CD4 Cell Lymphopenia and Atherosclerosis in Renal Transplant Recipients

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Abstract. Several animal studies suggest that T cell–mediated immunodeficiency may play a role in the progression of atherosclerosis. This study examined the association between lymphocyte subsets and atherosclerotic events in renal transplant recipients. A total of 302 consecutive renal transplant recipients were enrolled in this prospective study. Peripheral blood lymphocyte subsets were quantified and analyzed with respect to other known cardiovascular risk factors. The patients were followed for a mean duration of 23.5 ± 4.5 mo. Mean CD4, CD8, and CD19 cell levels were 511 ± 290/mm^3, 553 ± 596/mm^3, and 66 ± 62/mm^3, respectively. CD4 levels were positively related to transplant duration ($r = 0.32$; $P = 0.02$) and inversely related to age ($r = 0.35$; $P = 0.01$). Twenty-five atherosclerotic events (AE) occurred in 25 patients (8.3%). CD4 levels were lower in patients who experienced CVE (288 ± 170/mm^3 *versus* 531 ± 290/mm^3; $P < 0.0001$). Cox regression analysis showed that patients in the three upper quartiles of CD4 cell count had a decreased risk of CVE compared with those in the lowest quartile. There was a linear increase in risk of CVE with decreasing CD4 cell count ($P < 0.0001$). A CD4 cell count in the highest quartile (>663/mm^3) divided the risk of CVE by 10 as compared with the lowest quartile. In conclusion, CD4 lymphocytopenia is an independent risk factor for the development of cardiovascular complications in renal transplant recipients, suggesting that impaired immune response promotes accelerated atherogenesis in this population.

Stable renal transplant recipients (RTR) have disproportionately high rates of arteriosclerotic outcomes (1). An increased prevalence of traditional cardiovascular risk factors cannot fully explain this increased incidence of CVE in the transplant population (2), and our group has recently emphasized the role of nontraditional cardiovascular risk factors, such as hyperhomocysteinemia (3). A recent study from the USRDS registry showed an increased cardiovascular mortality in RTR having received polyclonal antilymphocyte globulins (4), suggesting either that intense immunosuppression may accelerate native atherosclerosis or that polyclonal antithymocyte globulins exerts specific long-term detrimental effects on the course of atherosclerosis. Nevertheless, interpretation of this finding is challenged by the fact that the atherosclerotic lesion contains large number of immune cells, particularly macrophages and T cells. Furthermore, atherosclerosis is associated with systemic immune responses, including inflammation.

On the other hand, several animal studies have shown that immunosuppression may accelerate native atherosclerosis (5–8). Moreover, an increased incidence of cardiovascular events has been reported in AIDS patients (9), and recent reports suggest a correlation between intensity of immunodeficiency and presence of atherosclerotic plaques (10). Lastly, a significant decrease in CD4 cells has been described in the blood of atomic bomb survivors, and an increased incidence of myocardial infarction in this population has been found to be associated with a lower proportion of CD4 cells (11).

Muller *et al.* (12) demonstrated that polyclonal antilymphocyte globulins may induce persistent changes in lymphocyte subsets characterized by low CD4 cell count and CD8 cell expansion. Our group has recently demonstrated that CD4 cell count is a potent marker of excessive immunosuppression in RTR (13,14). We postulated that T cell–mediated immunodeficiency as reflected by CD4 lymphocytopenia may be associated with atherosclerosis in RTR. We therefore prospectively examined the relation between peripheral blood CD4 cell counts and atherosclerotic events (AE) in a large population of stable RTR.

Materials and Methods

Patients Characteristics

Participants in the study were 302 consecutive, stable RTR (*i.e.*, transplant duration > 12 mo; no acute rejection, serum creatinine < 400 μmol/L).

Twenty patients were treated with azathioprine and prednisone alone, and 219 patients were treated with azathioprine and prednisone in similar doses as well as cyclosporine or tacrolimus. Thirty-one patients were treated with mycophenolate mofetil and prednisone, and

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32 patients were treated with mycophenolate mofetil and prednisone in similar doses as well as cyclosporine or tacrolimus.

