Modulation Factors of Oxidative Status in Stable Renal Transplantation

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ABSTRACT

Reactive oxygen species (ROS) trigger a biomolecular alteration that causes functional and structural changes. In renal transplantation, there is an increase in oxidative phenomena related to endothelial dysfunction, inflammation, and atherosclerosis, the main cause of cardiovascular complications and chronic allograft failure. The present study was designed to assess the oxidative state of transplant patients with stable renal function, in order to establish differences in oxidative, biochemical, and clinical parameters between patients treated with tacrolimus versus cyclosporine. We studied 67 stable kidney transplant patients treated with calcineurin inhibitors who were not receiving cholesterol-lowering therapy, and 14 healthy subjects. Data were collected on biochemical parameters: lipid profile (apoA, apoB, total cholesterol and fractions, and triglycerides); urea; and creatinine; oxidative parameters: malondialdehyde (MDA) as a lipid peroxidation marker, glutathione peroxidase (GPx), catalase, superoxide dismutase (SOD), glutathione reductase (GR), and antibodies against oxidized LDL; and clinical variables. Transplanted patients showed a higher oxidative status (MDA increase and GPx decrease) than healthy subjects. The oxidative status did not differ between the cyclosporine and tacrolimus cohorts. Some factors during the posttransplant period, such as delayed graft function, cytomegalovirus infection, and microalbuminuria, which may damage renal function, produce a decreased antioxidant capacity (lower GPx).
glomerular, and interstitial lesions. There do not appear to be differences in the oxidative status of patients depending on the type of anticalcineurin treatment, although there may be other factors that modify oxidative parameters during the transplant course. The present study was designed to assess the oxidative status of transplant patients with stable renal function, in order to establish differences in the oxidative, biochemical, and clinical parameters associated with tacrolimus versus cyclosporine.

PATIENTS AND METHODS

The study included 67 kidney transplant patients with stable renal function who were not receiving cholesterol-lowering treatment and 14 healthy subjects (controls). The inclusion criteria were: a minimum of 12 months since transplantation; mild-to-moderate hyperlipidemia; and immunosuppression treatment with cyclosporine or tacrolimus plus steroids. Exclusion criteria were diabetes mellitus, active liver disease, elevated hepatic enzymes (at least threefold the normal level), high steroid dosage in the previous 6 months, and increased creatinine kinase or lactate dehydrogenase. The age, gender, and cause of death of the donor were recorded. The following data were gathered on the recipient: age and gender; etiology of chronic renal failure; HBP; cardiovascular disease; vascular calcifications on plain X-ray; delayed graft function (DGF), defined as the need for hemodialysis within the first week posttransplantation; acute rejection, defined by biopsy; cytomegalovirus infection; microalbuminuria; hepatitis C virus infection; hyperparathyroidism; retransplantation; and antihypertensive treatment. The following biochemical variables were recorded: the lipid profile (apolipoprotein A, apolipoprotein B, total cholesterol, HDL, LDL particles, and triglycerides); urea; and creatinine. Oxidative status was established by measuring malondialdehyde (MDA) as a marker of lipid peroxidation, using the thiobarbituric acid method in serum, and by assessing the activity of the following antioxidant enzymes: catalase (by the modified Aebi [1984] method); superoxide dismutase (SOD) (by modified McCord and Fridovich method); glutathione peroxidase (GPx) (by the N.A. the Purchard method in serum); glutathione reductase (GR); and antibodies against oxidized LDL (oLab ELISA kit, Biomedical Group, Austria). The data were analyzed using the Statistical Package for Social Sciences (SPSS 11.0).

RESULTS

The transplanted patients showed significant differences with respect to the controls in total cholesterol, LDL, triglyceride and urea levels, and in oxidation parameters, with an increased MDA and reduced GPx (Table 1). The comparison between calcineurin inhibitor treatments (cyclosporine or tacrolimus) showed no significant differences in lipid peroxidation profile (MDA [P = .12], catalase [P = .17], SOD [P = .7], GPx [P = .16], GR [P = .51]), or in antibodies against oxidized LDL (P = .16). However, patients with cyclosporine treatment showed a higher lipid profile (total cholesterol [P = .012], LDL [P = .024], and HDL [P = .027]). Serum GPx and GR levels were significantly higher (P = .011) and lower (P = .016), respectively, in patients without delayed graft function versus those with delayed graft function. Patients infected with cytomegalovirus showed a reduced antioxidant capacity, with decreased GPx (P = .003) and increased GR (P = .021) levels versus those without this infection. A decreased GPx value (P = .002) was observed in transplant subjects with microalbuminuria. There was a significantly higher MDA level in patients with vascular calcifications on plain X-ray (P = .048), although the age of the recipient might have been a determinant factor.

The influence of renal function on oxidative status was analyzed using the Spearman correlation coefficient: there was a negative association between creatinine and GPx (r = −0.52; P = .0001) and a positive association between creatinine and GR (r = 0.30; P = .0125). Renal function was not significantly correlated with the levels of MDA (r = −0.12; P = .28), catalase (r = 0.012; P = .83), or SOD (r = −0.05; P = .69).

DISCUSSION

The modification of LDL particles due to oxidation, glycation, or MDA action is a determinant factor in the onset and progression of atherosclerosis. Oxidatively modified LDL is detected by a specific receptor (different from the LDL receptor) on the macrophage surface. Its uptake converts macrophages into foam cells, the accumulation of which under the vascular endothelium is considered to be the initial phase of atherosclerosis. Cholesterol is not toxic or immunogenic per se, but oxidized LDL particles have chemotactic, cytotoxic, and immunogenic properties, inducing the formation of polyclonal autoantibodies against these products.

The present study has shown that oxidative phenomena increase after renal transplantation, with a rise in the final products of lipid peroxidation (MDA) and a fall in the antioxidant capacity (GPx) compared with healthy controls. The excessive production of ROS increases the risk of vascular, glomerular, and interstitial injuries in chronic allograft...
failure. Immunosuppression, especially with a calcineurin inhibitor, plays an important role in hyperlipidemia and long-term allograft damage. In our study, patients receiving cyclosporine had a more pathologic lipid profile, although no differences in oxidative status were observed according to the cyclosporine or tacrolimus treatment.

Experimental studies in cultured human cells and uninephrectomized rats support the conclusion that extracellular GPx is secreted through the basolateral membrane of kidney proximal tubule cells, where it enters the blood plasma. However, cytomegalovirus infection has been associated with endothelial dysfunction and atherosclerosis. Our analysis of the risk factors for chronic nephropathy disclosed an increased GPx (antioxidant capacity) in patients without delayed graft function, microalbuminuria, or cytomegalovirus infection.

We conclude that transplant patients suffer increased oxidative stress, and that the negative factors associated with chronic renal allograft failure may be related to a reduced antioxidant capacity, as demonstrated by the inverse correlation between GPx and serum creatinine.

REFERENCES