

REVIEW

Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1

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Obesity is the central promoter of the metabolic syndrome which also includes disturbed fibrinolysis in addition to hypertension, dyslipidaemia and impaired glucose tolerance/type 2 diabetes mellitus. Plasminogen activator inhibitor-1 (PAI-1) is the most important endogenous inhibitor of tissue plasminogen activator and uro-plasminogen activator, and is a main determinant of fibrinolytic activity. There is now compelling evidence that obesity and, in particular, an abdominal type of body fat distribution are associated with elevated PAI-1 antigen and activity levels. Recent studies established that PAI-1 is expressed in adipose tissue. The greater the fat cell size and the adipose tissue mass, the greater is the contribution of adipose production to circulating PAI-1. Experimental data show that visceral adipose tissue has a higher capacity to produce PAI-1 than subcutaneous adipose tissue. Studies in human adipocytes indicate that PAI-1 synthesis is upregulated by insulin, glucocorticoids, angiotensin II, some fatty acids and, most potently, by cytokines such as tumour necrosis factor- α and transforming growth factor- β , whereas catecholamines reduce PAI-1 production. Interestingly, pharmacological agents such as thiazolidinediones, metformin and AT₁-receptor antagonists were found to reduce adipose expression of PAI-1. In addition, weight loss by dietary restriction or comprehensive lifestyle modification is effective in lowering PAI-1 plasma levels. In conclusion, impaired fibrinolysis in obesity is probably also due to an increased expression of PAI-1 in adipose tissue. An altered function of the endocrine system and an impaired auto-/paracrine function at the fat cell levels may mediate this disturbance of the fibrinolytic system and thereby increase the risk for cardiovascular disease.

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Introduction

Obesity is the most common nutritional disorder in the industrialized world. Approximately 60% of the adult population in these countries is overweight or obese.¹ This epidemic of excess body fat mass has far-reaching consequences as it is considered to be the most potent modifiable promoter of the metabolic syndrome which is characterized by the common occurrence of abdominal fat distribution, elevated blood pressure, lipid disturbances, and glucose intolerance. In an expanded definition, Reaven also allocated impaired fibrinolysis to the syndrome based on clinical data that suggest a close relationship between elevated plasma concentrations of plasminogen activator

inhibitor-1 (PAI-1) and variables of the metabolic syndrome including insulin resistance.²

There is now growing evidence that patients with features of the metabolic syndrome carry an elevated risk of developing cardiovascular disease.^{3,4} Other prospective studies have shown that a reduced fibrinolytic capacity, for example, caused by elevated PAI-1 activity, independently predicts cardiovascular events in young men after myocardial infarction,⁵ as well as in men and women with angina pectoris.⁶ Elevated plasma PAI-1 was also reported to be an independent predictor for sudden death in patients with angina pectoris.⁷

Fibrinolysis can be described as a cascade of enzymatic reactions that results in the degradation of fibrin and is determined by a variety of PAs and inhibitors. Among the inhibitory factors, the rapid acting PAI-1 is the most important inhibitor of plasma fibrinolytic activity. PAI-1 is a glycoprotein that is composed of 379 amino acids and has an apparent molecular weight of 48 kDa. PAI-1 is a member of the superfamily of serine-protease inhibitors (serpins) and serves as a pseudosubstrate for PA. The main production sites

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for PAI-1 known so far are liver, endothelial cells and thrombocytes. After release into the blood stream, PAI-1 is present either in an active form or, to a greater extent, complexed with either t-PA, one of the two main activators of fibrinolysis, or vitronectin which converts PAI-1 into an inactive, latent form.^{8,9}

Obesity and impaired fibrinolysis

During the last 15 y, there is growing evidence from clinical studies that overweight and obesity in humans are associated with impaired fibrinolysis.^{10–15} These studies have also revealed that elevated concentrations of PAI-1 are particularly evident in subjects with an abdominal pattern of body fat distribution.^{11,14,15} In addition, McGill *et al* have demonstrated that obese diabetic subjects show three-fold elevated concentrations of PAI-1 but no significant difference in plasma concentrations of tissue plasminogen activator (t-PA) compared to healthy lean subjects. The increased activity of PAI-1 in plasma was associated with increased concentrations of immunoreactive insulin and C-peptide, indicating a stimulatory effect of insulin.¹³ We have recently confirmed that PAI-1 antigen and activity levels

depend on BMI and the waist circumference in a sample of mildly hypertensive, overweight men (Figure 1).¹⁶ Such findings strongly indicate that an enlarged adipose tissue is closely associated with an impairment of fibrinolysis.