Cardiovascular Risk Factors

Age, gender, weight, size, BP, hemodialysis duration before transplantation, diabetes mellitus, smoking status, past history of cardiovascular events (CVE), immunosuppressive treatment (use of calcineurin inhibitors), and different biologic parameters were assessed upon inclusion.

Definition of Past History of CVE

Coronary heart disease: myocardial infarction; coronary revascularization including coronary artery bypass surgery or percutaneous transluminal coronary angioplasty; typical history of angina with abnormal coronarography or myocardial scintigraphy.

Stroke/Cerebrovascular disease: both non-hemorrhagic and hemorrhagic strokes; carotid endarterectomy.

Abominal aortic or lower extremity arterial disease: Abominal aortic repair; lower extremity amputation; intermittent claudication confirmed by Doppler or arteriography findings.

Nutritional Status

Albumin concentration was determined. Body mass index (BMI) was calculated (weight/[size]^2).

Smoking Behavior

Subjects were categorized as current smokers or nonsmokers.

Blood Pressure

BP was measured using a semiautomatic device, based on an oscillometric method with the patients in a sitting position after resting more than 5 min. Pulse pressure (Systolic BP −Diastolic BP) was calculated.

Left Ventricular Hypertrophy (LVH)

LVH was defined by a Sokolow index ≥ 35.

Lipid Profile

Triglycerides and total and HDL cholesterol serum concentrations were measured. LDL cholesterol was calculated using the method described by Friedwald.

Homocysteine

Total plasma homocysteine (tHcy) was measured using a previously described method (2). Briefly, venous blood samples were drawn after an overnight fast. The blood sample was centrifuged within 15 min, and plasma was stored frozen at −20°C. Hcy concentration, the sum of the acid-soluble (that is reduced Hcy, homocystine, disulphide, and homocysteine-cysteine mixed disulphide) and protein-bound moieties, was measured by HPLC. This assay involves the following steps: reduction of the sample with tri-n-butylphosphine, precipitations of proteins, alkalinization of the supernatant with sodium borate, derivitization with 7-fluoro-2-oxa-1,3 diazole-4 sulfonate, followed by 8-aminonaphtalene-1,3,6-trisulphonic acid, and HPLC separation with fluorescence detection. The normal values of plasma Hcy concentration ranged from 7 to 15 μmol/L. The precision of the assay corresponds to a coefficient of variation $< 3\%$.

C-Reactive Protein

C-reactive protein was measured by Nephelometry (Kit Beckman).

Renal Function

Serum creatinine concentration and urinary protein excretion were measured. Creatinine clearance was calcultated using the Gault-Cockcroft formula.

PTH, Vitamin D, Ca, Ph

PTHi was measured using an immunoradiometric assay, with a normal range between 15 and 80 pg/ml. Calcium and phosphorus were measured by standard autoanalyzer techniques.

Cytomegalovirus

CMV serology (ELISA) was performed at the entry in the study.

Lymphocyte Subsets

Lymphocytes subsets were measured by flow cytometry. Total blood samples were incubated with FITC-conjugated anti-CD4, phycoerythrin (PE)-conjugated, anti-CD8, FITC-anti-CD3 (5diaclone, Besançon, France), PE-anti-CD19 (Becton Dickinson, Mountain View, CA) monoclonal antibodies, and appropriate Ab controls. After red cell lysis, sample analysis was performed on a FACSCalibur (Becton-Dickinson) using CellOuest software(Becton-Dickinson).

Atherosclerotic Events

Coronary Heart Disease. Myocardial infarction documented by serial 12-lead electrocardiogram evidence or Q-wave infarction and appropriate myocardial enzyme elevations; coronary revascularization, including coronary artery bypass surgery or percutaneous transluminal coronary angioplasty; typical history of angina with abnormal coronarography.

