The Effects of Cyclosporine and Prednisone on Serum Lipid and (Apo)Lipoprotein Levels in Renal Transplant Recipients

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ABSTRACT
Disturbances of lipid metabolism are frequently encountered after renal transplantation and have been ascribed to the use of cyclosporine (CsA) and corticosteroids, but the individual contribution of each of these drugs remains uncertain. The individual effects of CsA and prednisone (Pred) on serum lipid and (apo)lipoprotein levels were compared in a prospective randomized trial. All patients received CsA and Pred during the first 3 months after transplantation. Subsequently, they were allocated to either withdrawal of Pred or conversion from CsA to azathioprine (Aza). Serum lipids and (apo)lipoproteins, including lipoprotein(a) (Lp(a)), were measured at regular intervals during the first year after renal transplantation. Analysis of variance for repeated measures of the first year results showed higher values for serum triglycerides (P < 0.001) and lower high-density lipoprotein (HDL) cholesterol levels (P < 0.05) in the CsA mono-therapy group (N = 59) as compared with the Aza-Pred group (N = 63). At 1 yr after transplantation, CsA-treated patients had significantly higher Lp(a) levels (CsA: median, 105 (interquartile range 42 to 340) mg/L; Aza-Pred: 46 (25 to 176) mg/L; P < 0.05). The withdrawal of Pred in the CsA group resulted in a large fall in HDL cholesterol (27 ± 30% at 5 months after transplantation) and an increase in triglycerides (49 ± 73% at 6 months). A reversion of these changes was observed in patients who were retreated with Pred. Multiple linear regression analysis showed an independent correlation between the use of Pred and HDL cholesterol level, whereas the use of CsA was independently associated with the concentration of Lp(a). The results indicate that with respect to risk for hyperlipidemia after renal transplantation, Aza-Pred treatment may be preferred above CsA monotherapy. These data do not support the general belief that the withdrawal of steroids in CsA-treated patients improves the serum lipid and lipoprotein profile.

Key words: Serum cholesterol, lipoprotein(a), hyperlipidemia, atherosclerosis, renal transplantation

Atherosclerosis is a major cause of morbidity and mortality after renal transplantation. One of the main risk factors for atherosclerosis is hyperlipidemia, and many studies have demonstrated that hyperlipidemia is frequently encountered in renal transplant recipients (1). Elevated levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) are frequently observed (1-3). High-density lipoprotein cholesterol (HDL-C) levels have been variously reported as high, normal, or low. In recent years, elevated lipoprotein(a) [Lp(a)] concentrations have been reported in renal transplant patients treated with cyclosporine (CsA) (4). In addition to other factors, there is strong evidence for a pathogenetic role of immunosuppressive drugs in post-transplant hyperlipidemia. The adverse effects of corticosteroids on serum cholesterol and TG levels are well established (2,5,6). The withdrawal of prednisone (Pred) in patients on CsA and azathioprine (Aza) led to significant decreases in total cholesterol levels (6-8). Numerous studies documented that treatment with CsA, alone or in combination with steroids, was associated with increased levels of total and LDL-C and serum TG (6,9-12), although there are also studies in which these effects of CsA could not be demonstrated (13,14). The individual contribution of either drug to disturbances in lipid metabolism as well as their distinct effects on the various lipoprotein subclasses are not clear.

To clarify this issue, we measured serum lipids and lipoproteins in patients who participated in a randomized prospective trial comparing CsA monotherapy with the combination of Aza and Pred from 3 months after renal transplantation. Because Aza is not known to influence lipid metabolism, this actually meant a comparison of the effects of CsA and Pred. In addition to most of the previous studies on this subject, we also measured apolipoprotein (apo) A-I, apo B, and Lp(a). Apo A-I and apo B are the major protein components...
within high density lipoprotein (HDL) and low density lipoprotein (LDL), respectively. Lp(a) resembles LDL but has an additional apolipoprotein [apo(a)] that is structurally homologous to plasminogen. In epidemiologic studies, apo B (15) and Lp(a) (16) were positively and apo A-I (15) was negatively associated with the risk for atherosclerotic cardiovascular disease. Because the initial treatment in all of our study patients consisted of CsA and Pred, the design of the trial also allowed the examination of the changes in lipid and apolipoprotein occurring after the withdrawal of Pred in CsA-treated patients, which we expected to be beneficial.

