Nephrol Dial Transplant (2011) 26: 2700–2705
doi: 10.1093/ndt/gfq791
Advance Access publication 1 February 2011

Thrombophilic factors in Stage V chronic kidney disease patients are largely corrected by renal transplantation

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Abstract

Background. The aim of our study was to evaluate the prevalence of acquired thrombophilic factors in Stage V chronic kidney disease (CKD) patients according to dialysis modality, the rate of correction of these factors 1 month after renal transplantation and their impact on cardiovascular or thromboembolic events at 1 year.

Methods. Three hundred and ten patients were prospectively screened for seven thrombophilic factors at transplantation; 215 of them were also assayed 1 month after.

All the patients received prophylactic acetylsalicylic acid, started before transplantation.

Results. The prevalence of thrombophilic factors was significantly higher in patients under dialysis ($n = 289$) than in patients not yet on dialysis ($n = 21$) (74 versus 52.4%; $P = 0.03$) but was similar in haemodialysis and peritoneal dialysis patients (74.2 versus 73.2%). One month after transplantation, the global prevalence of thrombophilic factors had dropped from 74.4 to 44.7% ($P < 0.001$). Most thrombophilic factors had disappeared after transplantation: antithrombin deficiency: 13.5 versus 0.9%; $P < 0.001$, protein C deficiency: 12.1 versus 1.9%; $P < 0.001$, protein S deficiency: 3.7 versus 1.4%; $P = 0.1$, lupus anticoagulant: 37.7 versus 8.4%; $P < 0.001$ and antiphospholipid antibodies: 29.3 versus 12.6%; $P < 0.001$. The prevalence of activated protein C resistance, which reflects inherited factor V (FV) Leiden, was unchanged (1.9%), while the prevalence of elevated factor VIIIc increased from 20.9 to 30.7%, $P < 0.001$. The incidence of cardiovascular or thromboembolic events 1 year after transplantation was similar in patients with more than or equal to one thrombophilic factor at 1 month (5.2%) versus thrombophilic-free patients (6.7%).

Conclusion. Acquired thrombophilic factors are highly prevalent among Stage V CKD patients. Most thrombophilic factors are corrected 1 month after transplantation.

Keywords: coagulation; haemodialysis; renal transplantation; thrombophilia

Introduction

Thrombophilia corresponds to well-known inherited and/or acquired hypercoagulability conditions that result in an increased risk of venous and/or arterial thromboses. Mutations or abnormal levels of coagulation factors result in either insufficient inhibition of the blood-clotting cascade (antithrombin, protein S, protein C and factor V mutation) or increased clotting activity (prothrombin mutation). High levels of factors VIIIc and IX are also associated with thromboembolic risk. In addition, antiphospholipid antibodies and lupus anticoagulant are the main acquired thrombophilic factors associated with an increased thromboembolic risk [1, 2]. For largely unknown reasons, the prevalence of acquired thrombophilic factors is higher in patients with Stage V chronic kidney disease (CKD) [3–10] than in the general population [2]. The possible impact of thrombophilic factors on the incidence of thromboembolic events, either during dialysis or early after kidney transplantation, is the subject of contradictory findings [3, 4, 11–19]. We recently reported on a cohort study where 310 renal transplant recipients were prospectively screened on the day of transplantation for a panel of 11 inherited and acquired thrombophilic factors. One crucial finding was that 80% of the patients from this cohort had at least one thrombophilic factor [3]. Important questions remain regarding CKD-acquired thrombophilic factors. Does the dialysis modality influence the prevalence of thrombophilic factors? Does renal transplantation lead to the correction of thrombophilic factors? What is the impact of thrombophilic factors present after transplantation on thromboembolic or cardiovascular events? Trying to answer these questions, we report here (i) the prevalence of seven thrombophilic factors according to the type of renal replacement therapy; (ii) the prevalence of factors assayed before and 1 month after renal transplantation to evaluate the possible correction of these factors by renal transplantation and (iii) the prevalence of cardiovascular or thromboembolic events 1 year after transplantation to evaluate the possible association with the presence of thrombophilic factors at 1 month.

