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Lipid abnormalities in stable liver transplant recipients – effects of cyclosporin, tacrolimus, and steroids

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Abstract Dyslipidemia is common after liver transplantation, but the underlying mechanisms are largely unknown. We studied the lipid profile of 27 liver transplant recipients randomized to receive either cyclosporin (CyA, $n = 14$) or tacrolimus ($n = 13$) and compared them with 20 healthy, matched controls. Before transplantation, patients presented low total and low-density lipoprotein (LDL) cholesterol (as compared to controls) that increased shortly, i.e., 3 months, after transplantation. Eighteen months post-transplantation, total and LDL cholesterol levels decreased to pretransplant values but tended to remain higher in CyA-treated patients. However, at that time, prednisone treatment was more prevalent among CyA-treated than tacrolimus-treated patients and fully accounted for the difference in cholesterol levels. Indeed, regardless of therapy, patients not receiving prednisone exhibited lower cholesterol levels than prednisone-treated patients and controls. We conclude that prednisone therapy, rather than CyA or tacrolimus immunosuppression, seems to be the major determinant of increased cholesterol levels.

Key words Lipoproteins, liver transplantation, immunosuppression · Liver transplantation, lipoproteins, immunosuppression · Immunosuppression, liver transplantation, lipoproteins

Introduction

Hyperlipidemia has been described as a complication in long-term survivors of liver transplantation and is associated with impaired liver [17, 18] and renal function, overweight, and hyperglycemia [17]. It has been suggested that immunosuppressive drugs may play a role in post-transplant dyslipidemia. In fact, some reports have shown that cyclosporin (CyA) is associated with increased cholesterol levels in liver transplant recipients more frequently than tacrolimus [1, 6, 9, 11, 15, 26]. Corticosteroids have also been implicated in the hyperlipidemia of these patients, and an improvement in the lipid profile has been described after corticosteroid withdrawal [2, 19, 23, 27]. Interestingly, the corticosteroid dose (daily and cumulative) in liver transplant recipients on CyA therapy is generally higher than in patients given tacrolimus. This fact may underlie the increased incidence of post-transplant hyperlipidemia described in CyA-treated patients.

The aims of this study were: (1) to evaluate the evolution of the lipid profile in short and long-term stable liv-

Table 1 Characteristics of liver transplanted patients randomized to cyclosporine or tacrolimus

	Cyclosporin $n = 14$	Tacrolimus $n = 13$	P
Age (years)	47.5 ± 8.9	42.3 ± 8.9	NS
Male (%)	10 (71)	9 (69)	NS
Body mass index (kg/m^2)	26.4 ± 2.4	25.1 ± 3.0	NS
Indications for transplantation:			NS
Alcoholic cirrhosis	4	5	
Postnecrotic cirrhosis	7	5	
Cryptogenic cirrhosis	1	1	
Primary biliary cirrhosis	1	1	
Hemangioendothelioma	0	1	
Idiopathic adult ductopenia	1	0	

Values are means ± SD or numbers of cases (%)
NS: not significant

er transplant recipients, (2) to compare the lipid abnormalities between patients receiving CyA and those receiving tacrolimus as immunosuppression therapy, and (3) to evaluate the potential role of corticosteroids in these alterations.

Patients and methods

Seventy-eight patients with end-stage liver disease underwent liver tranplantation between November 1993 and June 1995 in University Hospital "12 de Octubre" in Madrid, Spain. Twenty-seven of them (19 men and 8 women), in whom basal lipid profile (up to 3 months before tranplantation) was available, were randomized to receive either CyA ($n = 14$) or tacrolimus ($n = 13$) immunosuppression after liver transplantation. All patients were also treated with corticosteroids for at least 3 months after transplantation. Steroid treatment was as follows: methyl-prednisolone, 1000 mg i.v., was given intraoperatively; it was tapered from 2 to 0.3 mg/kg per day over a period of 8 days, and the patients were then switched to prednisone. This was gradually reduced to 0.1–0.2 mg/kg per day by 6 months post-transplantation. Prednisone withdrawal was done according to the clinical evolution. Patients on CyA therapy also received azathioprine during the first 3 months post-transplantation. The CyA dose was adjusted to blood levels between 100–250 ng/ml, as determined by radioimmunoassay (Instar, Stillwater, Minn., USA). Tacrolimus was adjusted to blood levels between 5–10 ng/ml, as determined by enzyme immunoassay (Abbot, Chicago, Ill., USA). All episodes of acute rejection were treated with pulse corticosteroids (3 g methylprednisolone in 3 days), followed by a rapid tapering (within 4 days) toward the previous prednisone maintenance dose. Corticoresistant cases were treated with the monoclonal antibody OKT3.