Stroke/Cerebrovascular Disease. Both nonhemorrhagic and hemorrhagic strokes confirmed by neurologic examination findings consistent with new-onset focal neurologic deficits, with or without computed tomography or magnetic resonance imaging evidence of cerebral infarction; symptomatic extracranial artery stenosis resulting in carotid endarterectomy.

Abdominal Aortic or Lower Extremity Arterial Disease. Abdominal aortic repair; lower extremity revascularization via bypass surgery or angioplasty; lower extremity amputation; new onset of intermittent claudication confirmed by Doppler or arteriography findings.

Two physicians independent of the study were responsible for CVE ascertainment. This analysis was performed without knowledge of baseline characteristics.

Statistical Analyses

Arithmetic mean was calculated and expressed as $\pm$ SD. Using log rank tests on Kaplan-Meier nonparametric estimates of the survival without AE distribution, we selected variables with a $P \leq 0.20$. The selected variables were included into a Cox proportional hazards model, and a backward stepwise selection process was performed, this time at a classical $\alpha = 0.05$. The time elapsed since kidney transplantation was bound to vary between patients; therefore, this duration was forced into the Cox model as a covariate. Gender and age being potential confounding variables, they were also entered into the Cox model, no matter the significance of their relationships with CVE. Age was split into two classes separated by the median age (51 yr) of the cohort, CD4 and CD8 counts were split into quartiles (CD4 limits: 299, 471, and 663/mm^3; CD8 limits: 283, 440, and 637/mm^3), as was serum homocysteine (limits: 13.1, 16.9, and 21.0 μmol/L). Tobacco consumption was accounted for as currently smoking *versus* nonsmoking. Variables that were split into quartiles were replaced by

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dummy variables in the Cox model, which tested quartile 2 *versus* quartile 1, quartile 3 *versus* quartile 1, and quartile 4 *versus* quartile 1. Results are expressed as relative risk (RR) and 95% confidence interval, with a *P* value testing the null hypothesis: RR = 1. Therefore, when *P* value is less than 0.05, RR is significantly different from 1, either greater than 1 (*i.e.*, risk of CVE is increased) or less than 1 (*i.e.*, risk of CVE is decreased). Assumptions of Cox models (log-linearity, proportionality of risk in time) were met in this analysis.

Results

The patients were followed for a mean duration of 23.5 ± 4.5 mo. Their mean age was 50 ± 13.5 yr, and 190 (63%) were men. Diabetes and LVH were present in 51 patients (17%) and 25 (8.2%), respectively. Seventy patients (23.1%) were current smokers. Mean transplant duration and hemodialysis duration were 72 ± 55 and 28 ± 37 mo, respectively. Two hundred and sixty-seven patients (88.4%) had a positive CMV serology, but no patient exhibited CMV replication. Categorical variables are described in Table 1, continuous variables in Table 2.

Lymphocyte Subsets

Mean CD4 and CD8 levels were 511 ± 290/mm^3 and 553 ± 596/mm^3, respectively. Mean CD4/CD8 ratio was 1 ± 0.92. Mean CD19 level was 66 ± 62/mm^3.

There was a positive correlation between CD4 levels and transplant duration ($r = 0.32$; $P = 0.02$). By contrast, CD4 cell count was inversely related to age ($r = 0.35$; $P = 0.01$).

Cardiovascular Events

Twenty-five AE (8.3%) occurred in 25 patients (cerebrovascular disease, 3; coronary heart disease, 16; peripheral vascular disease, 6). Ten patients (3.3%) died, four (1.3%) of cardiovascular causes. CD4 levels were lower in patients who experienced AE (288 ± 170/mm^3 *versus* 531 ± 290/mm^3; $P < 0.0001$).

Quartiles were defined according to CD4 cell count (Table 1). There was a linear increase in the risk of AE from the lower quartile to the higher quartile of CD4 cell (20.8% *versus* 8.1% in Q2 [<0.0001] and *versus* 4% in Q3 [<0.0001], 1.3% in Q4 [<0.0001]).

