Plasminogen Activator Inhibitor-1 Activity in Chronic Renal Disease and Dialysis

Ashley B. Irish

The activity of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis, is associated with insulin resistance (IR) and the risk of venous and arterial thrombotic cardiovascular disease (CVD) in the general population, and may behave as an acute-phase reactant. PAI-1 activity was measured in 124 patients with chronic renal disease, and its relationship with alterations in metabolic, lipid, and cytokine parameters and the prevalence of CVD complications was explored. Patients with chronic renal disease not requiring dialysis were divided into a low proteinuric ([LP] n = 30) or high proteinuric ([HP] n = 31) group and compared with patients on continuous ambulatory peritoneal dialysis ([CAPD] n = 32) or hemodialysis([HD] n = 31) and with 31 healthy controls. Patients on HD had significantly lower PAI-1 activity than HP, CAPD, and control groups, but no group had significantly higher values than the controls (AU/mL: 7.4 ± 3.8 HD, 11.2 ± 8.4 CAPD, 9.4 ± 5.4 LP, 12.1 ± 8.0 HP, 11.4 ± 6.6 controls, $P = .04$). Interleukin-6 (IL-6), the mediator of the acute-phase response, was determined in a subset of patients and was significantly increased in HD, CAPD, and LP groups compared with the controls (median, pg/mL: 4.6 HD, 4.0 CAPD, 2.9 LP, 2.4 HP, and 1.5 controls, $P < .001$), but did not correlate with PAI-1. PAI-1 independently correlated with body mass index (BMI), triglycerides, and lipoprotein(a) [Lp(a)] in stepwise regression for all patients. Dividing the whole patient group by tertiles of triglycerides and BMI, increased PAI-1 was confined to the subgroup of patients with both obesity (BMI > 26.7 kg/m^2) and hypertriglyceridemia (triglycerides > 2.5 mmol/L). These data suggest that PAI-1 activity in chronic renal disease and dialysis was more strongly associated with the common metabolic abnormalities of obesity and hypertriglyceridemia than with renal disease status, dialysis, or a chronic inflammatory state. This study does not support but does not exclude a major role for increased PAI-1 activity in CVD risk in chronic renal disease.

CARDIOVASCULAR DISEASE (CVD) is a frequent cause of mortality and morbidity in patients with chronic renal disease or nephrotic syndrome and in those receiving maintenance dialysis. Impairment of fibrinolytic activity due to an increase in plasminogen activator inhibitor-1 (PAI-1) activity has been shown to be associated with the risk for venous and arterial thrombotic vascular disease in the general population.[1] Increased PAI-1 was noted in survivors of acute myocardial infarction and predicted risk of reinfarction.[2,3] Decreased fibrinolytic activity measured by nonspecific global measures of fibrinolysis has also demonstrated that increased CVD risk is associated with impaired fibrinolysis, probably reflecting increased PAI-1.[4]

PAI-1 is a rapid inhibitor of tissue plasminogen activator and is derived from platelets, hepatocytes, and endothelium, but circulating PAI-1 activity is thought to reflect endothelial PAI-1 secretion, although this is still uncertain.[5] PAI-1 is under regulation by cytokines and may behave as an acute-phase reactant following surgery or acute illness.[5] It is associated with plasma triglycerides, low high-density lipoprotein (HDL) cholesterol, hypertension, hyperinsulinemia, and obesity, features of insulin resistance (IR).[6] The precise cause of this clustering of risk factors remains to be elucidated, but peripheral resistance to insulin and central obesity appear to be particularly important.[7] Insulin, very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and glucose can all stimulate PAI-1 in vitro.[8] The effect of renal disease on PAI-1 has not been comprehensively examined but is relevant, since global measures of fibrinolysis have suggested both impaired[9] and enhanced[10] fibrinolysis in renal disease. Specific measurement of fibrinolytic parameters has usually[11-13] but not always[14] shown increased tissue plasminogen activator with normal levels of PAI-1 in hemodialysis (HD) patients, and normal levels of PAI-1 activity or antigen[15-19] have been reported in patients receiving continuous ambulatory peritoneal dialysis (CAPD) or those with nephrotic syndrome. IR has been reported in HD,[20] predialysis,[21] and nephrotic syndrome.[22]

