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Risk factors for cardiovascular disease in renal transplant recipients: new insights

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Abstract Long-term survival of renal transplant recipients appears to be influenced by the occurrence of thromboembolic complications and cardiovascular disease. In order to investigate the prevalence of new hemostasis-related risk factors for venous and arterial thrombosis, we investigated 63 renal transplant recipients and 66 age- and sex-matched control subjects. We assayed antiphospholipid antibodies [lupus anticoagulant (LA) and anticardiolipin antibodies (aCL)], lipoprotein (a) [Lp(a)], plasminogen activator inhibitor-1 (PAI-1), and total homocysteine (tHcy) levels. We found a significantly higher prevalence of positivity for LA ($P < 0.001$); no difference was detected in the prevalence of aCL between patients and controls. PAI-1 levels were significantly higher in renal transplant recipients than in controls [12.3 IU/ml (2–45.5) vs 7.9 IU/ml (4–18.0); $P < 0.0001$] with an odd ratio (OR) of 11.8 (4.9–28.5) in univariate analysis and of 5.8 (2.1–15.4) in multivariate analysis. Lp(a) levels were higher in patients then in controls [159 mg/l (1–992) vs 100.5 mg/l (10–412); $P < 0.005$] with an OR of 5.9 (1.9–18.4) in univariate analysis and of 3.5 (0.9–13.4) in multivariate analysis. Fasting levels of tHcy were significantly higher in renal transplant recipients [7.0 μmol/l (4.0–68) vs 8.1 μmol/l (2.0–24.0); $P < 0.00001$] with an OR of 40.4 (14.7–111) in univariate analysis and of 33.1 (11.1–115.5) in multivariate analysis. After methionine loading test, we documented levels of tHcy above the 90th percentile of controls in 60/63 patients (95%). Finally, we found a significant correlation between tHcy and PAI-1 plasma levels ($r = 0.76$; $P < 0.000001$). Our results show a high prevalence of hemostasis-related risk factors for arterial and venous thrombosis in renal transplant recipients, suggesting the need for the investigation of these patients for the presence of these risk factors in order to improve their long-term survival and to tailor therapy.

Key words Renal transplantation · Cardiovascular disease · Risk factors · Hemostasis · Homocysteine

Introduction

At present, renal transplantation is an established method in the treatment of end-stage renal failure. The long-term survival of renal transplant recipients appears to be increasingly influenced by the occurrence of atherosclerotic lesions, and cardiovascular disease represents a major cause of both morbidity and mortality in these patients as in dialysis patients. However, there are surprisingly few reports defining risk factors for cardiovascular disease in renal transplant recipients [1–5]. The very high incidence of death due to ischemic heart dis-

ease makes primary and secondary intervention particularly beneficial in this group of patients. Several hemostasis-related risk factors have been associated with an increased risk for ischemic heart disease and thromboembolic events: antiphospholipid antibodies (aPL) [lupus anticoagulant (LA) and anticardiolipin antibodies (aCL)] [6], elevated plasminogen activator inhibitor-1 (PAI-1) [7] and lipoprotein (a) [Lp(a)] [8] levels, and mild hyperhomocysteinemia [9]. The prothrombotic effect of aPL has been postulated to be related to their interference with the protein C anticoagulant system, with fibrinolytic activity, and with the procoagulant activity of endothelial cells, monocytes, and platelets [10, 11].

In patients with established ischemic heart disease, prospective cohort studies [7] have indicated that high levels of PAI-1, the inhibitor of the fibrinolytic system, may predict cardiovascular disease. Furthermore, some studies [12] described, in renal transplant recipients, an imbalance in the fibrinolytic system documented by high levels of plasminogen activator inhibitor (PAI-1). Elevated plasma levels of Lp(a) [8] are a strong, independent predictor of myocardial infarction, intermittent claudication, and cerebrovascular disease. Several epidemiological prospective studies have provided strong evidence that hyperhomocysteinemia is a risk factor for ischemic heart disease: the enhanced risk associated with a 5-μmol/l rise in total plasma homocysteine (tHcy) was estimate to be comparable to that associated with a 0.5-mmol/l increase in total cholesterol [13, 14]. Furthermore, there is an increase of 7% for cardiovascular complications for each μmol increase of tHcy. Data from literature documented high levels of Hcy in patients with end-stage renal disease in which homocysteinemia was found to be associated with the impaired renal function [15]. More recently, some studies also reported high levels of Hcy in renal transplant recipients, with a recovered renal function and with creatinine levels within the normal range.