In univariate analysis, age ($P < 0.0001$), male gender ($P = 0.02$), a past history of cardiovascular disease ($P < 0.0001$), smoking status ($P = 0.04$), diabetes mellitus ($P = 0.11$), low creatinine clearance ($P = 0.01$), urinary protein excretion ($P = 0.03$), high phosphorus concentration ($P = 0.09$), low calcium concentration ($P = 0.02$), high fibrinogen concentration ($P = 0.07$), LDL cholesterol ($P = 0.07$), low HDL cholesterol ($P = 0.01$), tHcy ($P = 0.0002$), systolic BP ($P = 0.05$), pulse BP ($P = 0.06$), glycemia ($P = 0.07$), low CD4 level ($P < 0.0001$), high CD8 level ($P = 0.02$), low CD4/CD8 ratio ($P = 0.01$), low CD19 level ($P = 0.003$), CRP ($P = 0.0001$), and low albumin concentration ($P = 0.008$) were associated with AE.

After backward stepwise selection, the variables which remained in the Cox proportional hazards model, *i.e.*, which were linked to AE with *P* values < 0.05, were as follows: CD4 cell count, age, tobacco consumption, history of AE, serum homo-

Table 1. Description of categorical variables

Variable	Category	Frequency (%)
Gender		
	Male	191 (63.25%)
	Female	111 (36.75%)
History of cardiovascular event		
	Yes	25 (8.28%)
	No	277 (91.72%)
Tobacco consumption		
	Yes	72 (23.84%)
	No	230 (76.16%)
Diabetes		
	Yes	69 (22.85%)
	No	233 (77.15%)
Left ventricle diameter		
	≥35 mm	24 (7.95%)
	<35 mm	278 (92.05%)
CMV serology		
	Negative	35 (11.6%)
	Positive	267 (88.4%)

Table 2. Description of continuous variables

Variable	Mean	Standard Deviation	Median
Age (yr)	49.82	13.59	51.00
Transplant duration (mo)	72.48	55.75	68.50
SCt Clearance (ml/min)	49.68	18.02	49.03
UPE (g/d)	0.46	0.91	0.10
PTH (pg/ml)	97.00	133.87	61.50
Vitamin D (ng/ml)	17.07	14.49	13.00
Phosphorus (mmol/L)	1.17	0.21	1.16
Calcium (mmol/L)	2.44	0.14	2.44
Hemoglobin (g/100 ml)	12.94	1.76	13.00
Fibrinogen (g/L)	3.85	0.90	3.80
LDL cholesterol (g/L)	1.26	0.36	1.23
HDL cholesterol (g/L)	0.57	0.21	0.54
Total serum cholesterol (g/L)	2.13	0.47	2.11
Triglycerides (g/L)	1.54	1.11	1.28
Serum homocysteine (μmol/L)	18.15	6.96	16.90
BMI (kg/m^2)	24.42	4.35	23.81
SBP (mmHg)	135.85	19.07	140.00
DBP (mmHg)	80.56	10.09	80.00
PP (mmHg)	55.94	15.47	55.00
Glycemia (mmol/L)	5.49	1.52	5.10
CD3 (/mm^3)	1059.64	645.36	915.00
CD4 (/mm^3)	511.34	290.40	471.00
CD8 (/mm^3)	552.61	595.91	439.50
CD4/CD8 ratio	1.30	0.93	1.13
CD19 (/mm^3)	66.43	61.77	49.00
CRP (mg/L)	4.51	4.12	3.00
Serum albumin (g/L)	43.64	4.31	44.00

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cysteine. Gender and duration since transplantation were kept in the model.

Cox regression analysis revealed that age above the median (RR, 5.84; 95% CI, 1.64 to 20.75), a previous history of cardiovascular disease (RR, 4.24; 95% CI, 1.68 to 10.71), and current smoking (RR, 2.99; 95% CI, 1.27 to 7.02) were risk factors for AE. Patients in the higher quartile of tHcy have a significantly greater risk of AE than those in the lowest quartile (RR, 5.77; 95% CI, 1.28 to 26.08).