**PATIENTS AND METHODS**

**Patient Population**

All patients underwent a first or second cadaveric renal transplantation at our institution. Postoperatively, they were treated with CsA and Pred for 3 months. Afterwards, they volunteered to participate in a randomized prospective trial, comparing CsA monotherapy (N = 64) with the combination therapy of Aza and Pred (N = 63). Two patients with diabetes mellitus (both in CsA group) were excluded from this analysis, and another three patients in the CsA group could not be evaluated because of lacking data. The remaining 122 patients made up the study population.

**Study Protocol**

CsA was given iv (3 mg/kg per day) for the first 3 days postoperatively, followed by 12 mg/kg per day in two divided oral doses during the first month, gradually reduced to 4 mg/kg per day at 3 months after transplantation. The dosage was adjusted to maintain CsA trough blood levels between 200 and 400 ng/mL. Prednisolone was given at a dose of 100 mg/day iv during the first 2 days postoperatively, followed by an oral Pred dosage of 25 mg/day during the remainder of the first month and 20 mg/day during the second and third months after transplantation. In patients who were randomized to receive CsA monotherapy, CsA was continued in the same dosage with adjustments to reach trough blood levels between 100 and 200 mg/mL. The Pred dosage was reduced by 5 mg/day every 2 wk, resulting in CsA monotherapy after 6 wk. In patients allocated to Aza-Pred therapy, CsA was replaced without overlap by Aza in a dosage of 3 mg/kg. Their Pred dosage was temporarily increased from 20 to 25 mg/day and reduced by 5 mg/day every 2 wk until a maintenance dose of 10 mg/day was reached. In the CsA group, Pred was restarted if more than one acute rejection or chronic vascular rejection occurred after randomization. The same conditions led to the replacement of Aza by CsA in the Aza-Pred group. In case of severe and persistent side effects, attributable to one of the drugs, patients changed over to the alternative treatment regimen.

During the first 3 months after transplantation, acute rejection episodes were treated with methylprednisolone (1 g iv on three consecutive days) or antihymocyte globulin (ATG; RTVM Bilthoven, The Netherlands; 200 mg iv on alternate days for 10 days). An oral course of high-dose Pred (initial dosage 200 mg/day tapering to 25 mg/day in 12 days) was given after the failure of one or both of these treatments. From 3 months after transplantation (i.e., after randomization), acute rejections were primarily treated with ATG in all cases. High-dose Pred courses were given in case of the failure of ATG, bone marrow suppression, or previous treatment with ATG for rejection.

Hypertension, defined as diastolic blood pressure above 95 mm Hg on three consecutive occasions, was treated in a standard way with a 7-blocker (atenolol), followed by the successive addition of a calcium antagonist (nifedipine) and a diuretic (chlorothalidone) when necessary. None of the patients were treated with lipid-lowering drugs. There were no dietary recommendations given except for caloric restriction in patients with a large weight gain after transplantation.

Blood samples for the measurement of serum total cholesterol, HDL-C, TG, and plasma glucose were collected after an overnight fast at 2 and 3 months (baseline values), as well as at 5, 6, 9, and 12 months after transplantation. Apo A-I and apo B were measured in the samples obtained at 3, 6, and 12 months, whereas Lp(a) was measured at 3 and 12 months after transplantation. In the samples obtained at 12 months, very low-density lipoprotein (VLDL) cholesterol and TG were determined.

Body weight and blood pressure, as well as results from routine clinical chemistry, were recorded at regular intervals as part of the usual posttransplant patient evaluation. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Creatinine clearance was estimated with the formula given by Cockcroft and Gault (17). Proteinuria was defined as a urinary protein concentration of more than 0.1 g/L (24-h urinary protein excretion was not measured routinely). The study was approved by the Hospital Ethics Committee, and all patients gave written informed consent.

**Analytical Procedures**

Cholesterol and TG were measured by enzymatic methods (CHOD-PAP cholesterol reagent; Boehringer-Mannheim, Mannheim, Germany, and SERA-PAR TG, Miles, Italy with a centrifugal analyzer (Multistat III; Instrumentation Laboratory Inc., Lexington, MA). HDL-C was measured as described (18). LDL-C was calculated by the Friedewald formula (19). VLDL was isolated by ultracentrifugation at d = 1.006 g/mL with a Kontron TFR 45.6 rotor (Kontran Instruments AG, North Chicago, IL), initially with polyclonal antibodies directed against the parent molecule of CsA and some of its metabolites. The majority of blood levels was measured with a modified kit, with monoclonal antibodies against the CsA parent molecule without cross-reactivity. A conversion factor

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of 0.5 was used to adjust the initial values to those currently measured.