Subjects and methods

Coagulation analyses

On the day of transplantation and 1 month after transplantation, three trisodium citrate sample tubes (5 mL) and 1 EDTA-supplemented sample tube (8 mL) were collected from each enrolled patient. Blood samples were drawn by peripheral vein puncture, within 1–3 h prior to transplantation and 1 month later. From the 11 thrombophilic factors that we have previously assayed on the day of transplantation, seven were assayed 1 month later and were considered for the present analysis: levels of antithrombin, protein C, protein S and factor VIIIc; resistance to activated Protein C (APC); presence of lupus anticoagulant and antiphospholipid antibodies titres. For logistic reasons, only few patients were tested for factor IX both at transplantation and 1 month after and therefore, this factor was not included in the present analysis. Three inherited genetic variants, which could not be influenced by transplantation, were also left out of the present analysis: factor V Leiden (G1691A), prothrombin (G20210A) mutation and GPIIIa (T1565C) polymorphism of the GPIIIa/IIb receptor. Definition of the thrombophilic risk (cut-off values) and the method used for each coagulation assay are reported in Appendix Table, supplementary material.

Subjects

From September 2001 to December 2006, we prospectively screened 11 thrombophilic factors in 320 consecutive renal transplant recipients. We excluded 10 patients from the initial cohort because more than three values were missing [3]. The prevalence of thrombophilic factors according to dialysis modality was evaluated in the whole cohort of 310 patients. For the evaluation of the correction of thrombophilic factors after transplantation, we decided to exclude patients for whom one or more of the seven factors studied were missing at either baseline (at the day of transplantation) and/or at 1 month. From the 310 patients, 95 were excluded for the following reasons: more than or equal to one missing value at transplantation ($n = 41$); more than or equal to one missing value at 1 month ($n = 46$) and graft loss ($n = 7$) or death ($n = 1$) occurring during the first month posttransplantation. Finally, a total of 215 patients were screened for the seven thrombophilic factors at the day of transplantation and 1 month later and were eligible for the analysis of the correction of thrombophilic factors. Recipients were mostly Caucasian (75.2%), males (65.5%), with a mean age of 47.8 years, receiving a first renal graft (83.9%), mainly from a deceased donor (89.3%) and with a mean time in dialysis of 35.6 ± 2.6 months. The majority of patients received a calcineurin inhibitor (either tacrolimus: 81% or cyclosporine: 19%), mycophenolate mofetil (86.8%) and induction with anti-IL-2R antagonist (65.5%) or anti-thymocyte antibodies (15.8%). In the case of a personal history of thromboembolic event or a risk of graft vessel thrombosis discovered at surgery (multiple donor renal vessels, donor or recipient renal artery atheroma and donor renal artery reconstruction), patients were given low-molecular weight heparin (39%) or unfractioned heparin (3.5%) postoperatively for 3–5 days. In the core cohort ($n = 310$), 28 patients were given acenocoumarol prior to transplantation, for the following reasons: deep venous thrombosis/pulmonary embolism ($n = 3$), atrial fibrillation ($n = 6$), cardiac valve replacement ($n = 2$), vessel bypass ($n = 3$), prevention of dialysis access thrombosis ($n = 11$) and other ($n = 2$). Acenocoumarol was stopped prior to the surgical procedure in all patients. Twenty-three of them received heparin postoperatively during 3–5 days, while five received acetylsalicylic acid only. In heparin-treated patients,

acenocoumarol was restarted again in 13 of them, while acetylsalicylic acid was started in 15 patients. None of the 28 patients received acenocoumarol and acetylsalicylic acid in combination. The others received 100 mg of acetylsalicylic acid, started before surgery and continued *ad vitam*. In order to ascertain that our subpopulation tested for the seven thrombophilic factors at transplantation and 1 month after ($n = 215$) was comparable to the global cohort of 310 consecutive patients enrolled in the core study, we compared the baseline characteristics between the cohort of 215 patients and the group of patients who were excluded ($n = 95$) for the evaluation of the correction of thrombophilic factors. There were no significant differences (data not shown) except for acenocoumarol intake that, for unclear reasons, was more frequent among excluded patients versus those enrolled (17.0 versus 5.6%; P = 0.001).