The aim of this study was to evaluate the prevalence of hemostasis-related risk factors for cardiovascular disease, such as aPL, high plasma levels of Lp(a), PAI-1, and Hcy, which may contribute to the increased incidence of cardiovascular disease experienced by renal transplant recipients.

Materials and methods

Subjects investigated

We investigated 63 stable (at least 6 months after transplant and with no clinical evidence of renal graft rejection and normal liver transaminases) renal transplant recipients (33 M; 30 F), and 66 age- and sex-matched normal subjects as controls. For the renal transplant recipients, the specific current immunosuppressive drug regimen was documented. All patients were on prophylactic immunosuppressive therapy based either on triple therapy with cyclosporine, azathioprine, and steroids or on double therapy with cyclosporine and steroids. Mean serum creatinine levels were 1.36 ± 0.35 mg/dl and mean glomerular filtration rate (GFR) 74 ± 15.5 ml/min. Patients and controls were enrolled in this study after giving their informed consent to use part of their blood samples for an experimental study.

Experimental procedure

To determine Hcy, whole blood was collected in tubes containing ethylenediaminotetraacetate (EDTA) 0.17 mol/l as the anticoagulant, immediately put in ice, and centrifuged within 30 min at 4 °C (15000 *g* for 15 min). The supernatant was stored in aliquots at –80 °C until assay. The plasma levels of Hcy (free and protein bound) were determined by high-performance liquid chromatography (HPLC; LKB 2248 pump; Pharmacia, Uppsala, Sweden) and fluorescence detection (Waters 474). In brief, 100 μl plasma was incubated with 10 μl 10% tri-*n*-butylphosphine in dimethylformamide at 4 °C for 30 minto reduce homocystine and mixed disulfide and deconjugate Hcy from plasma proteins. Then, 100 μl of a 0.6-mol/l solution of trichloroacetic acid in 1 nmol/l EDTA 2Na was added. The mixture was kept for 10 min at room temperature and centrifuged in an Eppendorf microcentrifuge at 10000 rpm for 5 min. After a 60-min incubation in a 60 °C water bath, aliquots were cooled to room temperature and injected in HPLC. Separation was carried out at room temperature at a flow rate of 1.2 ml/min. HyperHcy was diagnosed when fasting plasma levels of Hcy or its postmethionine load absolute increments above fasting levels exceeded the 90th percentiles of distribution of values obtained in controls. Hcy after the methionine loading test was measured only in those patients with fasting Hcy levels below the 90th percentile of control distribution.

Blood for LA and other coagulation tests was collected in tubes containing trisodium citrate (0.129) 1:10, v/v. Platelet-poor plasma (PPP) for LA test was obtained by centrifuging twice at 1300 g for 10 minand was stored at –80 °C until used. For other tests, aliquots of citrated blood were immediately centrifuged at 1500 *g* for 10 min at 4 °C and stored at –20 °C until used. Sera for testing aCL were obtained by centrifuging blood collected without anticoagulant at 1300 *g* for 10 min and stored at –20 °C. The presence of aPL was assessed by performing four different tests for LA and an enzyme-linked immunoadsorbent assay (ELISA) for IgG and IgM aCL. Pooled PPP from 20 normal subjects was used as the reference. The tests used to detect the presence of LA were: (1) diluted (1:50) aPTT (Pathromtin; Behring Institute, Marburg Germany), (2) kaolin clotting time (Stago, Asnieres, France), (3) tissue thromboplastin inhibition test (using 1:1000 dilution; Calciplastina Baldacci, Pisa, Italy), and (4) dilute Russell's viper venom time (IL test LAC screen; Instrumentation Laboratory, Milan, Italy). Mixing studies with normal plasma (pooled PPP from 20 normal subjects) were employed to exclude clotting factor deficiences or the presence of antibodies against specific coagulation proteins. Specimens shown to be abnormal were also assayed according to the platelet neutralization procedure (PNP; Diagnostica Stago, Milan, Italy) as the confirmation test. We considered LA positive only those patients with tests confirmed by PNP. The aCL assay was performed by an ELISA method (First Cardiolipin; Eurospital, Trieste, Italy) and aCL levels were reported in GPL units (for IgG) and in MPL units (for IgM). On the basis of the analysis of several hundred normal serum specimens performed in our laboratory in the past, and according to the literature, values above 20 U for both IgG and IgM were considered abnormal.