Statistical Analysis

All data were analyzed with the SAS system (SAS Institute Inc., Cary, NC). Data are given as means ± standard deviations, unless stated otherwise. The logarithmic conversion of Lp(a) was performed to normalize the distribution. Comparison of the changes after randomization between both treatment groups was performed by analysis of variance for repeated measurements. Within-group comparisons and between-group comparisons at different times were carried out with paired or unpaired t tests. Proportions were compared with χ² analysis. Simple correlations within each treatment group were assessed by calculating Spearman’s correlation coefficient. Multiple linear regression analysis was used to examine the relative independent contributions of the use of CsA and Pred, as well as of several other clinical variables, to lipid levels at 1 yr after transplantation. A P value of less than 0.05 was considered statistically significant. No correction for the comparison of multiple outcomes was applied.

RESULTS

Between 3 and 12 months after transplantation, one patient died in each treatment group (CsA, 4 months; Aza-Pred, 6 months after transplantation). In addition, graft loss occurred once in each group (CsA, 6 months; Aza-Pred, 7 months after transplantation). The results obtained until the time of death or graft loss were included for analysis. In 37 patients, the initially assigned treatment had to be changed for a variety of reasons. Pred was added to CsA in eight patients because of the occurrence of more than one acute rejection or chronic rejection after steroid withdrawal (one of these patients received triple therapy). In another six patients, steroid withdrawal was not completed for a variety of reasons. CsA was replaced by Aza-Pred in nine cases, all but once because of CsA-induced renal dysfunction (in one of these patients, CsA was substituted for Aza again, with the continuation of Pred). In two patients, Aza was replaced by CsA because they had a second acute rejection episode after prior conversion from CsA to Aza. Bone marrow depression and liver function disturbances prompted switching from Aza to CsA in eight (one of these temporaril) and four additional patients, respectively. Seven of the latter 12 patients were off Pred at 1 yr after transplantation. To determine the clinical effect of the two therapeutic approaches on lipid metabolism and cardiovascular risk, the data of all patients were analyzed on an intention-to-treat basis.

Intention-To-Treat Analysis

The demographic and clinical characteristics of the patients are shown in Table 1. There were no differences in these parameters between both groups. The values for serum lipids and (apo)lipoproteins measured at 3, 6, and 12 months after transplantation are given in Table 2. In the CsA monotherapy group, total cholesterol and LDL-C did not change between 3 and 12 months after transplantation; however, the concentration of HDL-C decreased considerably, with a maximal reduction of 35 ± 30% at 5 months after transplantation, whereas TG levels increased significantly (maximal change of 49 ± 73% at 6 months). In the Aza-Pred group, there was also a significant decrease of the serum level of HDL-C (−13 ± 25% at 6 months). Analysis of variance showed that the changes after randomization differed significantly between both groups for HDL-C (a larger decrease in the CsA group; P < 0.05), for TG (an increase in the CsA group versus no change in the Aza-Pred group; P < 0.001), and for the ratio of total cholesterol to HDL-C (a larger increase in the CsA group; P < 0.01). At 1 yr after transplantation, VLDL cholesterol was higher in the CsA group (CsA, 1.15 ± 0.82 mmol/L; Aza-Pred, 0.68 ± 0.42 mmol/L; P < 0.01) as was the ratio of cholesterol to TG in the VLDL fraction (CsA, 0.76 ± 0.21; Aza-Pred, 0.61 ± 0.15; P < 0.001). The concentration of apo A-I was highly correlated with that of HDL-C (R² = 0.72, 0.69, and 0.72 at 3, 6, and 12 months; P < 0.001). Likewise, the level of apo B showed a strong correlation with that of LDL-C (R² = 0.82, 0.80, and 0.64 at 3, 6, and 12 months; P < 0.001). Consequently, significant decreases in apo A-I were observed in both groups. Lp(a) concentration increased in the CsA monotherapy group and did not change after replacing CsA-Pred by Aza-Pred, resulting in a significant difference between both treatment groups at 1 yr after transplantation.

