Changes in Oxidative Stress in Renal Graft Patients Receiving Calcineurin Inhibitors: Cyclosporine Versus Tacrolimus

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Abstract

Objectives: The effects of calcineurin inhibitors on oxidative stress after renal transplant are obscure. This study sought to investigate the changes in plasma oxidative stress and lipid levels in patients receiving cyclosporine or tacrolimus before and after renal transplant for 6 months.

Materials and Methods: Twenty-one patients and 15 healthy controls were involved in our study. Twelve of the patients were treated with cyclosporine and 9 were treated with tacrolimus. Plasma malondialdehyde, nitrite/nitrate, vitamin C, vitamin E, and plasma glutathione levels, as well as total cholesterol and triglyceride levels, were evaluated before and after transplant for 6 months.

Results: Before the transplant, patients had higher malondialdehyde and plasma glutathione levels than did healthy controls (3.76 ± 0.79 nmol/mL vs 3.21 ± 0.57 nmol/mL; P < .05, and 66.6 ± 23.2 µmol/L vs 43.3 ± 26.9 µmol/L; P < .05). In the overall group of patients, a significant increase in malondialdehyde levels was detected 3 and 6 months after transplant (3.76 ± 0.79 nmol/mL vs 4.38 ± 0.87 nmol/mL in the third month; P = .02 and 3.76 ± 0.79 nmol/mL vs 4.28 ± 0.69 nmol/mL in the sixth month; P = .04). A significant reduction in plasma glutathione levels 1 month after transplant and nitrite/nitrate levels 6 months after transplant was found. No changes in vitamin C and vitamin E levels were detected before and after transplant. After 3 and 6 months of transplant, cyclosporine-treated patients had higher levels of total cholesterol and triglycerides when compared with tacrolimus-treated patients.

Conclusions: An enhancement in plasma malondialdehyde levels was found after transplant at 6-month follow-up. However, no significant change in vitamin C, vitamin E, nitrite/nitrate levels between patients and controls was recorded. Although both calcineurin inhibitors showed similar effects on oxidative stress, cyclosporine-treated patients had higher levels of total cholesterol and triglycerides.

Key words: Kidney, Oxidative status, Antioxidants, Transplant, Immunosuppressant

Introduction

Oxidative stress and the antioxidant defense system deteriorate in patients with end-stage renal disease. This is because of several factors such as highly prevalent inflammatory situation, dialysis membranes, anemia, high homocysteine levels, parenteral iron therapy, and a significant reduction in antioxidant levels.1-3 Owing to an absence of dialysis and uremia-related factors, renal transplant patients seem to have less oxidative stress compared with routinely dialyzed patients. However, factors such as immune response to allograft, ischemia reperfusion injury, opportunistic infections, and immunosuppressive therapy may trigger oxidative stress in these patients.4-7 Calcineurin inhibitors (cyclosporine and tacrolimus) are the main group of drugs for solid-
organ transplant and have detrimental effects on endothelial cells and renal allograft. It has been recorded in some studies that cyclosporine causes enhancement in production of reactive oxygen species in kidney and heart transplant recipients.4, 8 Patients in these studies also demonstrate up-regulation of the nitric oxide (NO) system, as suggested by increased endothelial nitric oxide synthase (NOS) gene expression and nitrite/nitrate levels.9, 10 In another study, the effects of cyclosporine and tacrolimus on advanced oxidation protein products and total antioxidant status were compared for 6 months and no significant differences were found.11 Kanbay and associates also found no differences on serum uric acid levels in stable kidney transplant recipients using both calcineurin inhibitors.12 Cofan and associates compared the lipid profiles of renal transplant patients and found that tacrolimus had a better lipid profile.13 This was supported by several other studies.14-16 Current data on oxidative stress in renal transplant recipients is conflicting and there is not much detailed prospective data comparing both drugs’ influence. Therefore, we conducted this study to understand the oxidative stress in renal transplant recipients before and after transplant a 6-month follow-up.

