[Frontiers in Bioscience 12, 2957-2966, May 1, 2007]

Plasminogen activator inhibitor (PAI)-1 in vascular inflammation and thrombosis

Yoshimasa Aso

Department of Internal Medicine, Koshigaya Hospital, Dokkyo Medical University, Saitama, Japan

TABLE OF CONTENTS

1. ABSTRACT

Impaired fibrinolysis may be associated with development of atherothrombotic cardiovascular disease (CVD) in metabolic syndrome or type 2 diabetes. Plasma plasminogen activator inhibitor (PAI)-1, a potent inhibitor of fibrinolysis, is elevated in a number of clinical situations that are associated with high incidence of CVD. Impaired fibrinolysis resulting from high plasma PAI-1 can lead to excessive fibrin accumulation within vessels, resulting in atherothrombosis. Increased expression of PAI-1 is found in atherosclerotic lesions in humans, especially atherosclerotic plaques in patients with type 2 diabetes. This increased vascular expression of PAI-1 promotes neointima formation via accumulation of fibrin or fibrinogen as a result of inhibited clearance of platelet-fibrin thrombi. PAI-1, an acute phase protein, also could be involved in vascular inflammation. PAI-1 may be associated not only systemically but also locally with development of CVD.

2. INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality among adults worldwide (1). Over the past two decades, obesity, a major risk factor for cardiovascular disease (CVD) (2), has increased greatly in most countries, reflecting high-fat diet and sedentary life styles. Approximately 60% of adults in developed countries are reported to be overweight or obese (3). The increase in obesity is associated with a global epidemic of metabolic syndrome and diabetes (4). Patients with type 2 diabetes have a high incidence of atherosclerotic CVD, leading to increased morbidity and mortality due to CHD, stroke, and peripheral arterial disease (5, 6). CVD is the major cause of death in patients with type 2 diabetes in Western societies (7). Several epidemiologic studies have shown a 2- to 4-fold increase in risk of CVD among patients with type 2 diabetes compared to subjects without diabetes (5, 6, 8). The Framingham Heart Study has shown a 2- to 10-fold excess in risk of CAD, stroke, heart failure, and death from

CVD among subjects with diabetes compared with non-diabetic subjects (5, 8). Metabolic syndrome, also known as insulin resistance syndrome, is defined by clustering of several cardiovascular risk factors in an individual patient, including impaired glucose tolerance (diabetes), hypertension, dyslipidemia, and visceral obesity (9, 10). Several studies have demonstrated that this syndrome strongly predicts CVD, especially CHD (11, 12), independently of low-density lipoprotein (LDL)-cholesterol.

Hypercoagulability and reduced fibrinolysis may be associated with development of atherothrombotic vascular disease in metabolic syndrome or type 2 diabetes (13, 14). Plasma concentrations of plasminogen activator inhibitor (PAI)-1, a potent inhibitor of fibrinolysis, are elevated in patients with metabolic syndrome and type 2 diabetes. Among a number of hemostatic abnormalities (15), an increase in PAI-1 is considered a core feature of the metabolic syndrome (16). Thus, because of high plasma PAI-1, these patients have a well-described tendency toward relative hypercoagulability arising from impaired fibrinolysis (13, 17). Reduced fibrinolysis reflecting elevated plasma PAI-1 may increase risk of atherothrombotic events in metabolic syndrome and type 2 diabetes. Furthermore, evidence has been accumulating recently that increased vascular PAI-1 itself may contribute directly to acceleration of atherothrombosis formation by favouring neointimal formation within plaques.

3. ROLE OF INFLAMMATION AND THE COAGULATION-FIBRINOLYSIS SYSTEMS IN ATHEROTHROMBOSIS

Atherothrombosis is a complex disease in which inflammation, LDL cholesterol deposition, and plaque formation play significant roles (18). In particular, vascular inflammation as evidenced by accumulation of inflammatory cells may be responsible for disruption of plaques (18). Activated T lymphocytes associated with atherosclerotic lesions can inhibit collagen synthesis, thereby interfering with repair and maintenance of the fibrous caps of plaques (19). Macrophage activation can result in production of matrix metalloproteinases (MMPs), which promote breakdown of structural components within the extracellular matrix, weakening the fibrous cap and rendering plaques vulnerable to rupture (19). Finally, thrombus formation on exposed surfaces of ruptured atherosclerotic plaques is responsible for development of acute coronary syndromes such as unstable angina pectoris and acute myocardial infarction (20).

Disrupted plaques provoke thrombus formation through several mechanisms. Contact with collagen in the extracellular matrix of the plaque can trigger platelet activation. Tissue factor produced by macrophages and smooth muscle cells can activate the blood coagulation cascade, resulting in generation of thrombin, which can activate platelet aggregation. Finally, conversion of fibrinogen to fibrin can provide the cross-linking molecular bridge between platelets (21). Superimposition of thrombus on disrupted plaques contributes to development of acute coronary syndromes. Arterial thrombi are composed mainly of platelets and fibrin and therefore are called white thrombi (22).

Hypercoagulability, reduced fibrinolysis, and/or platelet activation which result from multiple factors including endothelial dysfunction, disturbed lipid metabolism, hyperglycemia, oxidative stress, and inflammation, may contribute to thrombus formation within vessels. Formation of fibrin deposits in arteries induced by relative hypercoagulation plays a crucial role in development of atherothrombosis (23).

4. ROLES OF PAI-1 IN VASCULAR INFLAMMATION AND ATHEROTHROMBOSIS

Chronic vascular inflammation plays a significant role in development of atherosclerotic vascular disease, because atherosclerotic plaques consist of monocyte-derive macrophages and T lymphocytes (18). In the initial stage of atherosclerosis, rolling and adherence of monocytes and T lymphocytes occur at the inflamed sites as a result of the upregulation of adhesion molecules on both the endothelium and leukocytes (18). Integrins then mediate its firmer attachment. Proinflammatory cytokines produced by atheroma provide a chemotactic stimulus to the adherent leukocytes, directing their migration into the intima (19). Vascular inflammation is also associated with the destabilization of the plaque. PAI-1 is the main physiological inhibitor of tissue-type and urokinase-type plasminogen activator and thereby regulates the fibrinolysis system, while PAI-1 can act as an acute phase protein. Several studies have demonstrated that PAI-1 is produced at the site of inflammation after tissue injury (24, 25), suggesting that PAI-1 plays a role in the regulation of local inflammatory process. The role of PAI-1 in vascular inflammation remains to be determined in humans. Renckens *et al* reported that PAI-1 deficiency mice showed a reduction in the early induction of IL-6, a main inflammatory cytokine, in plasma and tissues with subsequently lower acute phase protein levels (26). Thus, PAI-1 could have a proinflammatory property, thereby participating in vascular inflammation.