To determine PAI-1 activity, whole blood was drawn in Vacutainer test tubes containing sodium citrate 0.129 M (final ratio

1/10), centrifuged at 4 °C (1500 *g* for 10 min), and then rapidly frozen in liquid nitrogen and stored at –20 °C. Within 4 days, plasma aliquots were thawed and used for PAI-1 activity determinations by a chromogenic method (control range 2–15 IU/ml). Lp(a) was assayed by an ELISA method(TintElize Lp(a); Biopool, Umea, Sweden; control range 1–300 mg/l).

Statistical analysis

Unless otherwise indicated, the results are given as median and range. Spearman's rank correlation coefficient (for non-parametric data) was used for correlation analysis. The non-parametric test for unpaired data was used for comparison between single groups. To describe the relationship between PAI-1, Lp(a), and tHcy levels and renal transplant recipients, univariate analysis was used. To adjust for other IHD risk factors, creatinine levels, and GFR, logistic regression was used with diabetes, smoking status, hypertension, total cholesterol, triglycerides, creatininemia, and GFR as the independent variables. All odds ratios (ORs) are given with their 95% confidence interval (CI). All probability values reported are two-tailed, with values of less than 0.05 which are to be considered statistically significant.

Table 1 Clinical characteristics of renal transplant recipients

Number	63
Mean age (yrs)	49 ± 10.6
Gender (M/F)	34/29
Dialytic age (months)	39.2 ± 38.5
Graft duration (months)	44.6 ± 45.4
Mean serum creatinine (mg/dl)	1.36 ± 0.35
Glomerular filtration rate (ml/min)	74 ± 15.5

Table 2 Hemostasis-related risk factors in renal transplant recipients. [*LA* Lupus anticoagulant, *aCL* anticardiolipin antibodies, *PAI-1* plasminogen activator inhibitor 1, *tHcy* total homocysteine, *Lp(a)* lipoprotein (a)]

	Patients, $n = 63$	Controls, $n = 66$	P
LA positivity (%)	15.8	3	< 0.001
aCL positivity (%)	6.3	1.5	NS
PAI-1 (IU/ml)	12.3 (2–45.5)	7.9 (4–18)	< 0.0001
tHcy (μmol/l)	17.0 (4.0–68)	8.1 (2.0–24.0)	< 0.00001
Lp(a) (mg/l)	159 (1–992)	110.5 (10–412)	< 0.005

Results

Clinical characteristics of patients investigated are shown in Table 1.

Antiphospholipid antibodies

We found a significantly ($P < 0.001$) higher prevalence of positivity for LA among patients (10/63 patients; 15.5%) with respect to control subjects (2/66; 3%; Table 2). The prevalence of LA positivity was higher in female patients (44%) than in males (33%). aCL were present in 4/63 patients with a prevelence of 6.3% and in 1/66 control subjects (Table 2; NS).