Materials and Methods

A total of 24 renal allograft recipients from deceased- or living-related donors with a minimum follow-up of 6 months together with 15 healthy donors were enrolled into our study. Local ethics committee approved the study and the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all of our patients. None of the recipients or donors was older than 60 years or younger than 18 years of age, or had a history of cardiovascular disease and/or diabetes mellitus. Renal transplant patients had stable levels of plasma creatinine (≤ 177 μmol/L). Twelve patients were on antihypertensive treatment before the transplant (5 patients in the tacrolimus group and 7 patients in the cyclosporine group). None of our patients developed diabetes mellitus after transplant for 6 months. Two patients were excluded from our study owing to a switch from 1 calcineurin inhibitor to another, and 1 patient was excluded from our study owing to death related to aspergillus pneumonia after renal transplant. Of remaining 21 patients, 12 were under treatment with cyclosporine and 9 were under treatment with tacrolimus. Two patients had deceased-donor and 19 patients had living-related transplants. The cause of renal disease was 7 chronic glomerulonephritis, 7 chronic tubulointerstitial diseases, 6 unknown, and 1 polycystic kidney disease.

All of our patients received triple immuno-suppressive treatment with different calcineurin inhibitors. Twelve patients were treated with prednisolone (500 mg for 3 consecutive days and then tapered to a maintenance dosage), azathioprine (2-3 mg/kg/d) or mycophenolate mofetil (2 g/d) and cyclosporine (6-8 mg/kg/d initially; then adjusted to achieve a target C2 level as follows: 1500-1700 ng/mL on day 30, 1300-1500 ng/mL on day 60, 1100-1300 ng/mL on days 90-180). The remaining 9 patients received the same regimen but with tacrolimus (0.15 mg/kg/d initially; then adjusted to achieve and maintain a target trough level of 8-12 ng/mL). In deceased-donor transplant, it included anti-thymocyte globulin induction (100 mg/d for 5-10 d, depending on immediate graft function; if plasma creatinine dropped to 265 μmol/L, calcineurin was started). Patients were selected randomly. All kidneys were transplanted extraperitoneally into the iliac fossa in standard fashion. During the study, none of our patients received vitamin supplements or antilipidemic agents.

Peripheral blood samples were drawn after an overnight fast before transplant and at 30, 90, and 180 days after the transplant. Blood samples from controls were taken before the transplant. All bloods were collected in 10-mL ethylenediaminetetraacetic acid tubes and were centrifuged (3000 g at 4°C for 8 min). The plasma was removed, aliquoted, and stored at -80°C. Total cholesterol, triglyceride, and creatinine levels were measured with standard fashion in our laboratory. Oxidative stress was evaluated by determining (1) the end product of lipid peroxidation, malondialdehyde; and (2) the nonenzymatic antioxidants including plasma glutathione, plasma vitamin E, and plasma vitamin C. In addition, nitrite/nitrate levels as a marker of NO system were evaluated.

Measurement of plasma malondialdehyde
Malondialdehyde was measured according to the method of Yagi.17 Phosphotungstic acid (10%) and
sulfuric acid (N/12) were used to precipitate lipids and proteins. After suspending the sediment with distilled water, thiobarbituric acid was added, and the reaction mixture was heated for 60 minutes at 95°C. Substances reacted with thiobarbituric acid and were extracted with butanol. After centrifugation (3000 rpm for 15 min), the butanol layer was taken for fluorometric measurement (emission: 553 nm, excitation: 515 nm)

Measurement of plasma glutathione
Plasma glutathione levels were measured according to the method of Hu.18 Briefly, plasma proteins were precipitated with trichloroacetic acid (10%) on ice. After centrifugation (3000 rpm for 15 min at 4°C), supernatants were collected and suspended with 0.1 M phosphate/ethylenediaminetetraacetic acid buffer and o-phthalaldehyde was added. Plasma glutathione levels were determined fluorometrically (emission: 420 nm, excitation: 350 nm).

Measurement of plasma vitamin E
Plasma vitamin E levels were estimated using the spectrophotometric method of Martinek.19 Briefly, plasma samples were mixed with the equal amounts of ethanol and xylene for saponification. After mixing vigorously, samples were centrifuged at 2000 rpm for 5 minutes. Xylene layer was removed and mixed with equal amount of 0.12% 2,4,6 Tripiridil S-Triazin, and the absorbance values were read within the next 4 minutes at 460 nm. Ferric chloride solution (0.12%) was then added, and the absorbance values were read rapidly at 600 nm. Vitamin E levels were determined according to the below equation:

\[ \text{Vitamin E (mg/100 mL)} = \frac{\text{Absorbance at 600 nm} - (0.40 \times \text{absorbance at 460 nm})}{\text{Absorbance of standard at 600 nm}} \]

0.40 is a correction factor for interfering beta-carotene extract read at 460 nm.