Parameters evaluated in all patients were: age at transplantation, sex, presence of diabetes, arterial hypertension, number of acute rejection episodes, body mass index (BMI: kg/m^2), serum creatinine and glucose (mg/dl), prednisone dose (average in mg/day and cumulative in g), and fasting lipid profile. Lipid profile included: total serum cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, total serum triglycerides, VLDL triglycerides, and lipoprotein(a) [Lp(a)]. Lipoproteins were isolated by an ultracentrifugation method [5]. Cholesterol and triglycerides in the different fractions were assayed enzymatically (Boehringer Mannheim, Mannheim, Germany). Lp(a) was measured by nephelometry (Behringwerke, Marburg, Germany).

Pretransplant lipid profile was determined within the 3 months preceding transplantation. The first post-transplant lipid profile was obtained 3 months after transplantation (early) and the second one between 1.5 and 2.5 years (mean 22.4 ± 3.7 months) post-transplantation (late). Graft function was stable in all cases except for one tacrolimus-treated patient, who suffered a systemic vasculitis 16 months after transplantation and was excluded from long-term evaluation.

The control group consisted of 20 healthy volunteers who were matched for age (45.3 ± 9.5 years) and gender (70% males). None was receiving any medication known to alter lipid parameters. Their BMI (24.7 ± 2.8 kg/m^2) did not differ from that of patients at either short or long-term evaluation.

All statistical calculations were performed with the SAS software package (SAS 6.12, 1989–196, SAS Institute, Caryn, N.J., USA). The comparison of means for parametric variables was performed with Student's t-test or a one-way ANOVA for repeated measures, followed by the Student-Newman-Keuls test, when appropriate. Nonparametric variables were compared with the Wilcoxon test or a one-way ANOVA on ranks for repeated measures, followed by the Dunn test, as appropriate. Qualitative variables were compared with the chi-square and the Fisher exact tests. The association between continuous variables was assessed by linear regression. The differences were considered significant when P was less than 0.05.

Results

Clinical characteristics were similar in patients assigned to CyA and to tacrolimus immunosuppression (Table 1). Before liver transplantation, patients had reduced total and LDL cholesterol compared to controls (total cholesterol 160 ± 49 mg/dl vs 190 ± 33; $P = 0.015$; LDL cholesterol 97 ± 44 vs 125 ± 32; $P = 0.020$, Fig. 1). Basal lipid profiles were similar for the CyA and tacrolimus groups (Table 2).

In the early period after liver transplantation (3 months), when all patients were receiving prednisone, there was an increase in total, LDL, and VLDL cholesterol and VLDL triglyceride levels in the entire group of transplant recipients (Fig. 1) that approached that of controls. In contrast, HDL cholesterol and total triglyceride levels did not change significantly (Fig. 1). At this time, there were no significant differences be-

Table 2 Lipid profile in patients

	Cyclosporin $n = 14$	Tacrolimus $n = 13$[a]	P
Total cholesterol:			
Pre	154 ± 50	164 ± 46	0.57
Early	218 ± 47	195 ± 65	0.32
Late	195 ± 53	161 ± 34	*0.07*
LDL cholesterol:			
Pre	89 ± 45	106 ± 41	0.31
Early	152 ± 46	121 ± 61	0.18
Late	121 ± 42	92 ± 33	*0.08*
HDL cholesterol:			
Pre	53 ± 20	51 ± 21	0.78
Early	55 ± 11	59 ± 12	0.41
Late	54 ± 14	53 ± 18	0.90
VLDL cholesterol:			
Pre	9 ± 5	4 ± 3	*0.02*
Early	15 ± 10	15 ± 13	0.63
Late	20 ± 19	16 ± 13	0.58
Triglycerides:			
Pre	101 ± 51	76 ± 53	0.22
Early	116 ± 55	94 ± 57	0.35
Late	127 ± 87	97 ± 55	0.32
VLDL Triglycerides:			
Pre	19 ± 13	12 ± 8	0.17
Early	38 ± 27	36 ± 27	0.92
Late	46 ± 47	44 ± 46	0.89

All values are in mg/dl; LDL: low density lipoprotein; HDL: high density lipoprotein; VLDL: very low density lipoprotein; Pre: pretransplant; Early: 3 mo. post-transplant; Late: ≥18 mo. post-transplant; [a]N = 12 in Late.

