

Adipose Tissue and Atherothrombosis

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Abstract

Obesity is associated with increased cardiovascular mortality and morbidity mainly through insulin resistance. Dysregulation of protein secretion by adipose tissue is involved in obesity-related diseases. Adipose tissue contributes to create a subinflammatory status which could explain the disturbances in the haemostatic and fibrinolytic systems observed in obesity. Elevated plasma levels of PAI-1 demonstrated the strongest association with the degree of insulin resistance and could be an underlying mechanism for the thrombotic tendency and the progression of atherothrombosis during obesity. The effect of PAI-1 was examined on adipose tissue growth in several mouse models as well as on adipocyte differentiation *in vitro*. Most of the data indicate that PAI-1 can effectively modulate weight gain and may be a potential therapeutic target for controlling cardiovascular morbidity in obese subjects.

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Introduction

Obesity is associated with increased cardiovascular mortality and morbidity. Numerous observations suggest that biologically active molecules produced by adipose tissue constitute a critical link between obesity and cardiovascular complications. Adipose tissue controls energy metabolism, but also represents a secretory tissue for adipocytokines (leptin, adiponectin...) able to modify some vascular responses, for plasminogen activator inhibitor 1 (PAI-1) which favors fibrin accumulation and for proinflammatory cytokines. Here, we review new advances in our understanding of mechanisms which link adipose tissue to vascular risk. A particular focus is on PAI-1.

Leptin

Leptin is a glycoprotein produced by the mature adipocytes. It plays a key role in the control of body fat stores. During weight loss, its plasma level decreases and allows a positive feedback on food intake and anabolic pathways. Conversely, when adipose mass increases, plasma leptin concentration increases as well, leading to decreased appetite and increased energy expenditure.

However, despite high circulating levels of leptin, obese subjects remain obese and leptin administration only slight-

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ly influences weight. These data have introduced the concept of leptin resistance. This resistance could affect, primarily, leptin's metabolic effects with preservation of the cardiovascular ones. Among the latter, leptin exerts a balanced effect on arterial pressure. Hypertensive effects of leptin appear predominantly due to sympathetic activation whereas several studies have suggested that leptin has a direct vascular effect that tends to decrease arterial pressure [1]. The leptin receptor belongs to the cytokine superfamily. Short length isoforms are expressed by endothelial cells where they could play a transport role [2]. The full receptor appears to mediate most of the biological effects of leptin. It is expressed in the aorta of mice [3] and could be involved in the action of leptin on the vascular tone and the calcification process which affects some vascular cells [3].

Adiponectin

Adiponectin is an adipocyte secreted protein that circulates in human plasma as different molecular weight complexes consisting of two to six trimers. Human studies demonstrated a positive correlation between adiponectin and insulin sensitivity levels. Its plasma concentration decreases with the degree of insulin resistance. This supports its negative association with body weight [4] and its increase after weight loss and thiazolidinediones treatment. In mice, modulation of adiponectin was associated with that of the degree of insulin resistance suggesting a direct participation of adiponectin in development of the metabolic syndrome [5]. In Pima Indians, high plasma adiponectin levels are associated with increased insulin sensitivity and reduced risk of type 2 diabetes [6]. This effect could involve two transmembrane receptors [7] and the AMP activated protein kinase [8] and, as recently proposed, a control of energy homeostasis through the central nervous system [9].

Adiponectin is now considered as an anti-atherosclerosis and anti-inflammatory adipokine. It is able to link types I, III and V collagens and to accumulate in an injured vessel wall [10] as well as in the myocardium after ischemic injury [11]. It decreases the expression of endothelial adhesion molecules such as VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) [12]. Adiponectin suppresses macrophage-to-foam cell transformation [13], and inhibits Tumor necrosis factor (TNF) production [14]. It inhibits also oxidized low density lipoprotein-induced endothelial cell proliferation, suppresses cellular superoxide generation [15] and increases endothelial NO production [16].