Unexpectedly, a previous study reported that PAI-1 inhibits the attachment of cells to the extracellular matrix protein by blocking the adhesive sites of vitronectin (27). PAI-1 may act as a de-adhesive molecule rather than adhesive one. Furthermore, a previous study demonstrated that active PAI-1 inhibits SMC migration by blocking integrin the binding of vitronectin to the integrin receptor $\alpha v\beta 3$ (28). However, further study needs to be done to determine whether PAI-1 is associated with the attachment or detachment of cells to the extracellular matrix of arterial wall in humans.

The coagulation system is comprised of a complex cascade of coagulation molecules. Formation of stable, cross-linked fibrin, a main step in the coagulation cascade, occurs as a result of thrombin-induced cleavage of fibrinogen with concurrent activation of cross-linked fibrin polymers (29, 30). Thus, thrombin has a pivotal role in the

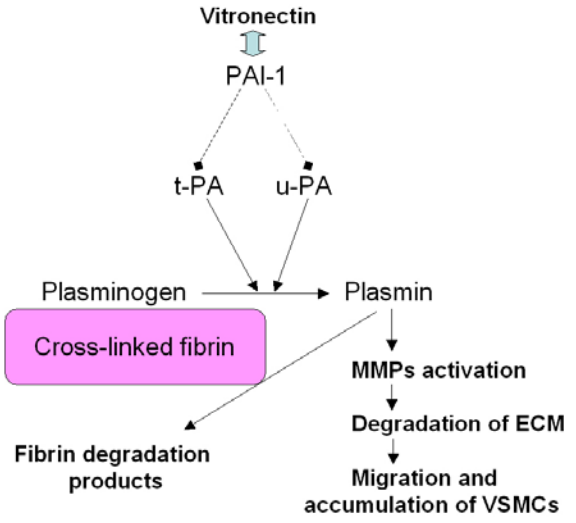

Figure 1. Fibrinolysis systems and plasmin pathways. Fibrinolysis is initiated by tissue plasminogen activator (t-PA), urinary-type plasminogen activator (u-PA), and plasmin. Plasminogen is activated by t-PA or u-PA. Binding of plasminogen and t-PA to the fibrin surface results in an increase in plasmin generation. Binding is mediated by specific interaction of C-terminal lysine residues of partially degraded fibrin and a lysine-binding site in plasminogen and t-PA. Plasminogen, t-PA, and fibrin form a ternary complex that promotes formation of plasmin, with subsequent lysis of cross-linked fibrin into fibrin-degradation products. The main fibrinolytic reactions can be affected by inhibition of fibrinolysis by plasminogen-activator inhibitor type 1 (PAI-1) or α2-antiplasmin. PAI-1 also binds to fibrin, when bound, it retains inhibitory activity against t-PA or u-PA. This function of PAI-1 is facilitated by vitronectin, a 75-kDa ECM glycoprotein. Plasmin generated from plasminogen in the ECM of the arterial wall activates MMPs, resulting in degradation of the matrix. Thus, plasmin facilitates migration of VSMCs into the intima, which may contribute to neoinitmal formation. MMPs, matrix metalloproteinases; ECM, extracellular matrix; VSMCs, vascular smooth muscle cells.

coagulation cascade with pleiotropic effects that result in formation of a cross-linked fibrin clot, and also platelet aggregation (29, 30).

The fibrinolytic system is activated after formation of fibrin, when both plasminogen and t-PA bind to the fibrin surface (Figure 1). Spontaneous dissolution of thrombus is regulated mainly by fibrinolytic activity, which ultimately is dependent on generation of plasmin (29, 30). During fibrinolysis, insoluble fibrin is digested by plasmin, which is converted from its inactive precursor plasminogen by the action of urokinase-plasminogen activator (u-PA) or tissue-PA (t-PA) on the surface of the fibrin clot. Thus, plasmin, the enzyme responsible for degradation of fibrin, plays a pivotal role in the fibrinolytic system. Hypercoagulability, reduced fibrinolysis, or both may contribute to the development of CVD via formation of occlusive thrombi within coronary and cerebral arteries. The two main inhibitors of fibrinolysis in the circulation are PAI-1, a rapidly acting inhibitor of t-PA and u-PA (31), and α2-antiplasmin (32), a specific plasmin inhibitor that is covalently bound to polymerizing fibrin by activated factor XIII.

PAI-1, a single-chain glycoprotein with a molecular weight of 50 kDa, is a member of the serpin (serine proteinase inhibitor) family (17). PAI-1 binds to t-PA or u-PA, forming an inactive complex, thus negatively regulating fibrinolysis in the blood by inhibiting t-PA (31). This important function of PAI-1 is facilitated by vitronectin, a 75-kDa extracellular matrix glycoprotein (33) (Figure 1). An increase in the PAI-1 concentration in the circulation impedes fibrinolysis by impairing the action of t-PA, so thrombi cannot be removed from the vascular wall (31). Immunohistochemical studies have demonstrated that macrophage infiltration and thrombus formation are more prominent in advanced coronary plaques from unstable angina patients with diabetes than plaques from those without diabetes (34, 35). Another study has shown that coronary artery thrombi from MI patients with diabetes contain more fibrin than thrombi from those without diabetes (36). Several studies have demonstrated increased PAI-1 expression in human atherosclerotic lesions. Thus, imbalance between coagulation and fibrinolysis may contribute to excessive fibrin deposition in the vascular wall. In this manner, impaired fibrinolysis due to high plasma PAI-1 may contribute to the pathogenesis of atherothrombosis, leading to CAD, stroke, and peripheral arterial disease in type 2 diabetes.