Measurement of plasma vitamin C
Plasma vitamin C levels were measured according to the modified method of Lowry.20 Trichloroacetic acid (5%) was mixed with plasma (4:1) and then centrifuged for 10 minutes at 3000 rpm. A standard solution of ascorbic acid (0.1 g/100 mL ascorbic acid is diluted 100 times) in 5% trichloroacetic acid (1:4) also was prepared. Both standard and supernatants were mixed (1:3) with reagent (2,4 dinitrophenylhydrazine [20 g/mL], thiourea [2.5 g/mL], and copper sulphate [0.3 g/mL]) dissolved in 9N sulfuric acid. After 30 seconds of vortex, all tubes were stood on their ends for 4 hours at 37°C and cooled on ice. Ice-cold sulfuric acid (65%) was added dropwise, incubated for 30 minutes at room temperature, and the absorbances were read spectrophotometrically at a wavelength of 554 nm.

Measurement of plasma nitrite/nitrate levels
Plasma nitrite/nitrate levels were determined according to the method of Green.21 Equal volumes of plasma and Griess reagent were mixed (equal amounts of 0.1% N-[1-Naphthyl]ethylenediamine dihydrochloride prepared in distilled water and 1% sulfanilamide prepared in 5% concentrated phosphoric acid), and the mixture was incubated for 45 minutes at 37°C. The absorbance values were read spectrophotometrically at a wavelength of 554 nm.

Statistical analyses
Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 10.0, IBM Corporation, Armonk, New York, USA). The t test was used as appropriate. Values for P less than .05 were considered statistically significant. Results are expressed as means ± standard deviation.

Results
Demographic and laboratory values in patients and control subjects
A total of 21 patients and 15 controls were included in this analyses. All patients were Turkish. There

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| Table 1. Demographic and Laboratory Values in Patients and Control Subjects |
|---------------------------|---------------------|---------------------|
| Patients (n=21) | Controls (n=15) | P Value |
| Age at transplant | 33.60 ± 9.90 | 39.00 ± 8.30 | NS |
| Sex ratio (% male) | 76.19 | 46.67 | NS |
| Dialysis duration (months) | 18.00 ± 10.00 | 18/3 |
| HD/CAPD | 18 | 3 |
| Total cholesterol (mmol/L) | 4.42 ± 1.22 | 4.81 ± 0.91 | NS |
| Triglycerides (mmol/L) | 2.01 ± 1.64 | 1.86 ± 0.88 | NS |
| Hemoglobin (g/L) | 111.00 ± 19.00 | 138.00 ± 13.00 | < .001 |
| MDA (nmol/mL) | 3.76 ± 0.79 | 3.21 ± 0.57 | < .05 |
| Nitrite/nitrate (mg/dL) | 2.24 ± 0.32 | 2.25 ± 0.59 | NS |
| Plasma GSH (µmol/L) | 66.60 ± 23.20 | 43.30 ± 26.90 | < .05 |
| Vitamin C (µmol/L) | 59.00 ± 8.00 | 59.00 ± 9.00 | NS |
| Vitamin E (µmol/L) | 11.00 ± 1.00 | 10.00 ± 1.00 | NS |

Values are expressed as means ± standard deviation.

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; GSH, glutathione; HD, hemodialysis; MDA, malondialdehyde
were more men in the patient group compared with controls (76.19% vs 46.67%). No significant difference was found between patients and controls in terms of lipid parameters (total cholesterol and triglyceride). Vitamin C, vitamin E, and nitrite/nitrate levels also were similar in both groups. Plasma malondialdehyde and glutathione levels were significantly higher in patients than in controls ($P = .04$; $P = .02$).

**Oxidative stress, creatinine, and lipid parameters in patients before and after transplant**

All renal allografts showed immediate function with a significant reduction ($P < .0001$) in creatinine levels after transplant. Total cholesterol levels increased significantly ($P < .005$) within 30 and 90 days after transplant. Triglyceride levels also increased on the 90th day of transplant, but this increase was not significant.

Transplant caused enhancement in the plasma malondialdehyde levels of patients that were significantly higher ($P < .05$) on days 90 and 180 after transplant. A significant reduction in plasma glutathione levels after 30 days of transplant and nitrite/nitrate levels after 180 days of transplant were found ($P < .005$ for both). Vitamin C and vitamin E levels did not show any significant change after transplant (Table 2).

