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Impact of long-term immunosuppression with cyclosporin A on serum lipids in stable renal transplant recipients

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Abstract. To determine the impact of long-term immunosuppression on serum lipids in stable renal graft recipients we measured serum lipids and apolipoprotein B concentrations in 20 patients receiving therapy with cyclosporin (CsA) and low-dose prednisolone (CsA/P) and in 18 patients on therapy with azathioprine and maintenance steroids (Aza/P). The patients were matched for age, body mass index, primary renal disease and dose of prednisolone, but not for the duration in transplantation and serum creatinine concentration. Triglyceride concentrations were significantly higher in the CsA/P group than in Aza/P-treated patients: 2.62 ± 0.35 vs 1.62 ± 0.23 mmol/l ($P < 0.05$). Similarly, total cholesterol (C) levels were significantly more elevated in the CsA/P recipients than in the other group: 7.44 ± 0.32 vs 5.84 ± 0.25 ($P < 0.02$). CsA/P patients had higher serum levels of LDL-C (4.79 ± 0.20 vs 3.43 ± 0.19 mmol/l ($P < 0.001$) and apolipoprotein B concentrations (191 ± 13 vs 128 ± 9 mg/dl; $P < 0.001$). CsA/P and Aza/P recipients had similar concentrations of HDL-C (1.73 ± 0.13 vs 1.52 ± 0.09 mmol/l; NS). We conclude that in stable renal graft recipients with good transplant function long-term immunosuppression with CsA/P is associated with a more atherogenic lipid status than therapy with Aza/P.

Key words: Serum lipids, cyclosporin A – Cyclosporin A, serum lipids – Kidney transplantation, serum lipids

Persistent post-transplant hyperlipidaemia is common and may contribute to the high incidence of cardiovascular complications in renal graft recipients [8, 18, 20]. Cardiovascular disease has now become the leading cause of death after renal transplantation [30, 39]. Factors believed to be important in the pathogenesis of post-transplant hyperlipidaemia include: glucose intolerance, poor graft function, proteinuria, medication with beta-blockers or diuretics, and immunosuppressive therapy with glucocorticosteroids [4, 8, 15, 16, 20].

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In the last 5 years cyclosporin A (CsA) has become an integral part of the immunosuppressive regimen of most patients following renal, hepatic, cardiac, or bone marrow transplantation. Because of its excellent immunosuppressive properties, CsA has considerably improved graft survival with reports from major transplant centres of more than 90% 1-year graft function in renal transplants [32]. However, a number of serious side-effects associated with the use of CsA has raised fears about its long-term safety. In particular, CsA nephrotoxicity and the frequent occurrence of hypertension make it a less desirable drug to use in cardiac and renal graft recipients who are already at a high risk for cardiovascular complications [17, 26, 33].

Recently, there have been reports about an adverse effect of CsA on serum lipids in cardiac, hepatic, bone marrow or renal graft recipients [9, 11, 13, 28, 31, 38]. While several studies looked at the first post-transplant year when high doses of CsA and prednisolone (P) were used [11, 13, 31, 38], there were only two reports that extended their observation period to 2 years [31] or 3 years [38] after transplantation. Only one study took into account other known risk factors for post-transplant hyperlipidaemia [38].

The goal of the present study was, therefore, to examine the long-term effects of two different types of immunosuppressive regimens on serum lipids and apolipoprotein B in renal transplant recipients selected for excellent graft function and a low and comparable risk profile for hyperlipidaemia.

Material and methods

Between March 1 and June 30, 1988, patients attending our transplant clinic were screened for the following criteria: (1) time since transplantation > 2 years; (2) stable clinical course for at least 1 year prior to this study, (3) serum creatinine ≤ 150 µmol/l; (4) fasting blood sugar ≤ 5.8 mmol/l, (5) normal thyroid function tests, (6) absence of liver disease (GPT ≤ 35 IU/l and normal serum electrophoresis), and (7) proteinuria ≤ 0.5 g/day. Eighteen patients receiving chronic immunosuppressive therapy with Aza (mean ± SEM, 1.8 ± 0.1 mg/kg per day; range, 0.6–2.5) and low-dose P (mean ± SEM, 7.7 ± 0.1 mg/day; range, 7.5–10) and 20 patients under chronic

therapy with CsA (mean ± SEM, 4.5 ± 0.3 mg/kg per day; range, 2.5–7.6) and maintenance P (mean ± SEM, 7.1 ± 0.1 mg/day; range: 2.5–7.5) met the inclusion criteria. Mean (± SEM) CsA whole blood level (monoclonal RIA kit, Sandoz, Basel) was 164 ± 13 ng/ml (range 84–277). All patients adhered to a normal Western diet.