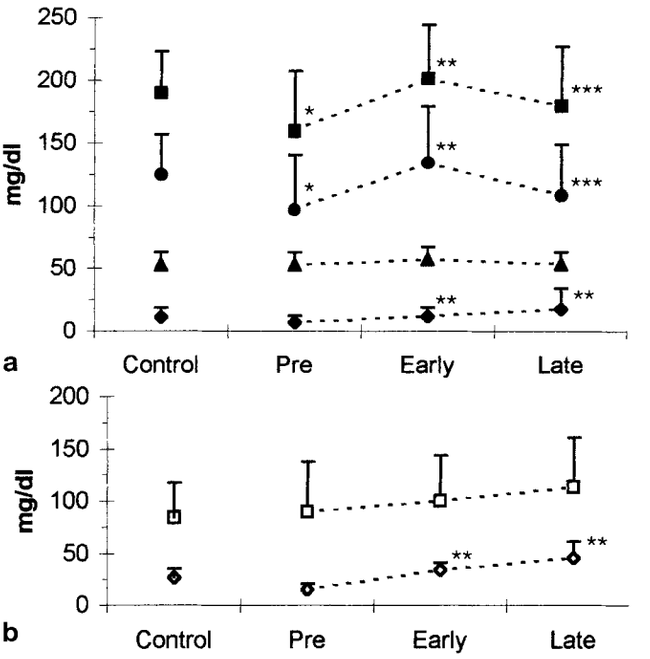

Fig. 1 Evolution of cholesterol and triglycerides in liver transplant recipients. The mean ± SD of cholesterol and triglycerides in different lipoprotein fractions in controls and patients before tranplantation (*Pre*) and in the early period (3 months) and the late period (≥ 18 months) after tranplantation are represented (*LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *VLDL* very low-density lipoprotein) $*P < 0.05$ vs control values; $**P < 0.05$ vs pretransplant values; $***P < 0.05$ vs early post-transplant values. **a** - -■- - Total cholesterol; - -•- - LDL cholesterol; - -▲- - HDL cholesterol, - -◆- - VLDL cholesterol. **b** - -□- - Total triglycerides; - -◇- - VLDL triglycerides

tween the CyA and tacrolimus groups with regard to the lipid profile (Table 2), BMI (23.7 ± 2.0 vs 24.0 ± 4.1 kg/m^2; $P = 0.97$), daily prednisone dose (19.6 ± 5.3 vs 16.6 ± 4.9 mg/dl; $P = 0.15$), serum creatinine levels (1.0 ± 0.2 vs 1.0 ± 0.0 mg/dl; $P = 0.69$), or serum glucose levels (116 ± 73 vs 108 ± 34 mg/dl; $P = 0.77$).

In the late period after liver transplantation (≥ 18 months), total and LDL cholesterol levels decreased to just above pretransplant values (Fig. 1). In contrast, VLDL cholesterol and VLDL triglyceride levels in the late period failed to decline, i.e., they remained similar to those early after transplantation, perhaps reflecting the recovery of liver synthetic function. HDL cholesterol and total triglycerides were not significantly different in the pretransplant early, post-transplant, and late post-transplant periods. There were no significant differences in Lp(a) levels between CyA- and tacrolimus-treated patients and controls (median values 14.5, 14, and 8.5 mg/dl, respectively; $P = 0.67$).

In the late period after transplantation, there was a trend towards higher total and LDL cholesterol levels in the CyA group than in the tacrolimus group ($P = 0.07$ and $P = 0.08$, respectively; Table 2). At this time, 11 patients on CyA and 4 patients on tacrolimus therapy were receiving prednisone ($P = 0.01$), the others having undergone prednisone withdrawal at least 2 months before the study period. There were no significant differences in the average prednisone dose, but there was a trend towards increased cumulative prednisone dose in patients given CyA. The interval post-transplantation, the number of acute rejection episodes, BMI, and serum creatinine and glucose levels did not differ between the two treatment groups. However, CyA-treated patients more frequently developed post-transplant diabetes and hypertension (Table 3). Antihypertensive treatment did not include beta-adrenergic antagonists in any case.

The lipid profile in the late period was also examined in terms of the presence or absence of active steroid treatment, regardless of the type of immunosuppression given (Table 4). Patients on active prednisone treatment showed total and LDL cholesterol levels similar to those of controls. In contrast, patients not receiving steroids exhibited lower total and LDL choles-

Table 3 Clinical data in late period in liver transplanted patients

	Cyclosporin ($n = 14$)	Tacrolimus ($n = 12$)	P
Time from transplantation (months)	21.2 ± 3.6	23.5 ± 3.8	0.13
No. of acute rejections	0.8 ± 0.7	0.8 ± 0.8	0.96
No. diabetes	5	0	*0.05*
No. hypertension	8	1	*0.04*
Body mass index (kg/m^2)	26.4 ± 2.1	26.2 ± 4.2	0.76
Serum creatinine (mg/dl)	1.2 ± 0.2	1.1 ± 0.1	0.24
Serum glucose (mg/dl)	114 ± 42	103 ± 23	0.56
Prednisone dose (mg/day)	6.3 ± 2.5	8.7 ± 4.7	0.22
Prednisone cumulative dose (g)	9.4 ± 2.4	7.2 ± 3.8	*0.09*
No. (%) on prednisone therapy	11	4	*0.01*

Values are means ± SD or numbers of cases (%)

Table 4 Lipid profile in the late post-transplant period in liver transplant recipients: impact of prednisone treatment.