**Cyclosporine-treated renal transplant patients have higher lipid profile and malondialdehyde levels**

Tables 3 and 4 reflect the data in cyclosporine- and tacrolimus-treated patients ($n=12$ and $n=9$) before and after transplant for 6 months. When the lipid parameters were evaluated in the cyclosporine- and the tacrolimus-treated patients, we found that total cholesterol levels increased in both groups after transplant, but only the values of the cyclosporine-treated group were significant ($P < .05$; $P < .01$). Patients treated with tacrolimus demonstrated a nonsignificant increase in their triglyceride levels after transplant. An enhancement in the levels of malondialdehyde was found in both groups after transplant, but it was only significant in the cyclosporine-treated group 6 months after transplant ($P < .05$). In the tacrolimus-treated group, first month total cholesterol levels and the third month malondialdehyde levels had borderline significance when compared to baseline levels ($P = .06$; $P = .07$). Nitrite/nitrate levels of patients reduced after 6 months of transplant in both groups, which was only significant ($P < .01$) for the cyclosporine-treated group. When the values of 9 patients treated with tacrolimus and 12 patients treated with cyclosporine were evaluated, there were no significant differences in vitamin C and vitamin E levels during the study. Plasma glutathione levels were significantly reduced after transplant.

### Table 2. Oxidative Stress, Creatinine, and Lipid Parameters in all Patients Before and After Transplant

<table>
<thead>
<tr>
<th></th>
<th>BT</th>
<th>AT30</th>
<th>AT90</th>
<th>AT180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (µmol/L)</td>
<td>964.00 ± 248.00*</td>
<td>97.00 ± 22.00*</td>
<td>115.00 ± 35.00*</td>
<td>115.00 ± 27.00*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.42 ± 1.22†</td>
<td>5.61 ± 1.14†</td>
<td>5.77 ± 1.40†</td>
<td>4.84 ± 0.67</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.01 ± 1.64</td>
<td>1.70 ± 0.56</td>
<td>2.47 ± 1.24</td>
<td>1.94 ± 0.80</td>
</tr>
<tr>
<td>MDA (nmol/mL)</td>
<td>3.76 ± 0.79‡</td>
<td>3.98 ± 0.74</td>
<td>4.38 ± 0.87‡</td>
<td>4.28 ± 0.69‡</td>
</tr>
<tr>
<td>Nitrite/nitrate (mg/dL)</td>
<td>2.24 ± 0.32‡</td>
<td>2.41 ± 0.47</td>
<td>2.17 ± 0.36</td>
<td>1.90 ± 0.40‡</td>
</tr>
<tr>
<td>Plasma GSH (µmol/L)</td>
<td>66.60 ± 23.20†</td>
<td>44.80 ± 14.90†</td>
<td>56.90 ± 19.10</td>
<td>52.40 ± 18.70</td>
</tr>
<tr>
<td>Vitamin C (µmol/L)</td>
<td>59.00 ± 8.00</td>
<td>54.00 ± 7.00</td>
<td>57.00 ± 6.00</td>
<td>58.00 ± 9.00</td>
</tr>
<tr>
<td>Vitamin E (µmol/L)</td>
<td>11.00 ± 1.00</td>
<td>10.00 ± 2.00</td>
<td>10.00 ± 2.00</td>
<td>10.00 ± 1.00</td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviation.

* $P < .0001$, † $P < .005$, ‡ $P < .05$

**Abbreviations:** AT30, 30 days after transplant; AT90, 90 days after transplant; AT180, 180 days after transplant; BT, before transplant; GSH, glutathione, MDA, malondialdehyde