Adipose expression of PAI-1

It was originally reported by Sawdey and Loskutoff that adipose tissue from mice expresses relatively high levels of PAI-1¹⁷ and that in obese animals plasma PAI-1 levels were several-fold increased compared to lean littermates due to increased expression in adipose tissue.⁸ TNF- α and TGF- β were found to be important stimulators of PAI-1 expression in the adipose tissue of obese mice.^{18,19} Subsequent studies in human adipose tissue confirmed that adipocytes are a source of PAI-1, indicating that an enlarged adipose tissue may directly contribute to circulating PAI-1 levels in humans.^{20–24} In two of these studies, an approximately two-fold higher expression and secretion of PAI-1 per fat cell were found in adipocytes from obese than from lean subjects.^{21,24} The contribution of adipose production of PAI-1 to circulating levels is yet unclear. In an elegant human study, Yudkin *et al* measured arterio-venous differences in PAI-1 over a subcutaneous adipose tissue bed. They found no evidence that subcutaneous adipose tissue contributes significantly to circulating PAI-1 levels in lean subjects.²⁵ However, it is also interesting to note that in another study a clear relationship between adipose tissue-derived PAI-1 expression and circulating plasma levels was established, further supporting a physiological role of PAI-1 produced by adipose tissue.²⁶ Thus, there is at least sufficient data to conclude that adipose tissue is an important source of circulating PAI-1. At least in obese subjects, adipose expression of PAI-1 may contribute to the elevated plasma concentrations.

It was first shown in obese rats that mesenteric fat cells produce significantly more PAI-1 than subcutaneous adipocytes and PAI-1 mRNA increased only in visceral fat during the development of obesity.²⁷ Using small human adipose tissue pieces in culture, Alessi *et al*²⁰ also reported that more PAI-1 is produced in visceral fat as compared to subcutaneous human fat. Very similar results were published by another group.²⁸ A subsequent study confirmed and extended this observation in isolated human adipocytes.²⁴ In the latter study, it was also clearly demonstrated that enlarged omental fat cells from obese donors express and release significantly more PAI-1 than omental fat cells from normal-weight subjects. Thus, the depot-specific difference in PAI-1 release was found in fat cells from lean and obese subjects as well as in both adipose tissue samples from men and women.²⁴ However, contradictory findings were reported in a more recent study. The secretion rate of PAI-1 was two-fold higher in subcutaneous than in visceral adipocytes. Likewise, subcutaneous adipose tissue contained higher PAI-1 mRNA levels than visceral adipose tissue.²⁹ Concerning the possible differences of PAI-1 expression in different regions

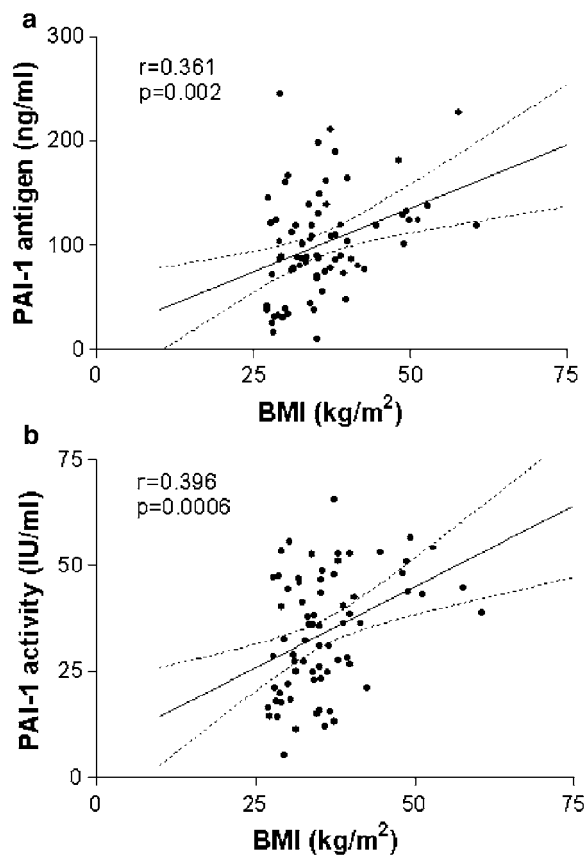


Figure 1 Association between BMI and PAI-1 antigen (a) and activity (b) in a selected population of 64 overweight/obese male subjects with moderate hypertension.