These beneficial effects observed *in vitro* were confirmed *in vivo*. Apolipoprotein E-deficient mice treated with recombinant adenovirus expressing human adiponectin

developed smaller lesions in aortic sinus than the control mice [17]. Conversely, adiponectin-deficient mice showed severe neointimal thickening and increased proliferation of vascular smooth muscle cells in injured arteries [18,19]. Discordant results have been published on the effects of adiponectin on angiogenesis and apoptosis [20-22]. Patients with atherosclerosis exhibit low circulating adiponectin levels [23,24], and high plasma adiponectin concentrations are associated with lower risk of myocardial infarction. Interestingly this relationship can be only partly explained by differences in blood lipids and is independent of inflammation and glycemic status [25]. In addition, some single nucleotide polymorphisms in the adiponectin gene were reported to be associated with an increased risk of type 2 diabetes and coronary artery disease [26,27].

Inflammatory Proteins

Obesity is associated with inflammation; including elevated levels of fibrinogen, C-reactive protein (CRP) and interleukin-6 (IL6) [28]. Thiazolidinediones decrease CRP levels [29] and chronic inflammation emerges as a new risk factor for the development of type 2 diabetes [30]. The monocyte infiltration of the adipose tissue could be the basis of this inflammatory process [31]. Monocyte chemoattractant protein 1 (MCP-1) mRNA is overexpressed in the adipose tissue of genetically obese mice compared with wild-type littermates and *in vitro* studies suggest that MCP-1 may contribute to the development of insulin resistance and induces adipocyte dedifferentiation [32].

Inflammatory cytokines such as TNF and IL6 have been involved in the development of insulin resistance [33-35] mainly in mice. In humans, although the demonstration of an association between TNF and insulin resistance gave discrepant results [36-40], the circulating levels of TNF receptors appear closely associated with the degree of insulin resistance [41-43]. IL6 is produced by human adipose tissue [44] mainly by the visceral territory [45]. As for TNF, the association between circulating levels of IL6 and insulin resistance in man is controversial. Obesity, and not insulin resistance, often appears the major determinant of serum IL6 levels.

Angiotensinogen

The renin-angiotensin system is an important regulator of blood pressure, and blockade of this system improves blood pressure in obesity and type 2 diabetes. The components of the renin-angiotensin system are fully represented in the adipose tissue. A growing body of evidence supports

the concept that alterations in adipocyte production of components of the renin-angiotensin system may contribute to disorders of the metabolic syndrome, including obesity and obesity-related hypertension, diabetes and atherosclerosis [46,47]. Results from genetically engineered mice overexpressing the angiotensinogen gene in adipose tissue support the concept that adipocyte-derived angiotensinogen can contribute to the circulating angiotensinogen concentration and modulate blood pressure [48]. Randomised controlled trials indicate that pharmacological renin-angiotensin system blockade improves insulin sensitivity and reduces the risk of type 2 diabetes. The concept that the local renin-angiotensin system plays a role in body-fat storage and in lipid and carbohydrate metabolism in humans is further supported by genetic studies showing that susceptibility to weight gain is greater in individuals carrying certain renin-angiotensin system allelic variants [49].

Resistin [50]

Resistin is secreted by adipose tissue. Whereas in mice modulation of resistin influences the insulin sensitivity, data obtained in humans are controversial. Resistin exerts some vascular effects. It induces the expression of endothelial adhesion molecules such as VCAM-1 and ICAM-1 [51,52], the endothelial production of endothelin 1 and the expression of CD40 ligand.

PAI-1

PAI-1 is a serpin which major function is to limit plasminogen activation and impair fibrinolysis. It occurs in plasma and tissues. Experimental data in mice have emphasised the role of PAI-1 in the development of thrombosis *in vivo* in the venous [53-56] and the arterial territories [57-61]. Data on the effect of PAI-1 on the development of atherosclerosis in mice [62-64] and on the influence of PAI-1 on the wound healing response to arterial injury [65-70] are sometimes contradictory mainly due to different degrees of thrombosis induced in the experimental models.

