregulation, contributes to major metabolic diseases such as insulin resistance and type 2 diabetes mellitus that are important risk factors for cardiovascular disease. However, obesity is also characterised by the expansion of perivascular adipose tissue that acts locally via diffusion of adipokines into the vascular wall. Local inflammation within blood vessels induced by adipokines contributes to the onset of endothelial dysfunction, atherosclerosis and thrombosis, but also to vascular remodelling and hypertension. A fast expansion of obesity is expected in the near future, which will rapidly increase the incidence of these cardiovascular diseases. The focus of this review is to summarise the link between metabolic and cardiovascular disease and discuss current treatment approaches, limitations and future perspectives for more targeted therapies.

Keywords

Obesity, adipokines, cardiovascular disease

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Introduction

Obesity is a major worldwide health problem due to its strong correlation with insulin resistance (IR), type 2 diabetes mellitus (T2DM) and its implication in coronary artery disease (CAD). The probability to develop CAD is increased in people with high plasma glucose levels, high blood pressure, increased low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) levels as well as elevated triglyceride levels (1). The metabolic syndrome (MS) is defined as a condition in which obesity associates with at least two of the above cited risk factors, and this increases the risk for cardiovascular events by two- to three-fold (2). The key role for obesity in the development of CAD and MS might be explained, at least in part, by overproduction of pro-inflammatory molecules (adipokines) within the perivascular adipose tissue (PVAT) giving rise to atherosclerosis. As a result, obesity is the fifth leading risk for developing major health problems and has become epidemic worldwide, with predictions of increased numbers of overweight or obese individuals by 2020 (3). In addition, development of obesity in young people is becoming a big concern. Nearly one out of three children from upper middle-income countries is already suffering from overweight, which will lead to economic and societal problems (3). In this review, we discuss the association between obesity and cardiovascular disease (CVD) risk factors, more particularly by focusing on the crucial role played by adipokines. Finally, we review the current lack of tailored treatment focusing specifically on the links between these two pathologies.

Obesity and the importance of visceral adipose tissue

Obesity is characterised by accumulation of fat resulting from an impaired energy balance whereby energy intake exceeds its expenditure, leading to increased triglyceride production and storage in adipocytes. A body mass index (BMI) ≥ 25 kg/m^2 is considered as overweight while a BMI ≥ 30 kg/m^2 indicates obesity and is associated with increased mortality (4). However, the metabolic defects caused by obesity are more linked to the location rather than the total amount of adipose tissue (AT). Abdominal AT can be more accurately measured by the waist circumference and the waist-to-hip ratio. Abdominal fat is subdivided into visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). VAT represents

around 10% of body fat (5) and is correlated with higher risk of developing IR, hypertension and CVD. In contrast, SAT (>85% of the total body fat) is only mildly associated with risk of developing CVD or related pathologies. In fact, a BMI ≥30 kg/m^2 does not inevitably induce IR and comorbid metabolic disorders as demonstrated by a prevalence of approximately 6-40% of obese individuals that are metabolically healthy (6). This hypothesis is strengthened by the fact that metabolically healthy obese (MHO) subjects have lower fat content in their VAT than regular obese people and that they display less cardiovascular events and normal insulin sensitivity (6). The mechanisms responsible for the development of "healthy obesity" are subject of intense research and it seems that factors involved in lipogenesis and lipid metabolism may (at least partly) explain this phenotype. Apart from VAT and SAT, fat can accumulate in other storage areas localised in various tissues (ectopic fat) or at the level of the cardiovascular system (myocardial, perivascular and epicardial fat depots) (7).

Inflammation in obesity: cellular responses

The historical viewpoint of obesity as a simple lipid storage disease has progressively been replaced by the concept that obesity is a chronic inflammatory disease implicating adipocyte dysfunction and endocrine activity of AT (8). Once entering adipocytes, free fatty acids (FFA) can be oxidised or transformed into triglycerides (9). When present in excess, FFA or triglycerides are metabolised into fatty acid intermediates that can activate pro-inflammatory kinases such as protein kinase C (PKC), IκB kinase (10) and c-Jun *N*-terminal kinase (JNK), which inhibit insulin receptor signalling by phosphorylating insulin receptor substrates (8). Moreover, FFA induce activation of the innate immune receptor toll-like receptor-4 (TLR4) and the downstream transcription factor nuclear factor κB (NF-κB), thereby leading to IR (11).

Other cellular key players involved in AT inflammation are macrophages and T-cells. Obese individuals express cytokines (interleukin [IL]-6, tumour necrosis factor α [TNF-α]), chemokines such as monocyte chemoattractant protein 1 (MCP-1, also named chemokine [C-C motif] ligand CCL-2), CCL-7, CCL-8, CXCL-14 as well as C-C and CXC chemokine receptors CCR-2 and CXCR-2 in VAT and SAT. Among all the chemokines implicated in macrophages chemotaxis, CCR-2 and its ligand CCL-2 seem to play a predominant role in the recruitment of monocytes into AT (12). The levels of pro-inflammatory molecules such as TNF-α, IL-6, IL-1 and CCL-2 are increased in the perivascular adipose tissue (PVAT) of subjects without CAD relative to those found in other AT depots (13).

However, these cytokines are expressed at low levels by adipocytes. Whole body AT (comprising VAT, SAT and PVAT) expression of IL-6, TNF-α and CCL-2 reaches only 15–30%, 5% and 10–15%, respectively, while the major expression is produced by non-adipose cells of the stromal vascular fractions, mainly macrophages (14–16).

AT of obese mice and humans contains distinct macrophage populations characterised by the expression of different surface markers and cytokines released (17) (►Table 1). Several macrophage phenotypes have been described depending on environmental signals. The classical M1 macrophage population displays pro-inflammatory properties and is induced by pro-inflammatory molecules such as interferon-γ (IFN-γ), lipopolysaccharide (LPS) or TNF-α. M2a macrophages exert anti-inflammatory properties and are induced by IL-4 and –13. The M2b type II phenotype is engendered by TLRs or IL-1 receptor (IL-1R) agonists and drives essentially T helper 2 cell (Th2) responses. Despite their anti-inflammatory function M2b macrophages concomitantly generate the pro-inflammatory cytokines TNF-α, IL-1 and IL-6. Finally, IL-10 is an inducer of the regulatory M2c macrophage phenotype (17). Obesity induces the switch of anti-inflammatory M2 macrophages to a pro-inflammatory M1 phenotype (17). M1 macrophages accumulate in AT of diet-induced obese mice where they adopt a crown-like shape around necrotic adipocytes (17) and participate to IR by the expression of pro-inflammatory cytokines TNF-α, IL-6, chemokine receptor CCR-7 and reactive oxygen species (ROS) (18).