Lipoprotein(a) [Lp(a)] is considered an independent predictor of CVD in the general and possibly renal population, although this is still controversial.[23,24] Its level is increased in CAPD, nephrosis, and predialysis, whereas normal or increased levels have been described in HD.[25] Lp(a) is atherogenic and, at least in vitro, prothrombotic, possibly by competition with plasminogen and/or fibrin for endothelial binding sites.[26] In vitro, increased Lp(a) levels have also been shown to increase PAI-1 mRNA expression in endothelial cells, suggesting another potential thrombotic mechanism for Lp(a).[27]

This cross-sectional study was undertaken to examine PAI-1 activity in 124 patients drawn from a broad cross-section of patients with chronic renal disease and representing all treatment modalities. The effect of dialysis or predialysis treatment on PAI-1 and other CVD and metabolic risk factors, particularly lipids, Lp(a), blood pressure, and prevalent CVD complications, was explored. In a subset of 51 patients, interleukin-6 (IL-6) measurements were available as a measure of the acute-phase response.

SUBJECTS AND METHODS

One hundred twenty-four (73 male, 51 female) outpatients with chronic renal disease (31 receiving HD, and 32 with CAPD, and 61 with chronic renal disease not requiring dialysis) were compared with 31 healthy controls. Patients with recent infection or malignancy were excluded. Diagnoses were glomerulonephritis (n = 52), reflux nephropathy (n = 13), polycystic kidney disease (n = 11), hypertension/vascular disease (n = 13), unknown (n = 19), and miscellaneous (n = 16). Seven patients were diabetic (four type I and three type II). Thirty-one

From the Oxford Renal Unit, The Churchill Hospital, Headington, Oxford, United Kingdom.

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Address reprint requests to Ashley B. Irish, FRACP, The Renal Unit, Bundaberg Base Hospital, PO Box 34, Bundaberg 4670, Queensland, Australia.

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healthy controls were drawn from the staff of the Oxford Renal Unit or their spouses. HD patients were dialyzed between 8 and 15 hours weekly on cuprophane dialysis membranes using bicarbonate (n = 25) or acetate (n = 6) concentrate. HD patients were studied a median of 24 hours (range, 10 to 84) following dialysis. The median time since commencing dialysis was 21 months (range, 3 to 264). Sixty-three percent of the patients were receiving antihypertensive medication, and four patients were on lipid-lowering therapies (Simvastatin or Pravastatin), and their lipid results have been excluded from analysis. Excluding vascular access complications, 44 patients (35%) had suffered either or both venous or arterial vascular occlusive or thrombotic complications defined by clinical history and confirmed with appropriate investigations.

Blood pressure was measured using automated sphygmomanometers (BP103N Mark III; Nippon Colin, Nippon, Japan) and recorded as the mean of the previous three consecutive clinical measurements. Patients were studied after a 12-hour overnight fast and underwent venesection with a 21-gauge needle between 8:30 and 11:30 AM, with minimal or no stasis. Blood for lipid and metabolic parameters was collected into heparin or EDTA vacutainer tubes. Blood for PAI-1 activity was collected into citrate 3.8% (1:9 by volume) and centrifuged at 3,000 × *g* for 15 minutes at room temperature before separation and stored at −70°C until assayed.

