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Renal allograft immunosuppression

IV. Comparison of lipid and lipoprotein profiles in blood using double and triple immunosuppressive drug combinations

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Abstract. Serum lipid and lipoprotein profiles were performed in order to investigate lipid abnormalities 2 years post-transplantation in first cadaveric renal allograft recipients immunosuppressed with cyclosporin (CyA), azathioprine (Aza), and methylprednisolone (MP), or with any combination of two drugs. CyA was used in low doses. Total serum cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, HDL2 cholesterol, HDL3 cholesterol, apolipoprotein A1, and apolipoprotein B were determined in 88 prospectively randomized patients with functioning grafts. When considering only the patients who remained on the original randomized treatment, there were no significant differences between the four groups in any of the measured variables. Mean total cholesterol was highest in the group receiving Aza and MP (6.8 mmol/l) and lowest in the group receiving triple therapy (5.8 mmol/l; NS). Mean triglyceride level was highest in the group receiving Aza and MP (2.3 mmol/l) versus 1.8–2.2 mmol/l in the groups receiving triple therapy, Aza + CyA, and CyA + MP. For all patients mean triglyceride level was highest in the group receiving Aza and MP (2.7 mmol/l) and lowest in the group receiving triple therapy (1.7 mmol/l; $P < 0.05$). Mean HDL cholesterol ranged from 1.5 to 1.6 mmol/l in all groups. Neither CyA concentration nor CyA or MP dose correlated with cholesterol or triglyceride concentration. However, the average MP dose was twice as high in the group receiving Aza and MP as in the other two groups employing steroids. Serum cholesterol and triglyceride concentrations were related to body mass index ($r = 0.28$, $P = 0.045$ and $r = 0.30$, $P = 0.029$, respectively). Hyperlipidemia was most common in the group receiving Aza and MP. The frequency of hypercholesterolemia (serum cholesterol level > 6.5 mmol/l) was 18%, 45%, 60%, and 35% for the patients continuing with the originally randomized treatment in the groups receiving triple therapy, Aza + CyA, Aza + MP, and CyA + MP, respectively. In a normal Finnish reference population, 35% of all males and 31% of all females have a serum cholesterol level above 6.5 mmol/l. Thus, only patients receiving Aza and MP had a clearly higher frequency of hypercholesterolemia than that found in a normal population. Taken together, this study shows no lipid abnormalities associated with the use of low-dose CyA for 2 years after transplantation. Hyperlipidemia occurring after transplantation is probably multifactorial and more associated with other risk factors than with the immunosuppressive therapy.

Key words: Immunosuppression, in kidney transplantation – Lipid profiles, immunosuppression, kidney – Double, triple immunosuppression, lipid profiles

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Atherosclerosis is one of the leading causes of mortality in renal transplant recipients according to the European Dialysis and Transplant Association Registry [31]. Persistent lipid abnormalities have been reported after renal transplantation even in patients with stable graft function [18, 21, 23]. Hypertriglyceridemia is the most common lipid abnormality in patients with chronic renal failure. After transplantation it becomes less prominent and hypercholesterolemia predominates [3, 18, 21]. The risk for coronary heart disease is influenced by several serum lipid abnormalities. A correlation between elevated serum cholesterol and coronary heart disease is well established [20], while the role of elevated serum triglycerides as an independent risk factor remains controversial [14]. On the other hand, serum HDL cholesterol concentrations [13], as well as HDL/total cholesterol and HDL/LDL cholesterol ratios [2], are inversely correlated with the risk for coronary heart disease.

The mechanism responsible for hyperlipidemia after transplantation is probably multifactorial. The role of immunosuppression is uncertain. Before the cyclosporin (CyA) era, many studies reported an association between corticosteroid dose and serum cholesterol in transplant patients [10, 12, 18]. Once the use of CyA had become widespread, hyperlipidemia associated with this drug was reported after renal transplantation [16, 32, 38] and after heart transplantation [22], as well as in CyA-treated patients with psoriasis [7] and amyotrophic lateral sclerosis [1].

