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Consuelo Fernández-Miranda
Marta Sanz
Angel dela Calle
Carmelo Loinaz
Ramón Gómez
Carlos Jiménez
Ignacio García
Agustín Gómez de la Cámara
Enrique Moreno

Cardiovascular risk factors in 116 patients 5 years or more after liver transplantation

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C. Fernández-Miranda (✉) · M. Sanz
Servicio de Medicina Interna,
Hospital Universitario 12 de Octubre,
Ctra. Andalucia km 5.4,
28041 Madrid, Spain
E-mail: cfmiranda@inicia.es
Tel.: +34-91-3908296
Fax: +34-91-3908358

A. de la Calle · C. Loinaz · R. Gómez
C. Jiménez · I. García · E. Moreno
Service of Surgery,
Hospital Universitario 12 de Octubre,
Madrid, Spain

A. Gómez de la Cámara
Epidemiology Unit,
Hospital Universitario 12 de Octubre,
Madrid, Spain

Abstract We assessed the cardiovascular risk factors (CVRFs) in 116 stable liver transplant patients surviving for 5 years or more (median: 102 months). The prevalence of smokers was 29.3%, hypertension 49.1%, obesity 22.4%, hypercholesterolemia 34.5%, hypertriglyceridemia 11.2%, and hyperhomocysteinemia 57.8%. Diabetes was found in 21.5% of the patients, being more frequent in patients with hepatitis-C-virus infection (31.8% vs 15.3%; $P=0.03$). Patients on cyclosporine therapy had a higher prevalence of hypertension, hypercholesterolemia and hyperhomocysteinemia than those treated with tacrolimus. Multivariate analysis showed only an association between cyclosporine therapy and cholesterol concentrations (odds ratio:1.02; 95% confidence interval (CI): 1.00–1.03; $P=0.01$). The prevalence of hypertension, diabetes, hypercholesterolemia and hypertriglyceridemia was lower at the time of the study than at 1 and 3 years after transplantation ($P<0.05$), probably related to steroid withdrawal. Comparing 87 patients' CVRFs with the general Spanish population, we found that the age–gender standardized prevalence ratio was not different: smoking 1.46 (95% CI: 0.88–1.76), obesity 1.16 (95% CI: 0.60–1.44), hypertension 1.55 (95% CI: 0.98–1.81), and hypercholesterolemia 0.64 (95%CI: 0.35–1.90). We conclude that the prevalence of CVRFs in liver transplant patients after 5 years or more is lower that found in the first years after the transplantation, and no different from that found within the Spanish population.

Keywords Liver transplantation · Cardiovascular risk factors · Immunosuppressive therapy · Hypertension · Hyperlipidemia · Diabetes · Hepatitis-C-virus infection

Introduction

Liver transplant patients share the same cardiovascular risk factors (CVRFs) as the general population and others associated with immunosuppressive therapy. It is known that steroids are involved in the development of diabetes, hypertension, hyperlipidemia, and overweight in liver transplant recipients, and their withdrawal reduces these metabolic complications [14, 17, 25, 30]. Cyclosporine is related to hyperlipidemia [20], and this drug and tacrolimus predispose the patient to hyperglycemia and hypertension [12, 32]. Studies of CVRFs in patients shortly after liver transplantation are frequent, but long-term studies are few [23, 27]. The evaluation and control of CVRFs are essential for avoiding atherosclerotic disease. Although this disease has previously not been considered a major problem in liver transplant patients, a recent wide study showed that cardiovascular

and cerebrovascular diseases were the second cause of late graft loss [1].

The aims of this study were: the evaluation of CVRFs in patients surviving for 5 years or more after liver transplantation, the correlation with immunosuppressive therapy, and a comparison with the Spanish population, if possible.