In human AT, the number of macrophages correlates with the BMI. Human adipose tissue macrophages (ATM) express M2 markers such as mannose receptor (MR) and CD163, but are also able to secrete pro-inflammatory mediators such as TNF-α, IL-6, IL-1 and CCL-2, thereby contributing to the development of IR (17). It has been shown that peroxisome proliferator-activated re-

Table 1: Macrophage heterogeneity in obese and lean adipose tissue.

Phenotype	Inducers	Adipose tissue state	Role in adipose tissue
M1	IFN-γ, LPS, TNF-α (17).	Obese (17).	Pro-inflammatory, production of TNF-α, IL-6, CCR-7 and ROS (17, 18).
M2a	IL-4, IL-13 (17).		
M2b	TLR ligands, IL-1R agonists (17).	Lean (17, 18).	Anti-inflammatory, predominantly production of IL-10 (18).
M2c	IL-10 (17).		

M1: classical pro-inflammatory macrophage; M2: alternative anti-inflammatory macrophage; IFN: interferon; LPS: lipopolysaccharide; TNF: tumour necrosis factor; IL: interleukin; IL-1R: interleukin-1 receptor; TLR: toll-like receptor; CCR: chemokine receptor; ROS: reactive oxygen species.

ceptor (PPAR)-γ activation modulates macrophage polarisation to an anti-inflammatory M2 state in mice and human (19).

Apart from macrophages, there is mounting evidence for the importance of T-cells in obesity-associated inflammation. T-cells are present at higher numbers in the VAT of diet-induced obese mice compared to chow fed mice. The recruitment of T-cells to AT is triggered by CCL-5 and its receptor CCR-5, which are upregulated in VAT of obese mice following TNF-α stimulation (20). Obesity is associated with increased T helper 1 (Th1) cell counts within AT, which secrete pro-inflammatory cytokines and enhance M1 macrophage recruitment/polarisation. A concomitant decrease in anti-inflammatory Th2 and regulatory T-cells (Tregs) within obese AT occurs favouring a pro-inflammatory environment (21). There is experimental evidence that Tregs control AT inflammation in ob/ob mice (22). Oral administration of anti-CD3 antibody in conjunction with the natural killer T-cell inducer, beta-glucosylceramide, into obese mice increased Treg numbers, while reducing the expression of TNF-α and macrophage content within AT. These findings suggest that adaptative immunity, via the involvement of T-cells, plays a crucial role in AT inflammation during the development of obesity.

Adipose tissue derived bioactive molecules

AT produces a plethora of bioactive molecules (adipokines) implicated in glucose and lipid metabolism as well as in the regulation of inflammation. An altered expression of these factors, as a consequence of obesity or adipocyte dysregulation, contributes to several diseases via dysfunctional immune reactions.

Pro-inflammatory adipokines

TNF-α is a cytokine secreted by adipocytes and pro-inflammatory macrophages and is over-expressed in obese animals and humans as compared to lean subjects (23), however, its levels in MHO individuals are still under debate (24, 25). TNF-α is correlated with waist-to-hip ratio rather than with BMI, suggesting a role of abdominal AT in the expression of this adipocytokine (26). An increased serum level of TNF-α is associated with enhanced lipolysis leading to IR and hyperinsulinaemia (27). In addition, TNF-α induces the production of other pro-inflammatory adipokines such as IL-6, leptin, resistin and CCL-2 (27).

IL-6 is a pro-inflammatory cytokine implicated in the regulation of inflammation in the acute phase by triggering the release of C-reactive protein (CRP), a major cardiovascular risk factor (28). Unhealthy obese display higher levels of IL-6 as compared to lean and MHO individuals (29).

Leptin is a pro-inflammatory adipokine, produced from the *ob* (or *Lep*) gene in adipocytes, which plays a role in appetite regulation, body weight monitoring and inflammation by activating its receptor in the hypothalamus (30). In sera of obese subjects, a two- to 30-fold increase of leptin levels is found as compared to those found in lean subjects (31). Interestingly, leptin levels are also higher in MHO subjects as compared to normal-weight individuals (24). Apart from regulation of appetite, another function of leptin is to stimulate the immune response. Leptin induces monocyte proliferation and their release of enhanced levels of TNF-α and IL-6 that in turn, can induce leptin expression (32). In macrophages, leptin also induces the release of CCL-3, CCL-4 and CCL-5 (32). Another effect of leptin is to enhance the production of ROS by monocytes and natural killer T-cells, leading to enhanced oxidative stress (33). Leptin also plays a role during the adaptive immune response by favouring Th1 cytokine production (33).

Resistin, also known as FIZZ3 (found in inflammatory zone) and ADSF (adipocyte-specific secretory factor), is a cystein-rich protein whose implication in obesity and IR are still not completely understood. Pro-inflammatory properties of resistin have been described, such as the activation of TNF-α and IL-6 production by monocytes and macrophages (34). In endothelial cells resistin has been found to favour leukocyte adhesion by increasing vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression as well as fractalkine and P-selectin (35).

The murine homolog of resistin is expressed as an adipokine in white adipocytes. In obese mice, circulating levels of resistin are increased compared to non-obese controls (36). In contrast, resistin deficiency was reported to worsen obesity in ob/ob mice. This effect was accompanied by a decrease in triglycerides, cholesterol as well as blood glucose and insulin levels (37).

In humans, there is no difference between resistin levels in obese and MHO subjects, even when both groups are compared to lean subjects (24). Human resistin was initially described as being produced by inflammatory cells located outside the AT and its expression seemed to be related to PPAR-γ activity (38). Further studies have shown that human resistin expression is induced by monocytes and macrophages via other pro-inflammatory adipokines, including IL-6 and TNF-α (39), and is inhibited by PPAR-γ expressed in macrophages (40). In keeping with a PPAR-γ-mediated inhibitory effect on resistin, the activation of PPAR-γ with thiazolidinediones (TZD) was shown to repress the expression of resistin from human macrophages (38). Resistin levels also increase in abdominal AT of obese humans (41). To date, there is still debate about the exact role played by resistin in obesity, IR and T2DM.