Statistical methods

The objectives of the present study were (i) to evaluate the prevalence of seven thrombophilic factors at the day of transplantation according to the modality of dialysis, haemodialysis, peritoneal dialysis or no dialysis (Stage V CKD) and (ii) to evaluate the correction of these thrombophilic factors 1 month after transplantation. We reported the prevalence of major cardiovascular events and thromboembolic events defined as follows: coronary heart disease with or without myocardial infarction, coronary artery bypass surgery or percutaneous transluminal coronary angioplasty, nonhaemorrhagic stroke, proximal or distal lower extremities arterial disease, deep venous thrombosis and pulmonary embolism. We compared the paired proportions by the Mc Nemar χ^2 and Mc Nemar exact test when the samples were too small. Categorical data were compared using the chi-square or Fisher's exact test as appropriate. We used the *t*-test when the variables had a normal distribution; otherwise, we used the Mann–Whitney test. In all cases, a bilateral P-value of <0.05 was used to reject the null hypothesis. All the analyses were performed with Stata 10.

Results

Prevalence of thrombophilic factors according to the dialysis modality

At the time of transplantation (baseline), 21 patients were not on dialysis (Stage V CKD patients who underwent preemptive transplantation), 248 were undergoing haemodialysis and 41 were on peritoneal dialysis (Table 1). The global prevalence of thrombophilic factors (at least one of seven thrombophilic factor assayed) at transplantation was higher in dialysed patients (either haemodialysis or peritoneal dialysis) than in patients not yet on dialysis (74.0 versus 52.4%; P = 0.03). The prevalence was similar in patients on haemodialysis versus under peritoneal dialysis (74.2 versus 73.2%; P = 0.89). There was no significant correlation between the presence of more than or equal to one thrombophilic factor at transplantation and the length on dialysis prior to transplantation. We then compared the prevalence of the seven individual factors at transplantation between the two dialysis modality groups and the group of Stage V CKD patients not on dialysis. Antithrombin deficiency was more frequent in patients on haemodialysis (P = 0.01), while high factor VIIIc was more frequent in patients on peritoneal dialysis (P = 0.01). Positive lupus anticoagulant (LA) was more frequent in patients on dialysis in comparison with patients not yet on dialysis (39.1 versus 14.3%; P = 0.02). The distribution of lupus anticoagulant (LA) was similar across the etiologies of graft failure and only one of three patients with systemic lupus erythematosus had a positive LA. Regarding the proportion of patients having a past history of cardiovascular or thromboembolic events before transplantation, there was no significant difference between patients with and without more than or equal to one thrombophilic factor at transplantation. Thromboembolic events (deep venous thrombosis, pulmonary embolism) or cardiovascular events (coronary heart disease, myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, nonhemorrhagic stroke and proximal/distal lower extremities arterial disease) occurred in 14.1% of patients free of thrombophilic factor (seven assayed) as compared to 16.9% of patients with more than or equal to one thrombophilic factor (P = 0.55). A past history of thromboembolic events developed in 3.5% of patients free of thrombophilic factor versus 4.9% of patients with more than or equal to one thrombophilic factor (P = 0.77).

Global prevalence, correction and de novo occurrence of thrombophilic factors 1 month after transplantation

Among the 215 patients screened both at the day of transplantation and 1 month after, 160 (74.4%) had at least one thrombophilic factor at the day of transplantation (Table 2). The most frequent abnormality was the presence of the lupus anticoagulant (37.7%), followed by antiphospholipid antibodies (29.3%), elevated factor VIIIc (20.9%), antithrombin deficiency (13.5%) and protein C deficiency (12.1%). Protein S deficiency and APC resistance were

Table 1. Prevalence of patients with single thrombophilic factor at transplantation, according to dialysis modality: haemodialysis ($n = 248$), peritoneal dialysis ($n = 41$) and no dialysis (Stage V CKD, $n = 21$)

Factor	Proportion of patients on haemodialysis, % (*n*)	Proportion of patients on peritoneal dialysis, % (*n*)	P[a]	Proportion of patients not on dialysis, % (*n*)	P[b]
Antithrombin deficiency	17.4 (43)	2.4 (1)	0.01	0 (0)	0.05
Protein C deficiency	15.1 (36)	7.3 (3)	0.2	0 (0)	0.09
Protein S deficiency	5.8 (14)	2.4 (1)	0.7	4.8 (1)	1
APC resistance	3.2 (8)	0 (0)	0.6	0 (0)	0.4
Elevated factor VIIIc	17.4 (43)	34.2 (14)	0.01	28.6 (6)	0.4
Lupus anticoagulant	39.7 (96)	41.5 (17)	0.8	14.3 (3)	0.02
Antiphospholipid antibodies	26.6 (61)	30.6 (11)	0.6	23.8 (5)	0.9
Proportion of patients with $\geq$1 factor, % (*n*)	74.2 (184)	73.2 (30)	0.9	52.4 (11)	0.03

[a]P-value of the comparison between patients under haemodialysis and under peritoneal dialysis.
[b]P-value of the comparison between dialysis patients (haemodialysis + peritoneal dialysis) and patients not on dialysis.