Materials and methods

One hundred and sixteen adult, clinically stable liver transplant patients who had undergone transplantation between November 1986 and March 1995 were studied at routine follow-up clinic visits. Within this period, 309 adult patients received a transplant, 140 of whom survived to when the study was carried out, 161 died, eight were lost for follow-up; a further 24 patients were not included in the study for various reasons (Table 1). The parameters assessed in all patients were: age, gender, time since transplantation, body mass index (BMI: kg/m^2), smoking (any cigarette smoking in the past month), the existence of diabetes, hypertension, cardiovascular disease, immunosuppressive therapy, serum creatinine, albumin, bilirubin, aspartate and alanine aminotransferase, lipoprotein concentrations after an overnight fast of 12 h, and creatinine clearance. Plasma homocysteine, serum folate, and vitamin B12 were determined in 102 patients who took neither vitamins nor other drugs that could alter their values. Obesity was defined as a BMI of ≥ 30 kg/m^2. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg more than twice during the year preceding the study, or the need for antihypertensive treatment. Hypercholesterolemia was defined as a fasting total cholesterol level of ≥ 200 mg/dl, and hypertriglyceridemia as a fasting total triglyceride level of ≥ 200 mg/dl or the need for anti-lipemic agents. Diabetes was defined as a fasting glycemia level of ≥ 126 mg/dl on 2 days during the year preceding the study, or the need for anti-diabetic agents. Hyperhomocysteinemia was defined as a fasting plasma homocysteine level of > 14.3 μmol/l in men and > 12 μmol/l in women.

Table 1 Patients not included in the study surviving 5 years or more after liver transplantation

Cause	Liver transplant indications
Unstable liver function ($n=6$)	Cirrhosis
	Alcoholic ($n=1$)
	Hepatitis C virus ($n=3$)
	Primary biliary ($n=1$)
	Secondary biliary ($n=1$)
Malignant disease ($n=5$)	Cirrhosis
	Alcoholic ($n=1$)
	Hepatitis C virus ($n=2$)
	Cryptogenetic ($n=1$)
	Secondary biliary ($n=1$)
Renal transplant ($n=10$)	Cirrhosis
	Alcoholic ($n=3$)
	Hepatitis C virus ($n=2$)
	Cryptogenetic ($n=3$)
	Polycystic kidney disease with hepatic involvement ($n=2$)
Refused study ($n=3$)	Cirrhosis
	Alcoholic ($n=1$)
	Hepatitis C virus ($n=1$)
	Secondary biliary ($n=1$)

Cardiovascular disease was defined as coronary disease (myocardial infarction, or angina and coronary angiography with stenosis of $> 50\%$ in one or more of the main arteries), cerebrovascular disease (transient ischemic episode and/or thrombotic stroke) or peripheral vascular disease (occlusive or subocclusive artery disease and/or abdominal aorta aneurysm). Plasma homocysteine was determined by fluorescence polarization immunoassay on an IMx analyzer (Abbott, Illinois, USA) [28]. Blood collected in Vacutainer tubes containing EDTA was immediately placed on ice and centrifuged within 1 h of collection at 1,200 g for 5 min. Plasma was stored frozen at –200 °C until required for analysis. Vitamin B12 and serum folate were determined by radioimmunoassay (Simul-TRAC-SNB; ICN Pharmaceuticals, New York, USA). Serum creatinine, albumin, bilirubin, aspartate and alanine aminotransferase analyses were performed according to the manufacturer's recommendations/instructions on a Hitachi 747-200 analyzer (Roche Diagnostics, Indianapolis, USA). Creatinine clearance was estimated from the Cockcroft-Gault formula [11]. Lipoproteins were isolated by an ultracentrifugation method [16]. Cholesterol and triglycerides in the various fractions were assayed enzymatically (Boehringer, Mannheim, Germany). Whole-blood cyclosporine was determined with radioimmunoassay (Incstar, Stilwater, Minnesota, USA), and whole-blood tacrolimus with fluorescence polarization immunoassay on an IMx analyzer (Abbott).

The protocol was approved by the local ethical committee, and informed consent was obtained from all participants.

Statistics

Means comparison of continuous numeric variables was tested with Student's *t*-test. Categorical variables were tested with chi-square statistics. Associations between continuous variables were assessed with Pearson's coefficients. *P* values below 0.05 were considered significant. Differences in the percentages of CVRFs at 1 and 3 years and at the time of the study were assessed with chi square for trends. Logistic regression analysis was performed to determine the correlation between cyclosporine- or tacrolimus therapy and the independent variables: age, gender, total cholesterol, homocysteine, creatinine concentrations, and post-transplant diabetes and hypertension.