PAI-1 and Lp(a) levels

PAI-1 plasma levels were significantly higher in renal transplant recipients than in controls [12.3 IU/ml (2–45.5) vs 7.9 IU/ml (4–18.0); $P < 0.0001$; Table 2]. The OR for PAI-1 levels above 15 IU/ml was increased in renal transplant recipients (OR 11.8; CI 4.9–28.5; $P < 0.000001$); this result was confirmed after adjustment for cardiovascular risk factors, creatinine levels, and GFR (OR 5.8; CI 2.1–15.4; $P < 0.0005$).

Similarly, we found higher Lp(a) levels in patients with respect to control subjects [159 mg/l (1–992) vs 100.5 mg/l (10–412); $P < 0.005$; Table 2]. In 15.8% of patients and 9% of controls, values higher than 300 mg/l have been observed. The OR for Lp(a) levels above 300 mg/l was 5.9 (CI 1.9–18.4; $P < 0.005$); after adjustment for cardiovascular risk factors, creatinine levels, and GFR, we found an OR of 3.5 (CI 0.9 –13.4; $P = 0.07$). We did not find any significant correlation between PAI-1 and Lp(a) levels ($r = 0.20$; $P = 0.09$).

Hcy levels

The fasting levels of plasma Hcy were significantly higher in renal transplant recipients than in controls [17.0 μmol/l (4.0–68) vs 8.1 μmol/l (2.0–24.0); $P < 0.00001$; Table 2]. Hyperhomocysteinemia, defined as a concentration of fasting plasma Hcy above the 90th percentile of controls, was diagnosed in 46/63 patients with a prevalence of 73%. In 17 patients with fasting Hcy levels within the normal value, we performed the methionine loading test. HyperHcy (defined as an increase of Hcy levels above the 90th percentile of controls) was diagnosed in 10/17 patients. Totally, in 60/63 renal ransplant recipients we documented high levels of Hcy with a prevalence of 95%. Fasting tHcy correlated well with serum creatinine levels and GFR; a significant correlation was also found between tHcy and folate levels as found by others (Table 3). The OR for fasting hyperhomocysteinemia was markedly increased in renal transplant recipients (OR 40.4; CI 14.7–111). Adjustment for prevalent cardiovascular risk factors, creatinine levels, and GFR by multivariable logistic regression did not alter this result significantly (OR 33.1; CI 11.1–115.5). Furthermore, we found a highly significant correlation between tHcy and PAI-1 plasma levels ($r = 0.76$; $P < 0.000001$; Fig. 1) while no significant correlation between tHcy and Lp(a) levels was documented ($r = 0.15$; $P = 0.20$).