CyA has improved graft survival of kidney transplants. The use of CyA, however, has been complicated by several significant side effects. Many of them, such as nephrotoxicity, are dose-dependent. As a result, protocols such as triple therapy, which allow a lower dose of CyA to be used, have been devised. Most earlier reports on the association of CyA with hyperlipidemia involved patients using high-dose CyA or dealt with short-term effects of CyA.

We have conducted a prospective, randomized trial to compare the long-term effects of triple immunosuppressive therapy with CyA, azathioprine (Aza), and methylprednisolone (MP) with different double drug regimens. One object of this trial was to investigate lipid abnormalities 2 years after renal transplantation in patients with functioning grafts, to correlate them to the type of immunosuppression used, and to clarify which one or more of the immunosuppressive drugs might be responsible for the abnormalities. We were especially interested in evaluating the possible effects of low-dose CyA on lipid metabolism during long-term therapy.

Patients and methods

Patients

Between January 1986 and May 1987, 128 adult consecutive recipients of a first cadaveric renal allograft entered a randomized, prospective trial. All patients had triple therapy for the first 10 weeks. After 10 weeks, according to randomization, one group continued with triple therapy, i.e., low-dose CyA, low-dose MP, and azathioprine, while in the remaining three groups, one of the three immunosuppressive drugs was discontinued. There were, thus, four final immunosuppressive treatment groups: one with triple therapy (group A), one with Aza and CyA (group B), one with Aza and MP (group C), and one with CyA and MP (group D). Randomization resulted in four similar groups [19].

Two years after transplantation, all patients with a functioning graft were readmitted to our hospital for a 3-day control. The lipid and lipoprotein profiles of patients were measured. Originally, each group consisted of 32 patients, 24 (75%), 25 (78%), 27 (84%), and 26 (81%) of whom had a functioning graft after 2 years in groups A, B, C, and D, respectively. There were, however, many deviations from the original drug protocol, mainly due to Aza intolerance and reversible rejections during the conversion period [19]. This resulted in drop-outs. Withdrawal of CyA or MP at 10 weeks caused some rejections, leading to readministration of triple therapy or CyA in these patients. These patients were considered drop-outs in the study even though they retained their transplants. After 2 years there were 14, 12, 12, and 23 patients who continued with their originally randomized treatment in groups A, B, C, and D, respectively. Blood lipid determinations, following informed consent, were available in 21, 22, 23, and 22 patients in groups A, B, C, and D, respectively, of whom 11, 11, 10, and 20 patients were on the originally randomized treatment.

This study includes all of the patients who had a functioning graft 2 years after transplantation but focuses especially on those patients who continued with the original randomized treatment protocol for up to 2 years.

Drug dosages

All patients received triple therapy during the first 10 weeks. The details of the initial immunosuppressive regimen and the withdrawal protocol at 10 weeks have been reported earlier [19]. In brief, CyA was started before the operation. The initial dose was 10 mg/kg per day and this was later adjusted according to CyA trough levels in whole blood. Aza was initiated at a dose of 2 mg/kg per day, decreased to 1 mg/kg per day on day 14, and adjusted later according to white blood cell count. MP was initiated at 1 mg/kg per day, with rapidly decreasing doses targeting to 0.25 mg/kg per day on day 10. Three months after transplantation, the maintenance level of CyA was between 60 and 120 ng/ml using the monoclonal parent molecule-specific radioimmunoassay method. Before conversion the mean CyA dose was 6.3 ± 2.4 (SD) mg/kg per day; at 1 year it was

Table 1. Clinical findings of patients following original treatment at 2 years. Values represent mean ± SD