of subcutaneous adipose tissue, there are data from only one study available. Mavri *et al* compared PAI-1 mRNA in the subcutaneous abdominal and subcutaneous femoral adipose tissue from lean and obese males and females. The results indicate that only PAI-1 expression in the subcutaneous abdominal depot contributes to plasma PAI-1 levels, whereas PAI-1 expression in the subcutaneous femoral adipose tissue was related neither to BMI nor to circulating PAI-1 protein.³⁰ Due to the above-mentioned discrepancy, it is currently not possible to draw firm conclusions concerning site differences in adipose production of PAI-1, but it is obvious that large fat cells produce more PAI-1 than small fat cells independently of the fat depot.

It is also well established now that not only are mature adipocytes a production site for PAI-1, but also that the stromal cell fraction of adipose tissue synthesizes substantial amounts of the inhibitor.^{18,23,31} In the most recent of these studies, stromal cells were even described as the main PAI-1-producing cells in human fat.³¹ The stromal cell fraction of adipose tissue consists mainly of specific adipocyte precursor cells but also contains other cell types such as endothelial cells, vascular smooth muscle cells and monocytes/macrophages, which are also possible sources of PAI-1, although the proportion of the latter is rather small. Bastelica *et al* recently reported that the stromal cell fraction from visceral fat contains five-fold more PAI-1-positive cells than the stromal cell fraction from subcutaneous adipose tissue of the same donors. In addition, the stromal cell fraction contained more PAI-1 mRNA than the adipocyte fraction.³² However, in a study by Birgel *et al*³³ using an established *in vitro* model of human stromal cells undergoing *in vitro* adipose differentiation, it was demonstrated that there is a two-fold increase in the production of PAI-1 during the course of adipose differentiation at least under these experimental conditions. Again, the reason for this inconsistency is unclear. One possible confounder could be that freshly obtained adipose tissue samples release substantial amounts of cytokines such as TNF- α and IL-6 possibly due to hypoxia, which may also affect PAI-1 synthesis³⁴ (Hauner *et al*, unpublished data). Although this aspect requires further investigation, it is clear that preadipocytes are also a source for PAI-1, but one has to keep in mind that adipocytes are the main constituent of adipose tissue and their number clearly exceeds the number of stromal cells.

Hormonal regulation of adipose tissue PAI-1 expression

Numerous studies were recently published which were dealing with the regulation of PAI-1 expression in adipose tissue. These studies convincingly indicated that a variety of specific hormones and/or cytokines are implicated in the increased expression of PAI-1 by adipose tissue in obesity.

Sawdey and Loskutoff¹⁷ were the first to report that cytokines such as TNF- α and TGF- β are involved in the

regulation of PAI-1. This is of particular interest as both cytokines and their receptors are produced in adipose tissue. Moreover, the expression of both cytokines is chronically elevated in adipose tissue both from obese rodents and humans.^{35,36} Administration of TNF- α to lean mice significantly increased PAI-1 mRNA in adipose tissue similar to the pattern found in obese mice.¹⁸ Using various *in vitro* models of human adipocytes, further studies suggested that TNF- α is also a potent stimulator of PAI-1 synthesis in human adipose tissue. In human adipose tissue explants, exposure to exogenous TNF- α resulted in increased PAI-1 mRNA and protein expression, whereas incubation of human fat biopsies with pentoxifylline or genistein, two inhibitors of endogenous TNF- α , markedly reduced PAI-1 mRNA.²² Similar stimulatory effects of TNF- α on PAI-1 production were observed in freshly isolated adipocytes²⁴ and in *in vitro* differentiated human adipocytes.³³ These and other studies¹⁹ support the hypothesis that the chronic elevation of TNF- α that occurs locally in the adipose tissue of obese rodents and humans may upregulate PAI-1 production in adipocytes and other cells of adipose tissue via an auto-/paracrine mechanism. Thus, this cytokine may substantially contribute to the elevated plasma concentrations of PAI-1 observed in obesity.