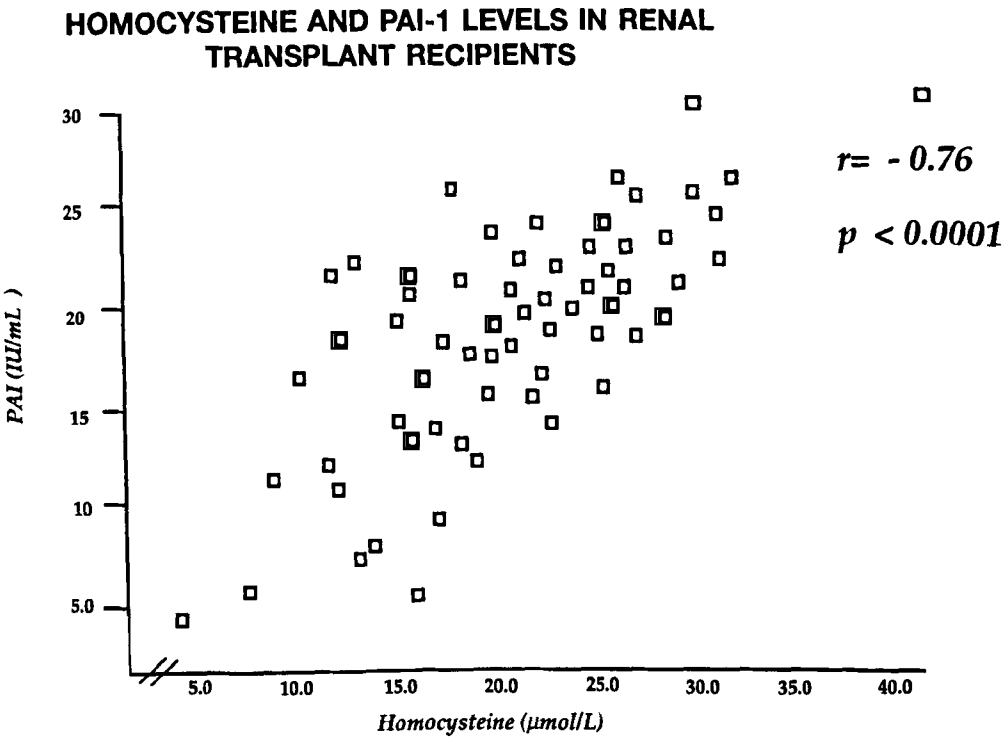

Fig. 1 Homocysteine and plasminogen activator inhibitor 1 (*PAI-1*) levels renal transplant recipients

Table 3 Crude Spearman correlations (with two-tailed *P* values) between fasting tHcy and PAI-1 levels and other covariates in 63 renal transplant recipients

	Fasting tHcy	PAI-1
Fasting tHcy	–	+ 0.68 (< 0.00001)
PAI-1	+ 0.68 (< 0.00001)	–
Folate	– 0.34 (0.04)	– 0.40 (0.01)
B12	– 0.19 (0.24)	– 0.36 (0.02)
Creatinine	0.81 (< 0.00001)	0.48 (< 0.00001)
Glomerular filtration rate (ml/min)	– 0.20 (< 0.05)	– 0.17 (= 0.05)
Age	– 0.14 (0.28)	– 0.18 (0.17)
Pretransplant dyalitic age (months)	– 0.03 (0.79)	– 0.04 (0.74)
Transplant duration (months)	– 0.07 (0.57)	– 0.01 (0.90)

Discussion

Thromboembolic and cardiovascular complications constitute an important risk after renal transplantation. The prevalence of thrombotic disease is very high in renal transplant recipients ranging from 0.9 to 24.1%. Long-term cyclosporine-treated renal transplant recipients manifest features of a hypercoagulable state as documented by the high levels of fibrinogen, FVIII, FVII, fragments 1 + 2 of prothrombin, and D-dimer found in these patients [16, 17]. In order to investigate the pathogenesis of cardiovascular disease experienced by renal transplant recipients, several studies reported, in these patients, high levels of some hemostasis-related risk factors such as Hcy and PAI-1 levels [12, 18]. In this study we offer the first evidence, to our knowledge, of a high prevalence of all the most important and emerging hemostatis-related risk factors for cardiovascular disease in renal transplant recipients.

We found a higher prevalence of LA positivity in renal transplant recipients with respect to controls. The prevalence of IgG and IgM aCL was similar in patients and controls. Only one patient was affected by systemic lupus erythematosus and no one by other connective tissue diseases. A connective tissue disease as the original renal disease could not be referred to in any patient. No patient had a history of previous arterial or venous thrombotic accidents, thrombocytopenia, or recurrent miscarriages suggesting a diagnosis of aPL syndrome. Our findings are rather surprising as cyclosporine is effective in the treatment of several autoantibody-mediated diseases such as systemic lupus erythematosus, rheumatoid arthritis, and psoriasis. Nevertheless, several studies found a permissive role of cyclosporine on the development of autoantibodies in renal transplant recipients. Autoimmune hemolytic anemia, autoimmune thrombocytopenia, Grave's disease, and the appearance of antineutrophil cytoplasmic autoantibodies have been reported [19–21] in transplanted patients on cyclosporine treatment. Some of these conditions can be re-

versed by conversion from cyclosporine to azathioprine therapy [22]. Similarly, in this group of patients a so high prevalence of LA positivity could represent one of the effects of the cyclosporine treatment: further studies are needed to explain the pathophysiology of this possible effect of the administration of cyclosporine. In addition, the lack of LA and aCL assay before renal transplantation does not allow us to evaluate the effect of the transplantation and/or of the immunosuppressive therapy on aPL appearance. aCl appearance has been previously described after kidney transplantation in patients without connective tissue disease [23]. Their presence, as indeed the presence of LA, may be related to altered immune functions in uremia, further aggravated by bioincompatibility of the dialyzer membrane, a condition that might possibly persist after transplantation. Finally, one could speculate that the antiphospholipid antibody response is secondary to the vascular damage in the transplanted kidney.