	Treatment group				Significance[a]
	A Triple	B Aza + CyA	C Aza + MP	D CyA + MP	*P*
Number of patients	14	12	12	23	
Age	47 ± 10	53 ± 9	46 ± 12	45 ± 14	NS
Body mass index (weight/height[a])	24 ± 3	26 ± 4	26 ± 4	24 ± 3	NS
Rejection episodes per patient	0.4	0.3	0.3	0.4	NS
Type 1 diabetes mellitus	14%	25%	33%	35%	NS
Graft function					
Serum creatinine (μmol/l)	128 ± 51	126 ± 47	137 ± 50	144 ± 69	NS
Creatinine clearance (ml/min)	60 ± 17	60 ± 23	50 ± 15	62 ± 24	NS
Urea (mmol/l)	8.3 ± 4.2	9.2 ± 4.4	8.7 ± 3.6	9.5 ± 5.9	NS
Immunosuppressive treatment at 2 years					
Azathioprine dose (mg/kg per day)	0.9 ± 0.3	1.2 ± 0.5	1.8 ± 0.6	–	0.001
Methylprednisolone dose (mg/kg per day)	0.05 ± 0.02	–	0.10 ± 0.05	0.06 ± 0.03	0.001
CyA dose (mg/kg per day)	3.1 ± 1.4	3.3 ± 1.9	–	3.2 ± 0.9	NS
Drug concentration					
CyA concentration (ng/ml)[b]	85 ± 52	112 ± 46	–	104 ± 36	NS
Other treatment (Number of patients using)					
Loop diuretics	3	5	3	9	NS
Calcium antagonist	4	2	5	8	NS
Beta blockers	8	7	7	14	NS

[a] Analysis of variance and chi-square

[b] Whole blood concentration with monoclonal RIA

Table 2. Lipid and lipoprotein values of different immunosuppressive groups (including the drop-outs). Values represent mean ± SD

	Treatment group				Controls[a]	
	A Triple ($n = 21$)	B Aza + CyA ($n = 22$)	C Aza + MP ($n = 23$)	D CyA + MP ($n = 22$)	Male	Female
Serum cholesterol (mmol/l)	5.9 ± 1.2	6.2 ± 2.0	6.6 ± 1.3	6.2 ± 1.7	6.1 ± 1.3	6.0 ± 1.3
Serum HDL (mmol/l)	1.6 ± 0.5	1.5 ± 0.4	1.5 ± 0.5	1.6 ± 0.5	1.3 ± 0.3	1.6 ± 0.4
Serum HDL2 (mmol/l)	0.50 ± 0.28	0.47 ± 0.29	0.44 ± 0.27	0.49 ± 0.22		
Serum HDL3 (mmol/l)	1.10 ± 0.37	1.03 ± 0.28	1.01 ± 0.36	1.10 ± 0.31		
Serum LDL (mmol/l)	3.7 ± 0.8	4.0 ± 1.8	4.3 ± 1.2	4.0 ± 1.3		
Serum triglycerides (mmol/l)	1.7 ± 1.5	2.1 ± 1.0	2.7 ± 1.5*	2.2 ± 2.1		
Apo A1 (mg/100 ml)	121 ± 24	112 ± 20	122 ± 21	122 ± 24		
Apo B (mg/100 ml)	102 ± 37	113 ± 40	123 ± 40	110 ± 39		
HDL/KOL ratio	0.28 ± 0.09	0.25 ± 0.08	0.23 ± 0.08	0.27 ± 0.09		
HDL/LDL ratio	0.46 ± 0.22	0.44 ± 0.22	0.37 ± 0.18	0.44 ± 0.20		

* $P < 0.05$ for group C versus group A; all other differences are nonsignificant (ANOVA, Fisher PLSD)
[a] Population mean in men and women aged 25–64 years

4.0 ± 2.0 (SD) mg/kg per day. The mean actual doses of CyA, Aza, and MP for the patients on the originally randomized treatment at 2 years are presented in Table 1.

Episodes of acute rejection were treated with oral MP, 3 mg/kg per day for 5 days, or with antithymocyte globulin (ATG, Fresenius, Bad Homburg, FRG), 3 mg/kg per day, for 3–8 days until the fine needle aspiration cytology became negative.