Laboratory methods

Early morning blood specimens were drawn after 12 h of fasting for all blood determinations. Autoanalysers were employed for measurements of serum creatinine, glucose and albumin. Cholesterol (C) and triglycerides (TG) were determined by routine enzymatic methods (Boehringer, Mannheim, FRG). Quantitative agarose electrophoresis with subsequent polyanion precipitation and densitometry was used for quantitation of lipoprotein classes according to Seidel et al. [34]. Apolipoprotein B was measured by ELISA techniques using monoclonal antibodies as previously described [2].

Statistical analysis

All results are expressed as mean ± SEM. For continuous variables, analysis of variance was used with serum creatinine as a covariate because of the small, but significantly higher serum creatinine in the CsA/P group. The multivariate approach (MANOVA) was taken because of the interdependency of serum lipids. Data for serum TG and VLDL-C were normalized using a logarithmic transformation. No other transformation of the data was used. Nominal data were analysed by the chi-squared test. All *P*-values were two-tailed, and levels less than 0.05 were considered to indicate significance. All analyses were done with the Statistical Package for the Social Sciences (SPSS).

Results

Table 1 shows major demographic data for the study groups. There was no significant difference in sex, age, body mass index, use of diuretic or β-blocker agents, serum levels of glucose and albumin, and degree of proteinuria. Serum-creatinine was higher in patients receiving CsA/P compared to patients receiving Aza/P medication (122 ± 21 vs 100 ± 21 μmol/l; $P < 0.01$).

Pertinent study results are presented in Table 2. TG concentrations were significantly higher in the CsA/P group than in Aza/P-treated patients: 2.62 ± 0.35 vs 1.62 ± 0.23 mmol/l ($P < 0.05$). Similarly, total C levels were also significantly higher in the CsA/P recipients than in patients receiving Aza/P therapy (7.44 ± 0.32 vs 5.84 ± 0.25 mmol/l; $P < 0.02$).

CsA/P patients had significantly higher concentrations of LDL-C than Aza/P recipients (4.79 ± 0.20 vs 3.43 ± 0.19 mmol/l; $P < 0.001$). There was no significant difference in HDL-C which was high normal in CsA/P- and Aza/P-treated patients (1.73 ± 0.13 vs 1.52 ± 0.09 mmol/l). The calculated LDL-C/HDL-C ratio was subsequently higher in the CsA/P-treated patients than in the other group (3.2 ± 0.02 vs 2.3 ± 0.3; $P < 0.05$). Apolipoprotein B concentrations were significantly increased in recipients of CsA therapy (191 ± 13 vs 128 ± 9 mg/dl; $P < 0.001$). Separate analysis for the group of patients without β-blockers and diuretics demonstrated that the differences in serum lipids were not due to this concomitant medication (Table 3).

When judged by the Lipid Research Clinics Prevalence Study hyperlipidaemia was much more common among CsA/P-treated patients [22]. Out of 20 CsA/P patients 18 (90%) had lipid values above the 90th percentile compared to 6 out of 18 (33%) in the Aza/P group. Of the CsA/P patients, six had an increased C, one an elevated TG, while 11 had both an elevated C and TG. In the Aza/P group two patients had an elevated C, two were hypertriglyceraemic and another two had increased C and TG levels.