Among the chemokines expressed in AT, CCL-2 seems to be the only one to be secreted in the extracellular space where it induces monocyte recruitment into AT. This chemotactic molecule is therefore one of the central mediators of inflammation during obesity. Obese diabetic and high-fat diet fed mice showed secretion of CCL-2 by adipocytes (42), and in mice lacking the CCL-2 receptor CCR-2, the development of obesity and inflammation was attenuated (43). However, CCL-2 deficiency did not induce a difference in macrophage infiltration in AT (44) suggesting that CCR-2-mediated effects on obesity is driven by other chemokines.

Anti-inflammatory adipokines

Adiponectin is an anti-inflammatory adipokine present at high levels in plasma (45) where it forms oligomers, resulting in the

presence of trimer, hexamer and other high-molecular-weight forms. Adiponectin acts on a large panel of tissues due to the expression of its three known receptors in various organs. While the adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) are expressed in muscle and liver, respectively, the third receptor T-cadherin is expressed in the cardiovascular and central nervous system and binds high-molecular-weight forms of adiponectin (46). Obese human subjects have significantly lower plasma adiponectin levels in comparison to lean individuals (47) but there are still some controversies concerning adiponectin levels in MHO individuals. In fact, some studies describe an increased concentration of adiponectin in MHO subjects as compared to unhealthy obese patients (48, 49) while other reports do not find any differences (24, 29). As opposed to the other adipokines, adiponectin improves insulin sensitivity and decreases the risk of developing T2DM. Reciprocally, it has been shown that adiponectin deficiency increases IR and the risk of developing T2DM (45). Mutations that block the multimerisation of adiponectin into high-molecular-weight forms have been found to correlate with T2DM suggesting a protective role for high-molecular-weight adiponectin in this disease (50). A potential mechanism for the beneficial effects of adiponectin is the activation of adenosine monophosphate-activated kinase (AMPK) and the inhibition of TNF-α and IL-6 (51). Adiponectin release from AT increases in response to PPAR-γ activation and is directly associated with the decrease in VAT (52). Adiponectin displays anti-inflammatory actions by inhibiting macrophage maturation into foam cells. Ohashi et al. showed enhanced pro-inflammatory M1 and decreased anti-inflammatory M2 macrophage accumulation in the AT of adiponectin-deficient mice (53). The mechanisms driving these anti-inflammatory properties of adiponectin still need to be established. In view of a therapeutic strategy for preventing obesity-induced diabetes, some drugs have been used to enhance adiponectin levels. For example PPAR-γ agonists have been shown to enhance adiponectin levels in mice and humans (54). The therapeutic potential of these molecules will be discussed below.

Other adipokines

FFA are released after AT lipolysis. Their blood levels are higher in subjects with abdominal fat accumulation and IR than in healthy subjects (55). Several hypotheses on the mechanisms underlying FFA trafficking have been proposed (56). One of these describes leptin resistance and an inappropriate expansion of AT as the source of comorbid metabolic alterations induced by obesity, resulting in an excess of lipids in peripheral tissues and IR (30, 56). A second hypothesis suggests a mechanism in which the hypertrophy of adipocytes impairs adipocyte behaviour, favouring apoptosis. FFA release is consequently exacerbated, leading to inflammation and IR (56). Altogether, these observations suggest that FFA release is a strong inducer of IR in tissues targeted by insulin. Nevertheless, a systematic review of the literature performed by Karpe et al. in 2011 suggests that the association between plasma FFA concentrations and obesity is not always present (57). In fact, as tissue mass develops, FFA release by AT is not increased but is rather decreased. In addition, the authors conclude that IR in the obese state does not necessarily imply an increase in FFA and *vice versa*. This observation is supported by a clinical study reporting elevated FFA levels in women as compared to men while having higher insulin sensitivity (58).

Plasminogen-activator inhibitor 1 (PAI-1) is an inhibitor of fibrinolysis. It is overexpressed in AT of obese individuals, thus enhancing the risk for thrombosis in these subjects (59). By contrast, lean and MHO subjects show lower PAI-1 concentrations (60). PAI-1 is produced and released into the circulation by endothelial cells and adipocytes and its blood concentration is dependent on the amount of VAT (61). The expression of PAI-1 is mediated by cytokines including TNF-α and the ligands of the glycoprotein 130 (gp130) receptor cytokine family such as oncostatin M, leukaemia inhibitory factor (LIF) and cardiotrophin-1 (CT-1). Interestingly, IL-6 is also member of this family. Rega et al. showed that oncostatin M and IL-6, which are produced by macrophages, induce a >10-fold increase in PAI-1 production in humans pre-adipocytes and adipocytes extracted from subcutaneous and visceral AT (62).

Elevated PAI-1 levels correlate with almost all factors contributing to MS, such as hyperinsulinaemia and occurrence of T2DM (61). As a consequence, weight loss and consequent decrease in IR is associated with a significant reduction in PAI-1 levels (63).

Perivascular adipose tissue-derived adipokines and cardiovascular disease

Apart from the correlation between VAT inflammation and atherosclerosis, the link between obesity and CVD is further supported by the existence of PVAT, allowing for the diffusion of adipokines into the vessel wall. In non-obese mice and human PVAT consists of a mixture of adipocytes, collagen fibers and resident macrophages (64). PVAT from obese animals was shown to contain increased numbers of $CD8^+$ T-cells and M1 activated macrophages with concomitant decrease of adiponectin levels (65, 66). It has been shown that adipocytes from coronary artery PVAT have a morphology comparable to VAT adipocytes and produce the same adipokines (67). CCL-2 is secreted by human aortic PVAT, where it exerts its chemotactic functions on monocytes (68). PVAT further releases a large variety of bioactive molecules including leptin, adiponectin, resistin, IL-6, PAI-1 and TNF-α (68). Moreover, FFA are released by PVAT (68). Importantly, obesity induces a decrease of adiponectin levels in PVAT, while expression of other adipokines is increased (66). In a paracrine manner, PVAT adipokines directly act on the vessel wall, thus contributing to CVD (69). The mechanisms allowing the diffusion of adipokines from PVAT into the vessel wall are still not understood. One hypothesis is that adipokines pass from PVAT into the vascular wall via *vasa vasorum* (70). PVAT adipokines are thought to affect vasoreactivity and vascular smooth muscle cell (VSMC) proliferation and migration, which is likely to affect vascular diseases such as hypertension, atherosclerosis and thrombosis (71) (▶Figure 1). The vascular effects of these adipokines secreted by PVAT in both obesity

and CVD are summarised in ▶Table 2 and will be discussed below.