5. HOW ENHANCED LOCAL PAI-1 EXPRESSION IN THE VASCULAR WALL MAY INFLUENCE ATHEROSCLEROTIC VASCULAR EVENTS

Several studies have demonstrated increased expression of PAI-1 in human atherosclerotic lesions (37-39). Immunohistochemical study demonstrated enhanced expression of PAI-1 in the macrophages and endothelial cells of atherosclerotic plaques (39). Patients with type 2 diabetes show higher expression of PAI-1 in the atherosclerotic vascular wall than those without diabetes (40, 41). Thus, increased PAI-1 in the arterial wall may contribute directly to development of CVD in type 2 diabetes. However, the causal role of arterial PAI-1 expression in atherothrombosis is controversial. Migration of vascular smooth muscle cells (VSMCs) from the media into the intima participates significantly in neointimal formation in atherosclerotic plaques or restenosis (18). Plasmin generated from plasminogen in the extracellular matrix of arterial wall activates MMPs, resulting in degradation of this matrix (42). By disrupting the arterial wall matrix, plasmin facilitates VSMC migration into the intima, which may contribute to neointima formation (42). Considering this, PAI-1 actually could attenuate plasmin-dependent proteolysis of the matrix by inhibiting t-PA or u-PA. In fact, in mouse studies, the VSMC migration was increased by the disruption of PAI-1 gene, and VSMC accumulated in the neointima after intraluminal electrical injury (43, 44). Furthermore, PAI-1 overexpression attenuated migration of VSMCs in response to injury (44). Considering these results together, increased PAI-1

expression in the arterial wall unexpectedly could inhibit migration of VSMCs into the intima, thus diminishing luminal obstruction.

In contrast, several studies demonstrated that increased expression of PAI-1 in the arterial wall augmented neointimal formation in mice (45-47). As mentioned previously, PAI-1 promotes fibrin accumulation in the vascular lumen by inhibiting activation of t-PA or u-PA. Increased expression of PAI-1 may augment neointimal formation by favoring fibrin deposition within vessels (42). In fact, in mice PAI-1 overexpresssing, PAI-1 promoted neointimal formation in association with fibrin or fibrinogen accumulation by inhibiting clearance of platelet-fibrin thrombi (45). Furthermore, in atherosclerosis-prone mice, increased vascular expression of PAI-1 is associated with enhanced thrombosis (48). Increased PAI-1 expression in the arterial wall could decrease local fibrinolysis, and also promote thrombus formation and unfavorable change in atherosclerotic plaques. Thus, results in animal models of neointimal formation concerning PAI-1 show disagreement. In the absence of obvious reasons for this discrepancies, Konstantinides *et al.* speculated that in the early stage of vascular remodeling in the absence of thrombi and fibrin, PAI-1 limits migration and proliferation of VSMCs, stabilizing the extracellular matrix; while in an advanced stage, where thrombus is present, PAI-1 correlates consistently with neointimal formation, which narrows the lumen (49).

6. ASSOCIATIONS OF HIGH PLASMA PAI-1 CONCENTRATIONS IN TYPE 2 DIABETES AND IN METABOLIC SYNDROME

High plasma PAI-1 concentrations have been associated with development of CHD. Many investigators have reported that plasma PAI-1 concentrations are elevated in type 2 diabetic patients (50-53). Elevated plasma PAI-1 now is considered a main component of metabolic syndrome, a pre-diabetic state (16, 17). Plasma PAI-1 also is strongly correlated in subjects with metabolic syndrome and type 2 diabetes with metabolic syndrome components such as BMI, visceral fat, blood pressure, plasma insulin, triglyceride, free fatty acids, and HDL cholesterol (54-56). Interestingly, the Insulin Resistance Atherosclerosis study demonstrated that elevated plasma PAI-1 predicted development of type 2 diabetes (57). Thus, high plasma PAI-1 in subjects with normal glucose tolerance may help to identify a high-risk population, which could prevent both atherosclerotic disease and type 2 diabetes by targeting shared antecedents.

We confirmed that despite similar degrees of excessive coagulation between lean and obese diabetic patients, endogenous fibrinolytic activity was lower in the obese than the lean group (51). Fibrinolytic compensation for hypercoagulation proved inadequate in obese patients with type 2 diabetes. Thus, relatively deficient fibrinolysis in a hypercoagulable state may contribute to high risk of CAD in obese, insulin-resistant diabetic patients. Accumulation and expression of PAI-1 has been found to be significantly higher in coronary atheromas removed from diabetic patients than from nondiabetic patients (40, 41). Plasma concentrations of PAI-1 correlate negatively with plasma concentrations of plasmin-α2-antiplasmin complex (PAP), a measure of fibrinolytic activity in blood, in type 2 diabetes (51). Elevated plasma PAI-1 may play a role in development of atherothrombosis in obese patients with type 2 diabetes, independently of other known cardiovascular risk factors (58).

7. REGULATION OF PAI-1 GENE EXPRESSION

The *PAI-1* gene, located on chromosome 7 (bands q21.3 to q22), has an extent of approximately 12.2 kb and consists of 8 or 9 exons (17). Two distinct species PAI-1 mRNA, 2.3 kb and 3.3 kb, are expressed on human cells, resulting from alternative polyadenylation to yield an additional 3' untranslated region (17). The 5'-flanking region (promoter) of the human PAI-1 gene contains the transcription initiation site, a TATA box, and a regulatory sequence that confer transcriptional responsiveness to a number of mediators, including a glucocorticoid response element (59) that can mediate aldosterone responsiveness, a VLDL response site (60), a glucose response site (61), as well as sites for TGF-β and TNFα (62).

PAI-1 is produced by several tissues including endothelial cells (63), adipose tissue (64), and liver (65). Human studies suggest that the liver ordinarily may be a main source. In subjects with obesity, adipose tissue is the main source of circulating PAI-1, since the mRNA for PAI-1 is up-regulated in adipose tissues of obese persons. A previous study reported that intensity of adipose tissue PAI-1 expression is related to plasma PAI-1 concentrations in human subjects (66). Platelets also synthesize and store PAI-1, which is released after platelet activation (67). A platelet-rich clot therefore is resistant to fibrinolysis.

In vitro studies have demonstrated that gene expression and synthesis of PAI-1 can be induced in cultured cells by a number of factors. Glucose induces PAI-1 synthesis and release by human endothelial (68) and smooth muscle (61). Both insulin and proinsulin can increase expression of PAI-1 in hepatocytes (69). Very low-density lipoprotein (VLDL) and free fatty acid stimulate secretion of PAI-1 by endothelial cells (70, 71). A number of cytokines have been found to induce the synthesis and release of PAI-1 *in vitro*. Tumor necrosis factor (TNF)-α and interleukin (IL)-1, both inflammatory cytokines, can produce PAI-1 in adipocytes (72). Growth factors, including transforming growth factor (TGF)-β, are known to stimulate synthesis of PAI-1 in endothelial cells (73). Components of the renin-angiotensin- aldosterone system can contribute to synthesis of PAI-1 *in vitro*. Angiotensin (Ang) II and Ang IV, a hexapeptide metabolite of Ang II, increase PAI-1 mRNA expression in vascular tissue (74). Aldosterone enhances the effects of Ang II on PAI-1 expression in vascular smooth muscle cells, as shown by transfection with a luciferase reporter construct containing variable lengths of the human PAI-1 promoter (75).