Urinary protein concentration was measured from 24-hour urinary collections (n = 38) or first-morning void samples (n = 23) in patients not receiving dialysis. The correlation between (log-transformed) urinary protein concentration and 24-hour protein excretion was .93. Lipids were assayed by standard enzymatic techniques.[28] LDL cholesterol level was measured after precipitation of VLDL using sodium dodecyl sulfate and subtraction of the measured HDL. HDL cholesterol level was measured after precipitation of other fractions by heparin and manganese chloride. VLDL cholesterol was calculated as the difference [total − (LDL + HDL)]. Lp(a) was determined by an enzyme-linked immunosorbent assay (TintElize; Biopool, Umea, Sweden). The interassay coefficient of variation for Lp(a) using Biopool QC was 7.9%. Samples above the upper limit of detection (600 mg/L) were assayed in dilution. IL-6 was assayed by an enzyme-linked immunosorbent assay using an antibody raised against recombinant human IL-6 (Human IL-6 Quantikine HS; R&D Systems, Minneapolis, MN) in 51 renal patients randomly drawn from all the groups and 27 controls. PAI-1 activity was measured by a chromogenic assay (Coatest PAI; Chromogenix, Mölndal, Sweden).

Statistics

Comparison of group means or log-transformed medians was made by ANOVA, and for comparisons where the F test was significant, the Fisher protected test for least-significant difference was used to determine which pairs of groups differed at the 95% significance level. Lp(a), IL-6, triglycerides, and urinary protein concentrations that were not normally distributed were log-transformed before analysis. Linear correlations were assessed by Pearson's correlation. Forward stepwise multiple linear regression was used to assess independent contribution to the dependent variable PAI-1. A two-factor ANOVA was used to assess the interaction between triglycerides and BMI on PAI-1. $P < .05$ was considered significant. Statistical analyses were performed by Statview II (Abacus Concepts, Berkley, CA) computer software.

RESULTS

Metabolic, demographic, and categorical data by mode of treatment are shown in Table 1. To compare the effects of protein loss on the parameters of interest, the chronic renal disease group was divided into a low (LP) and high (HP) proteinuric group according to the median urinary protein concentration (1.6 g/L), which was 0.6 (LP) and 4.0 (HP) g/L, respectively. The patient groups had comparable sex, smoking, and CVD distribution and BMI was similar for all groups, but LP subjects were substantially older than all other groups and the controls. Plasma albumin was significantly reduced and total white blood cell count and platelet count were higher in the CAPD and HP groups than in the LP and HD groups. All groups were hypertensive compared with the controls.

Values for lipids, Lp(a), IL-6, and PAI-1 are shown in Table 2. The lipid profile showed the typical hypertriglyceridemia of chronic renal disease and the progressive decline in HDL cholesterol with worsening renal function. VLDL cholesterol was increased in all groups, but only the HP group had elevated total and LDL cholesterol. Lp(a) was increased for the whole population compared with the controls (median, 290 *v* 113 mg/L, $P < .01$), and by each treatment mode except for the HD group. IL-6 was increased in HD, CAPD, and LP groups compared with the controls. PAI-1 activity showed a barely significant variation in means across the patient groups. No group had significantly higher values than the controls, but the

Table 1. Metabolic Data by Mode of Treatment (mean ± SD)

Variable	HD (n = 31)	CAPD (n = 32)	LP (n = 30)	HP (n = 31)	Controls (n = 31)	*P*
Sex (M:F)	21:10	15:17	18:12	19:12	16:15	>.2
CVD total (n)	11	16	9	8	0	>.2*
Erythropoietin (n)	22	12	3	1	—	—
Age (yr)	51 ± 13	52 ± 15	61 ± 11†	48 ± 13	47 ± 11	.003
BMI (kg/m²)	24.7 ± 3.9	25.1 ± 3.9	24.5 ± 4.3	26.5 ± 4.8	25.3 ± 3.1	>.3
Creatinine (μmol/L)	780 ± 170	790 ± 250	510 ± 230†	260 ± 200†	—	.0001
Albumin (g/L)	43.0 ± 3.9†	35.7 ± 3.3†	40.3 ± 3.1†	31.2 ± 6.9†	—	.0001
Glucose (mmol/L)	5.5 ± 1.0	5.9 ± 1.4	5.7 ± 1.0	6.0 ± 0.9	—	>.2
White blood cell count (×10⁹/L)	5.9 ± 1.9†	8.0 ± 2.2	7.4 ± 2.1	8.1 ± 1.6	—	.0001
Platelet count (×10⁹/L)	206 ± 65†	276 ± 71	256 ± 95¶	304 ± 87	—	.0001
Systolic BP (mm Hg)	148 ± 26	152 ± 22	162 ± 18†	148 ± 19	134 ± 15†	.0001
Diastolic BP (mm Hg)	80 ± 14	88 ± 9¶	85 ± 9	82 ± 10	72 ± 11†	.0001