Table 1. Patient characteristics. Values are means ± SE. BMI, Body mass index

	Aza/P ($n = 18$)	CsA/P ($n = 20$)	*P* value
Year of transplantation	1979–1981	1982–1985	
Male	8 (44%)	9 (45%)	NS
Age (years)	42.6 ± 3.3	41.5 ± 2.6	NS
BMI (kg/m^2)	24.2 ± 0.9	24.8 ± 0.8	NS
Primary renal disease:			
Chronic glomerulonephritis	6	9	
Chronic pyelonephritis	7	6	
Polycystic kidney disease	3	2	
Alport syndrome	1	1	
Renal dysplasia	1	1	
Renovascular disease		1	
Unknown			
Years since transplantation	7.7 ± 0.8	3.8 ± 1.3	0.0001
Diuretics	5 (23%)	5 (25%)	NS
Beta-blockers	5 (28%)	7 (35%)	NS
Prednisolone (mg/day)	7.1 ± 0.1	7.1 ± 0.3	NS
Serum creatinine (μmol/l)	100 ± 5	122 ± 5	0.01
Serum albumin (g/l)	44.5 ± 0.9	44.7 ± 1.0	NS
Serum glucose (mmol/l)	4.5 ± 0.2	4.7 ± 0.2	NS
Urinary protein (g/24 h)	0.18 ± 0.03	0.18 ± 0.03	NS

Table 2. Serum lipids, lipoproteins and apolipoprotein B. Values are means ± SE

	Aza/P ($n = 18$)	CsA/P ($n = 20$)	*P* value
TG (mmol/l)	1.62 ± 0.23	2.62 ± 0.35	0.05
C (mmol/l)	5.84 ± 0.25	7.44 ± 0.32	0.02
LDL-C (mmol/l)	3.43 ± 0.19	4.79 ± 0.20	0.001
HDL-C (mmol/l)	1.73 ± 0.13	1.52 ± 0.09	NS
VLDL-C (mmol/l)	0.72 ± 0.16	1.12 ± 0.24	NS
LDL-C/HDL-C	2.30 ± 0.30	3.20 ± 0.20	0.05
Apolipoprotein B (mg/dl)	128 ± 9	191 ± 13	0.001

Table 3. Serum lipids, lipoproteins and apolipoprotein B in patients without beta-blockers and diuretics. Values are means ± SE

	Aza/P ($n = 9$)	CsA/P ($n = 10$)	*P* value
TG (mmol/l)	1.23 ± 0.15	2.30 ± 0.35	0.02
C (mmol/l)	5.84 ± 0.30	6.94 ± 0.25	0.02
LDL-C (mmol/l)	3.18 ± 0.25	4.55 ± 0.19	0.002
HDL-C (mmol/l)	1.93 ± 0.16	1.53 ± 0.12	0.05
VLDL-C (mmol/l)	0.44 ± 0.08	0.89 ± 0.15	0.02
LDL-C/HDL-C	1.90 ± 0.26	3.10 ± 0.25	0.005
Apolipoprotein B (mg/dl)	121 ± 9	195 ± 8	0.001

Discussion

Our study demonstrates that compared to renal graft recipients receiving Aza/P therapy, hyperlipidaemia is common and quite severe in stable CsA/P-treated patients, even when other known risk factors for post-transplant hyperlipidaemia, such as impaired graft function, proteinuria, diabetes mellitus, liver disease or potentially lipogenic comedication, such as diuretics of β-blockers, are excluded.

It seems unlikely that, because of the longer time since transplantation, the Aza/P group carries a smaller risk for hyperlipidaemia. Most graft losses in the pre-CsA era occurred early after transplantation and were due to acute rejection or severe infection, factors not known to be linked with hyperlipidaemia [36]. In a recent retrospective study by Vathsala et al. there was only a minor reduction of total C levels in an Aza/P-population between 12 and 36 months post-transplant [38]. A similarly mild decrease in total C was found in their CsA/P group during the same period. Serum TG in the Aza/P patients tended to increase during the same period.