8. REGULATION AND DETERMINANTS OF PLASMA PAI-1 CONCENTRATIONS

PAI-1 is present in blood as three different molecular forms: latent (inactive), active, and complexed to t- or u-PA (29). PAI-1 binds rapidly to t-PA or u-PA at a ratio of 1:1, forming a stable complex that is cleared from the circulation by liver (29, 76). PAI-1 extensively binds t-PA, acting to limit fibrinolysis. PAI-1 plasma concentrations exceed t-PA concentrations by a 4:1 ratio (29, 62). The half-life of PAI-1 in the circulation is about 10 min. PAI-1 circulates at a plasma concentration of 10 to 50 ng/ml (62), showing circadian variation; plasma PAI-1 concentrations peak in the early morning, corresponding to a nadir in fibrinolytic activity, while plasma PAI-1 concentrations fall in the afternoon (75).

In clinical studies, plasma concentrations of PAI-1 have shown relationships with components of the metabolic syndrome, especially the fasting plasma insulin concentration and central obesity (76,77). Chronic hyperinsulinemia secondary to insulin resistance is believed to be the primary determinant of elevated plasma PAI-1 in individuals with metabolic syndrome and type 2 diabetes; on the other hand, hyperglycemic state generally is not considered to be a main regulator of plasma PAI-1 (52, 78). An insulin infusion in rats increases activity of PAI-1 in plasma, resulting in deceased fibrinolytic function (79). In contrast, a human study demonstrated that short-term insulin administration reduced plasma PAI-1 by inhibiting intranuclear nuclear factor kB (80). Most likely, synergistic actions of hyperglycemia, dyslipidemia, and hyperinsulinemia drive elevated plasma PAI-1 concentrations in type 2 diabetes (81). Several recent studies have demonstrated that plasma PAI-1 correlated negatively with serum adiponectin (82, 83), an adipocyte-derived protein that has antidiabetic and anti-atherosclerotic effects, suggesting a potential relationship between PAI-1 and adiponectin in adipocytes.

Plasma PAI-1 concentrations can be affected by several polymorphisms in the promoter region of the PAI-1 gene, including a common single-base polymorphism (4 or 5 guanine) in the promoter region of the gene, 675 base pairs upstream of the transcriptional start site (84). Subjects homozygous for the 4G allele have plasma PAI-1 concentrations approximately 25% higher than those of subjects who are homozygous for the 5G allele (85). PAI-1 also has a genotype-specific interaction with plasma triglyceride (86).

Several interventional studies demonstrated a decrease in plasma PAI-1 concentration in obese subjects after weight reduction with low-calorie diet (87, 88). In a previous study we also found that in patients with type 2 diabetes, weight reduction by intensive metabolic control decreased in plasma PAI-1, resulting in a reciprocal increase in plasma plasmin-α2-antiplasmin complex (PAP) (89). Indeed, PAI-1 is released directly from adipose tissues, especially visceral fat, in subjects with obesity (64). Insulin sensitizing drugs such as metformin and thiazolidinedione (TZD) decrease plasma PAI-1 concentrations in type 2 diabetes. Metformin, which acts by decreasing hepatic glucose production and improving insulin sensitivity through peripheral glucose utilization, can reduce triglyceride and body weight. Grant *et al.* showed that plasma PAI-1 concentrations and activity fell significantly in diabetic patients treated with metformin compared with placebo-treated controls (90). TZDs, which are peroxisome proliferator-activated receptor-γ agonists, promote adipocyte differentiation, converting insulin-resistant adipocytes to insulin-sensitive adipocytes (91). Several studies reported that troglitazone, a TZD, decreased plasma PAI-1 concentrations and activity in patients with type 2 diabetes (92, 93).

Inhibition of the renin-angiotensin-aldosterone system by an angiotensin-converting enzyme (ACE) inhibitor or an Ang II receptor blocker (ARB) may decrease plasma PAI-1 concentrations. Short-term treatment with fosinopril, an ACE inhibitor, significantly reduced PAI-1 compared with amlodipine, a calcium antagonist, in a dose-dependent fashion in type 2 diabetic patients with hypertension (94). Short-term interruption of the renin-angiotensin-aldosterone system by either ACE inhibition or ARB decreases PAI-1 antigen, but the duration of this effect is greater for ACE inhibition than for Ang II receptor (AT_1) receptor antagonism (95). Aldosterone blockade by spironolactone also decreases plasma PAI-1 in hypertensive patients (96). Unexpectedly, fenofibrate, a fibric acid derivative that lowers serum triglyceride, slightly increases PAI-1 activity in hyperlipidemic patients (97).

Our group and other investigators have shown that in poorly controlled patients with type 2 diabetes, insulin therapy decreased plasma PAI-1 concentrations with concurrent improvement in insulin sensitivity (89, 98), suggesting that exogenous insulin replacement may have no deleterious effect on fibrinolysis. In a crossover study in poorly controlled patients with type 2 diabetes, sulfonylurea therapy increased PAI-1 activity and antigen compared with insulin therapy (99).

9. SUMMARY AND PERSPECTIVE

Mechanisms by which PAI-1 may induce atherothrombotic events are summarized in Figure 2. Systemically, elevated plasma concentrations of PAI-1 induce hypofibrinolysis by impairing the action of t-PA, to prevent removal of thrombi from the vascular wall. Thus, elevated plasma PAI-1 may contribute to an excess of atherothrombotic events in metabolic syndrome or type 2 diabetes. Locally, PAI-1 promotes fibrin accumulation in the vascular lumen through its capacity to inhibit activation of t-PA or u-PA. Increased expression of PAI-1 may augment neointimal formation by promoting fibrin deposition within vessels. Enhanced local PAI-1 expression within the arterial wall may induce luminal obstruction via neointimal formation, leading to an atherothrombotic event. Medications that counteract impaired fibrinolysis by decreasing circulating concentrations of this inhibitor may