A variety of data suggest that TGF- β also stimulates PAI-1 biosynthesis in adipose tissue both from rodents^{8,17} and humans^{24,33,36}. These studies clearly indicated that TGF- β stimulates PAI-1 synthesis to an at least similar extent as TNF- α . It was demonstrated in a study in both *ob/ob* and *db/db* mice that the levels of adipose expression of TGF- β mRNA are elevated in obese as compared to lean animals, arguing again for a local regulation of PAI-1 expression in adipose tissue. In humans with severe obesity, a proportional increase in PAI-1 and TGF- β mRNA expression was observed in the visceral and subcutaneous adipose tissues.³⁶ Furthermore, it was shown in *in vitro* differentiated human adipocytes that these cells express TGF- β and two of the three receptor subtypes.³³ Thus, it is plausible to assume that the upregulation of PAI-1 in the obese state is also mediated by TGF- β in a paracrine fashion. There is some evidence that the elevated expression of TGF- β is at least partly due to the action of TNF- α ^{19,33} and other cytokines such as interleukin-1 β (IL-1 β).³³ However, there may also exist other cytokines which directly contribute to PAI-1 upregulation in adipose tissue. Among these, IL-1 β was found to significantly increase the expression of PAI-1 in human adipocytes.³³

Another potent auto-/paracrine regulator is angiotensin II, which is also produced by fat cells. It was recently demonstrated that the expression of angiotensinogen mRNA in adipose tissue is elevated in obese as compared to lean subjects.³⁷ In addition, a higher expression level of angiotensinogen mRNA was reported in omental as compared to subcutaneous abdominal adipose tissue from humans.³⁸ We have recently shown that angiotensin II, the biologically active product of angiotensinogen processing, is able to stimulate PAI-1 expression in human adipocytes at the

transcriptional level. This effect is mediated via the AT₁-receptor subtype as the presence of selective AT₁-receptor antagonists completely prevented this stimulation.³⁹ Thus, locally produced angiotensin II is another candidate that may mediate the increased synthesis of PAI-1 in human obesity in an auto-/paracrine fashion.

Apart from signals from the adipose cell, circulating factors could also contribute to the regulation of PAI-1 production. Insulin, proinsulin and IGF-1 were previously found to stimulate PAI-1 synthesis in liver cells.⁴⁰ Similar findings concerning the effect of insulin were also reported for fat cells.²⁶ In the latter study, a stimulatory effect of insulin on PAI-1 production was seen in human adipose tissue explants but not in isolated human adipocytes nor in stromal cells from human adipose tissue. We also observed only a weak stimulatory effect of insulin on PAI-1 synthesis in human adipocytes (unpublished data), arguing against a major role of insulin in the upregulation of adipose PAI-1 synthesis in obesity. In a recent study in HepG2 cells, the effect of insulin on PAI-1 gene expression was found to be exerted at the transcriptional level via activation of the MAP kinase pathway.⁴¹ In a cross-sectional study in humans, IGFBP-1 but not IGFBP-3 and IGF-1 concentrations were related to PAI-1 activity, which may be explained by a direct effect of insulin on IGFBP-1 production.⁴² Thus, at the present state of knowledge, insulin is a modulator of PAI-1 production in humans, but this stimulatory action appears to be exerted via other tissues rather than adipose tissue.

Likewise, glucocorticoids were found to induce PAI-1 biosynthesis in adipose tissue *in vitro*,^{26,28} which is also supported by clinical data obtained in patients under treatment with glucocorticoids^{43,44} and in Cushing patients.⁴⁵ The stimulatory effect of glucocorticoids was most pronounced in isolated human adipocytes and *in vitro* differentiated 3T3 F442A adipocytes, whereas no effect was observed in cultured human preadipocytes.²⁶ In another study, it was additionally elaborated that the stimulatory effect of glucocorticoids occurs within the physiological concentration range and that there was a preferential promotion of PAI-1 synthesis in omental as compared to subcutaneous fat.²⁸ This stimulation could be mediated through the binding of the steroid-receptor complex to the glucocorticoid response element that has been identified in the regulatory region of the human PAI-1 gene.^{28,46} Recent studies indicate that 11 β -hydroxysteroid dehydrogenase which converts cortisone into the biologically active cortisol is expressed in adipose tissue, preferentially in the visceral depot.⁴⁷ Thus, the possibility may also arise that locally produced cortisol contributes to the elevated expression of PAI-1 in the omental fat depot.