Patients in the three upper quartile of CD4 cell count had a decreased risk of AE compared with those in the lowest quartile (Table 3). Importantly, the RR for AE progressively decreased from the lowest to the highest quartile with RR values of 0.34 (CI, 0.13 to 0.92), 0.10 (CI, 0.02 to 0.46) and 0.10 (CI, 0.01 to 0.80) for the 2nd, 3rd, and 4th quartiles, respectively.

RR and their 95% CI of CVE for each variable in the Cox model are displayed in Table 3, along with *P* values.

Discussion

There is a high incidence of cardiovascular complications in the organ transplant population. In our cohort of RTR, the cumulative risk for developing AE was 4.1% within 1 yr, which is comparable to a previous report of our group (3). Both traditional and nontraditional CV risk factors are prevalent in our population and contribute for this increased incidence of atherosclerotic events. Nevertheless, we postulated that immunosuppression by itself may contribute *per se* to accelerate atherogenesis in this RTR population.

Our major result is the demonstration of a negative independent relationship between posttransplant peripheral blood CD4 cell counts and the occurrence of AE. Importantly, this relationship persisted after adjustment for traditional and nontraditional cardiovascular risk factors. However, the association between CD4 cell counts and occurrence of AE demonstrated in our study does not prove causal relationship.

The probability of AE increased linearly with the decrease in CD4 cell levels, and a CD4 cell count in the highest quartile ($>663/mm^3$) divided the risk of AE by 10 as compared with the lowest quartile. Our group has previously demonstrated that CD4 lymphocytopenia is a marker of over-immunosuppression in the renal transplant population (13,14). As a consequence, our results may suggest that immunosuppression by itself contributes to accelerated atherosclerosis in renal transplant recipients.

Our study provides new insight into the pathogenesis of accelerated transplant-related atherosclerosis. In a study by Fyfe *et al.* (5), atherosclerosis developed at an accelerated rate in class I MHC-deficient mice. Furthermore, Nilsson *et al.* (6) demonstrated a 58% decrease in degree of atherosclerosis in rabbits immunized against oxidized or native LDL. Other animal studies have also suggested that T lymphocytes may have a protective role against atherosclerosis progression (7). Rats in which T lymphocytes have been eliminated by a monoclonal antibody treatment develop larger proliferative arterial lesions after balloon-catheter injury. Larger lesions also develop in athymic rnu/rnu rats when compared with rnu/+ littermates with normal T cell levels. These results strongly suggest that T lymphocytes can modulate smooth muscle proliferation during vascular repair in experimental models. Lastly, Roselaar *et al.* (8) demonstrated that Cyclosporin A-induced suppression of cell-mediated immunity increased the development of macrophage-rich atherosclerotic lesions in cholesterol-fed rabbits. Nevertheless, these results remained difficult to interpret because Cyclosporin also interacts with numerous traditional cardiovascular risk factors such as hypertension and hyperlipidemia (15,16). However, a direct role of Cyclosporin is unlikely in our study. Treatment with Cyclosporin was not associated with AE, and our previous reports did not support a link between CD4 cell counts and Cyclosporin treatment.

Table 3. Cox model: relative risks (RR) of cardiovascular event (CVE) and 95% CI

Variable		RR[a]	95% CI	*P*
CD4 ($/mm^3$)	<299 (1st quartile)	1	–	–
	299; 471 (*versus* 1st quartile)	0.34	0.13 to 0.92	0.033
	471; 663 (*versus* 1st quartile)	0.10	0.02 to 0.46	0.003
	≥663 (*versus* 1st quartile)	0.10	0.01 to 0.80	0.030
Age	<51 yr	1	–	–
	≥51 yr	5.84	1.64 to 20.75	0.006
Tobacco consumption	No	1	–	–
	Yes	2.99	1.27 to 7.02	0.012
History of CVE	No	1	–	–
	Yes	4.24	1.68 to 10.71	0.002
Serum homocysteine (μmol/L)	<13.1 (1st quartile)	1	–	–
	13.1; 16.9 (*versus* 1st quartile)	2.35	0.46 to 12.03	0.307[b]
	16.9; 21.0 (*versus* 1st quartile)	1.31	0.21 to 8.02	0.772[b]
	≥21.0 (*versus* 1st quartile)	5.77	1.28 to 26.08	0.023