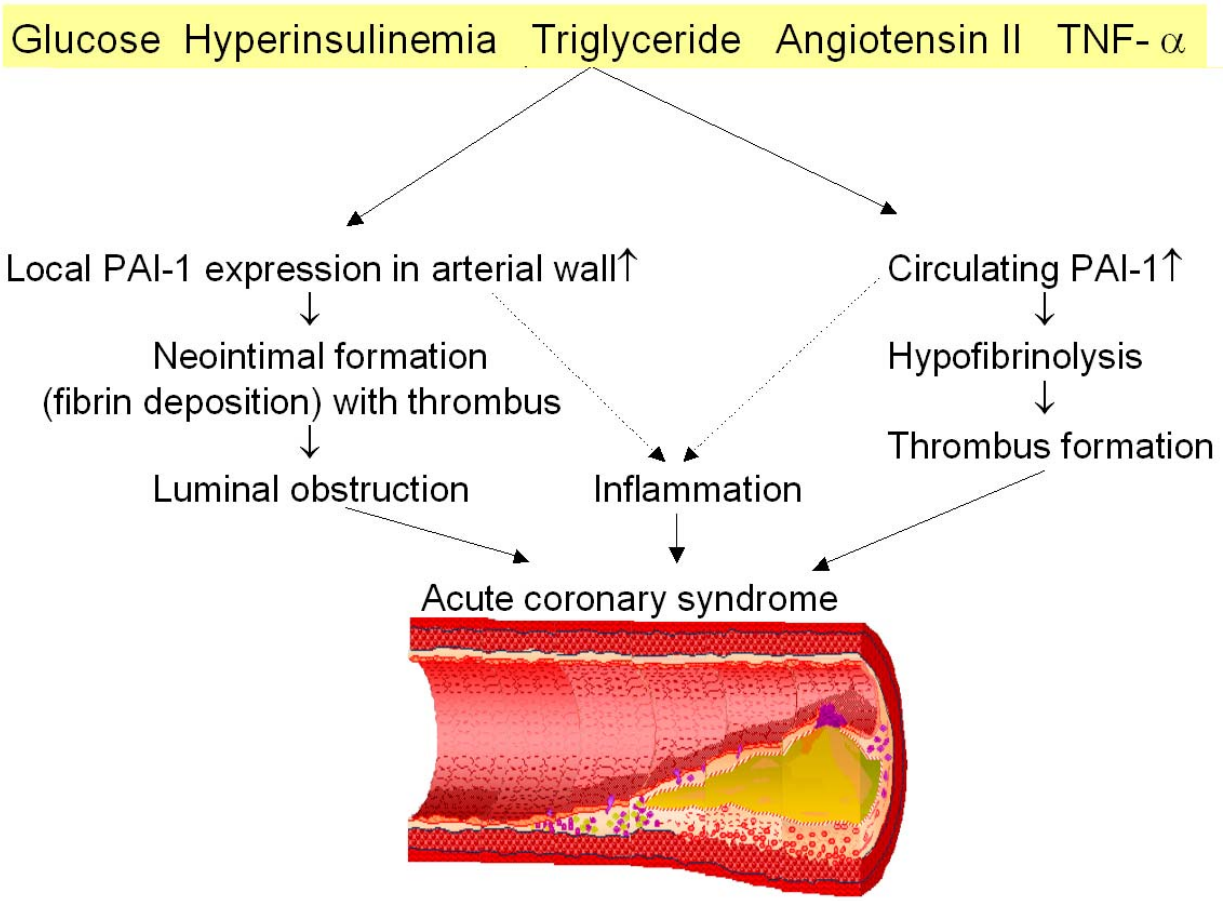

Figure 2. Proposed roles of local and circulating plasminogen activator inhibitor (PAI)-1 in development of atherothrombotic cardiovascular disease. Several factors associated with glucose and lipid metabolism, including hyperglycemia, hyperinsulinemia, hypertriglyceridemia, angiotensin II, and TNF-α, stimulate local expression of PAI-1 in the arterial wall and increase plasma concentrations of PAI-1. Increased PAI-1 expression in the arterial wall could decrease local fibrinolysis, promoting thrombus formation and unfavorable evolution of atherosclerotic plaques. Elevated plasma concentrations of PAI-1 induce hypofibrinolysis by impairing the action of t-PA, resulting in a state where thrombi cannot be removed from the vascular wall. TNF, tumor necrosis factor; t-PA, tissue-type plasminogen activator.

reduce risk of cardiovascular disease in metabolic syndrome or type 2 diabetes. Excessive intravascular PAI-1 expression may represent an ideal target for therapeutic interventions to prevent atherothrombotic events. Accordingly, a long-term clinical study should be undertaken to investigate the effects of pharmacologic inhibition of PAI-1 on atherothrombotic events.

10. ACKNOWLEDGEMENTS

I wish to thank Prof. T. Inukai at our department for reviewing this manuscript, Drs. K. Morita and K. Takebayashi for critical suggestions, and my colleagues for helping to carry out our work.

11. REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 364:937-52 (2004)

2. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS; INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 366:1640-9 (2005)

3. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 288:1723-7 (2002)

4. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. *Nat Med*. 12:75-80 (2006)