Adipokines in endothelial dysfunction and hypertension

A frequent complication of obesity is increased blood pressure and subsequent arterial hypertension, which is also a cardiovascular risk factor by itself (72). Endothelial dysfunction contributes to the onset of hypertension. The vascular endothelium releases factors regulating the vascular tone such as nitric oxide (NO), endothelin-1 (ET-1), prostacyclin and cyclooxygenase (73). However, this normal endothelial function is impaired in obese and insulin resistant individuals (74).

The contribution of TNF-α to endothelial dysfunction has been highlighted in obese and T2DM mice (75). Increased TNF-α expression was found to induce NF-κB signalling, activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and production of ROS, thereby promoting endothelial dysfunction. Increased release of TNF-α and FFA also contributes to en-

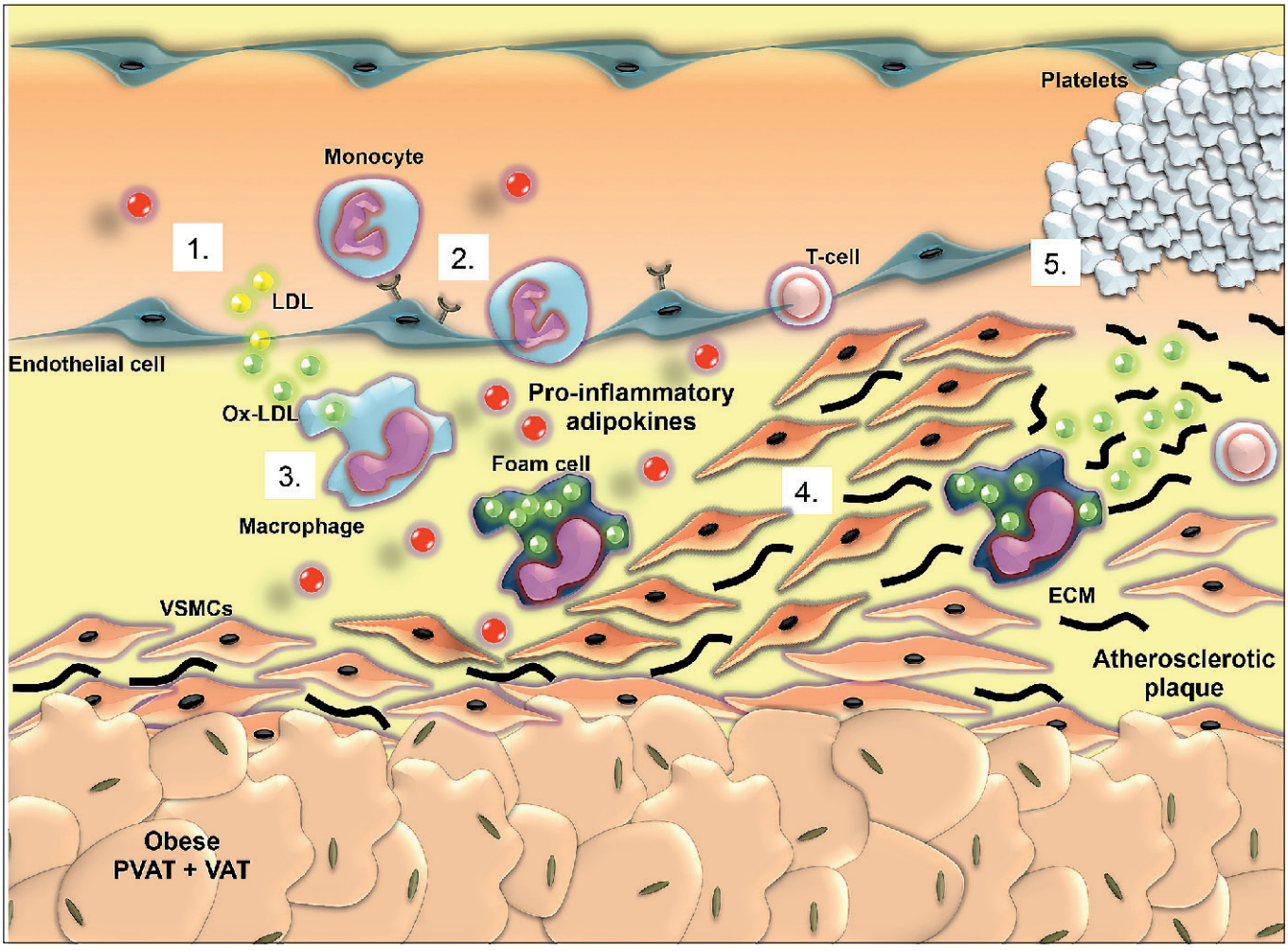

Figure 1: Implication of adipokines in the process of atherosclerosis and thrombosis. In the obese state, perivascular adipose tissue (PVAT) and visceral adipose tissue (VAT) express and release adipokines implicated in atheroma formation and thrombosis. The mechanism leading from atherosclerosis to thrombosis is initiated by endothelial dysfunction (step 1), triggered by pro-inflammatory adipokines, that will increase endothelial cell permeability to facilitate LDL entry. Once entering the vascular intima LDL undergoes oxidation. Resistin stimulates adhesion molecule expression on endothelial cells, which facilitates monocyte adherence (step 2). Monocyte recruitment into the intima is enhanced by CCL-2 that is released by PVAT in response to IL-6. Monocytes differentiate into macrophages that will accumulate modified LDL and transform into foam cells (step 3). This phenotypic change is favoured by resistin and leptin. The pro-inflammatory activity of macrophages as well as adipokines (FFA, TNF-α, resistin and leptin) induces the proliferation and migration of vascular smooth muscle cells (VSMC) from the media to the intima where they produce extracellular matrix components (ECM) thus contributing to the formation of a fibrous cap (step 4). TNF-α, FFA and leptin contribute to the release of PAI-1 from adipose tissue. PAI-1 in concomitance with resistin induces plaque destabilisation, thus increasing the risk of plaque rupture. When a plaque ruptures, it releases its thrombogenic content into the blood-stream, thereby inducing platelet aggregation that is enhanced by the action of TNF-α and IL-6. At this step thrombosis occurs. The levels of the anti-inflammatory adiponectin which counteracts all these effects is decreased in obese PVAT and VAT (step 1–4).

Table 2: Role of adipokines in obesity and in cardiovascular disease.