NOTE. Comparison of means was made by ANOVA.
Abbreviation: BP, blood pressure.
*Excluding controls.
†Significantly different from all other groups.

Table 2. Lipid Fractions (mmol/L), Lp(a), IL-6 (measured in 51 patients and 27 controls), and PAI-1 Activity by Treatment Modality

Variable	HD	CAPD	LP	HP	Controls	P
Cholesterol (mmol/L)						
Total	4.5 ± 1.3‡	5.7 ± 1.2	5.3 ± 1.8	8.1 ± 3.7*	5.1 ± 0.9	.0001
LDL	2.6 ± 0.9‡	3.6 ± 1.2	3.2 ± 1.6	5.6 ± 3.6*	3.4 ± 0.8	.0001
HDL	0.9 ± 0.3	0.9 ± 0.2	1.0 ± 0.3	1.1 ± 0.4†‡	1.2 ± 0.3†‡§	.0001
VLDL	1.1 ± 0.7	1.3 ± 0.7	1.1 ± 0.4	1.3 ± 0.7	0.5 ± 0.3*	.0001
Triglycerides (mmol/L)	1.8 ± 1.1	2.4 ± 1.4	2.0 ± 1.4	3.2 ± 2.4†§	1.1 ± 0.6*	.0001
Lp(a) (mg/L)	187 (1-1,372)	309 (12-1,610)	318 (15-1,030)	280 (9-1,965)	113 (1-1,180)‡§‖	.017
IL-6 (pg/mL)	4.6 (2.0-14.1)	4.0 (0.5-12.4)	2.9 (1.4-17.6)	2.4 (0.3-16.7)†	1.5 (0.3-6.5)†‡§	.0004
PAI-1 (AU/mL)						
All patients	7.4 ± 3.8	11.2 ± 8.4†	9.4 ± 5.4	12.1 ± 8.0†	11.4 ± 6.6†	.04
Males	7.3 ± 4.2	10.2 ± 7.5	9.1 ± 5.5	10.8 ± 6.3	10.2 ± 5.8	NS
Females	7.6 ± 3.3	12.1 ± 9.3	10.0 ± 5.5	14.1 ± 10.2	12.7 ± 7.3	NS

NOTE. Results are the mean ± SD or median (range). Comparison of means or log-transformed medians was made by ANOVA.
*Significantly different from all other groups.
†Significantly different from HD.
‡Significantly different from CAPD.
§Significantly different from LP.
‖Significantly different from HP.

HD group had significantly lower values than the CAPD, HP, and control groups. There was no significant difference between PAI-1 in males and females (9.2 ± 5.9 for males *v* 11.2 ± 8.0 for females, $P = .12$) for the whole patient population, the control group, or within each renal grouping.

Current smokers had slightly increased PAI-1 (11.6 ± 7.1 *v* 9.4 ± 6.7, $P = .11$). The prevalence of erythropoietin use is shown in Table 1. There was no difference in PAI-1, hemoglobin, white blood cell count, or platelet count between all patients receiving erythropoietin (n = 38) and those not receiving erythropoietin (n = 86) or when examined by mode of dialysis (data not shown), nor was there any difference in PAI-1 in patients receiving antihypertensive medication compared with those not receiving antihypertensive treatment (data not shown). Neither PAI-1 activity nor Lp(a) differed between patients with CVD complications (CVD^+, n = 44) and those without CVD complications (PAI-1, 9.6 ± 7.0 CVD^+ *v* 10.2 ± 6.9 AU/mL, $P = .6$; Lp(a), 214 CVD^+ *v* 306 mg/L, $P = .18$).