Methods

Blood samples were taken 2 years after transplantation and were obtained after overnight fasting. Total serum cholesterol, high-density lipoprotein (HDL) cholesterol, HDL 2 cholesterol, HDL 3 cholesterol, low-density lipoprotein (LDL) cholesterol, serum triglyceride, apolipoprotein A1 (Apo AI), and apolipoprotein B (Apo B) were assessed as follows. Cholesterol and triglyceride concentrations in whole serum and in lipoprotein fractions were determined by enzymatic methods (Bochringer Mannheim, FRG). Serum HDL cholesterol was determined after precipitation of Apo B containing lipoproteins by heparin-manganese chloride, followed by separation of HDL 2 and HDL 3 by addition of dextran sulfate [11]. LDL cholesterol was calculated using the Friedewald formula [9], except in markedly hypertriglyceridemic (triglycerides > 4 mmol/l) patients. In such patients lipoprotein fractions were separated from sera by a sequential ultracentrifugation technique [17], using Beckman L-70 ultracentrifuge and Type 50.3 Ti Beckman rotor (Beckman Instruments, Palo Alto, Calif.). The concentrations of Apo AI and Apo B were measured using commercial immunoassay kits (Orion Diagnostica Espoo, Finland).

Definition of lipid abnormalities

Hyperlipidemia was defined in this study according to the recommendations of the European Atherosclerosis Society (EAS) [8]. Patients with cholesterol levels above 6.5 mmol/l or with triglyceride levels above 2.3 mmol/l were considered hyperlipidemic. HDL cholesterol levels below 0.9 mmol/l were considered subnormal [8], and the normal lower limit for HDL/total cholesterol ratio was defined as 0.2.

Statistical analysis

Differences between the groups were evaluated with an analysis of variance, with Student's *t*-test, the chi-square test, and the nonparametric Mann-Whitney test. Data for serum triglyceride, Apo B, and LDL were normalized using logarithmic transformations where indicated in the text. Other lipid data were normally distributed. Differences were considered significant at the level of $P < 0.05$. Correlation coefficients *(r)* were calculated via linear regression analysis.

Results

Characteristics of patients

The backgrounds of the four groups were similar and have been presented in detail previously [19]. All patients had a first cadaveric graft. Clinical data for patients following the original treatment schedule at 2 years is presented in Table 1. There were no significant differences between the four study groups with regard to sex ratio, age, body mass index, or rejection episodes per patient. Type I diabetes frequency varied between 14% and 35%. Approximately equal proportions of patients in different groups were using calcium antagonists, loop diuretics, and beta blockers.

Graft function did not differ significantly between the four groups and graft function was stable in patients following the original treatment schedule (Table 1).

At 2 years the average CyA dose and concentration were equal in the groups using CyA. The mean daily MP

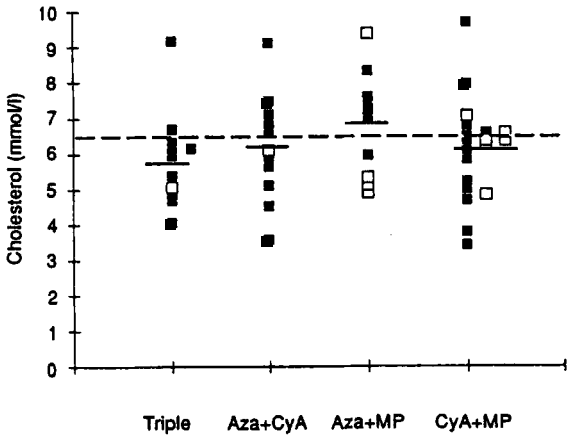

Fig. 1. *Cholesterol* values of each patient in a group following the original randomized treatment. *Solid lines* indicate mean cholesterol values of each group. *Broken lines* indicate the level of markedly increased coronary heart risk according to the European Atherosclerosis Society. □ Patients with diabetes; ■ patients without diabetes