Table 2. Prevalence of patients with thrombophilic factor at transplantation and 1 month after ($n = 215$)

Factor	Prevalence at transplantation, % (n)	Proportion with persistent factor at 1 month, % (n)	P[a]	Proportion with *de novo* factor at 1 month, % (n)	Total proportion with thrombophilic factor at 1 month, % (n)	P[b]
Antithrombin deficiency	13.5 (29)	0.9 (2)	<0.001	0 (0)	0.9 (2)	<0.001
Protein C deficiency	12.1 (26)	0.5 (1)	<0.001	1.4 (3)	1.9 (4)	<0.001
Protein S deficiency	3.7 (8)	0.5 (1)	0.016	0.9 (2)	1.4 (3)	0.1
APC resistance	1.9 (4)	1.4 (3)	>0.99	0.5 (1)	1.9 (4)	0.6
Elevated factor VIIIc	20.9 (45)	12.1 (26)	<0.001	18.6 (40)	30.7 (66)	0.02
Lupus anticoagulant	37.7 (81)	6.1 (13)	<0.001	2.3 (5)	8.4 (18)	<0.001
Antiphospholipid antibodies	29.3 (63)	8.8 (19)	<0.001	3.7 (8)	12.6 (27)	<0.001
Proportion of patients with ≥1 factor, % (n)	74.4 (160)	26.0 (56)	<0.001	26.0 (56)	44.7 (96)	<0.001

[a]P-value of the comparison between prevalence at transplantation and prevalence of patients with thrombophilic factor persisting at 1 month.
[b]P-value of the comparison between prevalence at transplantation and prevalence at 1 month.

found in <5% of patients. One month after transplantation, most of the patients were free of their thrombophilic factor, except for APC resistance, which reflects factor V Leiden mutation. Among 45 patients with increased factor VIIIc before transplantation, 19 (42%) normalized blood levels during the first month ($P < -0.001$). The proportion of patients with at least two thrombophilic factors dropped from 31.2% at the day of transplantation to 11.6% 1 month after ($P < 0.001$). Of note, some patients (56/215; 26%) did acquire *de novo* new thrombophilic factors at 1 month. These patients either had no thrombophilic factor ($n = 14/55$) or had another thrombophilic factor present at transplantation ($n = 42/160$). The newly acquired *de novo* thrombophilic factor was in most cases an elevated factor VIIIc, which developed in 18.6% of patients. The total prevalence of thrombophilic factors was 44.7% 1 month after transplantation as compared with 74.4% before transplantation ($P < 0.001$).

Acenocoumarol may be responsible for decreased levels of protein C, protein S and false-positive lupus anticoagulant. Indeed, the prevalence of these three factors was significantly higher in patients under acenocoumarol ($n = 14$) than in patients without acenocoumarol ($n = 201$), respectively (protein C deficiency: 50 versus 9.5%; $P < 0.001$, protein S deficiency: 21.4 versus 2.5%; $P = 0.01$ and positive lupus anticoagulant: 71.4 versus 35.3%; $P = 0.01$). Therefore, the correction of these thrombophilic factors at 1 month might be due in part to discontinuation of anticoagulation therapy after transplantation. We analysed the correction of these three factors in the subgroup of patients who did not receive acenocoumarol neither at transplantation nor 1 month after transplantation ($n = 201$). After transplantation, protein C deficiency dropped from 9.5 to 0.5% ($P < 0.001$), protein S deficiency from 2.5 to 0.5% ($P = 0.13$) and positive lupus anticoagulant from 35.3 to 4% ($P < 0.001$). These data suggest that transplantation *per se* plays a role in the normalization of thrombophilic factors.

There was no significant correlation between the correction of thrombophilic factors and glomerular filtration rate (GFR) in our cohort. One month after transplantation, the median GFR was 65 mL/min in the whole cohort of 215 patients. A total of 59 patients (53.6%) with a GFR ≤65 mL/min and 52 patients (49.5%) with GFR >65 mL/min were still positive for thrombophilic factor after 1 month ($P = 0.59$).