Adipokine	Function in obesity	Function in cardiovascular disease
TNF-α	↑ IR , hyperinsulinaemia, inflammation (27).	↑ endothelial dysfunction (75, 76), ↑ hypertension (77), ↑ VSMC proliferation and migration (142, 143), ↑ atheroma formation (104), ↑ thrombosis (127, 128).
IL-6	↑ CRP release, inflammation (28).	↑ endothelial dysfunction (80, 81, 102), ↑ hypertension (81), ↑ adhesion molecules and inflammation (102), ↑ thrombosis (125, 126).
Leptin	Regulates appetite (30), ↑ inflammation (32, 33), ↑ ROS production (32).	↑ endothelial dysfunction (83), ↑ VSMC proliferation and migration (147, 148), ↑ hypertension (84–87), ↑ foam cell and atheroma formation (109, 110, 113, 114), ↑ thrombosis (135–137).
Resistin	↓ glucose homeostasis and insulin sensitivity (34, 37, 38), ↑ T2DM (37), ↑ inflammation (41).	↑ endothelial dysfunction (90, 93), hypertension (89, 93), ↑ VSMCs proliferation (106, 142), ↑ foam cell formation (107), ↑ thrombosis (138).
Adiponectin	↓ IR and T2DM (45, 50), ↓ inflammation (51, 53).	↓ endothelial dysfunction (94, 96), ↓ VSMCs proliferation (121, 144) and migration (121, 146), ↓ hypertension (97–100), ↓ inflammation (117, 118), ↑ plaque stability (123), ↓ thrombosis (139–141).
CCL-2	↑ monocyte recruitment (42, 43, 68).	↑ monocyte recruitment (102).
FFA	↑ inflammation and IR (17, 30, 56).	↑ endothelial dysfunction (77), ↑ hypertension (77), ↑ VSMC migration (146), ↑ thrombosis (129).
PAI-1	Correlates with IR and T2DM (59, 61).	↓ VSMC migration (133), ↑ thrombosis (128), ↑ thrombosis by blocking fibrinolysis (58, 59).

IR: insulin resistance; VSMC: vascular smooth muscle cell; CRP: C-reactive protein; T2DM: type-2 diabetes; ROS: reactive oxygen species.

dothelial dysfunction by reducing the expression of endothelial nitric oxide synthase (eNOS), and thus NO synthesis, leading to reduced vasorelaxation (76, 77). Compared with individuals with normal blood pressure, circulating levels of TNF-α and IL-6 are augmented in hypertensive subjects (78). Endothelial cells can produce IL-6 (79), but do not express IL-6 receptor (IL-6R). It is thought that the effects of IL-6 in endothelial cells are mediated through trans-signalling, which induces an increased expression of adhesion molecules which promotes inflammation (80). Schrader et al. investigated the role of IL-6 in the regulation of oxidative stress and vascular dysfunction in response to angiotensin II (Ang-II) in IL-6 deficient mice (81). They found that chronic infusion of Ang-II (1.4 mg/kg/d for 14 days) induced less endothelial dysfunction in carotid arteries of IL-6-deficient mice compared to controls as measured by vascular responses to acetylcholine. Moreover, they found that Ang-II treatment decreased eNOS expression in the controls but not in IL-6-deficient mice (81). Leptin receptors are expressed in vascular endothelial cells and their activation by leptin was reported to induce eNOS expression and vasodilation (82). But there is also controversial evidence that hyperleptinaemia induces a decrease in NO release and up-regulation of ROS in aortas of obese mice (83). Overexpression of leptin has been described to increase blood pressure in mice, even in non-obese state (84), whereas leptin-deficient ob/ob mice do not develop hypertension (85). Apart from its effects on the release of endothelial factors, hyperleptinaemia is linked to hypertension through a mechanism mediated by the central effects of leptin on the sympathetic nervous system (SNS) activity, as SNS activation is increased in obesity and may provoke an enhancement in blood pressure (86). In humans, correlations between plasma leptin levels and hypertension have been found in both hyperleptinaemic men and women (87). Strikingly, human leptin deficiency caused by missense mutation is associated with decreased blood pressure, but severe obesity (88).

Resistin also plays a role in hypertension. High plasma resistin levels were associated with an increased risk of developing hyper-

tension in non-diabetic women (89). Like for the other adipokines, the effects of resistin on blood pressure are also linked to its action on endothelial cells. Incubation of human umbilical vein endothelial cells (HUVECs) with resistin-rich supernatants harvested from epicardial AT of patients with acute coronary syndrome was shown to stimulate endothelial cell permeability (90). Resistin further activates the production of ET-1, an effective vasoconstrictor in endothelial cells, via an Extracellular signal-Related Kinase (91) 1/2 dependent pathway (92). Chen et al. reported that resistin reduces eNOS expression and increases ROS in human coronary artery endothelial cells through the activation of p38 and JNK (93). Conversely, adiponectin plays a protective role in endothelial function. Adiponectin-deficient mice displayed reduced eNOS expression and decreased NO production compared to the levels found in wild-type (WT) mice. Moreover, these effects were reversed upon administration of recombinant adiponectin (94). In humans, adiponectin induces NO production and endothelial-dependent vasodilation in lean subjects but not in obese patients suffering of MS (95). Adiponectin exerts its beneficial effects on NO production via AMPK-induced phosphorylation of eNOS (96). As a consequence, adiponectin improves blood pressure. Hypertensive rats exhibit impaired vascular AMPK activation in response to adiponectin. This effect is reversed by caloric restriction, which improves adiponectin levels and consequently decreases blood pressure by favouring eNOS expression and NO release (97). In other experimental settings performed in hypertensive adiponectin-deficient mice, adiponectin supplementation was shown to decrease blood pressure (98). Moreover, infusion of different adiponectin concentrations in rats induced a decrease of renal sympathetic nerve-induced blood pressure in a dose-dependent manner (99). Finally, there is a positive correlation between plasma adiponectin levels and endothelium-dependent vasorelaxation in humans, suggesting relevance for human pathology (100).

Adipokines in atherosclerosis and thrombosis

Impairment in PVAT function resulting from adipocyte expansion induces the release of adipokines and the infiltration of inflammatory cells which altogether contributes to atherogenesis (101). IL-6 triggers the expression of adhesion molecule VCAM-1 and chemokine CCL-2 in vascular endothelial cells, thus allowing the recruitment of inflammatory cells into the vascular intima (102). Adhesion molecule expression on endothelial cells is also induced by TNF-α whose concentration is increased together with IL-6 and leptin in CAD patients (103). There is a positive correlation between plasmatic TNF-α elevation and early atheroma formation in middle-aged healthy men (104).

In vitro and animal studies further support an implication of resistin in atherosclerosis. Human recombinant resistin was shown to play a pro-atherogenic role by increasing the production of ET-1, adhesion molecules and CCL-2 in endothelial cells, thus allowing the recruitment of monocytes to the endothelium (105). Despite its stimulatory actions on VSMC proliferation and migration (106), another important feature of resistin is that it increases lipid absorption by macrophages and consequently foam-cell development (107). In addition, there is evidence for a positive correlation between increased plasma resistin levels, atherosclerosis and CAD (108).