5. Kannel WB, MacGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 2: 120-126 (1979)

6. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular

mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 16: 434-44 (1993)
7. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *JAMA*. 290: 1884-90 (2003)
8. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 241: 2035-8 (1979)
9. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 37:1595-607 (1988)
10. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation.* 109:433-8 (2004)
11. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 288:2709-16 (2002)
12. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation.* 108:414-9 (2003)
13. Sobel BE. Fibrinolysis and diabetes. *Front Biosci*. 8:1085-92 (2003)
14. Juhan-Vague I, Thompson SG, Jespersen J. Involvement of the hemostatic system in the insulin resistance syndrome. A study of 1500 patients with angina pectoris. The ECAT Angina Pectoris Study Group. *Arterioscler Thromb*. 13:1865-73 (1993)
15. Schneider DJ. Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coron Artery Dis*. 16:473-6 (2005)
16. Skurk T, Hauner H. Obesity and impaired fibrinolysis: role of adipose production of plasminogen activator inhibitor-1. *Int J Obes Relat Metab Disord*. 28:1357-64 (2004)
17. Dellas C, Loskutoff DJ. Historical analysis of PAI-1 from its discovery to its potential role in cell motility and disease. *Thromb Haemost*. 93:631-40 (2005)
18. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med*. 340: 115-26 (1999)
19. Libby P. Molecular bases of the acute coronary syndromes. *Circulation*.91:2844-50 (1995)
20. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation*. 111:3481-8 (2005)
21. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol*. 46:937-54 (2005)
22. Ross JM, Alevriadou BR, McIntire L V. Rheology. In: Loscalzo J, Schafer AI, eds. Thrombosis and Hemorrhage. Baltimore, Md: Williams and Wilkins; 405–421 (2002).
23. Rentrop KP. Thrombi in acute coronary syndromes: revisited and revised. *Circulation*. 101: 1619–1626 (2000)
24. Juhan-Vague I, Moerman B, De Cock F, Aillaud MF, Collen D. Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathological conditions. *Thromb Res*. 33:523-30 (1984)
25. Kluft C, Verheijen JH, Jie AF, Rijken DC, Preston FE, Sue-Ling HM, Jespersen J, Aasen AO. The postoperative fibrinolytic shutdown: a rapidly reverting acute phase pattern for the fast-acting inhibitor of tissue-type plasminogen activator after trauma. *Scand J Clin Lab Invest*. 45:605-10 (1985)
26. Renckens R, Roelofs JJ, de Waard V, Florquin S, Lijnen HR, Carmeliet P, van der Poll T. The role of plasminogen activator inhibitor type 1 in the inflammatory response to local tissue injury. *J Thromb Haemost*. 3:1018-25 (2005)
27. Czekay RP, Aertgeerts K, Curriden SA, Loskutoff DJ. Plasminogen activator inhibitor-1 detaches cells from extracellular matrices by inactivating integrins. *J Cell Biol*. 160:781-91 (2003)
28. Stefansson S, Lawrence DA. The serpin PAI-1 inhibits cell migration by blocking integrin alpha V beta 3 binding to vitronectin. *Nature*. 383:441-3 (1996)
29. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med*. 342:1792-801 (2000)
30. Aso Y: Fibrinolysis and cardiovascular disease in type 2 diabetes: roles of plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor. Future Lipidology 1: 429-40 (2006)
31. Sprengers ED, Kluft C. Plasminogen activator inhibitors. *Blood*. 69:381-7 (1987)
32. Wiman B, Collen D. On the mechanism of the reaction between human alpha 2-antiplasmin and plasmin. *J Biol Chem*. 254:9291-7 (1979)
33. Declerck PJ, De Mol M, Alessi MC, Baudner S, Paques EP, Preissner KT, Muller-Berghaus G, Collen D. Purification and characterization of a plasminogen activator inhibitor 1 binding protein from human plasma. Identification as a multimeric form of S protein (vitronectin). *J Biol Chem*. 263:15454-61 (1988)
34. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V, Fallon JT. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation*. 102:2180-4 (2000)
35. Burke AP, Kolodgie FD, Zieske A, Fowler DR, Weber DK, Varghese PJ, Farb A, Virmani R. Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study. *Arterioscler Thromb Vasc Biol*. 24:1266-71 (2004)
36. Sato Y, Hatakeyama K, Yamashita A, Marutsuka K, Sumiyoshi A, Asada Y. Proportion of fibrin and platelets differs in thrombi on ruptured and eroded coronary atherosclerotic plaques in humans. *Heart*. 91:526-30 (2005)
37. Schneiderman J, Sawdey MS, Keeton MR, Bordin GM, Bernstein EF, Dilley RB, Loskutoff DJ. Increased type 1 plasminogen activator inhibitor gene expression in atherosclerotic human arteries. *Proc Natl Acad Sci U S A*. 89:6998-7002 (1992)