In patients, the between-person variability of fibrinolytic activity is unlikely to be an important risk factor for venous thrombosis in the general population [71]. In contrast, there are clinical evidences for an association between increased PAI-1 levels and myocardial infarction. It was shown that the acute release of PAI-1 in patients with ST-segment elevation myocardial infarction (difference between PAI at admission and 24 hours later) was dramatically higher in patients who died than in those who survived. Postangioplasty TIMI-3 flow and the acute release of PAI-1

were the only two independent predictors of death at 30 days [72]. Plasma concentrations of fibrinolytic factors in the subacute phase of myocardial infarction predict recurrent myocardial infarction or sudden cardiac death [73]. In large epidemiological studies, elevated plasma PAI-1 levels have been identified as a predictor of cardiovascular risk [74-78]. Co-exposure to high plasma PAI-1 activity and smoking synergistically interacts to predict myocardial infarction in men [79]. Post procedural plasma PAI-1 has also been implicated in the risk of restenosis after percutaneous coronary angioplasty. Most of the studies have described a deleterious effect of high plasma PAI-1 levels which may predict restenosis [80-84]. The same effect was obtained in a group of 251 consecutive patients who underwent femoro-popliteal percutaneous transluminal angioplasty [85]. However, in two studies decreased PAI-1 antigen (and not increased) levels exhibited a high predictive power of deleterious events [86,87].

In contrast to the association observed between plasma PAI-1 levels and the risk of an acute vascular event, the demonstration of an association between plasma PAI-1 and the degree of atherosclerosis is less evident. Significant upregulation of PAI-1 in the vessel wall was demonstrated in human atherosclerotic plaques [88-90]. Sobel et al [91] and Pandolfi et al [92] have provided evidence that type II diabetes is associated with an increased PAI-1 expression in arterial wall. In the Danish Glostrup study including 325 men and 370 women of 60 years, subjects with high Intima Media Thickness (IMT) had higher CRP but not PAI-1 levels. Association between fibrinogen and D-dimer but not PAI-1 concentrations and number of plaques was observed [93]. However, in a population of 200 subjects, multivariate logistic regression analysis confirmed the associations between greater than normal mean IMT and plasma concentrations of LDL cholesterol and PAI-1 as well as total ultrasonographic score [94]. These discrepancies could be related to the variables controlled for. Indeed, Folsom et al showed that adjustment for lifestyle and medical covariates essentially eliminated these associations suggesting that PAI-1 may partly mediate the effects of other risk factors on carotid atherosclerosis [95].

The increased PAI-1 expression in patients prone to acute vascular events has been related to several mechanisms. PAI-1 is known to be upregulated by several inflammatory cytokines such as TNF and Transforming Growth Factor beta (TGF- β). Thus, the healing process which accompanies atherosclerosis could explain the upregulation of PAI-1 in this pathology. A strong relationship between activation of the renin-angiotensin-aldosterone system (RAAS) and plasma PAI-1 [96] has also been described, and increased PAI-1 may represent a circulating marker of activation of the RAAS that may be indirectly related to infarct

size. Interestingly, PAI-1 has been shown to predict myocardial events in univariate analysis but the predictive power was not affected by adjustment for inflammatory parameters and disappeared after adjustment for Body Mass Index (BMI), triglycerides and High Density Lipoprotein (HDL) cholesterol, markers of the metabolic syndrome (MS) [97]. This suggests that the metabolic syndrome is a prerogative to high plasma PAI-1 levels in patients prone to atherosclerosis.

The MS consists of a cluster of metabolic abnormalities, which includes obesity with a distribution of the fat in the central part of the body (visceral or android obesity), impaired glucose tolerance, hyperinsulinaemia, dyslipidaemia with elevated triglycerides, low HDL cholesterol concentration, increased proportion of small dense lipoparticles, and hypertension [98]. Recently, more components of this syndrome have been proposed, including subclinical inflammation, hyperuricaemia and microalbuminuria. Furthermore, haemostatic abnormalities, with increased PAI-1 levels, are also a core feature of the MS [99]. Paradoxically, the observed metabolic disturbances are similar to those observed during lipodystrophy and could be the witness of a deficiency in the peripheral fat storage process leading to a redistribution of fat in "lean tissues" such as visceral tissues (mainly the liver) causing lipotoxicity.