Table 3 summarizes the values of other clinical and laboratory parameters that could have influenced lipoprotein metabolism. As expected, Aza-Pred-treated patients had higher creatinine clearances. Except for a negative correlation between creatinine clearance and apo A-I at 12 months after transplantation in the Aza-Pred group (R² = −0.28; P < 0.05), there were no significant correlations between creatinine clearance and lipid or (apo)lipoprotein levels at 6 or 12 months in either group. Proteinuria was more frequent in the Aza-Pred group at 6 months after transplantation. A

![Table 1. Characteristics of patients assigned to treatment with CsA monotherapy or combination therapy of Aza and Pred from 3 months after renal transplantation](image-url)

- **Parameter**
  - **CsA** (N = 59)
  - **Aza-Pred** (N = 63)
- **Sex (M/F)**
  - 38/21
  - 41/22
- **Age (yr)**
  - 42 ± 12
  - 42 ± 14
- **First/second transplantation**
  - 48/11
  - 53/10
- **Body mass index (kg/m²)**
  - 23.7 ± 3.2
  - 24.3 ± 3.9
- **Creatinine clearance**
  - 57 ± 18
  - 56 ± 19
- **(ml/min)**
  - Patients with proteinuria
    - 8 (14%)
    - 10 (16%)
  - Patients using antihypertensive drugs
    - 45 (76%)
    - 47 (75%)

*Data at 3 months after transplantation.*
comparison of patients with and without proteinuria revealed a difference for LDL-C at 12 months in the CsA group (5.23 ± 2.72 versus 3.97 ± 1.83 mmol/L; P < 0.05). A significant correlation between changes in creatinine clearance or urinary protein excretion on the one hand and changes in lipid or (apo)lipoprotein levels on the other hand was only observed in the CsA group for the change in creatinine clearance between 3 and 6 months and the concurrent change in TG (R = −0.32; P < 0.05). Body weight increased to the same extent in both treatment groups. Although plasma glucose was slightly higher in the CsA group at 3 months, there were no significant differences in plasma glucose after randomization. The use of the different classes of antihypertensive drugs was comparable. CsA blood levels tended to decline over time and showed no significant correlation with lipid or (apo)lipoprotein levels at 3, 6, or 12 months after transplantation. The number of acute rejection episodes during the first year after transplantation did not differ between both groups (CsA: mean, 0.83 [range 0 to 4]; Aza-Pred: 0.65 [0 to 3]), nor did the number of patients who received a methylprednisolone course (CsA, N = 9; Aza-Pred, N = 11). The cumulative dose of Pred was higher in the Aza-Pred group (5,747 ± 845 versus 4,169 ± 1910 mg; P < 0.001).

Multiple linear regression was performed to assess the independent effects of immunosuppressive treatment and other clinical variables on lipid and (apo)lipoprotein levels at 1 yr after transplantation. Because a number of patients did not keep to their originally assigned treatment, the actual use of CsA and of Pred (0 if the patient did not take the drug and 1 if he/she did) instead of group membership formed explanatory variables. Other independent variables were: age, sex (0 = male, 1 = female), body mass index, creatinine clearance, proteinuria (0 = absent, 1 = present), cumulative doses of corticosteroids (arbitrarily defined as the cumulative dose of Pred plus 0.1 times the cumulative dose of methylprednisolone), and use of β-blockers and calcium antagonists. Table 4 gives

### Table 2. Lipid and (apo)lipoprotein concentrations at 3, 6, and 12 months after renal transplantation in patients assigned to treatment with CsA monotherapy or with Aza-Pred

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA</th>
<th>Aza-Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>6.31 ± 1.63</td>
<td>6.19 ± 1.40</td>
</tr>
<tr>
<td>Serum TG (mmol/L)</td>
<td>1.91 ± 0.97</td>
<td>2.53 ± 1.42a</td>
</tr>
<tr>
<td>LDL-Cholesterol (mmol/L)</td>
<td>4.23 ± 1.51</td>
<td>4.12 ± 1.16</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.31 ± 0.38b</td>
<td>1.01 ± 0.34a</td>
</tr>
<tr>
<td>Total/HDL-C</td>
<td>5.23 ± 2.05</td>
<td>6.82 ± 2.78a</td>
</tr>
<tr>
<td>apo A-I (mg/L)</td>
<td>1,538 ± 325</td>
<td>1,350 ± 328c</td>
</tr>
<tr>
<td>apo B (mg/L)</td>
<td>1,295 ± 399</td>
<td>1,314 ± 347</td>
</tr>
<tr>
<td>Lp(a) (mg/L)f</td>
<td>61 (25-168)</td>
<td>105 (42-340)c</td>
</tr>
</tbody>
</table>

a P < 0.001 for difference versus 3 months.
b P < 0.01 for difference with CsA group.
c P < 0.01 for difference versus 3 months.
d P < 0.05 for difference with CsA group.
e P < 0.05 for difference versus 3 months.
f Given as median with Interquartile range.