We calculated the standardized prevalence ratio (SPR) [9] (ratio between the observed and the expected number) for smoking, obesity, hypertension, and hypercholesterolemia in 87 liver transplant patients with an age range from 35–64 years, using age and gender-specific data from reports of the Spanish population [6, 7].

Results

Of the participants, 75 were men and 41 women. Their mean age was 51.2 ± 12.6 years without difference between the genders. The elapsed time after transplantation was 101 ± 25 months (median: 102; range: 60–168 months). The immunosuppressive treatment was cyclosporine in 78 patients, and tacrolimus in 36. Moreover, eight patients were treated with mycophenolate, six with azathioprine and one with prednisone. Patients treated with cyclosporine had a longer follow-up, because some of them were from an earlier era. In 14 patients, cyclosporine had produced nephrotoxicity, and medication was changed to tacrolimus in 12 patients later than 2 years after the study; the remaining two patients received only mycophenolate as immunosuppressant therapy. The prevalence of treatment with

steroids at 1 year after transplantation was 89.6%, at 3 years 45.2%, and at the time of the study 0.9% ($P < 0.001$) (Fig. 1). The mean steroid dose was 11.0 mg/day at 1 year and 8.5 mg/day at 3 years ($P = 0.007$). The dose of the only patient on steroid therapy at the time of the study was 10 mg/day. Liver transplant indications are shown in Table 2. Sixteen patients needed two liver transplants, one further patient, four liver transplants.

In 54 patients, liver-function tests were abnormal (aspartate aminotransferase >45 U/l, and/or alanine aminotransferase >45 U/l, and/or total bilirubin >2 mg/dl) (46.5%), and 34 of them had hepatitis-C-virus (HCV) infection. Clinical characteristics of the patients are shown in Tables 3 and 4.

Table 2 Liver transplant indications in the 116 patients

Indication	*n*
Fulminant liver failure	7
Liver cirrhosis	
Hepatitis B virus	5
Hepatitis C virus	24
Hepatitis B and C virus	6
Alcoholic	26
Alcoholic and Hepatitis C virus	14
Cryptogenetic	17
Chronic cholestasis	
Primary biliary cirrhosis	8
Secondary biliary cirrhosis	4
Budd-Chiari syndrome	2
Hepatocarcinoma	1
Wilson disease	1
Hemangioendothelioma	1

Tobacco

There were 38 smokers (32.7%) (Table 3), with a higher prevalence among men (42.6% vs 14.6%; $P = 0.001$). There was no difference between transplant patients on cyclosporine and those on tacrolimus therapy (Table 4). Compared with the Spanish population adjusted for age and gender, the prevalence of smokers in patients was not higher (SPR: 1.46; 95% confidence interval (CI) 0.88–1.76) (Table 5).

Hypertension

Fifty-seven transplant patients (49.1%) had hypertension at the time of the study (Table 3), the percentage being the same for men and women. Patients treated with cyclosporine had a higher prevalence than those treated with tacrolimus (57.7% vs 33.3%; $P = 0.01$) (Table 4), but multivariate analysis did not show a correlation between post-transplant hypertension and cyclosporine therapy. Twenty six patients were treated with calcium channel blockers, 14 with angiotensin-converting enzyme inhibitors, four with angiotensin receptor antagonists, four with diuretics, and two with beta-adrenergic blocking agents. Excluding 48 patients (41.4%) with pre-transplant hypertension, the prevalence of hypertension at 1 year after transplantation was 54.2%, at 3 years 42.4%, and at the time of the study 7.8% ($P < 0.001$) (Fig. 1).