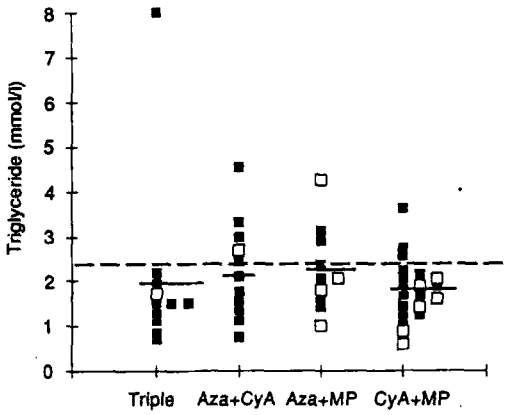

Fig. 2. *Triglyceride* values of each patient in a group following the original randomized treatment. *Solid lines* indicate mean triglyceride values of each group. *Broken lines* indicate the level of hypertriglyceridemia according to the European Atherosclerosis Society

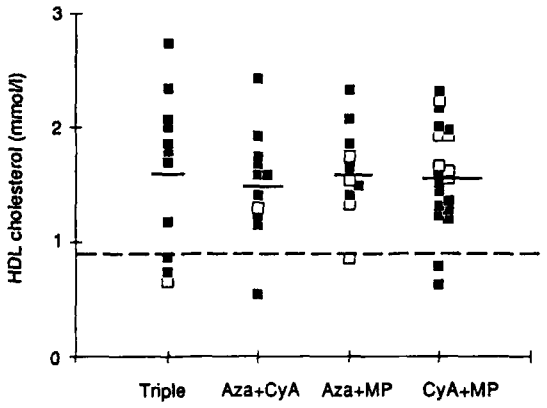

Fig. 3. *HDL cholesterol* values of each patient in a group following the original randomized treatment. *Solid lines* indicate mean cholesterol values of each group. *Broken lines* indicate the lowest level of HDL recommended by the European Atherosclerosis Society

dose was twice as high in group C, using Aza and MP, as in the other groups using MP ($P = 0.001$).

Lipid and lipoprotein values of all patients in different treatment groups

Lipid and lipoprotein mean values are presented in Table 2. Serum triglyceride in the Aza and MP group (2.7 ± 1.5 mmol/l) differed significantly from that in the triple therapy group (1.7 ± 1.5 mmol/l; $P < 0.05$). There were no other significant differences between the four groups in any of the measured variables.

Lipids in patients on the originally randomized treatment regimen

There were no significant differences in serum triglyceride, total cholesterol, HDL, HDL2, HDL3, and LDL cholesterol, or in Apo AI or B concentrations between the four groups of patients. Mean total cholesterol was highest (6.8 mmol/l) in group C (Aza + MP) and lowest (5.8 mmol/l) in group A (triple therapy; NS). This difference was mainly due to a higher LDL cholesterol level (4.5 mmol/l versus 3.5 mmol/l, group C versus group A). HDL cholesterol and its subfractions HDL2 (range of mean 0.44–0.50 mmol/l) and HDL3 (range of mean 1.06–1.18 mmol/l) were similar in each group.

The mean cholesterol value in group C (Aza + MP) was above 6.5 mmol/l, but in all other groups the mean cholesterol fell slightly below this level (Fig. 1). Three of four patients with diabetes in this group had the lowest cholesterol values. The mean triglyceride value in group C (Aza + MP) was 2.27 mmol/l, with lower levels in all other groups (Fig. 2). The median triglyceride values were 1.5, 2.1, 2.1, and 1.8 in groups A, B, C, and D, respectively.

In patients following the original schedule, the intervention level of 6.5 mmol/l (EAS) for cholesterol was exceeded by 18%, 45%, 60%, and 35% of the patients in groups A, B, C, and D, respectively (Table 3). In the Finnish population, 35% of all males and 31% of all females have a cholesterol level above 6.5 mmol/l [35]. A few patients in each group had subnormal HDL cholesterol (< 0.9 mmol/l) [8] as well as subnormal HDL/total cholesterol ratios (< 0.2). However, the mean HDL cholesterol concentrations (Fig. 3) and HDL/total cholesterol ratios (Fig. 4) were clearly above the recommended lower limit in every group.