### Table 3. Evaluation of Oxidative Stress in Patients Treated With Cyclosporine ($n=12$) for 6 Months After Transplant

<table>
<thead>
<tr>
<th></th>
<th>BT</th>
<th>AT30</th>
<th>AT90</th>
<th>AT180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.34 ± 1.16*, †</td>
<td>5.61 ± 1.09*</td>
<td>6.21 ± 1.66†</td>
<td>5.02 ± 0.78*</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.47 ± 1.93</td>
<td>1.59 ± 0.49</td>
<td>2.83 ± 1.37</td>
<td>2.13 ± 0.88</td>
</tr>
<tr>
<td>MDA (nmol/mL)</td>
<td>3.64 ± 0.74*</td>
<td>3.81 ± 0.76</td>
<td>4.11 ± 0.92</td>
<td>4.22 ± 0.75*</td>
</tr>
<tr>
<td>Nitrite/nitrate (mg/dL)</td>
<td>2.38 ± 0.37†</td>
<td>2.49 ± 0.48</td>
<td>2.14 ± 0.35</td>
<td>1.92 ± 0.34†</td>
</tr>
<tr>
<td>Plasma GSH (µmol/L)</td>
<td>65.40 ± 22.30†</td>
<td>43.20 ± 11.10†</td>
<td>65.30 ± 16.80</td>
<td>60.50 ± 19.70</td>
</tr>
<tr>
<td>Vitamin C (µmol/L)</td>
<td>58.00 ± 9.00</td>
<td>54.00 ± 7.00</td>
<td>57.00 ± 6.00</td>
<td>57.00 ± 11.00</td>
</tr>
<tr>
<td>Vitamin E (µmol/L)</td>
<td>11.00 ± 1.00</td>
<td>11.00 ± 2.00</td>
<td>10.00 ± 2.00</td>
<td>10.00 ± 2.00</td>
</tr>
</tbody>
</table>

Values are expressed as means ± standard deviation.

* $P < .05$, † $P < .01$

**Abbreviations:** AT30, 30 days after transplant; AT90, 90 days after transplant; AT180, 180 days after transplant; BT, before transplant; GSH, glutathione, MDA, malondialdehyde
in the tacrolimus-treated group ($P < .05$) after 6 months, and were significantly reduced in the cyclosporine-treated group ($P < .01$) after the first month of transplant.

**Discussion**

In end-stage renal disease, patients develop uremia that leads to oxidative-stress–related atherosclerosis because of an imbalance between free radical formation and the antioxidant defense system.22 Even though uremia- and dialysis-related factors are eliminated by a transplant, other detrimental factors substitute them such as drugs (cyclosporine and tacrolimus), ongoing immunologic reaction, opportunistic infections, posttransplant diabetes, hypertension, and lipid abnormalities.3-5 Owing to hyperlipidemia and an increase in low-density lipoprotein oxidation, cardiovascular disease remains the major cause of morbidity and mortality in patients under dialysis treatment and renal transplant patients.23, 24 Therefore, in this study, we decided to evaluate the effects of renal transplant on oxidative stress for 6 months after transplant.

Cyclosporine and tacrolimus are calcineurin inhibitors, fundamental for the immunosuppressive treatment after transplant. Numerous studies have investigated the role of both drugs in posttransplant hypertension, lipid abnormalities, endothelial dysfunction, renal toxicity, and NO up-regulation.25-29 However, there have been only a few studies evaluating the roles of cyclosporine and tacrolimus in oxidative stress. Our findings suggest that cyclosporine and tacrolimus have similar effects on oxidative stress. An enhancement of oxidative stress was found in renal transplant patients within a 6-month follow-up.

Cyclosporine-induced oxidative stress has been discussed in several studies. Zahmatkesh reported higher levels of malondialdehyde in 19 patients treated with cyclosporine 48 hours after renal transplant. This was significantly reduced on the seventh and twelfth day after transplant.30 In our study, patients were evaluated for 6 months after transplant, and an enhanced level of malondialdehyde was found in both cyclosporine- and tacrolimus-treated patients. The enhancement was only significant in the cyclosporine-treated patients 6 months after transplant ($P < .05$). Similar to our study, Calò and associates reported an increase in the levels of oxidative stress in 16 cyclosporine- or tacrolimus-treated allograft recipients with posttransplant hypertension.10 In a short-term study, Vural and associates found a reduction in malondialdehyde levels in both cyclosporine- and tacrolimus-treated patients 28 days after transplant.31 These results conflict with our results, as we demonstrated an increase in malondialdehyde levels even at 30 days after transplant. When both groups of calcineurin inhibitors were compared, oxidative stress reached the maximal level in the sixth month after transplant in the cyclosporine-treated group and in the third month after transplant in the tacrolimus-treated group. Oxidative stress has been defined as an imbalance between production and manifestation of reactive oxygen species and the detoxification mechanisms, mostly implemented by antioxidants. When we evaluated the antioxidant levels in our study, there was no change in vitamin C and E levels within 6 months, whereas, there is a reduction in the levels of nitrite/nitrate and plasma glutathione. Therefore, we believe that the enhanced reactive oxygen species cannot effectively be intercepted by the present amounts of antioxidants. Administration of vitamin C and E after transplant might be an alternative to improve oxidative stress.