Fat cells are also a target of catecholamines, which are provided either via the blood supply or are released by sympathetic nerve fibres surrounding the adipocytes. Recent studies found that catecholamines suppress PAI-1 production via a β -adrenergic mechanism.^{28,48} In addition, compounds that elevate cAMP levels induce a similar reduction

in PAI-1 secretion from adipose cells. The fact that omental fat cells are more densely innervated by sympathetic nerve fibres than subcutaneous fat cells would suggest that higher concentrations of catecholamines are present in omental than subcutaneous adipose tissue. However, the relative contribution of locally released catecholamines vs locally produced stimulators of PAI-1 expression is unknown (Figure 2).

Regulation of PAI-1 production by dietary factors

In addition to studies in other cell types that express PAI-1, there is currently only rather limited information on the role of dietary factors on PAI-1 gene expression in adipose tissue. Previous studies have demonstrated that both fatty acids and glucose are able to induce PAI-1 production in various cell types. For example, Chen *et al*⁴⁹ recently showed that glucose activates the PAI-1 promoter via Sp1 sites in vascular smooth muscle cells. Likewise, experiments in human endothelial cells indicate that several types of lipoproteins, in particular of oxidized low-density lipoproteins, are able to contribute to impaired fibrinolysis in obesity and/or type 2 diabetes.⁵⁰ In HepG2 cells, addition of different types of fatty acids was found to stimulate PAI-1 release.⁴¹ In recent experiments, we were able to demonstrate a direct stimulatory effect of Intralipid[®] on PAI-1 expression and secretion from human adipocytes (Figure 3). In a clinical study, hyperinsulinaemia combined with hyperglycaemia and hypertriglyceridaemia, by infusion of high glucose and Intralipid[®] in normal subjects which induced characteristic changes like in type 2 diabetes, significantly increased PAI-1 concentrations.⁵¹ In a recent study in isolated rat adipocytes, carbonyl stress was used to induce the formation of advanced glycation endproducts (AGE) and to promote lipid peroxidation. Under these conditions, PAI-1 expression and

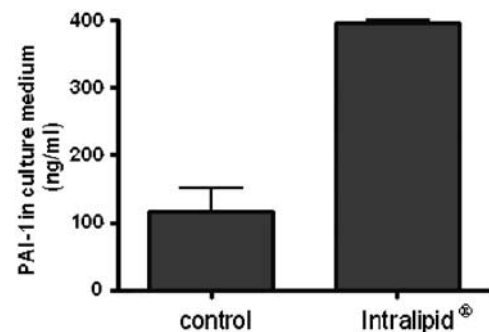


Figure 2 Schematic summary of the regulation of PAI-1 expression in adipose tissue: PAI-1 is produced and released by both preadipocytes and mature fat cells. PAI-1 synthesis is upregulated both by locally produced factors such as TNF- α , TGF- β and angiotensin II and by circulating hormones such as insulin and cortisol. In addition, high glucose and fatty acids also promote PAI-1 production, at least particularly by the generation of reactive oxygen species. In contrast, exposure of adipocytes to catecholamines as well as to specific antidiabetic and antihypertensive drugs reduces PAI-1 production in adipose tissue.