Clinical correlates to cholesterol and triglyceride levels

Serum cholesterol was related to body mass index ($r = 0.28$, $P = 0.045$) and age ($r = 0.32$, $P = 0.0212$). Triglyceride (after logarithmic transformation) correlated with body mass index ($r = 0.36$, $P = 0.0005$) but not with age. CyA concentration, CyA dose, and steroid dose did not correlate with cholesterol or with triglyceride concentration. Serum creatinine level correlated with triglyceride level ($r = 0.32$, $P = 0.0021$) and negatively with HDL-cholesterol ($r = 0.257$, $P = 0.0169$) in all patients; however, there were no correlations when looking only at the patients following the original treatment schedule (these patients had stable and good graft function).

Significant relationships existed between total cholesterol and Apo B ($r = 0.74$, $P = 0.0001$) and between triglyceride (log) and Apo B ($r = 0.79$, $P = 0.0001$). HDL was correlated to Apo A1 ($r = 0.63$, $P = 0.0001$).

Cholesterol levels for all females ($n = 42$) were higher (6.6 ± 1.7 mmol/l) than for males ($n = 46$; 5.9 ± 1.4

Table 3. At 2 years, percentage of patients over critical lipid values for patients on originally randomized treatment

	Treatment group			
	A Triple (%)	B Aza + CyA (%)	C Aza + MP (%)	D CyA + MP (%)
S-cholesterol > 6.5 mmol/l	18	45	60*	35
S-triglyceride > 2.3 mmol/l	9	45	40	15
HDL cholesterol < 0.9 mmol/l	27	9	10	10
HDL/s-cholesterol < 0.2	36	18	30	20
LDL cholesterol > 4 mmol/l	27	55	60	60
Hyperlipidemia[a]	18	54	60*	45

* $P < 0.05$ for triple therapy versus group C; all other differences are nonsignificant

[a] Total cholesterol > 6.5 mmol/l and/or triglyceride > 2.3 mmol/l (according to European Atherosclerosis Society)

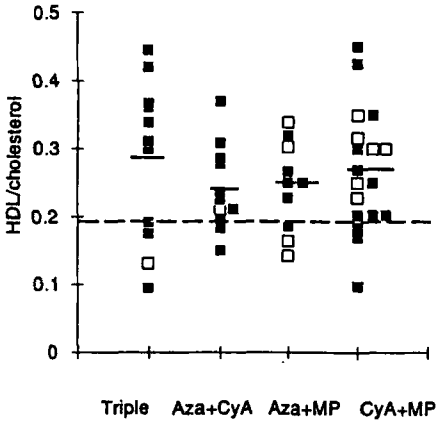

Fig. 4. *HDL cholesterol and total cholesterol ratio* of each patient in a group following the original randomized treatment. *Solid lines* indicate mean ratio of each group. *Broken lines* indicate the lowest level of ratio recommended by the European Atherosclerosis Society

mmol/l). The average HDL cholesterol level was also higher for women than for men (NS).

Discussion

Our observations do not confirm the earlier suggestions that CyA adversely influences serum lipid levels. The group with conventional treatment (Aza and MP), without CyA, had the highest cholesterol and triglyceride values and the highest percentage of hyperlipidemic patients. In our study, 2 years after transplantation, CyA administration was not associated with either hypercholesterolemia or hypertriglyceridemia. This finding is in agreement with a recent study that reported no differences in the incidence of hypertriglyceridemia or hypercholesterolemia in CyA-treated patients compared to patients with conventional treatment 3 years after transplantation [30]. The earlier studies, in which the use of CyA was correlated to high lipid levels, involved either high CyA doses [16, 33] or changes in lipid metabolism that were reported after short-term use of CyA [1, 16, 27, 32]. In such studies, CyA was used in nephrotoxic doses, as indicated by a marked reduction in creatinine after discontinuation of CyA [16, 32, 38]. In our study, low doses of CyA were used in all three of the regimens containing CyA. At 2 years the mean CyA dose was only 3 mg/kg per day for these patients.