Compared with the Spanish population, adjusted according to age and gender, the prevalence of hypertension in patients was not different (SPR: 1.55; 95% CI

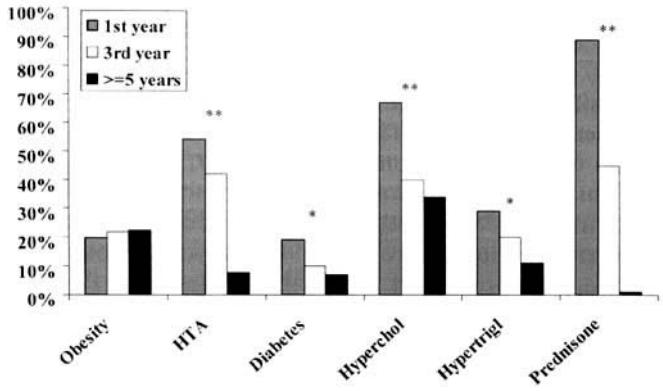

Fig. 1 Prevalence of obesity, post-transplant hypertension and diabetes, hypercholesterolemia, hypertriglyceridemia and prednisone treatment, at 1, 3, and ≥5 years after liver transplantation. *$P < 0.05$; **$P < 0.01$

Table 3 Clinical characteristics of the 116 patients. Values are means ± SD (median and ranges) or numbers of cases (%)

Characteristic	Value
Age (years)	51.2 ± 12.6 (52.0; 19.0–76.0)
Gender (men)	75 (64.6)
Time since transplant (months)	101 ± 25 (102; 60–168)
BMI (kg/m^2)	26.2 ± 4.8 (25.9; 15.8–38.8)
Smokers	38 (32.7)
Hypertension	57 (49.1)
Diabetes	25 (21.5)
With Hepatitis C virus ($n = 44$)	14 (31.8)*
Without Hepatitis C virus ($n = 72$)	11 (15.3)
Obesity	26 (22.4)
Hypercholesterolemia	40 (34.5)
Hypertriglyceridemia	13 (11.2)
Hyperhomocysteinemia ($n = 102$)	59 (57.8)
Homocysteine (μmol/l) ($n = 102$)	15.5 ± 5.7 (15.1; 5.2–31.8)
Total cholesterol (mg/dl)	189 ± 48 (188; 94–403)
LDL cholesterol (mg/dl)	118 ± 39 (114; 45–347)
HDL cholesterol (mg/dl)	48 ± 17 (46; 15–112)
Triglycerides (mg/dl)	126 ± 62 (105; 39–389)
Lipoprotein(a) (mg/dl)	18 ± 21 (11; 2–122)
Creatinine (mg/dl)	1.3 ± 0.5 (1.2; 0.7–5.0)
Creatinine clearance (ml/min)	77.5 ± 28.0 (77.0; 19.0–178.0)
Bilirubin (mg/dl)	1.0 ± 0.8 (0.8; 0.2–5.2)
Albumin (g/dl)	4.0 ± 0.3 (4.0; 3.0–5.2)
Aspartate aminotransferase (U/l)	43 ± 34 (31; 3–208)
Alanine aminotransferase (U/l)	59 ± 57 (40; 3–301)

*$P = 0.03$ compared with patients without Hepatitis C virus

Table 4 Clinical characteristics of the 114 patients treated with cyclosporine or tacrolimus. Values are means ± SD (median and ranges) or numbers of cases (%)

