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# Lipid Profile During Azathioprine or Mycophenolate Mofetil Combinations With Cyclosporine and Steroids

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ABSTRACT

Background. Immunosuppressive therapy is the major cause of hyperlipidemia after renal transplantation. We sought to compare the effects of an azathioprine (AZA) combination ($n = 26$) with corticosteroid and cyclosporine (CyA; group 1) with a mycophenolate mofetil (MMF) combination ($n = 71$; group 2) in the first year following renal transplantation.

Methods. Ninety-seven renal transplant patients (71 men, 26 women; aged 34.7 ± 13.1 years; renal transplantation duration, 44.9 ± 12.9 months) underwent serum lipid profiles—total cholesterol, triglyceride, high-density lipoprotein (HDL); low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) at the initiation of as well as 3-month intervals after grafting for 1 year retrospectively. Serum creatinine for each patient was recorded at 12 months. We evaluated possible risk factors for hyperlipidemia.

Results. For all patients, the prevalence of hypercholesterolemia (>200 mg/dL) was 36.1% during the pretransplant period, 60.8% at month 3, 50.5% at month 6, and 38.1% at month 12 after renal transplantation. Total cholesterol and triglyceride levels significantly increased in both groups in the first year ($P = .001$ and $P = .02$, respectively). Three-month values for total cholesterol were higher in group 2 than group 1 ($P = .001$). No significant difference was observed between the groups with respect to total cholesterol and triglyceride levels ($P > .05$). In both groups, HDL, LDL, and VLDL levels did not change during the 12-month study ($P > .05$ for all).

Conclusions. Independent of hyperlipidemia risk factors, serum total cholesterol and triglyceride levels tended to increase during CyA and steroid therapy among patients undergoing renal transplantation. Combination with MMF or AZA showed no advantage over one another regarding their effects on the lipid profile.

CARDIOVASCULAR DISEASE is the main cause of death among renal transplant recipients. Optimal control of cardiovascular risk factors, especially hyperlipidemia, is important in the long-term management of these patients. Although hyperlipidemia after renal transplantation is multifactorial, immunosuppressive therapy plays an important role. Immunosuppressive therapy alters serum lipid levels starting from the first 3 to 6 months after renal transplantation. Calcineurin inhibitors, particularly cyclosporine (CyA), and corticosteroids increase serum cholesterol levels, an effect that is more prominent in the first year after renal transplantation when these agents are used at maximal dosages.[1–5] The effects of azathioprine (AZA) and mycophenolate mofetil (MMF) on lipid levels have been studied either as single drugs in animal models[6,7] or as combination therapies with corticosteroids, CyA, and tacrolimus/sirolimus.[8] There is some information about the effects of AZA versus MMF on lipid profile when combined with both corticosteroids and CyA. Also the additive effects of other hyperlipidemia risk factors on the lipid levels of renal transplant recipients receiving AZA or MMF combination therapies with corticosteroids and CyA were the purposes of this study.

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**Table 1. Multivariate Logistic Regression Analysis of Hyperlipidemia Risk Factors in Renal Transplant Recipients**

| Hyperlipidemia Risk Factors | OR | 95% CI | *P* |
|---|---|---|---|
| Age | 2.113 | 0.451–9.887 | >.05 |
| Gender | 0.459 | 0.121–1.735 | >.05 |
| Smoking | 0.053 | 0.004–1.574 | >.05 |
| Blood pressure ≥ 140/90 mm Hg | 2.318 | 1.006–5.342 | >.05 |
| Family history of hyperlipidemia/ atherosclerosis | 0.655 | 0.050–1.200 | >.05 |
| Type of immunosuppressive therapy (AZA or MMF combined with steroids and CyA) | 0.566 | 1.130–2.465 | >.05 |

## MATERIALS AND METHODS

We selected 97 renal transplant patients (71 men, 26 women; aged 34.7 ± 13.1 years; time after renal transplantation, 44.9 ± 12.9 months) prescribed either AZA-CyA-prednisolone (group 1, $n$ = 26; 19 men, 7 women; aged 36.1 ± 14.1 years; time after renal transplantation, 49.7 ± 11.0 months) or MMF-CyA-prednisolone (group 2, $n$ = 71; 52 men 19 women; aged 31.0 ± 9.2 years; time after renal transplantation, 31.7 ± 7.4 months) in the first year after renal transplantation. We excluded patients who had received higher-dose steroid therapy than our usual regimen, had been given antilipidemic drugs, antihypertensive drugs (beta-blockers or diuretics) or diabetic in the first year of renal transplantation. Possible risk factors for hyperlipidemia, which was defined as total cholesterol > 200 mg/dL) were evaluated for each patient: age, gender, smoking, blood pressure ≥140/90 mm Hg, or family history of hyperlipidemia/atherosclerosis.