### Table 3. Clinical and biochemical parameters at 3, 6, and 12 months after renal transplantation in patients assigned to treatment with CsA monotherapy or with Aza-Pred

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA</th>
<th>Aza-Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 11</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>57 ± 18</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.9 ± 1.0</td>
<td>5.0 ± 0.7</td>
</tr>
<tr>
<td>Patients with proteinuria (%)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Patients using a β-blocker (%)</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Patients using a calcium antagonist (%)</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Patients using a diuretic (%)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>CsA trough level (ng/mL)</td>
<td>220 ± 82</td>
<td>197 ± 87</td>
</tr>
</tbody>
</table>

a P < 0.01 for difference with CsA group.
b P < 0.001 for difference with CsA group.
c P < 0.05 for difference with CsA group.
TABLE 4. Results of multiple linear regression analysis of data obtained at 1 yr after transplantation

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Predictor Variable</th>
<th>Partial Regression Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol</td>
<td>Sex (female = 1)</td>
<td>0.86</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Use of calcium-antagonist</td>
<td>0.79</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>0.026</td>
<td>0.049</td>
</tr>
<tr>
<td>Serum TG</td>
<td>Use of calcium-antagonist</td>
<td>0.53</td>
<td>0.043</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>Creatinine clearance (mL/min)</td>
<td>-0.009</td>
<td>0.048</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Sex (female = 1)</td>
<td>0.028</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²)</td>
<td>-0.028</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Use of Pred</td>
<td>0.23</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance (mL/min)</td>
<td>0.0045</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>0.0058</td>
<td>0.032</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Sex (female = 1)</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²)</td>
<td>-0.028</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Use of Pred</td>
<td>0.23</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance (mL/min)</td>
<td>0.0045</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>Age (yr)</td>
<td>0.0058</td>
<td>0.032</td>
</tr>
<tr>
<td>apo A-I</td>
<td>Sex (female = 1)</td>
<td>282</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Use of CsA</td>
<td>176</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>Use of Pred</td>
<td>181</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Use of calcium-antagonist</td>
<td>163</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²)</td>
<td>-13</td>
<td>0.047</td>
</tr>
<tr>
<td>apo B</td>
<td>Use of CsA</td>
<td>0.86</td>
<td>0.036</td>
</tr>
</tbody>
</table>

a Only the variables that showed a significant, independent correlation with a particular lipid outcome are shown.
b The regression coefficient shows the expected change in the dependent variable each time the predictor variable increases by 1 U, holding the values of the other predictor variables constant.

Those explanatory variables that showed an independent association with the respective lipid outcome variables. The use of Pred retained a significant relationship with HDL-C and apo A-I, whereas the use of CsA was an independent predictor of (log-normalized) Lp(a) and apo A-I. Somewhat surprisingly, the use of a calcium antagonist (nifedipine) was independently correlated with serum cholesterol, serum TG, and apo A-I.

Additional information on the individual effects of CsA and Pred on serum lipid and lipoprotein levels was obtained in patients who received steroid courses for acute rejection. In seven patients who were treated with high doses of Pred for acute rejection after prior steroid withdrawal, blood samples were obtained before and within 3 months after restarting treatment with Pred. The effects on serum lipid patterns are shown in Figure 1a. The cessation of Pred at 3 months after transplantation was followed by a decrease in HDL-C and an increase in TG, resembling the results mentioned above. The steroid course was accompanied by a reversion of HDL-C and TG levels to values observed during previous Pred treatment. In contrast, the treatment of acute rejection with ATG in patients on CsA monotherapy was not followed by comparable changes (Figure 1b). In 10 of the 23 patients who were switched to the other treatment group, the blood sampling schedule allowed the evaluation of the changes in the serum lipid profile after conversion from CsA monotherapy to Aza-Pred treatment or vice versa (Table 5). The decrease in HDL-C and the rise in TG characteristic of steroid withdrawal disappeared after the cessation of CsA and the reinstition of Pred in all cases. In addition, the data presented in Table 4 suggest that both treatment regimens have opposite effects on the levels of LDL-C.