Prevalence of major cardiovascular events or thromboembolic events 1 year after transplantation

One year after transplantation, 5.2% (95% CI: 2.2–11.6%) patients with more than or equal to one thrombophilic factor assayed at 1 month developed a major cardiovascular event or a thromboembolic event (cardiovascular event: $n = 0$, thromboembolic event: $n = 5$) versus 6.7% (95% CI: 3.4–12.7%) patients (cardiovascular event: $n = 6$, thromboembolic event: $n = 2$) without thrombophilic factor ($P = 0.65$).

Discussion

Two main findings emerge from our study. First, we found a high prevalence of seven thrombophilic factors in our cohort of Stage V CKD patients in comparison with the prevalence reported in the general population. In addition, the proportion of patients with a least one thrombophilic factor was significantly higher in patients undergoing dialysis as compared with patients not yet on dialysis. Second, 1 month after renal transplantation, the proportion of patients with at least one thrombophilic factor dropped from 74.4 to 44.7%, and most of the single thrombophilic factors considered separately were significantly corrected.

Patients with kidney dysfunction have complex coagulation abnormalities, with underlying mechanisms not well understood to date. We observed that the prevalence of seven thrombophilic factors in Stage V CKD patients was higher than in the general population and was consistent with previous reports on this issue [4–10]. The prevalence in our cohort of rare thrombophilic factors like antithrombin, protein C and protein S deficiencies was 13.5, 12.1 and 3.7% versus 0.02–0.5, 0.3–0.5 and 0.03–0.13%, respectively, in the general population [2, 20, 21]. These three thrombophilic factors are due to rare mutations in the general population but may be acquired in certain circumstances like liver disease (deficiency of the three factors), use of oral anticoagulants (protein C and protein S), use of heparin (antithrombin), the presence of autoantibody (protein C and

protein S) or nephrotic syndrome (protein S and antithrombin) [1]. Likewise, the prevalence of more frequent thrombophilic factors like high level of factor VIIIc, positive lupus anticoagulant and antiphospholipid antibodies was 20.9, 37.7 and 29.3% versus 11, 8 and 6.5%, respectively, in the general population [2, 22]. The high level of factor VIIIc in the general population is at least in part congenital but may also be acquired (stress, acute phase response and older age). False-positive lupus anticoagulant may be observed during oral anticoagulation therapy, while antiphospholipid antibodies may be promoted by infectious disease in the general population [1]. Most of these acquired conditions are more frequent in a Stage V CKD population than in the general population, possibly playing a role in the high prevalence observed. Moreover, we showed that coagulation abnormalities were more frequent in dialysed patients than in patients with Stage V CKD. Of note, antithrombin deficiency was more frequent in haemodialysed patients than in patients on peritoneal dialysis and this abnormality was absent in Stage V CKD patients. This might be due to consumption of antithrombin during haemodialysis, either by the injected heparin or by activation of the coagulation by dialysis filters, leading to the generation of thrombin–antithrombin complexes [23]. In contrast, elevated factor VIIIc was less frequent in patients undergoing haemodialysis in comparison with peritoneal dialysis (17.4 versus 34.2%; $P = 0.01$). Peritoneal dialysis modality *per se* does not seem to explain this difference as a high proportion of Stage V CKD patients not on dialysis also had elevated factor VIIIc level (28.6%). One may hypothesize that haemodialysis by itself was responsible for a decrease in factor VIIIc. Indeed, one study evaluating coagulation parameters before and after haemodialysis reported a significant decrease in plasma concentrations of von Willebrand factor (factor associated with factor VIII) and fibrinogen after haemodialysis. The authors suggest a consumption of these factors by coagulation activation and adsorption by the dialyser membrane and the tubing system [24].