On the other hand, there is a study with long-term follow-up showing no correlation between cholesterol and CyA but rather a correlation between cholesterol and steroid dose [37]. Some conversion studies have also suggested that serum lipids correlated with the doses of steroids, rather than with doses of CyA, when patients originally treated with CyA and steroids were converted to CyA and Aza [24] or to CyA monotherapy [6]. After complete steroid withdrawal, both cholesterol and triglyceride levels decreased. Moreover, significant reductions in cholesterol and triglyceride concentrations were recently demonstrated after steroid withdrawal in triple therapy [25] and in conventional therapy [15] of living related donor transplant recipients. Strong correlations between steroid doses and elevated cholesterol and/or triglyceride levels have also been reported in recipients of kidney transplants in several [18, 4, 29], but not all, studies [5] during conventional treatment. Furthermore, it has been suggested that LDL cholesterol is increased in transplant patients if a threshold dose of 12.5 mg prednisolone per day is exceeded [26]. Our steroid doses were markedly lower at 2 years. It is, therefore, not unexpected that we did not observe a statistically significant correlation between steroid dose and lipid levels in linear regression analysis, despite the fact that the group with Aza and MP had a mean dose of MP that was twice as high as that of the two other groups using MP. This group also had the highest mean cholesterol (6.8 mmol/l versus 5.8–6.2 mmol/l in the other groups).

The number of patients with hypercholesterolemia or hypertriglyceridemia was considerable in every group according to the criteria set forth by the EAS [8] (Table 3). The risk for fatal coronary heart disease is markedly increased when total serum cholesterol exceeds 6.5 mmol/l [28]. It is worthwhile noting that the mean serum cholesterol level of the population in Finland is very high in relation to other countries. In 1987 the population mean was 6.1 ± 1.3 mmol/l in men and 6.0 ± 1.3 mmol/l in women aged 25–64 years. Thirty-five percent of all males and 31% of all females had serum cholesterol levels above 6.5 mmol/l [35]. In our study, the groups using CyA had cholesterol values exceeding the 6.5 mmol/l risk level in proportions varying from 18% to 45% for patients following the original treatment schedule. In this respect, the percentages did not markedly differ from those in the overall population.

Unfortunately, the number of patients who continued on the originally randomized schedule during the whole 2-year period was limited. Yet, the characteristics of patients in the four groups were similar and their graft function was stable. The greater number of diabetic patients in group C was not the reason for elevated lipid levels since most of the diabetics had lower than average lipid levels (Figs. 1, 2).

Changes in lipid levels in our patients were similar to those reported for patients on conventional immunosuppressive therapy. Hypercholesterolemia was the most common lipid abnormality, irrespective of treatment regimen, while some patients had hypertriglyceridemia, too. The mean HDL cholesterol levels were relatively high. HDL cholesterol is known to be reduced in chronic renal failure and has been reported to become normalized after successful renal transplantation [34, 36]. Mean HDL cholesterol values were remarkably high in every study group, varying from 1.5 to 1.6 mmol/l. The mean HDL cholesterol value in Finland for males in a normal population is 1.3 ± 0.3 mmol/l and for females 1.6 ± 0.4 mmol/l. As in normal subjects, age, sex, and body mass index influenced cholesterol values in transplant patients. HDL cholesterol was higher in females than in males, again as in a normal population [35].

One may conclude that low-dose CyA does not seem to influence lipid levels during long-term use, in contrast to the reported changes after short-term use of high doses of CyA. Lipid disorders after transplantation are probably multifactorial, and the immunosuppressive treatment regimens used nowadays, with the possible exception of steroids, contribute little to this type of hyperlipidemia.

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