[a] Cox model is adjusted for duration since kidney transplant and gender.
[b] Nonsignificant at $\alpha = 5\%$

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Lesser data concerning a potential role for immunodeficiency in the pathogenesis of atherosclerosis progression are available in humans. Nevertheless, recent studies have focused on an increased incidence of AE in AIDS patients (9,17) with findings suggesting that lymphopenia could be associated with an increased risk of AE. An increased prevalence of traditional cardiovascular risk factor is observed in this population. However, this increase in risk factors is apparently not sufficient to explain the observed difference in AE and a matched population (10). A role for protease inhibitor–induced hyperlipidemia has been evoked (17) but not confirmed by more recent reports (18,19). Constans *et al.* (10) have reported that HIV-positive patients with atherosclerotic plaques had significantly lower CD4 cell count than those without plaques, suggesting a relationship between the intensity of immunodeficiency and the progression of atherosclerosis. Lastly, as previously reported in atomic bomb survivors, the intensity of CD4 lymphocytopenia in atomic bomb survivors has been found to be associated with an found increased incidence of myocardial (11). These findings observed both in AIDS patients and in atomic bomb survivors therefore strongly suggest an association between CD4 lymphocytopenia and atherosclerosis.

Hypothetically, a type 2 immune polarization could be occurring in RTR who undergo lymphocyte reconstitution post-polyclonal antithymocyte globulins-related lymphocyte depletion. In such cases, the lack of Th2 expansion in RTR with CD4 lymphocytopenia might contribute to the increased incidence of AE in this group of recipients. Indeed, T1 immune response, as induced in response to bacteria pathogens, has been reported to play a role in promoting atherosclerosis (20). On the other hand, a predominantly type 2 response mitigates the course of atherosclerosis. Indeed, IL-10−/− C57BL/6J mice exhibit increased fatty streak development (21) and overexpression of IL-10 inhibits atherosclerosis in LDL receptor-deficient mice (22). Furthermore, BALB/c mice, a mouse strain skewed toward $CD4^+$ Th2 type immune responses, are atherosclerosis resistant (23). Studies to examine this hypothesis are presently underway.

The reasons for the persistence of low CD4 cell count in some renal transplant recipients and not in others remain unclear. In addition, polyclonal antilymphocyte globulins (12) and suppression of cell-mediated immunity by infectious agents other than HIV has long been recognized as a cause of CD4 lymphocytopenia. A variety of acute and chronic infections may be associated with CD4 cell depletion, which is usually transient and accompanied by CD8 lymphocytosis (24). As mentioned previously, bacterial and viral pathogens have been also identified as inciting agents in the pathogenesis of atherosclerosis. *In vitro*, cytomegalovirus and chlamydia pneumoniae promote a proinflammatory and a procoagulant phenotype in vascular cells (25) Moreover, viruses can augment cell accumulation through apoptosis alterations (26). Thus, one can also speculate that CD4 lymphocytopenia could be a surrogate marker for the presence of viral or bacterial infections. Alternatively, diminished cell-mediated immune response may favor chronic infections involved in the pathogenesis of atherosclerosis. However, one must stress that we found no relationship between CMV status and CVE.

To conclude, our study strongly suggests that CD4 lymphocytopenia is an independent cardiovascular risk factor in RTR. Factors such as polyclonal anti-lymphocyte globulins treatment, quality of immune reconstitution, bacterial or viral infections may be directly or indirectly contributive. Further studies should better characterize the associations between CD4 lymphocytopenia and AE in RTR.

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