In the first posttransplant year, patients received AZA (150 mg/d, MMF (2 g/d), prednisolone (10 mg/d), and CyA (adjusted to maintain whole blood trough levels between 200 and 300 ng/dL). Corticosteroids (prednisolone) was administered at 1 mg/kg for up to 5 to 10 days posttransplantation, then tapered to 20 mg/d at day 10. The patients received corticosteroids 20 mg/d till month 3 after transplantation. After month 3 the corticosteroid dose was 10 mg/d. All patients had total cholesterol levels 200 to 250 mg/dL and were prescribed a low (<300 mg) fat diet.

Blood specimens were drawn after an overnight fast. Serum lipid levels (total cholesterol, triglyceride, high-density lipoprotein [HDL], low-density lipoprotein [LDL], very low-density lipoprotein [VLDL]) were estimated at the initiation of and at 3-month intervals for 1 year retrospectively. Serum creatinine for each patient was recorded at 12 months. Serum levels of total cholesterol, triglyceride, HDL, LDL, VLDL were measured by direct quantitative colorimetric method (Human Gesellchaft für Biochemica und Diagnostica mbH, Germany). Serum creatinine levels were analyzed by standard biochemical methods.

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA). All numeric variables are expressed as mean values ± standard deviations (SD). Intergroup differences were compared using Student $t$ test and analysis of variance for repeated measures. Nominal parameters were analyzed using chi-square tests. Multivariate logistic regression analysis was performed to evaluate the risk factors for hyperlipidemia (including AZA and MMF effects). A $P$ value less than .05 was considered significant.

## RESULTS

The groups were comparable in terms of age, sex distribution, and pretransplant total cholesterol levels ($P > .05$ for all). There was no difference in terms of hyperlipidemia risk factors ($P > .05$ for all). Also multivariate logistic regression analysis revealed no difference in hyperlipidemia risk, when the age, gender, smoking, blood pressure ≥ 140/90 mm Hg, family history of hyperlipidemia/atherosclerosis, AZA and MMF combinations with corticosteroids or CyA were considered ($P < .05$ for each; Table 1). The 12-month serum creatinine levels were not different in group 1 (AZA-CyA-prednisolone) and group 2 (MMF-CyA-prednisolone; $P > .05$; Table 2). When all 97 renal transplant recipients were evaluated, the prevalence of hypercholesterolemia (>200 mg/dL) was 36.1% in the pretransplant period; 60.8% in month 3; 50.5% in month 6; and 38.1% in month 12 after renal transplantation. We observed a significant increase in total cholesterol and triglyceride levels during the first year after renal transplantation in group 1 (AZA-CyA-prednisolone) and group 2 (MMF-CyA-prednisolone) ($P = .001$ and $P = .02$, respectively). Third-month values for total cholesterol were significantly higher in group 2 than in group 1 ($P = .001$). However, no significant difference was observed between the groups with respect to total cholesterol and triglyceride levels at the 12 months ($P > .05$). In groups 1 and 2, HDL, LDL, VLDL levels did not change during the study period