As to the role for leptin in atherosclerosis, some controversies exist. The fact that leptin was shown to promote oxidised lipid absorption by foam cells and ROS production suggests a pro-atherogenic role (109). In the same direction, leptin- and leptin-receptor deficient mice were protected against neointima formation after arterial injury (109). Leptin deficiency in low-density receptor deficient ($LDLR^{-/-}$) mice reduced the lesions by 2.2– to six-fold when compared with mice with matched cholesterol levels and decreased Th1 responses together with improved Treg activity (110). By contrast, daily injection of leptin for two months in apolipoprotein E deficient ($ApoE^{-/-}$) mice did not affect the lesion size, as compared to non-treated mice, but increased vascular calcification, thereby increasing plaque instability (111). Other animal studies reported protective effects of leptin in atherosclerosis. Hasty et al. showed that $LDLR^{-/-}$ mice lacking (ob/ob) display severe hypercholesterolaemia, hypertriglyceridaemia and atherosclerosis (112). Similar discrepancies concerning the role of leptin in atherosclerosis are found in humans. Correlations between high leptin levels and CAD have been reported by several studies (113, 114), while other failed to confirm this association (115, 116).

As opposed to leptin, high levels of adiponectin are protective against atherosclerosis due to anti-inflammatory effects on cellular key players of atherosclerosis. In particular, adiponectin blocks adhesion molecule expression in endothelial cells by inhibiting NF-κB (117) and activates reverse cholesterol transport in macrophages (118). Moreover adiponectin has been shown to inhibit VSMC proliferation and migration by blocking the ERK 1/2 pathway (119). Overexpression of adiponectin in $ApoE^{-/-}$ mice reduces atherosclerotic lesions (119). Moreover, adiponectin-deficient mice respond to external vascular cuff injury with a two-fold higher neointima formation compared to WT mice (120). In humans, lower plasma levels of adiponectin are a prognostic marker of CVD, independently of obesity (121). The carotid intima-media thickness is inversely correlated to adiponectin concentrations (122). Pioglitazone, a PPAR-γ agonist, leads to increased adiponectin levels and the formation of more stable plaques by reducing necrotic core composition (123).

Plaque stability is an important factor bridging between atherosclerosis and thrombosis. Unstable plaques are more susceptible to rupture. When such an event occurs, the lipidic and vascular matrix content of the plaque is released in the blood flow. This induces platelet adhesion, activation and aggregation leading eventually to thrombosis, the major cause of myocardial infarction. Some evidence indicates that obesity and IR may participate in the mechanisms leading to pro-thrombotic events. In the obese state, AT produces numerous adipokines involved in thrombus formation. Among these, TNF-α and IL-6 enhance the synthesis of tissue factor (TF), a coagulation factor allowing thrombin formation (124). In humans, *in vivo* administration of IL-6 leads to increased platelet numbers (125). Moreover, IL-6 favours the release and the activation of thrombin by decreasing the synthesis of the potent anti-coagulatory factor anti-thrombin (126). So far, the

contribution of TNF-α to thrombosis in humans is not clear. TNF-α enhances platelet aggregation (127) and induces the synthesis of PAI-1 and leptin in AT (128). PAI-1 is a pro-thrombotic agent associated with increased cardiovascular risk (128). PAI-1 expression is also induced by FFA (129). On the other hand, insulin favours fibrinolysis by suppressing PAI-1 (130). The levels of PAI-1 are enhanced in obese compared to lean individuals and correlate with visceral obesity (61, 74). This in part explains the pro-thrombotic state of obese individuals displaying IR. In addition to its pro-thrombotic properties, PAI-1 inhibits VSMC migration and neointima formation (131). Conversely, Samarakoon et al. described PAI-1 as an inducer of VSMC migration (132). A different study again reported inhibitory effects of PAI-1 on intimal hyperplasia following balloon injury in rat carotids (133). In particular, PAI-1 reduced VSMC migration by promoting apoptosis. However, the effects of PAI-1 on neointima formation were not accompanied by thrombosis. More recently, a role for leptin in endothelial PAI-1 expression was described (134). It was shown that ApoE$^{-/-}$ mice treated with recombinant leptin had increased atherosclerosis and thrombosis (135). Nakata et al. demonstrated that leptin at concentrations comparable to plasma levels in obese subjects was able to enhance adenosine 5-diphosphate (ADP)-induced aggregation of human platelets *in vitro* (136). Moreover, a role for leptin in TF activation was described. In obese subjects, the increased leptin levels were associated with elevated levels and activation of TF in monocytes (137). In human coronary artery endothelial cells, resistin was found to induce TF expression via production of ROS and activation of NF-κB (138).

Finally, adiponectin displays antithrombotic effects. AdipoR1 and AdipoR2 receptors are expressed in mouse and human platelets (139). Platelets from adiponectin-deficient mice are more reactive to ADP activation (139). In human adiponectin inhibits platelet aggregation and thrombus formation (140). However, adiponectin was also shown to inhibit TF expression in human endothelial cells (141). Given the above described anti-inflammatory properties of adiponectin, it is likely that its anti-thrombotic effects are due to its inhibitory action on pro-inflammatory cytokines.

Adipokines in vascular remodelling and restenosis

Published data suggest that adipokines secreted by PVAT participate in vascular remodelling (142). For example, there is substantial evidence for stimulatory effects of TNF-α and resistin in the activation of VSMC growth. While TNF-α-mediated effects on VSMC seem to be mediated through NF-κB pathway (143), resistin induces cell proliferation through activation of the ERK 1/2 and the protein kinase B (Akt) pathways (106).

In contrast to the pro-inflammatory role of TNF-α and resistin, adiponectin was described to inhibit VSMC proliferation in mice via the AMPK pathway (144). In human, adiponectin release by epicardial AT is decreased in both MS and CAD patients, suggesting that reduced concentrations of adiponectin in PVAT could contribute to atherosclerosis development (145). As reported by Lamers et al., VSMC migration was activated when cells were cultured in adipocyte-conditioned media produced from human adipocytes supplemented with oleic acid. Conversely, treatment with recombinant adiponectin had the opposite effect (146). Finally, there is evidence for a pro-inflammatory role of leptin in VSMC proliferative and migratory activities in a model of neointima formation after vascular injury (147). Another *in vivo* study of intimal hyperplasia revealed that VSMC proliferation and migration was increased in response to leptin via MAPK and PI3K pathways (148). However, in human VSMC leptin exhibited an inhibitory effect on cellular growth (149).