Our trial was not designed to measure parameters of atherosclerosis in depth, but of both patients who died, one patient died from an acute myocardial infarction (Aza-Pred) and the other died from Pneumocystis carinii pneumonia (CsA). None of the remaining patients developed clinical signs of cardiovascular disease during the first year after transplantation.

**Continued-on-Therapy Analysis**

To investigate the separate effects of maintenance doses of CsA and Pred on lipid and (apo)lipoprotein levels, as well as the changes in lipid levels after steroid withdrawal, we analyzed the data again after the exclusion of patients who died or experienced graft loss (N = 4), patients who did not strictly adhere to their assigned treatment protocol (N = 37), and patients who were treated with high-dose steroids for acute rejection (CsA, N = 6; Aza-Pred, N = 6). The demographic and clinical characteristics of the remaining 69 patients were not different from those of the whole study population given in Table 1. The course of the concentrations of serum lipids and (apo)lipoproteins is shown in Table 6. Differences between both groups are more pronounced in this subgroup analysis, especially for HDL-C and Lp(a). The proportion of patients with a Lp(a) value above 300 mg/L (generally used as a cut-off point for increased risk) was 36% in the CsA group and 10% in the Aza-Pred group (P < 0.01). In the CsA group, the
Effects of CsA and Prednisone on Lipid Metabolism

**DISCUSSION**

This study demonstrates that CsA monotherapy and Aza-Pred treatment markedly differ in their effects on serum lipid and (apo)lipoprotein levels during the first year after renal transplantation. Because the influence of Aza on serum lipid levels has not been demonstrated (22), the design of our study allowed a direct comparison of the effects of CsA and Pred on lipid metabolism. During the first 3 months after transplantation, all patients received both CsA and Pred, which was followed by the cessation of either drug. Concentrations of total cholesterol and LDL-C remained elevated in both groups and were comparable to those reported earlier in posttransplant patients on various immunosuppressive regimens (12,13). However, significant differences between both groups were noted for HDL-C, serum TG, and Lp(a). Differences in HDL-C or TG were not observed in previous, relatively small studies comparing the effects of CsA monotherapy and Aza-Pred treatment on lipid metabolism (9,10).

Diabetic patients were excluded from this study because preexisting secondary hypertriglyceridemia as well as the influence of Pred on already disturbed glucose metabolism would hamper the interpretation of the data obtained in these patients. The results may therefore not apply to diabetics, who represent a substantial part of the renal transplant recipients in some countries.

One of our most striking findings was the considerable decrease in HDL-C concentration, especially in CsA-treated patients. The fall in HDL-C may in part have been secondary to the rise in serum TG, but in the Aza-Pred group, both HDL-C and TG appeared to decrease, which suggests that other mechanisms are involved. In general, low HDL-C levels can result from a decreased hepatic synthesis or from an increased removal from the circulation. The urinary loss of HDL has been suggested to occur in patients with the nephrotic syndrome (23). It is, however, not a likely cause of low HDL levels in our patients because there were only a few patients with proteinuria and there was no correlation between the degree of proteinuria and HDL levels. The time course of the alterations in HDL-C and serum TG on CsA monotherapy, with the most dramatic changes between 3 and 5 months after transplantation, suggests a relation with the cessation of Pred during exactly the same period. This was supported by the normalization of reduced HDL and increased TG levels in patients treated with steroid courses for acute rejection after prior steroid with-

**Figure 1.** Effects on serum lipids and lipoproteins of steroid withdrawal and subsequent treatment with steroids or ATG for rejection. Mean (±SE) values of serum lipids and lipoproteins before the withdrawal of Pred at 3 months after renal transplantation (Tx), after cessation of Pred, and either after treatment with high doses of Pred for acute rejection in seven patients (a) or after treatment with ATG for acute rejection in five patients (b). Data are presented as percentages with an index value of 100% for the first lanes. TC, serum total cholesterol; *P < 0.05 for differences with values at 3 months after transplantation.