Characteristic	Cyclosporine ($n=78$)	Tacrolimus ($n=36$)
Age (years)	53 ± 13 (55; 19–76)*	46 ± 11 (46; 20–62)
Gender (men)	50 (64.1)	23 (63.8)
Time since transplant	105 ± 23 (105; 60–165)**	93 ± 28 (84; 60–168)
Blood level (ng/ml)	87.2 ± 40.9 (83.0; 26.0–292.0)	7.6 ± 2.9 (7.8; 3.7–17.1)
BMI (kg/m^2)	26.8 ± 4.9 (26.9; 15.8–38.8)**	24.5 ± 4.1 (24.6; 17.0–33.0)
Smokers	22 (28.2)	14 (38.8)
Hypertension	45 (57.7)**	12 (33.3)
Diabetes	18 (23.1)	6 (16.6)
Obesity	19 (24.3)	5 (13.8)
Hypercholesterolemia	35 (44.9)*	5 (13.8)
Hypertriglyceridemia	10 (12.8)	3 (8.3)
Hyperhomocysteinemia($n=102$)	47 (68.1)*	11 (35.5)
Homocysteine (mmol/l)($n=102$)	16.0 ± 5.0 (15.6; 6.5–31.8)	13.9 ± 5.8 (12.4; 5.2–28.8)
Total cholesterol (mg/dl)	199 ± 47 (197; 111–403)*	171 ± 45 (171; 94–315)
LDL cholesterol (mg/dl)	124 ± 41 (123; 46–347)**	105 ± 30 (104; 45–190)
HDL cholesterol (mg/dl)	49 ± 17 (46; 26–110)	46 ± 18 (42; 15–112)
Triglycerides (mg/dl)	130 ± 59 (111; 39–350)	139 ± 59 (92; 39–389)
Lipoprotein(a) (mg/dl)	19 ± 23 (11; 2–122)	15 ± 18 (8; 2–64)
Creatinine (mg/dl)	1.3 ± 0.3 (1.3; 0.7–2.6)	1.3 ± 0.7 (1.2; 0.7–5.0)
Creatinine clearance (ml/min)	71.5 ± 25.2 (71.0; 27.0–157.0)*	91.6 ± 29.5 (90.5; 19.0–178.0)
Vitamin B12 (pg/ml) ($n=102$)	745 ± 433 (629; 196–2000)	723 ± 283 (699; 266–1324)
Folate (ng/ml) ($n=102$)	7.8 ± 3.3 (6.6;2.5–20.0)	7.8 ± 3.0 (7.5; 2.7–18.1)

*$P<0.01$; **$P<0.05$ compared with patients treated with tacrolimus

0.98–1.81) except in those aged 45–54 years. There was no difference between men and women (Table 5).

Obesity

The mean BMI was 26.2 ± 4.8 kg/m^2 (Table 3), being higher in men (27.2 ± 4.4 vs 24.6 ± 5.0; $P=0.006$). Obesity was found in 26 patients (22.4%) (BMI: 32.9 ± 2.3 kg/m^2), without difference regarding gender and immunosuppressive therapy (Table 4). Obesity prevalence at 1 year after transplantation was 19.8%, at 3 years 21.8%, and at the time of the study 22.4% ($P=0.67$) (Fig. 1).

Compared with the Spanish population, adjusted according to age and gender, the prevalence of obesity in patients was not higher (SPR: 1.16; 95% CI 0.60–1.44) (Table 5).

Hyperlipidemia

The levels of total cholesterol, low-density-lipoprotein (LDL) cholesterol, high-density-lipoprotein (HDL) cholesterol, triglycerides and lipoprotein(a) are shown in Table 3. Hypercholesterolemia was found in 40 patients (34.5%), without difference in gender, and only three patients had a bilirubin concentration of >2 mg/dl. Thirteen patients (11.2%) had hypertriglyceridemia, with a higher prevalence in men (16% vs 2.4%; $P=0.03$). Patients treated with cyclosporine had a higher total and LDL-cholesterol level than those treated with tacrolimus, but HDL-cholesterol, triglyceride and lipoprotein(a) concentrations were not different in either group (Table 4). The logistic regression showed that cyclosporine was associated with total cholesterol (odds ratio: 1.02; 95% CI: 1.00–1.03; $P=0.01$). Five patients were treated with statins (pravastatin or atorvastatin) and one with fibrates, without deleterious effects. Hypercholesterolemia prevalence at 1 year after transplantation was 66.6%, at 3 years 40.3%, and at the time of the study 34.5% ($P=0.002$) and hypertriglyceridemia prevalence was 29.0% at 1 year, 20.3% at 3 years and 11.2% at the end ($P=0.01$) (Fig. 1). The prevalence of hypercholesterolemia in our series compared with the Spanish population, adjusted according to age and gender, was not significantly different (SPR: 0.64; 95% CI: 0.35–1.90) (Table 5).