Altogether the above-mentioned effects of adipokines on VSMC proliferation and migration also suggest a role for these proteins in restenosis. In a recent study, Manka et al. provide some evidence for a participation of PVAT in this pathology (150). The authors transplanted thoracic aortic PVAT from donor mice fed a high-fat diet to the carotid artery of LDL$^{-/-}$ mice fed a high-fat diet and performed wire injury two weeks after. After two additional weeks vessel observation revealed an increased neointima formation that was dependent of CCL-2. In fact, depletion of CCL-2 in PVAT reduced neointimal hyperplasia in recipient mice (150).

In a different study, wire-induced endovascular injury of WT mouse femoral arteries induced increased mRNA levels of TNF-α, IL-6, CCL-2 and PAI-1 and decreased levels of adiponectin in the PVAT (151). Similar results were obtained after ballooning of rat iliac artery (151). Similar experiments in CCL-2$^{-/-}$ mice induced an increase in PVAT adiponectin levels, while TNF-α$^{-/-}$ mice had decreased IL-6, CCL-2 and PAI-1 levels (151). Moreover, TNF-α depletion reduced neointima formation while local delivery of TNF-α in the PVAT enhanced hyperplasia (151). Elevated TNF-α levels are also associated with increased incidence of restenosis in humans (152). Likewise, serum resistin levels have been associated with restenosis in patients who underwent percutaneous coronary intervention (153) and have been proposed as potential biomarkers for this pathology (154).

A potential role of leptin in the regulation of restenosis after arterial injury has been evidenced in diabetic mice in which the depletion of leptin receptor induces a decrease in neointima formation of about 90% (155). In humans, the levels of leptin are increased in non-diabetic patients with restenosis after stenting while no differences are observed in patients without restenosis or in control individuals (156).

As to the role of adiponectin, many studies describe this anti-inflammatory adipokine as protective against restenosis. In mice, adiponectin deficiency induces acute formation of neointima after arterial injury (157). The inverse effect has been observed when adiponectin was supplemented with an adenovirus to the animals (157). Low levels of adiponectin in patients undergoing coronary stenting have been described as potential predictor of in-stent restenosis (158, 159). However, published data suggest that changes in adiponectin levels may predict the severity of restenosis within six months but not at a late stage after stenting (160).

Therapeutic implications

Restoring the balance between pro- and anti-inflammatory adipokines could represent a therapeutic strategy to treat or prevent CVD linked to obesity. Both life style changes and pharmacological approaches could be useful for this purpose, including weight loss or treatment with anti-inflammatory drugs.

Weight loss

Physical exercise, caloric restriction and lifestyle changes lead to the reduction of visceral obesity and IR, delay the onset of T2DM and prevent CVD. Exercise and diet efficiently reduce TNF-α and IL-6 levels with concomitant increase in IL-10 levels in obese patients (161). Moreover, it has been shown that 12 weeks of restrictive diet accompanied by a program of exercise decreased TNF-α, IL-6, resistin and leptin levels, while increasing IL-10 and adiponectin in obese patients (162). However, the effects may not be solely due to caloric restriction and exercise, as patients enrolled in this study received sibutramine, an inhibitor of noradrenaline/serotonin reuptake and anti-obesity drug. Despite its long-term effects on body weight loss and its capacity to improve glucose, insulin and lipid levels, major safety concerns have been raised since sibutramine was associated with increased incidence of myocardial infarction and stroke in obese or overweight patients (163). To date, orlistat is the only approved drug for the long-term treatment of obesity in the clinical practice despite safety concerns about the risk to mediate severe liver injury (164). Besides their role in weight loss, sibutramine and orlistat were reported to reduce TNF-α, IL-6 and resistin and to increase adiponectin levels (165, 166). This suggests that weight loss via caloric restraint, exercise or using drugs increasing adipokine expression could limit the occurrence of CVD. However, in morbid obese people these strategies are often inefficient, and these patients need to undergo bariatric surgery to ensure effective weight loss and significantly improve or resolve diabetes, hyperlipidaemia, hypertension and other risk factors for CVD (167). In addition to loss of AT, bariatric surgery also induces beneficial changes in the levels of hormones and cytokines, including adipokines. For example, leptin levels have been shown to decrease about two weeks after bariatric surgery in a long-term manner (168). Similar observations were made for other pro-inflammatory adipokines such as IL-6 and CRP (168). According to animal studies, TNF-α levels also followed this pattern but there was no statistically significant decrease in patients who underwent bariatric surgery (168). The effects of bariatric surgery on plasma resistin levels are less clear as some studies report a decrease of resistin levels in obese subjects 12 months after the intervention while others do not find any significant change (reviewed in [169]).

Importantly, weight loss after bariatric surgery has been shown to reduce the levels of monocyte-platelet aggregates, which are markers of platelet overactivity and a source of pro-thrombotic factors such as TF (170). In accordance with a role for bariatric surgery in decreased risk of thrombosis, a study performed on thirty-seven obese adults showed that 18 months after the intervention there was a concomitant decrease of the visceral fat diameter and PAI-1 adipokine levels (171).

Confirming the benefits of weight loss on the production of adiponectin, animal studies show that the levels of this adipokine increase after bariatric surgery and correlate with delayed onset of T2DM and IR (168). The same effects were confirmed in patients in which post-surgical increase of adiponectin levels were significantly associated with improvement of dyslipidaemia and insulin sensitivity (168).

In conclusion, the decrease of visceral AT mass and chronic inflammation by modulating pro-inflammatory/pro-thrombotic and anti-inflammatory cytokines after surgical intervention participates in the reduction of IR, T2DM and CVD.

Anti-inflammatory therapies

The link between obesity-induced inflammation and CVD suggests that targeting inflammatory pathways limits the incidence of cardiovascular risk associated with excess of VAT or PVAT. Several anti-inflammatory drugs have been proposed in the context of obesity-associated inflammation, such as statins and TZD.