38. Raghunath PN, Tomaszewski JE, Brady ST, Caron RJ, Okada SS, Barnathan ES. Plasminogen activator system in human coronary atherosclerosis. *Arterioscler Thromb Vasc Biol*. 15:1432-43 (1995)
39. Lupu F, Bergonzelli GE, Heim DA, Cousin E, Genton CY, Bachmann F, Kruithof EK. Localization and production of plasminogen activator inhibitor-1 in human healthy and atherosclerotic arteries. *Arterioscler Thromb*. 13:1090-1100 (1993)
40. Sobel BE, Woodcock-Mitchell J, Schneider DJ, Holt RE, Marutsuka K, Gold H. Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor predisposing to thrombosis and its persistence. *Circulation*. 97:2213-21(1998)
41. Pandolfi A, Cetrullo D, Polishuck R, Alberta MM, Calafiore A, Pellegrini G, Vitacolonna E, Capani F, Consoli A. Plasminogen activator inhibitor type 1 is increased in the arterial wall of type II diabetic subjects. *Arterioscler Thromb Vasc Biol*. 21:1378-82 (2001)
42. Sobel BE, Taatjes DJ, Schneider DJ. Intramural plasminogen activator inhibitor type-1 and coronary atherosclerosis. *Arterioscler Thromb Vasc Biol*. 23:1979-89 (2003)
43. Carmeliet P, Moons L, Ploplis V, Plow E, Collen D. Impaired arterial neointima formation in mice with disruption of the plasminogen gene. *J Clin Invest*. 99:200-8 (1997)
44. Carmeliet P, Moons L, Lijnen R, Janssens S, Lupu F, Collen D, Gerard RD. Inhibitory role of plasminogen activator inhibitor-1 in arterial wound healing and neointima formation: a gene targeting and gene transfer study in mice. *Circulation*. 96:3180-91 (1997)
45. Zhu Y, Farrehi PM, Fay WP. Plasminogen activator inhibitor type 1 enhances neointima formation after oxidative vascular injury in atherosclerosis-prone mice. *Circulation*. 103:3105-10 (2001)
46. DeYoung MB, Tom C, Dichek DA. Plasminogen activator inhibitor type 1 increases neointima formation in balloon-injured rat carotid arteries. *Circulation*. 104:1972-7 (2001)
47. Peng L, Bhatia N, Parker AC, Zhu Y, Fay WP. Endogenous vitronectin and plasminogen activator inhibitor-1 promote neointima formation in murine carotid arteries. *Arterioscler Thromb Vasc Biol*. 22:934-9 (2002)
48. Schafer K, Muller K, Hecke A, Mounier E, Goebel J, Loskutoff DJ, Konstantinides S. Enhanced thrombosis in atherosclerosis-prone mice is associated with increased arterial expression of plasminogen activator inhibitor-1. *Arterioscler Thromb Vasc Biol*. 23:2097-103 (2003)
49. Konstantinides S, Schafer K, Loskutoff DJ. Do PAI-1 and vitronectin promote or inhibit neointima formation? The exact role of the fibrinolytic system in vascular remodeling remains uncertain. *Arterioscler Thromb Vasc Biol*. 22:1943-5 (2002)
50. Schneider DJ, Nordt TK, Sobel BE. Attenuated fibrinolysis and accelerated atherogenesis in type II diabetic patients. Diabetes. 42:1-7 (1993)
51. Aso Y, Matsumoto S, Fujiwara Y, Tayama K, Inukai T, Takemura Y. Impaired fibrinolytic compensation for hypercoagulability in obese patients with type 2 diabetes: association with increased plasminogen activator inhibitor-1. *Metabolism*. 51:471-6 (2002)
52. Juhan-Vague I, Roul C, Alessi MC, Ardissone JP, Heim M, Vague P. Increased plasminogen activator inhibitor activity in non insulin dependent diabetic patients--relationship with plasma insulin. *Thromb Haemost*. 61:370-3 (1989)
53. Walmsley D, Hampton KK, Grant PJ. Contrasting fibrinolytic responses in type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes. *Diabet Med*. 8:954-9 (1991)
54. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. *J Thromb Haemost*. 1:1575-9 (2003)
55. Mavri A, Alessi MC, Juhan-Vague I. Hypofibrinolysis in the insulin resistance syndrome: implication in cardiovascular diseases. *J Intern Med*. 255:448-56 (2004)
56. Aso Y, Wakabayashi S, Yamamoto R, Matsutomo R, Takebayashi K, Inukai T. Metabolic syndrome accompanied by hypercholesterolemia is strongly associated with proinflammatory state and impairment of fibrinolysis in patients with type 2 diabetes: synergistic effects of plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor. *Diabetes Care*. 28:2211-6 (2005)
57. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM; Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes*. 51:1131-7 (2002)
58. Thogersen AM, Jansson JH, Boman K, Nilsson TK, Weinehall L, Huhtasaari F, Hallmans G. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation*. 98:2241-7 (1998)
59. van Zonneveld AJ, Curriden SA, Loskutoff DJ. Type 1 plasminogen activator inhibitor gene: functional analysis and glucocorticoid regulation of its promoter. *Proc Natl Acad Sci U S A*. 85:5525-9 (1988)
60. Eriksson P, Nilsson L, Karpe F, Hamsten A. Very-low-density lipoprotein response element in the promoter region of the human plasminogen activator inhibitor-1 gene implicated in the impaired fibrinolysis of hypertriglyceridemia. *Arterioscler Thromb Vasc Biol*. 18:20-6 (1998)
61. Chen YQ, Su M, Walia RR, Hao Q, Covington JW, Vaughan DE. Sp1 sites mediate activation of the plasminogen activator inhibitor-1 promoter by glucose in vascular smooth muscle cells. *J Biol Chem*. 273:8225-31 (1998)
62. De Taeye B, Smith LH, Vaughan DE. Plasminogen activator inhibitor-1: a common denominator in obesity, diabetes and cardiovascular disease. *Curr Opin Pharmacol*. 5:149-54 (2005)
63. Nordt TK, Klassen KJ, Schneider DJ, Sobel BE. Augmentation of synthesis of plasminogen activator inhibitor type-1 in arterial endothelial cells by glucose and

its implications for local fibrinolysis. *Arterioscler Thromb*. 13:1822-8 (1993)
64. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, Yamashita S, Miura M, Fukuda Y, Takemura K, Tokunaga K, Matsuzawa Y. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med*. 2:800-3 (1996)
65. Kooistra T, Bosma PJ, Tons HA, van den Berg AP, Meyer P, Princen HM. Plasminogen activator inhibitor 1: biosynthesis and mRNA level are increased by insulin in cultured human hepatocytes. *Thromb Haemost*. 62:723-8 (1989)
66. Morange PE, Alessi MC, Verdier M, Casanova D, Magalon G, Juhan-Vague I. PAI-1 produced *ex vivo* by human adipose tissue is relevant to PAI-1 blood level. *Arterioscler Thromb Vasc Biol*. 19:1361-5 (1999)
67. Konkle BA, Schick PK, He X, Liu RJ, Mazur EM. Plasminogen activator inhibitor-1 mRNA is expressed in platelets and megakaryocytes and the megakaryoblastic cell line CHRF-288. *Arterioscler Thromb*. 13:669-74 (1993)
68. Nordt TK, Klassen KJ, Schneider DJ, Sobel BE. Augmentation of synthesis of plasminogen activator inhibitor type-1 in arterial endothelial cells by glucose and its implications for local fibrinolysis. *Arterioscler Thromb*. 13:1822-8 (1993)
69. Nordt TK, Sawa H, Fujii S, Sobel BE. Induction of plasminogen activator inhibitor type-1 (PAI-1) by proinsulin and insulin *in vivo*. *Circulation*. 91:764-70 (1995)
70. Stiko-Rahm A, Wiman B, Hamsten A, Nilsson J. Secretion of plasminogen activator inhibitor-1 from cultured human umbilical vein endothelial cells is induced by very low density lipoprotein. *Arteriosclerosis*. 10:1067-73 (1990)
71. Nilsson L, Banfi C, Diczfalusy U, Tremoli E, Hamsten A, Eriksson P. Unsaturated fatty acids increase plasminogen activator inhibitor-1 expression in endothelial cells. *Arterioscler Thromb Vasc Biol*. 18:1679-85 (1998)
72. Sakamoto T, Woodcock-Mitchell J, Marutsuka K, Mitchell JJ, Sobel BE, Fujii S. TNF-alpha and insulin, alone and synergistically, induce plasminogen activator inhibitor-1 expression in adipocytes. *Am J Physiol*. 276(6 Pt 1):C1391-7 (1999)
73. Sawdey M, Podor TJ, Loskutoff DJ. Regulation of type 1 plasminogen activator inhibitor gene expression in cultured bovine aortic endothelial cells. Induction by transforming growth factor-beta, lipopolysaccharide, and tumor necrosis factor-alpha. *J Biol Chem*. 264:10396-401 (1989)
74. Kerins DM, Hao Q, Vaughan DE. Angiotensin induction of PAI-1 expression in endothelial cells is mediated by the hexapeptide angiotensin IV. *J Clin Invest*. 96:2515-20 (1995)
75. Brown NJ, Kim KS, Chen YQ, Blevins LS, Nadeau JH, Meranze SG, Vaughan DE. Synergistic effect of adrenal steroids and angiotensin II on plasminogen activator inhibitor-1 production. *J Clin Endocrinol Metab*. 85:336-44 (2000)
76. Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). *Circulation*. 79:101-6 (1989)
77. Anand SS, Yi Q, Gerstein H, Lonn E, Jacobs R, Vuksan V, Toe K, Davis B, Montague P, Yusuf S; Study of Health Assessment and Risk in Ethnic Groups; Study of Health Assessment and Risk Evaluation in Aboriginal Peoples Investigators. Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. *Circulation*. 10:420-5 (2003)
78. Juhan-Vague I, Alessi MC, Vague P. Increased plasma plsaminogen activator inhibitor 1 levels. A possible link between insulin resistance and atherothrombosis. *Diabetologia* 34: 457-462 (1991)
79. Pandolfi A, Giaccari A, Cilli C, Alberta MM, Morviducci L, De Filippis EA, Buongiorno A, Pellegrini G, Capani F, Consoli A. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta Diabetol*. 38:71-6 (2001)
80. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab*. 86:3257-65 (2001)
81. Calles-Escandon J, Mirza SA, Sobel BE, Schneider DJ. Induction of hyperinsulinemia combined with hyperglycemia and hypertriglyceridemia increases plasminogen activator inhibitor 1 in blood in normal human subjects. *Diabetes*. 47:290-3 (1998)
82. Pellme F, Smith U, Funahashi T, Matsuzawa Y, Brekke H, Wiklund O, Taskinen MR, Jansson PA. Circulating adiponectin levels are reduced in nonobese but insulin-resistant first-degree relatives of type 2 diabetic patients. *Diabetes*. 52:1182-6 (2003)
83. Maruyoshi H, Kojima S, Funahashi T, Miyamoto S, Hokamaki J, Soejima H, Sakamoto T, Kawano H, Yoshimura M, Kitagawa A, Matsuzawa Y, Ogawa H. Adiponectin is inversely related to plasminogen activator inhibitor type 1 in patients with stable exertional angina. *Thromb Haemost*. 91:1026-30 (2004)
84. Dawson S, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. *Arterioscler Thromb*. 11:183-90 (1991)
85. Eriksson P, Kallin B, van 't Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. *Proc Natl Acad Sci U S A*. 92:1851-5 (1995)
86. Mansfield MW, Stickland MH, Grant PJ. Environmental and genetic factors in relation to elevated circulating levels of plasminogen activator inhibitor-1 in Caucasian patients with non-insulin-dependent diabetes mellitus. *Thromb Haemost*. 74:842-7 (1995)
87. Folsom AR, Qamhieh HT, Wing RR, Jeffery RW, Stinson VL, Kuller LH, Wu KK. Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII, and other hemostatic factors in moderately overweight adults. *Arterioscler Thromb*. 13:162-9 (1993)
88. Kockx M, Leenen R, Seidell J, Princen HM, Kooistra T. Relationship between visceral fat and PAI-1 in