**TABLE 5. Direction of changes in serum lipids and lipoproteins after conversion from CsA monotherapy to Aza-Pred or vice versa**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Increase/decrease</th>
<th>CsA → Aza-Pred (N = 5)</th>
<th>Aza-Pred → CsA (N = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>↑ / ↓</td>
<td>1/4</td>
<td>2/3</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↑ / ↓</td>
<td>1/4</td>
<td>4/1</td>
</tr>
<tr>
<td>HDL-C</td>
<td>↑ / ↓</td>
<td>5/0</td>
<td>2/3</td>
</tr>
<tr>
<td>TG</td>
<td>↑ / ↓</td>
<td>0/5</td>
<td>3/2</td>
</tr>
</tbody>
</table>

The relative decrease in HDL-C after steroid withdrawal was larger than the accompanying decrease in apo A-I, resulting in a significant reduction in the HDL-C-to-apo A-I ratio.
TABLE 6. Continued-on-therapy analysis of lipid and (apo)lipoprotein concentrations at 3, 6, and 12 months after renal transplantation in patients treated with CsA monotherapy (N = 28) or with Aza-Pred (N = 41)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CsA 3 months</th>
<th>CsA 6 months</th>
<th>CsA 12 months</th>
<th>Aza-Pred 3 months</th>
<th>Aza-Pred 6 months</th>
<th>Aza-Pred 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>6.16 ± 1.53</td>
<td>5.90 ± 1.06</td>
<td>5.85 ± 1.17</td>
<td>6.26 ± 1.37</td>
<td>5.84 ± 1.21</td>
<td>5.86 ± 1.17</td>
</tr>
<tr>
<td>Serum TG (mmol/L)</td>
<td>1.70 ± 0.84</td>
<td>2.54 ± 1.57</td>
<td>2.19 ± 1.18</td>
<td>2.10 ± 0.97</td>
<td>1.81 ± 0.86</td>
<td>1.76 ± 0.83</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>4.20 ± 1.32</td>
<td>3.93 ± 0.80</td>
<td>3.94 ± 1.01</td>
<td>4.06 ± 1.12</td>
<td>3.99 ± 1.17</td>
<td>3.96 ± 1.02</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.35 ± 0.36</td>
<td>0.90 ± 0.25</td>
<td>0.99 ± 0.36</td>
<td>1.32 ± 0.45</td>
<td>1.16 ± 0.44</td>
<td>1.16 ± 0.39</td>
</tr>
<tr>
<td>Total/HDL-C</td>
<td>3.03 ± 1.53</td>
<td>3.09 ± 2.24</td>
<td>3.03 ± 2.87</td>
<td>3.06 ± 1.54</td>
<td>3.04 ± 1.67</td>
<td>3.05 ± 1.64</td>
</tr>
<tr>
<td>apo A-I (mg/L)</td>
<td>1.58 ± 0.27</td>
<td>1.31 ± 0.24</td>
<td>1.38 ± 0.25</td>
<td>1.50 ± 0.25</td>
<td>1.43 ± 0.30</td>
<td>1.38 ± 0.23</td>
</tr>
<tr>
<td>HDL-C/apo A-I (mmol/L)</td>
<td>0.85 ± 0.17</td>
<td>0.68 ± 0.13</td>
<td>0.70 ± 0.17</td>
<td>0.88 ± 0.18</td>
<td>0.81 ± 0.18</td>
<td>0.82 ± 0.18</td>
</tr>
<tr>
<td>apo B (mg/L)</td>
<td>1.31 ± 0.39</td>
<td>1.23 ± 0.26</td>
<td>1.28 ± 0.29</td>
<td>1.25 ± 0.27</td>
<td>1.25 ± 0.26</td>
<td>1.21 ± 0.28</td>
</tr>
<tr>
<td>Lp(a) (mg/L)</td>
<td>84 (38-378)</td>
<td>166 (71-479)</td>
<td>166 (71-479)</td>
<td>72 (25-277)</td>
<td>38 (21-176)</td>
<td>38 (21-176)</td>
</tr>
</tbody>
</table>

a P < 0.05 for difference versus 3 months.
b P < 0.001 for difference versus 3 months.
c P < 0.01 for difference versus 3 months.
d P < 0.01 for difference with CsA group.
e P < 0.05 for difference with CsA group.
f Given as median with interquartile range.