We observed a high PAI-1 activity in renal transplant recipients as compared to control subjects. High levels of PAI-1 mirror a defective fibrinolytic potential due to the inhibitory effect of PAI-1 on plasminogen activator activity. These results are consistent with data given by Patrassi et al. [12] documenting high PAI-1 levels both after kidney transplantation and in patients affected by Cushing's disease. In fact, they correlated the decreased fibrinolytic activity with the steroid treatment. Our results again demonstrate not only an impairment of fibrinolytic potential, in which certainly steroid treatment plays a role, but also a strict correlation between Hcy and PAI-1 plasma levels. This suggests that the high PAI-1 plasma levels may represent more the effect of the endothelial damage due to the oxidation stress induced by high levels of Hcy than the effect of the steroid treatment. In order to investigate the influence of steroid treatment and homocysteinemia on PAI-1 levels, we analyzed tHcy and PAI-1 plasma levels in eight renal transplant recipients on steroid-free immunosuppressive treatment. In this subgroup of patients we were able to confirm elevated PAI-1 levels strictly correlating with tHcy levels (data not shown), supporting our hypothesis on the relevant effect of Hcy on PAI-1 levels.

Another important finding is the elevated levels of Lp(a) found in our group of patients. Lp(a) contributes to a defective fibrinolytic activity enhancing the effect of the high levels of PAI-1. In fact, Lp(a) contains a unique apolipoprotein, apolipoprotein (a), that has a striking homology with plasminogen. Lp(a) binds to plasminogen binding sites on fibrin, fibrinogen, and cell surfaces. In in vitro studies it has been shown that high levels of Hcy seem to be able to promote the binding of Lp(a) on fibrin, causing a decreased fibrinolysis.

Our findings show an increase in tHcy plasma levels in the large majority of renal transplant recipients in comparison with healthy control subjects. The mechanism of hyperhomocysteinemia in renal transplant recipients has not yet been elucidated. Nutritional factors, in particular vitamin B12 and folate, may influence Hcy levels as well as the renal function. This is documented by the significant positive relationship found between folate, creatinine levels, GFR, and homocysteinemia. Our transplanted patients had a good renal function as documented by their GFR. Data from literature [24] documented that renal transplant recipients on cyclosporine had significantly higher plasma Hcy concentrations than those not on cyclosporine, probably based on an interference with the folate-assisted remethylation of Hcy. Therefore, an additional mechanism seems to operate in renal transplant recipients treated with cyclosporine.

These results may play a crucial prognostic and therapeutic role as high levels of homocysteinemia can be corrected by a simple and inexpensive diet integration based on folic acid, vitamin B6, and vitamin B12. In order to evaluate the effect of the vitamin supplementation on tHcy levels, 20 patients have been treated for 2 months with folic acid (5 mg/days), vitamin B6 (2 mg/days) and vitamin B12 (0.5 mg/days). We obtained a significant reduction (–59.6%) of tHcy levels in all patients (data not shown). Intervention studies are guaranteed to evaluate the effect of Hcy-lowering therapy on the incidence of cardiovascular disease and thromboembolic complications after renal transplantation. In conclusion, our results add further weight to the need of investigating renal transplant recipients for the presence of the most important hemostasis-related risk factors, such as aPL, Lp(a), PAI-1, and tHcy levels, in order to prevent any possible future cardiovascular or thromboembolic accident and to tailor the therapy to the single patient.

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