The effect of statin treatment on adipokine levels observed in clinical studies is controversial. Two months of simvastatin treatment decreased plasma concentrations of adiponectin in hypercholesterolaemic patients (172). By contrast, Qu et al. demonstrated that 12 weeks of therapy with atorvastatin or rosuvastatin in sixty-nine hypercholesterolaemic patients reduced LDL, matrix metalloproteinase (MMP)-9 and PAI-1 levels, and significantly increased adiponectin levels (173). Rosuvastatin more potently increased adiponectin levels than atorvastatin (67 % vs 15 %, respectively) (173). However, a long-term study enrolling 36 patients with MS and 20 healthy subjects did not reveal any effect of atorvastatin (10 mg/day for 6 months) on adiponectin, leptin or resistin levels (174). Some limitations of this study exist, such as variations in the body weight of the patients, lack of placebo group and low dosage of atorvastatin.

Of note, a new LDL-lowering strategy implicating resistin blocking is emerging. In fact, resistin stimulates the proprotein convertase subtilisin/kexin type 9 (PCSK9), a major player in cholesterol homeostasis (175). In $ApoE^{-/-}$ mice sirtuin 1 (Sirt1) activation provides atheroprotection by decreasing PCSK9 secretion and enhancing LDLR expression (176). In addition, phase I and II trials showed that monoclonal antibodies targeting PCSK9 significantly decrease LDL levels (177). Moreover, these antibodies directly interact with resistin that bears a similar cysteine-rich C-terminal domain than PCSK9. According to these findings, resistin inhibitors could offer new strategies to lower LDL levels in specific conditions like hereditary hypercholesterolaemia or in case of statin intolerance (175).

Another anti-inflammatory strategy is the use of PPAR-γ agonists (TZD) such as pioglitazone and rosiglitazone. These drugs improve metabolic parameters via their beneficial effects on adipocytes and have been implicated in the reduction of FFA and in the repression of pro-inflammatory gene expression (178). However, although TZD display positive effects on metabolic factors, some

indications render their use challenging in patients with heart failure or increased cardiovascular risk. In particular, rosiglitazone, but not pioglitazone, was reported to enhance myocardial ischaemia (179). Apart from their inhibitory action on FFA and pro-inflammatory molecules, TZD activate adiponectin expression in obese and healthy individuals (54). It has been proposed by Iwaki et al. that TZD could regulate adiponectin expression by inducing the binding of PPAR-γ to a potential PPAR-γ-responsive element in its promoter (180). Remarkably, TZD improve metabolic profile, without necessitating weight loss (181).

Apart from TZD, other molecules also activate adiponectin expression via PPAR-γ, including resveratrol and metformin (182, 183). Resveratrol, a product of grapes, is an anti-diabetic agent that improves insulin sensitivity by inhibiting inflammation and enhancing adiponectin levels (182). A recent study suggested that resveratrol up-regulates adiponectin expression and multimerization via DsbA-L, a newly identified protein that interacts with adiponectin (184). Resveratrol was shown to induce adiponectin polymerisation in 3T3L1 adipocytes. Interestingly, when Akt signalling was blocked, DsbA-L and adiponectin expression was enhanced. Conversely, inhibition of AMPK decreased DsbA-L and adiponectin levels. These observations suggest that these three pathways are implicated in the regulation of adiponectin expression. The second agent, metformin, is a biguanide commonly used to treat T2DM. Metformin decreases neoglucogenesis and reduces PPAR-γ-coactivator 1α in an AMPK-dependent manner (183). This suggests that metformin, like resveratrol, could induce adiponectin expression via AMPK. Zulian et al. indeed provided evidence that metformin can enhance adiponectin expression *in vivo* and *in vitro* (185). Incubation of SAT and VAT obtained from non-diabetic obese patients with metformin induced adiponectin expression solely in SAT explants. Moreover, treatment of 22 obese patients with metformin associated with lifestyle changes increased adiponectin levels and decreased inflammation (185).

Omega-3 polyunsaturated fatty acid (n-3 PUFAs) intake reduces triglyceride levels (9). n-3 PUFAs, comprising docosahexaenoic (DHA, 22: 6*n*-3) and eicosapentaenoic (EPA, 20: 5*n*-3) acids, act as anti-obesity agents by improving low-grade inflammation in AT related to NF-κB and PPAR-γ inhibition (186). Some indications also suggest that n-3 PUFAs are able to control adipokine synthesis in rodents and humans. *In vivo* and *in vitro* studies have shown a modulatory function of n-3 PUFAs on leptin levels. EPA at a concentration of 1 mM blocks leptin release from white adipocytes (187). Wistar rats fed with a high-fat diet containing 10% n-3 PUFAs for three weeks increased the oxidation of fatty acids and reduced plasmatic leptin levels (188). In humans, an eight week consumption of fatty seafood (150 g salmon, three times per week) associated with weight loss was shown to lower leptin concentration in men with a BMI of about 30 kg/m^2, thereby supporting the inhibitory effect of n-3 PUFAs on leptin secretion (189). In addition to the inhibitory effects of PUFAs on leptin expression, Flachs et al. demonstrated that mice fed a high-fat diet complemented with EPA/DHA for five weeks had increased adiponectin levels (190). This was recently confirmed by experiments performed on Sprague-Dawley rats fed a high saturated fatty acid diet associated with n-3 PUFAs for four weeks, which showed an increase in adiponectin expression in the soleus muscle (191). In human, a double-blind trial including 50 overweight subjects receiving daily oral administration of fish oil (1.1 g marine n-3 PUFAs) or olive oil, reported an increase of adiponectin serum levels after six weeks (192). However, these effects were small and did not imply any effect on other pro-inflammatory molecules, suggesting that the dose should be increased. Further studies are required in order to allow drawing firm conclusions on a potential effect of n-3 PUFAs on inflammatory markers.

Conclusion

Obesity induces adipocyte dysfunction, which is the key step in the development of pro-inflammatory state and FFA release. Macrophages and T-cells are major players of the systemic inflammation. Their number increases dramatically in human AT in correlation with the BMI, and their polarisation towards a pro-inflammatory phenotype in the AT favours atherogenesis and obesity. The subsequent adipocyte dysregulation induces an altered expression pattern of pro- and anti-inflammatory adipokines that are linked to several cardiovascular risk factors such as endothelial dysfunction and vascular remodelling, as well as clinical manifestations of atherosclerosis such as heart failure, myocardial infarction or stroke. Counterbalancing adipocyte dysfunction is an important therapeutic goal for which targeted strategies are urgently needed. Pharmacological interventions allowing either the blocking of signalling pathways involved in pro-inflammatory adipokine production, or the inhibition of FFA release show some limitations. Even if dietary supplements derived from fish oil seem to be promising tools to enhance anti-inflammatory response in AT, their use should imperatively be accompanied by the imposition of life-style changes, that are, at the moment, the safest way to reduce cardiovascular risk factors linked to obesity.

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Conflicts of interest

None declared.

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