overweight men and women before and after weight loss. *Thromb Haemost*. 82:1490-6 (1999)
89. Aso Y, Okumura KI, Yoshida N, Tayama K, Takemura Y, Inukai T. Enhancement of fibrinolysis in poorly controlled, hospitalized type 2 diabetic patients by short-term metabolic control: association with a decrease in plasminogen activator inhibitor 1. *Exp Clin Endocrinol Diabetes*. 112:175-80 (2004)
90. Grant PJ. The effects of metformin on the fibrinolytic system in diabetic and non-diabetic subjects. *Diabete Metab*. 17:168-73 (1991)
91. Okuno A, Tamemoto H, Tobe K, Ueki K, Mori Y, Iwamoto K, Umesono K, Akanuma Y, Fujiwara T, Horikoshi H, Yazaki Y, Kadowaki T. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest*. 101:1354-61 (1998).
92. Ehrmann DA, Schneider DJ, Sobel BE, Cavaghan MK, Imperial J, Rosenfield RL, Polonsky KS. Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 82:2108-16 (1997)
93. Kruszynska YT, Yu JG, Olefsky JM, Sobel BE. Effects of troglitazone on blood concentrations of plasminogen activator inhibitor 1 in patients with type 2 diabetes and in lean and obese normal subjects. *Diabetes* 49:633-9 (2000)
94. Pahor M, Franse LV, Deitcher SR, Cushman WC, Johnson KC, Shorr RI, Kottke-Marchant K, Tracy RP, Somes GW, Applegate WB. Fosinopril versus amlodipine comparative treatments study: a randomized trial to assess effects on plasminogen activator inhibitor-1. *Circulation*. 105:457-61 (2002)
95. Brown NJ, Agirbasli M, Vaughan DE. Comparative effect of angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor antagonism on plasma fibrinolytic balance in humans. *Hypertension*. 34:285-90 (1999)
96. Yalcin AI, Dincer M, Aslan V, Gulbas Z. Effect of spironolactone on impaired fibrinolysis of hypertensive patients. *Kidney Blood Press Res*. 25:260-4 (2002)
97. Durrington PN, Mackness MI, Bhatnagar D, Julier K, Prais H, Arrol S, Morgan J, Wood GN. Effects of two different fibric acid derivatives on lipoproteins, cholesteryl ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type IIb hyperlipoproteinaemia. *Atherosclerosis.* 138:217-25 (1998)
98. Lormeau B, Aurousseau MH, Valensi P, Paries J, Attali JR. Hyperinsulinemia and hypofibrinolysis: effects of short-term optimized glycemic control with continuous insulin infusion in type II diabetic patients. *Metabolism*. 46:1074-9 (1997)
99. Panahloo A, Mohamed-Ali V, Andres C, Denver AE, Yudkin JS. Effect of insulin versus sulfonylurea therapy on cardiovascular risk factors and fibrinolysis in type II diabetes. *Metabolism*. 47:637-43 (1998)

Key Words: Plasminogen Activator Inhibitor 1, Cardiovascular Disease, Atherothrombosis, Type 2 Diabetes, Metabolic Syndrome, Review

Send correspondence to: Yoshimasa Aso, MD, Department of Internal Medicine, Koshigaya Hospital, Dokkyo Medical University, 2-1-50 Minami-Koshigaya, Koshigaya, Saitama 343-8555, Japan, Tel: 81-48-965-1111, Fax: 81-48-965 –1127, E-mail: yaso@dokkyomed.ac.jp

http://www.bioscience.org/current/vol12.htm