The link between PAI-1 and the MS was established many years ago. During the last decade, strong associations between plasma PAI-1 levels and parameters of the MS were repeatedly shown [for review see 100]. Interventional studies have provided data that by improving insulin resistance, plasma PAI-1 levels decrease [101-103].

Most of the predictive power of PAI-1 for cardiovascular events depends on the MS. The ECAT study has shown that the prognostic value of PAI-1 in predicting coronary events is related principally to insulin resistance [97]. The mechanisms involved in increased PAI-1 production in the MS are not completely explained and the origin of PAI-1 is also uncertain. Obviously, induction of PAI-1 overexpression in the MS is a complex process and it is possible that several inducers are involved at the same time as well as at several sites of synthesis. Many of the metabolic parameters, which are disturbed in the MS, induce PAI-1 synthesis in different cultured cell lines [for review see 104]. Human adipose tissue, abundant in the MS, has attracted considerable attention as a possible source of PAI-1. Indeed, PAI-1 is synthesised in human adipose tissue proportionally to the BMI [for review see 104]. Visceral fat produces more PAI-1 than subcutaneous abdominal fat and subcutaneous femoral fat produces less PAI-1 than the latter [105] suggesting that visceral tissue, a core feature of the MS, could be a potential source of PAI-1. Fat accumulation in the liver is also a common feature of the MS. Some clinical evidence

has been provided that steatotic liver or the mechanisms leading to liver steatohepatitis may be involved in increased PAI-1 expression in the MS [106]. Liver steatohepatitis might be important also in conditions where insulin resistance is not accompanied with obesity, but in spite of it, plasma PAI-1 levels are elevated (i.e. in patients with lipodys(a)trophy). This leads to the assumption that increased plasma PAI-1 levels during obesity may reflect the ectopic fat storage process (visceral fat, liver steatosis..) which is associated with the MS.

Evidence has emerged that the TNF pathway plays a particular role in PAI-1 overexpression in the MS. In ob/ob mice, the inhibition of TNF with neutralising antibodies or deletion of TNF receptors (RI and RII), leads to significant reduction of plasma PAI-1 levels and adipose tissue PAI-1 expression [107]. On the other hand, parallel increases in TNFRI and PAI-1 in adipose tissue or plasma indicate that this receptor may be involved in the induction of PAI-1 synthesis during the MS [108]. TGF- β , a multifunctional cytokine which regulates cells growth and differentiation, could also be involved in the regulation of PAI-1 during insulin resistance [109].

The demonstration that PAI-1 levels predicted diabetes independently from other known risk factors [110] as well as the involvement of PAI-1 in tissue remodelling has led to speculate that the increased expression of PAI-1 in obesity influences the remodelling and expansion of the adipose tissue and the course of the metabolic syndrome. Recent experiments in animal models elucidated this issue partly.

Three studies in mice have examined the role of PAI-1 deficiency in weight gain. Two of them, a genetically and a nutritionally model of induced obesity demonstrated that PAI-1 deficient mice developed less obesity and concomitantly less insulin resistance and that downregulation of PAI-1 by an angiotensin type 1 receptor antagonist in wild type mice ameliorated diet-induced obesity [111,112]. The third study did not induce strong adiposity changes [113]. Furthermore, PAI-1 transgenic mice, which overexpress PAI-1 in adipose tissue, gained weight slower than their wild-type controls and developed hyperinsulinaemia [114]. From these experiments it could be proposed that increased plasma PAI-1 levels observed in patients during the MS could represent an induced counter-regulatory mechanism to limit excessive adiposity. This needs however further confirmation.

Conclusion

There is now evidence that adipose tissue may have a strong impact on most obesity related complications. A clustering between insulin resistance, adipocyte secreted protein, hypofibrinolysis, inflammation, thrombosis and ather-

osclerosis becomes more and more evident, but also renders the situation more and more complex with numerous possible feedback loops.

Further efforts with experimental and clinical studies are needed to better understand this complex interplay. Nevertheless, it is tempting to propose that adiponectin,

PAI-1 represent interesting targets for therapeutic intervention that aim to decrease the risk of both: type 2 diabetes and cardiovascular diseases.

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