The mechanism by which corticosteroid administration increases HDL-C levels is not clear. Animal studies have shown increases in the hepatic production of nascent HDL-C after corticosteroid administration (29). Furthermore, increased activity of lipoprotein lipase during the administration of Pred has been associated with a rise in HDL-C and may also contribute to a decrease in TG (25,26). Alternatively, decreased activity of hepatic lipase, enhanced activity of lecithin-cholesterol acyltransferase (24), or changes in cholesteryl ester transport could be involved. In patients with nephrotic syndrome, corticosteroid therapy has been associated with a reduction in plasma cholesterol ester transfer protein (CETP) (30). CETP mediates the transfer of cholesteryl esters from HDL to apo B-containing lipoproteins, and patients with genetic CETP deficiency have increased HDL-C levels (31). A reduction in CETP activity by Pred therapy as a possible cause of increased HDL-C levels is supported by our observation of a significantly smaller cholesteryl content of VLDL in Aza-Pred-treated patients as compared with their CsA-treated counterparts.

Taken together, we have strong arguments to assume that in our CsA-treated patients, the reduction of the Pred dosage from 20 mg/day to 0 contributed to the observed fall in HDL-C. The persistence of high levels of total cholesterol, LDL-C, and TG is probably related to treatment with CsA. In accordance with this view, the moderate decrease in HDL-C that occurred in the Aza-Pred group may be caused by the reduction of the Pred dosage from 20 to 10 mg/day. The tendency for decreases in total cholesterol and TG in these patients is in line with the observations in previous conversion studies (32,33) and may be attributed to either the discontinuation of CsA or again to the reduction of the Pred dosage.

The remarkable increase in Lp(a) levels in CsA-treated patients, but not in Aza-Pred-treated patients, is in keeping with the results of several recent studies (4,34), although opposite data have been reported too (35). Multiple linear regression analysis showed an independent relationship between the use of CsA and (log normalized) Lp(a). The mechanism by which CsA increases the concentration of Lp(a) is unknown. Lp(a) levels were demonstrated to be related to the genetically determined apo(a) phenotype (36). Although apo(a) phenotyping was not performed in our study, the results indicate that in renal transplant patients,
Lp(a) levels are not only a function of the phenotype but also of the immunosuppressive treatment regimen that is used. A recent study showed decreases in Lp(a) levels during treatment with glucocorticoids in patients with rheumatic diseases (28), but the use of Pred appeared not to be an independent predictor of Lp(a) levels in our multivariate analysis.

What is the clinical significance of our findings? Atherosclerosis is a common problem in renal transplant recipients, with coronary heart disease being the main cause of death in this population (37). Hyperlipidemia plays an important role in the pathogenesis of atherosclerosis, and from large epidemiologic studies, it is known that low HDL-C levels, as well as high total cholesterol and LDL-C levels, are independent risk factors for coronary heart disease (15,38,39). Hypertriglyceridemia has been found to be an independent risk factor in some studies (40). Kasiske demonstrated an independent association between serum cholesterol and ischemic heart disease in a large population of renal transplant recipients (41). Regarding the magnitude of the effect of a decrease in HDL-C, it was estimated from the Framingham Heart Study that a decrease of 10 mg/dL [0.26 mmol/L] was associated with an increase in the risk for mortality due to coronary heart disease of 18.9 and 28.1% for men and women, respectively (39). Similarly, in the Physician’s Health Study, a change of 1 U in the ratio of total cholesterol to HDL-C, like the difference between the means of our study groups at 1 yr after transplantation, was associated with a 53% change in the risk of myocardial infarction (15). Despite these persuasive figures for the general population, we have to be cautious in concluding that a decrease in HDL-C after steroid withdrawal will equally worsen the cardiovascular risk in renal transplant patients. If steroids would alter the composition of HDL in a nonbeneficial way, the improved composition of HDL after steroid withdrawal could outweigh the potentially negative effects of lower HDL-C levels. However, the rise in the lipid-to-protein ratio of HDL, as well as previously observed increases in the HDL₂ subfraction (26,42), points to favorable changes in the composition of HDL after the administration of Pred (15). Lp(a) is not only positively associated with coronary heart disease but may also have detrimental effects on hemostasis and thrombosis (16).

In conclusion, the resulting lower HDL-C, higher serum TG, and higher Lp(a) levels suggest that CsA monotherapy is a less attractive immunosuppressive treatment strategy than Aza-Pred treatment in terms of risk for coronary heart disease. Moreover, the changes in HDL-C and TG that we observed after the cessation and resumption of Pred in CsA-treated patients indicate that the widespread assumption that steroid withdrawal improves the serum lipid pattern after renal transplantation may be false. In this regard, Pred may even exert some protective effect in CsA-treated patients. Currently, we are performing a prospective study to compare the effects of CsA-Aza treatment with that of CsA-Pred treatment on serum lipids and lipoproteins.

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REFERENCES