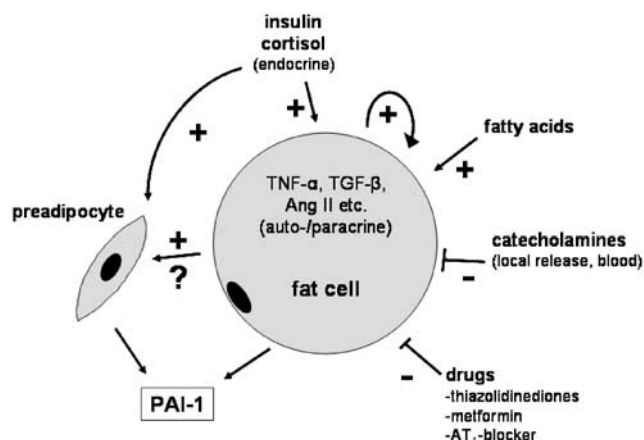


Figure 3 Effect of Intralipid[®] on PAI-1 secretion into the culture medium of human adipocytes. Intralipid[®] was added at a concentration of 0.2%. After an incubation period of 24 h, PAI-1 antigen was measured in the medium by ELISA. mean \pm s.d. of three experiments (unpublished observation).

release into the culture medium was clearly upregulated. Inhibition of oxidative stress by antioxidants or the reactive oxygen scavenger probucol prevented the stimulatory effect of AGE or high glucose, suggesting a pivotal role of oxidative stress on PAI-1 production in adipocytes.⁵²

Effects of weight loss and dietary intervention on fibrinolysis

As demonstrated, body fat mass seems to be a major determinant of the fibrinolytic activity. Thus, the best strategy to improve the obesity-related impairment of fibrinolysis may be to reduce body weight. In fact, it was repeatedly shown that weight loss is associated with a partial or complete normalization of disturbed fibrinolytic parameters (for a review, see Ref. ⁵³). In these studies, a reduction in plasma PAI-1 concentrations was found relative to the extent of weight loss. A similar favourable effect of weight loss on fibrinolysis was also found in children and adolescents.^{54–56} In an intensive lifestyle intervention study in subjects with impaired glucose tolerance, a programme consisting of a low-fat, high-fibre diet, regular physical exercise and behaviour modification conducted in a full-board wellness centre produced a greater reduction in PAI-1 activity than a usual care programme (decrease after 12 months by 31 vs 12%). In this study, the intensive intervention group had a mean weight decline after 1 y by 5.4 kg compared to 0.5 kg in the usual care group.⁵⁷ Interestingly, different types of physical exercise were also shown to significantly improve an impaired fibrinolytic activity.^{58–60}

As weight loss is accompanied with an improvement in insulin resistance detectable by a decrease in insulin concentrations, as well as by a fall in plasma triglycerides and glucose, it cannot be excluded that these metabolic

changes are responsible for the improvement in fibrinolytic activity. Available data do not allow dissecting whether the relationship between weight loss and decrease in PAI-1 levels is causal or indirect. This issue needs to be elucidated in future studies.

The improvement in fibrinolytic variables during weight loss is not generally paralleled at the adipose tissue level. In the study by Mavri *et al*,³⁰ an average weight loss of 20.7 kg in obese women and men during a 3-month weight reduction programme was associated with a decrease in PAI-1 mRNA levels in the abdominal subcutaneous adipose tissue along with a similar decrease in plasma PAI-1, whereas no change in mRNA levels was observed in the femoral subcutaneous fat. In contrast, Bastard *et al*⁶¹ reported a marked increase in PAI-1 mRNA and protein abundance in subcutaneous abdominal adipose tissue by 87 and 44%, respectively, after a mean weight loss of 5.8 kg during a very-low-calorie diet, although serum levels of PAI-1 decreased by 26% at the same time. There is no explanation for this discrepancy, but it is apparent that mRNA levels measured in one fat depot do not reflect the changes in all fat depots nor are representative of plasma PAI-1 concentrations. Thus, additional efforts are required to investigate the changes in PAI-1 mRNA in adipose tissue and their relationship to protein concentrations during weight loss.