	Prednisone treatment	
	Yes ($n = 15$)	No ($n = 11$)
Total cholesterol	200 ± 49	152 ± 30*
LDL cholesterol	127 ± 40	85 ± 29*
HDL cholesterol	53 ± 14	54 ± 18
VLDL cholesterol	23 ± 18	11 ± 11
Triglycerides	133 ± 82	86 ± 53
VLDL triglycerides	57 ± 49	31 ± 39

All values are in mg/dl. Included are all patients on cyclosporin and tacrolimus therapy. (*LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *VLDL* very low-density lipoprotein)
* $P < 0.05$ for patients not on prednisone treatment versus those on prednisone and controls

terol than both steroid-treated patients and controls ($P < 0.01$ for both).

As mentioned, CyA treatment was associated with a trend towards increased cholesterol levels in the late period. We used a two-way ANOVA to evaluate the relative contribution of the type of immunosuppression (CyA or tacrolimus) and late steroid treatment to the long-term increase in cholesterol levels. When the effect of steroids was taken into account, the contribution of the type of immunosuppressant used to increased total or LDL cholesterol levels completely disappeared ($P = 0.51$ for total cholesterol, $P = 0.59$ for LDL cholesterol). In contrast, allowing for the effect of the immunosuppressant, the effect of steroids remained significant for both total ($P = 0.034$) and LDL cholesterol ($P = 0.048$). The two-way ANOVA did not detect any significant interaction effect between the type of immunosuppression and steroids on the late cholesterol levels ($P = 0.181$ for total cholesterol, $P = 0.387$ for LDL cholesterol). In addition, steroid-treated patients had higher serum triglycerides than controls ($P = 0.02$). BMI and other lipid parameters did not differ between the groups.

There were no significant correlations during either the early or late post-transplant periods between total and LDL cholesterol and CyA, tacrolimus blood levels, or prednisone dose.

Discussion

End-stage liver disease is associated with abnormalities in lipid metabolism that generally subside within a few months after transplantation [16, 21]. In this study, total and LDL cholesterol levels were lower in patients prior to liver transplantation than they were in controls. This was no longer true during the early or late period after transplantation. Lipid levels in the pretransplant and early post-transplant periods were similar in CyA- and tacrolimus-treated patients. In contrast, late after transplantation, CyA-treated patients tended to have higher total and LDL cholesterol levels than patients assigned to tacrolimus.

CyA has been implicated in the hyperlipidemia of renal [7, 14, 24] and liver [1, 6, 9, 11, 15, 20, 26] transplant recipients, although other studies have failed to find such a relationship [3, 4, 10]. Some authors have described tacrolimus treatment as being less commonly associated with hypercholesterolemia than CyA therapy in liver transplant recipients [1, 6, 9, 11, 15, 26]. However, corticosteroid therapy (number of patients and dose) is also generally higher in patients given CyA. In addition, Krentz et al. [13] have reported that, shortly after liver transplantation and following steroid withdrawal (6 weeks before the study), total cholesterol is similar in CyA and tacrolimus-treated patients and that it is even lower than in age-matched, healthy controls. In our study, when treatment with CyA or tacrolimus and steroids was analyzed simultaneously with a two-way ANOVA, only steroids were associated with increased total and LDL cholesterol levels. Moreover, some authors have reported a positive correlation between prednisone dose and total cholesterol in renal transplant recipients [8, 12, 28], and steroid withdrawal has been associated with improvement in the lipid profile in renal [22, 25] and liver [19, 23] transplant recipients.

Altogether, and in agreement with the results of the present paper, these data suggest that corticosteroid therapy may be the main factor responsible for increased cholesterol levels after liver transplantation. If immunosuppression with tacrolimus makes complete steroid withdrawal increasingly possible, then the use of this agent may offer better control of lipid abnormalities [6].

Accordingly, hyperlipidemia in liver transplant recipients does not seem to be a major problem after corticosteroid withdrawal. However, the presence of hypercholesterolemia could predispose patients with it to cardiovascular disease. Moreover, as in our series, corticosteroid therapy is associated with an increased prevalence of diabetes and hypertension, which could further increase the cardiovascular risk in liver transplant recipients.

In conclusion, the lipid profile of liver transplant recipients seems to basically reflect the effect of steroid treatment, which is associated with the development of diabetes and hypertension. The use of immunosuppressants that require lower doses of steroids, such as tacrolimus, may therefore keep cardiovascular risk factors under control. These data further underscore the need for new immunosuppressive therapies lacking adverse metabolic effects.

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