**Table 2. Changes in Lipid Profile in Groups 1 and 2 During the First Year After Renal Transplantation**

| Lipid Profile | Group 1 ($n$ = 26) | Group 2 ($n$ = 71) | *P* |
|---|---|---|---|
| Total cholesterol (mg/dL) | | | .001 |
| Baseline* | 190.4 ± 50.4 | 197.1 ± 44.9 | |
| Month 3 | 208.6 ± 43.9 | 235.7 ± 22.4 | |
| Month 6 | 205.9 ± 49.3 | 229.5 ± 28.5 | |
| Month 12 | 207.2 ± 50.5 | 210.6 ± 32.7 | |
| Triglyceride (mg/dL) | | | .02 |
| Baseline* | 152.5 ± 71.3 | 155.9 ± 74.5 | |
| Month 3 | 164.2 ± 68.1 | 196.4 ± 83.6 | |
| Month 6 | 158.2 ± 78.1 | 150.8 ± 54.6 | |
| Month 12 | 170.5 ± 83.9 | 209.6 ± 66.4 | |
| HDL (mg/dL) | | | >.05 |
| Baseline* | 41.6 ± 11.1 | 43.5 ± 13.4 | |
| Month 3 | 51.3 ± 14.8 | 46.1 ± 11.4 | |
| Month 6 | 43.0 ± 14.8 | 62.0 ± 10.1 | |
| Month 12 | 42.4 ± 11.5 | 46.0 ± 11.8 | |
| LDL (mg/dL) | | | >.05 |
| Baseline* | 119.4 ± 42.4 | 123.3 ± 47.2 | |
| Month 3 | 115.0 ± 37.5 | 123.1 ± 45.0 | |
| Month 6 | 117.1 ± 37.2 | 126.5 ± 39.1 | |
| Month 12 | 120.6 ± 40.4 | 128.0 ± 19.3 | |
| VLDL (mg/dL) | | | >.05 |
| Baseline* | 38.2 ± 17.8 | 38.0 ± 17.5 | |
| Month 3 | 35.4 ± 17.0 | 26.6 ± 16.7 | |
| Month 6 | 26.6 ± 6.6 | 36.0 ± 10.0 | |
| Month 12 | 37.0 ± 11.6 | 37.1 ± 10.1 | |

*Baseline, pretransplant; group I, AZA-CyA-prednisolone; group II, MMF-CyA-prednisolone.

($P > .05$ for all). There were no significant differences between the groups in terms of HDL, LDL, or VLDL levels in the first year after transplantation ($P > .05$ for all).

## DISCUSSION

The prevalence of hyperlipidemia is high after transplantation. According to the guidelines of the National Cholesterol Education Program, about 60% of all transplant patients display cholesterol levels in the high-risk category (>6.3 mmol/L).[9] In our study, the 60.8% prevalence of patients with total cholesterol levels greater than 200 mg/dL in month 3 tended to decrease toward the month 12. However, the prevalence of patients with hypercholesterolemia was still higher at 12 months (38.1%) than pretransplantation (36.1%).

Corticosteroids and CyA are known to alter lipid profiles after renal transplantation. Corticosteroids increase both total cholesterol and LDL levels, but they also increase HDL and triglyceride levels.[10] VLDL synthesis from the liver is also increased by corticosteroids. On the other hand, CyA increases total cholesterol, triglyceride, LDL, and VLDL levels and decreases HDL levels.[11] The hyperlipidemic effect of CyA is dose-dependant and reversible.[11] One study reported a change in total cholesterol (0.5 to 1 mmol/L decrease) after CyA withdrawal and conversion to AZA or MMF.[11] HDL levels did not change after CyA to AZA conversion, but decreased after CyA to MMF conversion.[11]

The separate actions of corticosteroids and CyA are well known when they are used in combination, they potentiate each other's hyperlipidemic effects.[2,12] The atherogenetic potential of immunosuppressive agents has been reported as steroids > CyA > sirolimus > tacrolimus > AZA > MMF.[13] Although AZA and MMF are known to have minimal effects on lipid levels separately,[13,14] they may have distinct modes of action in combination with corticosteroids and CyA. The highest risk of developing hyperlipidemia is during the first year after renal transplantation. If there was a greater effect of MMF or AZA in combination with corticosteroid-CyA, it would be beneficial to know it. In the current study, we eliminated some risk factors for hyperlipidemia: higher-dose steroid therapy, antilipidemic drugs, antihypertensive drugs, or diabetes mellitus in the first year of renal transplantation. By multivariate regression, we analyzed the remaining hyperlipidemia risk factors: age, gender, smoking, blood pressure ≥ 140/90 mm Hg, family history of hyperlipidemia/atherosclerosis. As the groups were similar in terms of the above hyperlipidemia risk factors, we can clearly state that AZA and MMF had no effects on plasma lipid levels during combination therapy with corticosteroids and CyA. At month 3, total cholesterol levels peaked and then decreased in both groups which may be explained by the tapering of corticosteroid doses after the month 3.

In conclusion, independent of the hyperlipidemia risk factors, serum total cholesterol and triglyceride levels increased during corticosteroid-CyA therapy among patients undergoing renal transplantation. When corticosteroid-CyA were combined with MMF or AZA, there was no advantage of these drug regimens regarding their effects on lipid profiles.

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