Our results are in agreement with a recent prospective study by Raine et al. who found an increase in total C and LDL-C in CsA/P-treated patients followed up for 2 years after transplantation [31]. In contrast, total C levels remained unchanged in patients receiving Aza/P therapy when compared to pretransplant concentrations. In a retrospective study, looking at a large cohort of patients, there was an equal incidence of hyperlipidaemia in CsA/P-treated renal transplant recipients vs Aza/P patients as late as 36 months after transplantation [38]. Studies looking at the effect of CsA on serum lipids sooner after transplantation also showed discrepant results. Hodel et al. found that frequency and degree of lipid disturbances were similar in 16 Aza/P-treated patients and in 17 renal graft recipients under CsA monotherapy [13]. In contrast, Harris et al. observed a significant fall in C, LDL-C, and TG concentrations when their patients were converted from CsA to Aza 3 months after renal transplantation leaving the P dosage unchanged [11]. It is difficult to explain these discrepancies, but they may be due to the different prednisolone doses used between the two groups and other differences such as degree of renal dysfunction and of proteinuria. In a double-blind, randomized, placebo-controlled trial in 36 men with amyotrophic lateral sclerosis, only in the cyclosporin group were there significant increases of 21% in total C, 31% in LDL-C and 12% in apolipoprotein B levels [1]. This study clearly shows that cyclosporin alone adversely affects lipid levels.

The mechanism of CsA-associated hyperlipidaemia is not yet known. CsA is a highly lipophilic drug which is largely bound to LDL and HDL in plasma [10, 35]. It has been speculated that binding of CsA to LDL may interfere with the normal removal of LDL from the circulation [31]. In a preliminary report, Derfler et al. found a decreased activity of hormone-sensitive lipoproteinlipase in hyperlipidaemic CsA-treated renal graft recipients [5]. Although this may explain the hypertriglyceridaemia in these patients, it probably does not account for their high levels of C and LDL-C. Mild glucose intolerance has been observed in some CsA-treated patients, but the effect seems to be too minor to explain the rather severe lipid disturbances associated with CsA therapy [27]. In another preliminary report, early post-transplant hyperlipidaemia correlated with the pretransplant lipid status [23]. Unfortunately, for our patients no data were available as to their serum lipids prior to transplantation.

In a recent retrospective study examining risk factors for accelerated atherosclerosis in 403 renal transplant recipients, multivariate analysis showed that known risk factors for the non-transplant population such as age, sex, diabetes, cigarette smoking, hypertension, and serum C were also independently associated with post-transplant vascular disease [18]. Epidemiological data in normal middle-aged men demonstrated that a serum cholesterol level of 7.4 mmol/l, as found in our CsA/P-treated renal graft recipients, resulted in a 6-year mortality rate for coronary heart disease at least 3.4 times higher than in the baseline risk group with a serum cholesterol of less than 4.7 mmol/l, or at least 1.6 times higher than in our Aza/P transplant patients with a serum cholesterol of 5.8 mmol/l [24]. Apolipoprotein B concentrations in our CsA/P-treated patients were in the range of middle-aged men with early onset of ischaemic heart disease [6].

In one study, the use of CsA in renal graft recipients for up to 5 years has been associated with a significant increase in cardiovascular mortality, when compared to treatment with Aza/P [3]. In view of the high incidence of hypertension in CsA-treated renal graft recipients, we feel that long-term use of this drug should be reconsidered in those patients who show a marked deterioration of their cardiovascular risk profile under CsA therapy [33].

Very little data are currently available on how to treat CsA-related hyperlipidaemia. Antihyperlipidaemic therapy by fibrates may be dangerous in the presence of renal insufficiency and, like the new class of HMG-CoA-reductase inhibitors, they have been associated with acute rhabdomyolysis in CsA-treated transplant recipients [7, 29, 37]. Use of cholestyramine may influence gastrointestinal uptake of CsA [21]. Conversion of CsA/P to Aza/P therapy may result in a significant improvement in serum lipids [11], but has also been associated with increased risk of acute rejection, which in itself may accelerate the atherosclerotic process [18, 25]. Changes in serum lipids after conversion to immunosuppressive triple drug therapy using a reduced dose of CsA have not been explored in controlled studies. However, in our own transplant clinic, a more than 40% reduction in CsA-dosage did not result in a significant fall in serum cholesterol levels in 17 long-term renal graft recipients (unpublished observation). Dietary fish oil supplementation is effective in lowering TG levels in hyperlipidaemic renal transplant recipients and may even reduce CsA-associated renal dysfunction [14, 19]. However, because of fish-oil-induced increases in LDL-C levels in non-transplant hypertriglyceraemic patients a cautious approach to the use of fish oil supplements in the transplant population seems to be warranted [12].

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