A correlation between lipid abnormalities and oxidative stress already has been shown in some
studies. Cristol and associates found a significant increase in total cholesterol, triglyceride, and apolipoprotein B levels together with a significant increase in malondialdehyde levels in patients treated with cyclosporine.4 In our study, a significant enhancement was found only in the total cholesterol levels of the cyclosporine-treated patients at 30, 90, and 180 days after transplant. This correlates with other studies that report a better lipid profile for renal transplant recipients under the treatment of tacrolimus than the ones treated with cyclosporine.14-16 The mechanisms for the actions of these 2 calcineurin inhibitors on lipid profile remains to be elucidated. Although increasing evidence supports an important role for lipid abnormalities in the pathogenesis of chronic allograft nephropathy and cardiovascular mortality, none of our patients experienced these complications within 6 months after transplant.32, 33

It is well known that the 3 isoforms of NOS: endothelial, neuronal, and inducible produce NO from the guanidine nitrogen of L-arginine. Nitric oxide has a short half life, as it can rapidly oxidize to nitrite and nitrate, which are reliably measurable compounds. Nitric oxide production and NOS expression have been shown to be involved in acute rejection and cyclosporine toxicity. Studies in cultured bovine aortic endothelial cells showed a decrease in endothelium-derived NO synthesis after cyclosporine administration, which then causes arterial stiffness.34 These results support our study, as we also found an increase in nitrite/nitrate levels 30 days after transplant, and a decrease 180 days after transplant. A reduction in the levels of nitrite/nitrate was only significant after 180 days of transplant in patients treated with cyclosporine. The mechanism behind the reduction of NOS after cyclosporine administration is explained by Lungu and associates34 as a consequence of translocation of endothelial NOS from caveolae owing to decreased amounts of caveolae cholesterol content caused by cyclosporine. Enhancement of nitrite/nitrate levels 1 month after transplant could be related with increased levels of total cholesterol. In their report, Calò and associates, found that cyclosporine-induced endothelial dysfunction, the role of NO in vascular tone, and cyclosporine-mediated vasoconstriction also were evaluated. Similar to our study, they also found cyclosporine induced up-regulation of the NO system in transplanted patients.9

Antioxidant defense system is important for counter-balancing increased oxidative stress; however, using antioxidants for the long term and in high levels can cause their consumption and make them insufficient to overcome the increased burden. In our study, plasma glutathione levels before transplant were higher in patients than in controls. After transplant, in the cyclosporine-treated group, plasma glutathione levels reduced significantly in 30 days and then increased to the baseline level. In tacrolimus-treated patients, a significant reduction was found after 180 days of transplant. Baseline high plasma glutathione levels and a significant decrease after transplant might be explained by a shortage of this compensatory mechanism secondary to using it at high levels after transplant. Lake and associates administered vitamin C (500 mg twice a day) and vitamin E (400 IU twice a day) orally and found a significant reduction in cyclosporine concentration, but no effect in tacrolimus concentration in heart transplant recipients.35 In our study, we measured the plasma levels of vitamin C and vitamin E in patients under cyclosporine and tacrolimus therapy, and found no significant difference before and after transplant. As mentioned earlier, administration of vitamin C and E to renal transplant patients might improve oxidative stress.

A small number of patients and relatively short follow-up (6 months) after transplant are the main limitations of this study. We know that dialysis duration is an important risk factor for cardiovascular events. Patients enrolled in our study had a relatively low duration of dialysis treatment owing to living-related transplant. In addition, patients were exposed to higher dosages of calcineurin inhibitors, especially during the first months after transplant. These factors may explain why the transplant did not cause any significant improvement in the oxidant status of patients with renal disease.

In conclusion, there is an enhancement of oxidative stress in renal transplant patients. We observed no change in vitamin C and vitamin E levels. We did find significant reductions in plasma glutathione levels 1 month after transplant and nitrite/nitrate levels 6 months after transplant. Overall, within 6 months after the transplant, calcineurin inhibitors (cyclosporine and tacrolimus) have similar effects on oxidative stress. Longer follow-ups and evaluations should be performed.
References