Diabetes

There were 25 patients (21.5%) with diabetes at the time of the study, without differences in gender and therapy (cyclosporine or tacrolimus) (Tables 3 and 4). Six patients were treated with insulin, and five with oral anti-diabetic agents. The diabetes of the remaining patients was controlled with diet. Except for 17 patients with pre-transplant diabetes (14.6%), the prevalence of diabetes was 19.6% 1 year after transplantation, 9.8% at 3 years, and 6.9% at the time of the study ($P=0.03$) (Fig. 1). In a multivariate analysis, neither cyclosporine nor tacrolimus was related to post-transplant diabetes.

Diabetes was found in 14 of 44 patients with HCV hepatitis and in 11 of 72 patients without this virus (31.8% vs 15.3%; $P=0.03$) (Table 3).

Table 5 Standardized prevalence ratio (*SPR*)

Parameter	Men			Women			Total		
Age	*n*	Cases	SPR (95% CI)	*n*	Cases	SPR (95% CI)	*n*	Cases	SPR (95% CI)
Smoking									
35–44	8	6	1.32 (0.24–2.11)	7	3	1.33 (0.05–2.64)	15	9	1.44 (0.42–2.12)
45–54	23	12	1.10 (0.21–1.51)	9	0	0	32	12	1.46 (0.53–2.02)
55–64	32	12	0.87 (0.31–1.21)	8	0	0	40	12	1.46 (0.53–2.02)
35–64	63	30	0.96 (0.54–1.17)	24	3	0.75 (0.03–2.78)	87	33	1.46 (0.88–1.76)
Obesity									
35–44	9	2	1.33 (<0.01–3.12)	6	0	0	15	2	0.80 (<0.01–1.88)
45–54	23	6	1.43 (0.27–2.29)	9	3	1.11 (0.22–2.93)	32	9	1.10 (0.60–1.61)
55–64	32	11	1.72 (0.58–2.41)	8	2	0.69 (<0.01–1.62)	40	13	1.10 (0.41–1.49)
35–64	64	19	1.62 (0.75–2.08)	23	5	0.79 (0.11–1.33)	87	24	1.16 (0.60–1.44)
Hypertension									
35–44	9	4	1.66 (0.16–2.98)	6	2	2.0 (<0.01–4.7)	15	6	2.00 (0.38–3.19)
45–54	23	17	2.10 (0.92–2.74)	9	5	1.78 (0.25–2.99)	32	22	2.11 (1.05–2.67)*
55–64	32	15	0.96 (0.39–1.27)	8	3	0.71 (0.14–1.87)	40	18	0.88 (0.40–1.14)
35–64	64	36	1.55 (0.92–1.85)	23	10	1.33 (0.42–1.90)	87	46	1.55 (0.98–1.81)
Hypercholesterolemia									
35–44	9	2	0.40 (<0.01–0.94)	6	2	0.71 (<0.01–1.67)	15	4	0.54 (0.05–0.97)
45–54	23	7	0.53 (0.12–0.81)	9	5	0.90 (0.13–1.51)	32	12	0.68 (0.24–0.94)
55–64	32	8	0.42 (0.11–0.63)	8	5	0.89 (0.12–1.49)	40	13	0.50 (0.19–0.68)
35–64	64	17	0.46 (0.20–0.60)	23	12	0.89 (0.17–1.23)	87	29	0.64 (0.35–1.90)

*Significant difference

Hyperhomocysteinemia

For the study of plasma homocysteine, 14 patients on treatment with vitamins, anticonvulsants, fibrates, or trimethoprim sulfamethoxazole were excluded, because these drugs alter homocysteine concentrations. Increased homocysteine was found in 61 patients (59.2%) (Table 3), with no differences between men and women. The Pearson correlation showed that homocysteine was correlated with age ($r=0.20$; $P=0.03$), creatinine ($r=0.43$; $P<0.001$), creatinine clearance ($r=-0.46$; $P<0.001$) and folate ($r=-0.24$; $P=0.01$). The prevalence of hyperhomocysteinemia was higher in patients treated with cyclosporine, but in these patients clearance creatinine was decreased ($P<0.001$) and creatinine concentration showed a decreasing trend ($P=0.06$), compared with patients treated with tacrolimus (Table 4). Multivariate analysis did not show an association between cyclosporine therapy and homocysteine concentration.