One month after renal transplantation, the global prevalence of antithrombin deficiency, protein C deficiency, the presence of lupus anticoagulant and of antiphospholipid antibodies were all significantly lower. To the best of our knowledge, one single study has reported on the correction of thrombophilic factors after renal transplantation. Nampoory *et al.* [5] observed in 16 patients that protein C, protein S, antithrombin deficiencies and APC resistance were significantly corrected 9 months after renal transplantation. In our study, the prevalence of the single thrombophilic factors assayed after 1 month comes close to that found in the general population. Thus, in the subgroup of patients without acenocoumarol ($n = 201$), the prevalence of protein C deficiency, protein S deficiency and positive lupus anticoagulant dropped to 0.5, 0.5 and 4% respectively, similar to the prevalence found in the general population [25]. The prevalence of antithrombin deficiency dropped to 0.9%, again close to the 0.02–0.5% observed in the general population [2, 20]. Antiphospholipid antibodies (IgG) were still present in 12.6% of the patients. As the half-life of IgG antibodies is ~3 weeks, it is possible that the prevalence of antiphospholipid antibodies and lupus anticoagulant would have been even lower if tested after 2 or 3 months. Finally, the lower GFR found in renal transplant patients may contribute to the slightly higher prevalence of thrombophilic factors in comparison with general population.

Interestingly, and similar to our observations related to coagulation factors, a group evaluating kinetics of microparticles with procoagulant activity (MP-PCA) during haemodialysis and 3, 6, 9 and 12 months after renal transplantation showed that (i) the level of MP-PCA in haemodialysis was significantly higher than in healthy controls, (ii) MP-PCA decreased significantly at 3 months after transplantation and remained stable but higher than controls thereafter, and (iii) microparticle (MP) levels were negatively correlated with renal function [26]. Along this line, the presence of inflammatory and procoagulant biomarkers (fibrinogen, factor VIIc, factor VIIIc, D-dimer and plasmin–antiplasmin complex levels) has also been correlated with renal impairment in several reports [27–29]. MP resulting from cell activation and apoptosis are increased by uremic toxins, inflammatory state, oxidative stress and complement activation. In addition to being a marker of endothelial cell damage, platelet-derived MP can activate coagulation *via* the exposition of phosphatidylserine and tissue factor on the outer membrane and the interaction with factors Va, VIII and IXa, thereby facilitating assembly of prothrombinase complex [30]. Therefore, one may hypothesize that MP-PCA accounts for the global coagulation activation that we and others observed in Stage V CKD patients.

A high level of factor VIIIc was more frequent after than before transplantation (30.7 versus 20.9%; $P = 0.02$). In fact, only 12.1% of patients had a persistently high level of factor VIIIc after 1 month, which is comparable to the prevalence in the general population [2]. Nearly 20% of patients developed this factor *de novo*. High factor VIIIc levels have been previously observed in renal transplant patients, with a peak level following the transplantation [31, 32]. One can hypothesize that the acute phase response associated with surgery may trigger the synthesis of factor VIIIc.

In contrast to what has been observed by others [4, 6, 13, 15, 33], in our cohort, the presence of more than or equal to one thrombophilic factor assayed at 1 month was not associated with the occurrence of major cardiovascular events or thromboembolic events 1 year after transplantation ($P = 0.65$). The low incidence of events in our series (5.2%; 95% CI: 2.2–11.6) might be due to the fact that our patients were taking aspirin prophylaxis. Therefore, a prospective study adequately powered (0.80) to detect a reduction in risk by 30% (3.5% global incidence at 1 year) would require the inclusion of 4857 patients (Stata 10). Adequately powered prospective studies to detect risk differences of 1–2% for rare outcomes such as thromboembolic events are basically impossible to conduct in renal transplant recipients, and the medical significance of the absolute reduction in risk is questionable.

In summary, ~50% of Stage V CKD patients display thrombophilic factors, and the prevalence is even higher among dialysis patients. Uraemia- and dialysis-associated chronic microinflammation are probably involved in the

global activation of coagulation, while heparin and acenocoumarol use can promote specific acquired thrombophilic factors. The vast majority of single thrombophilic factors were corrected 1 month after transplantation. In addition, the presence of thrombophilic factors 1 month after transplantation was not associated with major cardiovascular or thromboembolic events.

Supplementary data

Supplementary Appendix Table is available online at http://ndt.oxfordjournals.org.

Acknowledgements. The authors thank gratefully Ms Brigitte Borre, Ms Françoise Bernard and Ms Sylvie Arias Lopez for samples and clinical data collection. The study was supported by the Renal Transplantation Clinic of the ULB-Hopital Erasme. L. Ghisdal, D. Abramowicz and V. Donckier are supported by the Erasme Fund transdisciplinary grant.

Conflict of interest statement. None declared.

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Received for publication: 30.7.10; Accepted in revised form: 6.12.10