Effect of pharmacological interventions on fibrinolysis

Drug therapy for obesity and the metabolic syndrome has to consider a variety of aspects. To date, normalization of impaired fibrinolysis has not been among the primary goals of pharmacological treatment in patients with this syndrome. However, there is now growing evidence that some of the drugs that are currently used for the treatment of the metabolic syndrome may also distinctly modify impaired fibrinolysis. It was demonstrated in clinical studies that thiazolidinediones such as troglitazone have favourable effects on the fibrinolytic system in addition to their effect on other components of the metabolic syndrome.^{62,63} These studies documented that in patients with type 2 diabetes troglitazone treatment was associated with a reduction in plasma PAI-1 concentrations by 30–40%. We recently reported that troglitazone exerts a dose-dependent inhibitory effect on PAI-1 expression and secretion in cultured human adipocytes.⁶⁴ This effect was not restricted to *in vitro* differentiated adipocytes, but was also present in freshly isolated fat cells. Additionally, troglitazone reduced PAI-1 mRNA expression in adipocytes both from the subcutaneous and visceral depot to a similar extent.⁶⁴ In additional experiments, we found that the two thiazolidinediones approved for the treatment of type 2 diabetes, rosiglitazone and pioglitazone, are equally effective to reduce PAI-1 mRNA levels in human adipose tissue (unpublished data). However, in another *in vitro* study using human preadipocytes and

adipocytes, no direct effect of thiazolidinediones such as troglitazone, pioglitazone and ciglitazone on PAI-1 production was found.⁶⁵ In addition, troglitazone was found to reduce PAI-1 expression in human aortic smooth muscle cells, but induced an accumulation of PAI-1 in human liver cells.⁶⁶ Furthermore, in human umbilical vein endothelial cells, a similar reduction in basal and TNF- α -stimulated PAI-1 secretion and PAI-1 expression was observed in the presence of troglitazone.⁶⁷ These rather consistent data allow concluding that thiazolidinediones also improve impaired fibrinolysis in patients with the metabolic syndrome.

In an analysis of the BIGPRO-1 study, Charles *et al* demonstrated a positive effect of metformin, another frequently used drug to induce insulin resistance, on different haemostatic variables including not only PAI-1 antigen and activity, but also t-PA antigen and von Willibrand factor in patients with obesity. These favourable changes were independent of weight loss if 850 mg metformin was administered twice a day,⁶⁸ thereby confirming early observations on the beneficial effect of metformin on PAI-1 levels in healthy subjects.¹⁰ Again, cell culture experiments in human adipose tissue indicated that this effect may occur at the transcriptional level.⁶⁵

Fibrates are another group of compounds that were found to have a beneficial effect on PAI-1 antigen and activity in clinical studies, although the results were not consistent.⁶⁹ Finally, treatment with AT₁ receptor antagonists was found to improve fibrinolytic activity,^{70,71} although a short-term treatment of mildly hypertensive men with candesartan was not associated with significant changes of impaired fibrinolysis.¹⁶ Nevertheless, there is a lack of clinical data concerning the role of AT₁ receptor antagonists in the regulation of fibrinolysis in man.

Other effects of PAI-1

Although the inhibitory action of PAI-1 in fibrinolysis is well characterized and beyond dispute, there is rapidly accumulating literature that PAI-1 has additional biological effects with special reference to angiogenesis and tumour growth, possibly by interacting with vitronectin. However, PAI-1 was found to promote and inhibit tumour growth and angiogenesis.⁷² To date, there is one study on a possible involvement of PAI-1 in cell migration in adipose tissue. In addition to PAI-1, the authors showed that human preadipocytes express the vitronectin receptor alpha V beta 3 in a pattern similar to human umbilical vein endothelial cells. Active, but not latent, PAI-1 inhibited preadipocyte attachment to vitronectin and thus preadipocyte migration. Such data indicate that PAI-1 could contribute to the regulation of cell cluster formation and extracellular matrix remodelling required for adipogenesis.⁷³ Nevertheless, more investigations are required to unravel the possible local effects of PAI-1 in adipose tissue. In addition, the possible role of elevated concentrations of PAI-1 in cancer risk and progression remains to be determined.

In conclusion, there is now compelling evidence that adipose tissue is an important site of PAI-1 production, which may also affect circulating levels. This is particularly evident in patients with overweight/obesity and/or an abdominal pattern of fat distribution. Factors which mediate this overexpression include cytokines such as TNF- α and TGF- β and classical hormones such as insulin and glucocorticoids. In addition, angiotensin II which is overexpressed in adipose tissue in the obese state is another possible mediator of increased adipose PAI-1 expression. Weight loss by conventional measures and administration of selected drugs frequently used for the treatment of the metabolic syndrome such as thiazolidinediones and metformin also have a beneficial effect on impaired fibrinolysis and may thereby reduce the cardiovascular risk in patients with obesity and/or the metabolic syndrome.

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