Cardiovascular disease

Seven cardiovascular events occurred in six (5.2%) patients (coronary disease in one, cerebrovascular disease in three and peripheral arterial disease in three) between 3 and 84 months after liver transplantation (median: 24 months). All these patients were men, with a mean age of 54.0 ± 7.1 years (median: 53; range: 45–66 years). All of them had at least two of the CVRFs studied.

Discussion

Our study of liver transplant patients after 5 years or more of follow-up show a high prevalence of CVRFs. However, it was lower for diabetes, hypertension, and hyperlipidemia that found in the first years after transplantation, when the number of patients treated with steroids and the dose administered were higher. Steroid therapy has been related to the development of some CVRFs, and its reduction or withdrawal produce weight loss [17], decrease in the cholesterol and triglyceride concentrations [14, 17, 30], and decrease in diabetes [25, 30] and hypertension [30].

Cyclosporine therapy is associated with the development of hypertension [31] and hyperlipidemia [22] in liver transplant recipients. In our study, patients treated with cyclosporine had a higher prevalence of hypertension and hypercholesterolemia than those treated with tacrolimus, but multivariate analysis showed only an association between cyclosporine therapy and cholesterol concentration. Hypertriglyceridemia, which has recently been considered as a predictor of coronary disease [3] and related to cyclosporine administration [24], was not frequent in our patients, even in those treated with this drug. Hyperhomocysteinemia is an independent CVRF very prevalent in liver transplant recipients, and associated with renal dysfunction and folate concentration [15], as we found in the present study. Although hyperhomocysteinemia was more prevalent in patients treated with cyclosporine, multivariate analysis showed no association between

cyclosporine therapy and homocysteine concentration, consistent with other studies [8, 15]. The influence of cyclosporine on renal function is known, and possibly, renal dysfunction confers an influence of cyclosporine on homocysteine.

Tacrolimus is a further immunosuppressive drug involved in the hyperglycemia and hypertension of transplant patients, and it has been suggested that tacrolimus could be more diabetogenic than cyclosporine therapy [12, 32]. However, we found the same prevalence of diabetes in patients of both groups of immunosuppressive therapy. In another recent work, a low maintenance dose of cyclosporine and tacrolimus did not show a significant difference in insulin sensitivity and insulin secretory reserves in liver transplant recipients [13]. In our series, multivariate analysis did not find a relationship between tacrolimus treatment and post-transplant diabetes and hypertension.

Diabetes prevalence in our study was higher in patients with HCV infection. An association between diabetes and HCV infection has been described in recent years, but the etiology of this association is not well known. As HCV has been related to autoimmune disease [26], some authors suggest that an autoimmune mechanism for diabetes in HCV infection cannot be excluded [21, 29]. Others suggest that HCV can induce direct injury to the pancreas [18, 33]. An improvement in glycemic control has been described in liver transplant recipients with HCV hepatitis and diabetes after transplantation who responded to antiviral therapy [5].

Although a high prevalence of CVRFs was found in the present study, the SPR was not the same as for the general Spanish population, adjusted according to age and gender [6, 7]. Despite this, strict control of each CVRF is necessary to avoid cardiovascular diseases. These diseases have not been considered a noteworthy medical complication in liver transplant patients [2, 4], but in a recent study of these patients, Abbasoglu et al. [1] found that cardiovascular and cerebrovascular diseases were the second cause of late graft loss. In our study, atherosclerotic disease was present in six patients (5.2%) whose mean age was 54 years. The incidence of this complication increases with the liver transplant patient's age [34]. In our series, 53.4% of the patients were < 55 years, which could explain the low prevalence of cardiovascular events.

The prevalence of CVRFs in the present study with long follow-up liver transplant patients is high, but lower than that found in the first years after transplantation, and not different from the Spanish population. Cyclosporine therapy is associated with cholesterol concentrations, and diabetes is more frequent in patients with HCV infection.

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