PAI-1 correlated significantly with BMI ($r = .39$, $P < .0001$), VLDL cholesterol ($r = .28$, $P < .01$), white blood cell count ($r = .25$, $P < .01$), triglycerides ($r = .39$, $P < .0001$), and Lp(a) ($r = .20$, $P < .05$) and inversely with creatinine ($r = .20$, $P < .05$) and albumin ($r = .20$, $P < .05$), but not with urinary protein concentration ($r = .15$), 24-hour urinary protein excretion ($r = .16$), platelet count ($r = .15$), or IL-6 ($r = .04$). In stepwise regression with PAI-1 as the dependent variable and BMI, triglycerides, creatinine, albumin, white blood cell count, Lp(a), sex, and mode of therapy as the independent variables, BMI (partial F = 11.0), triglycerides (F = 9.1), and Lp(a) (F = 4.9) were independently correlated with PAI-1 and explained 24% of the variance of PAI-1. To examine the interaction between triglycerides and BMI on PAI-1, the 117 nondiabetic patients were divided by tertiles of these parameters (Table 3). This shows that the increase in PAI-1 was confined to patients within the group defined by the upper tertile of triglycerides (2.5 mmol/L) and BMI (26.7 kg/m^2).

DISCUSSION

This study shows that PAI-1 activity measured in a large and heterogeneous group of patients with chronic renal disease was not significantly greater than in a group of healthy controls, in agreement with the majority of reports to date.[15-19] Patients on HD had PAI-1 levels significantly lower than the control, HP, and CAPD groups, which could contribute to their enhanced fibrinolysis noted in other studies.[11-13] In contrast, Gris et al[14] described increased PAI-1 activity in French HD patients and postulated that it was related to cytokine activation and endothelial dysfunction. However, they did not report lipid fractions or a measurement of body weight, so it is difficult to compare these studies. Compared with this study, their patients had significantly lower albumin levels, perhaps reflecting a greater increase in inflammatory cytokines such as IL-6, IL-1, and TNFα, altered nutrition, or differences in the dialysis procedure. Similar to the problem with the lack of standardization of Lp(a) assays that makes comparisons between studies difficult, variability in the measurement of PAI-1 remains of concern, with great variability in the reproducibility of assay methods,[30] but providing a control group is used, this should restrict internal comparisons. In the present study, HD patients had the highest albumin level and lowest white blood cell and platelet counts of all groups, suggesting a reduced inflammatory response despite evidence of increased IL-6, the principal mediator of the acute-phase response.[31] PAI-1 correlated neither with IL-6 or with the platelet count, suggesting that it was not influenced by a persistent inflammatory response or related to the platelet-derived pool of PAI-1. HD patients are subjected to intermittent cytokine activation due to exposure to the dialysis membrane, but it has been shown that the extent of chronic circulating cytokine activation is equivalent between CAPD and HD populations[29,32] (in agreement with the finding of a similar degree of increase in IL-6 levels in HD and CAPD groups in the

Table 3. Interaction Table for PAI-1 by BMI and Triglycerides in 117 Nondiabetic Patients (two-factor ANOVA, $P = .07$)

	Tertiles of Triglycerides (mmol/L)		
Tertiles of BMI (kg/m^2)	≤1.34	1.35-2.5	>2.5
≤23.1	7.8	9.0	6.5
23.2-26.7	6.5	8.7	11.1
>26.7	8.7	7.8	15.2

present study) and that no significant increment in PAI-1 activity occurred during the HD procedure despite cytokine release.[11,13,19] Therefore, the regulation of PAI-1 by cytokines in chronic renal disease may differ from the acute changes described in the general population. Factors such as increased insulin release in CAPD patients due to instillation of dextrose-containing dialysate into the peritoneum and/or the loss of protein across the peritoneal membrane or into the urine that occur in CAPD or HP groups may contribute to the variation in PAI-1, white blood cell count, and albumin seen across the renal groups. The finding that patients without heavy proteinuria but with significant chronic renal failure (the LP group) had PAI-1 levels not significantly different from the HD group is consistent with this hypothesis.

Renal disease groups share many features also found in the metabolic or IR syndrome, including hypertension, elevated triglycerides, and low HDL cholesterol. IR is found in obesity, non–insulin-dependent diabetes, hypertriglyceridemia, and hypertension, and also in up to 25% of healthy populations with normal glucose tolerance.[8] Increased PAI-1 is also considered a feature of IR states and is proposed to contribute to the increased CVD risk of these populations, although the mechanism remains uncertain.[1] Weight loss reduces PAI-1 antigen independently of insulin and triglyceride levels, suggesting that obesity is central to these associations.[33] In this study, neither fasting insulin measurements nor methods to quantify IR were available. However, BMI and triglyceride level independently correlated with PAI-1 regardless of treatment modality, and only patients in the highest tertiles for triglycerides and BMI had increased PAI-1 levels, suggesting that factors common to IR states in the general population also define a population at risk of increased PAI-1 in renal disease. Dzúrik et al[21] have demonstrated increased IR and dyslipidemia in patients with mild to moderate renal failure, but in their study the IR group was characterized by increased BMI compared with the insulin-sensitive group. Stenvinkel et al[22] have shown increased IR in a nephrotic group but not in a nonnephrotic group with mild renal impairment, perhaps related to reduced albumin binding of free fatty acids. The results of this study and published studies to date suggest that increased PAI-1 is not a typical feature of renal disease states or dialysis per se, and occurs only in patients who are metabolically or genetically at risk irrespective of the development of renal disease. This can only be definitively answered when both parameters are measured concurrently.

Patients with arterial or venous CVD complications did not have increased PAI-1 compared with those without CVD. This study may have underestimated the CVD risk because of the temporal dislocation between blood sampling and the disease event, and because patients most at risk may have died. It remains possible that despite the findings in this study, prospective studies could identify a subgroup of patients at increased risk for CVD due to increased PAI-1, such as patients with both obesity and hypertriglyceridemia. Genetic variability in PAI-1 has also been described due to a polymorphism in the promoter region of the PAI-1 gene, which may respond differently to acute-phase cytokines and possibly triglycerides by differential binding of nuclear transcription factors.[34,35] Genotyping was not available in this study, but may have provided additional information relevant to the interaction between environment and genotype in determining susceptibility to CVD risk.

Increased Lp(a) is well described in renal disease and has been suggested to contribute to CVD risk. Increased Lp(a) was confirmed in this study for all treatment groups except the HD group, in agreement with other reports.[24,25] In vitro, Lp(a) induced PAI-1 mRNA expression in cultured endothelial cells, suggesting that high Lp(a) may interfere with endothelial-controlled fibrinolysis by mechanisms apart from competitive inhibition of plasminogen for binding sites.[27] In the present study, although PAI-1 and Lp(a) showed an independent correlation, the significance is uncertain. However, high concentrations of Lp(a) and PAI-1 at the endothelial surface could contribute to impaired fibrinolysis and thrombotic risk.

In summary, in a large heterogeneous cohort of patients drawn from all causes of renal failure and renal replacement therapy, and despite dyslipidemia and evidence of a persistent acute-phase response, PAI-1 activity was not significantly increased. Patients receiving HD had the lowest PAI-1 and Lp(a) of all renal disease groups, which could favor enhanced fibrinolysis, but the mechanism for this is uncertain. The data presented here suggest that, as in the general population, obesity and hypertriglyceridemia identify a subgroup of patients who may be at increased risk for elevated PAI-1 activity, but that chronic renal disease or dialysis per se does not significantly increase PAI-1 activity.

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