

RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF DYSLIPIDEMIA AFTER HEART TRANSPLANTATION

FATEMEH AKHLAGHI,^{1,5} CHRISTOPHER H. JACKSON,⁴ JAYAN PARAMESHWAR,³ LINDA D. SHARPLES,^{2,4}
AND ANDREW K. TRULL¹

College of Pharmacy, University of Rhode Island, Kingston, RI 02881; Department of Pharmacology, Research & Development and Transplant Units, Papworth Hospital, Cambridge, CB3 8RE; and MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Robinson Way, Cambridge CB2 2SR, UK

Background. Hyperlipidemia is an important complication after organ transplantation and contributes to the development of posttransplant accelerated coronary artery diseases.

Methods. We have retrospectively evaluated the relative contribution of various risk factors associated with the development and progression of hyperlipidemia in 194 heart transplant recipients by the use of mixed effects multiple linear regression analysis. The demographic characteristics evaluated were primary diagnosis of ischemic heart disease (IHD), gender, and age. Postoperative characteristics included number of treated rejections, dosage of cyclosporine (CYA), tacrolimus (TAC), prednisolone and azathioprine, and concentration of serum creatinine and glucose. The effects of administration of antihypertensive agents, diuretics, and lipid lowering agents were also studied.

Results. The total cholesterol concentration increased significantly in the first 3 months posttransplant but gradually decreased thereafter. Total cholesterol and the ratio of low density lipoprotein (LDL) cholesterol to high density lipoprotein (HDL) cholesterol (LDL-C/HDL-C) increased to a greater extent in patients with IHD although female transplant recipients had a greater increase in the total cholesterol concentration. Each episode of rejection increased serum cholesterol by 0.306 mmol/liter (0.258, 0.355) [mean (95% C.I.)] and serum triglyceride by 0.164 mmol/liter (0.12, 0.209) although switching to TAC improved total cholesterol and LDL-C/HDL-C. Administration of frusemide, increased the total cholesterol and LDL-C/HDL-C whereas administration of bumetanide or metolazone increased the concentration of serum triglyceride. Serum glucose was associated with hypertriglyceridemia whereas serum creatinine was associated with increases in the total cholesterol, LDL-C/HDL-C and triglyceride.

Conclusions. We have identified demographic and postoperative covariables that predispose heart transplant recipients to hyperlipidemia. Some of these risk factors, such as the effect of diuretics, have not been identified before in this group of patients and may be amenable to modification or closer control. TAC rather than CYA may be the immunosuppressive of choice for patients who are at greater risk of developing hyperlipidemia.

INTRODUCTION

Hyperlipidemia, as defined by elevation in the concentration of serum lipids, is a frequent complication after organ transplantation (1). Although some reports indicate that up to 80% of heart transplant recipients become hyperlipidemic at some stage posttransplant, the recent registry report produced by the International Society for Heart and Lung Transplantation (ISHLT) reveals that by the end of first year post transplant, 39.3% of heart transplant recipients had developed hyperlipidemia (2). In the nontransplant population, hyperlipidemia is a well-established risk factor for the development of coronary artery diseases (3). In transplant recipients it is believed that hyperlipidemia, in association with immunological and inflammatory factors (4), is the driving mechanism behind the development of accelerated allograft and nonallograft vascular diseases (1). Hyperlipidemia may also predispose patients to acute allograft rejection (5), possibly by reducing the unbound concentration of cyclosporine (CYA) (6).

Posttransplant hyperlipidemia is a multifactorial phenomenon and has been attributed to genetic predisposition, diet, and diabetes (7) in addition to the use of immunosuppressive agents including CYA and corticosteroids. The concentration of serum lipids after organ transplant are also influenced by many other nutritional, metabolic, and pharmacological factors, for example, the relative contribution of other medications, including diuretic and β -blocking agents, which are known to induce dyslipidemia in nontransplant population, has never been investigated (8–11) in transplant recipients.

The objective of our study was to comprehensively describe the pattern of development and progression of posttransplant dyslipidemia in heart transplant recipients and to identify the relative contribution of the various risk factors for development of this condition.

METHODS

Clinical and laboratory information from heart allograft recipients transplanted between February 1993 and September 1998 was retrospectively reviewed and collected in a database. A total of 194 patients who survived beyond 6 months posttransplant and had a complete record of clinical and laboratory investigations during both in- and outpatient hospital periods were included in the study.

The lengths of follow-up were as follows: 6 to 12 months (16 patients, 8.2%), 13 to 18 months (28 patients, 14.4%), 18 to 24 months (18 patients, 9.3%), and more than 24 months (132 patients, 68.0%). The total number of cholesterol observations was 3123. In addition to the pretransplant total cholesterol concentration, between 4 and 40 observations (median 14) were available for each patient. Concentration of serum cholesterol and triglyceride was

¹ Department of Pharmacology.

² Research and Development Unit.

³ Transplant Unit.

⁴ MRC Biostatistics Unit.

⁵ Address correspondence to: Fatemeh Akhlaghi PhD, College of Pharmacy, University of Rhode Island, 41 Lower College Road, Kingston, RI 02881.

measured using standard enzymatic methods and CYA concentration was determined using EMIT 2000 Cyclosporine Specific Assay (Syva/Behring, Inc, San Jose, CA).

Statistical analysis. Preliminary statistical analyses were carried out by the use of the SPSS computer program (ver 9.0, SPSS Inc, Chicago, IL). Risk factors for hyperlipidemia were analyzed by mixed effects linear regression analysis using S-Plus package (Mathsoft, Seattle, WA). The main outcome variable was the total cholesterol concentration although separate analyses were performed for low-density lipoprotein cholesterol (LDL-C) (1948 observations), high-density lipoprotein cholesterol (HDL-C, 2075 observations), LDL-C/HDL-C (1948 observations), and triglyceride (3081 observations) concentrations. Within each patient, these concentrations were assumed to be time related increasing during the first 90 postoperative days and decreasing after this time. Patient-specific risk factors were gender, date of transplant, a primary diagnosis of ischemic heart disease, and the presence of diabetes at the time of transplantation. Time-dependent risk factors included weight adjusted immunosuppressive drug doses [CYA, prednisolone, azathioprine, tacrolimus (TAC)], cumulative number of acute rejection episodes, body mass index (BMI), serum glucose and creatinine concentrations, and the administration of diuretic, lipid-lowering, β blocking, and calcium channel blocking agents.

The association between hyperlipidemia and the above risk factors was first investigated by univariate regression analysis, adjusted for time after transplantation. A multiple regression model was then developed to assess the predictive value of each risk factor independently on the lipid level by adjusting for the effects of the other factors and for time after transplantation. The multiple regression models were subsequently improved by accounting for "random effects," a method that adjusts for any correlation between successive measurements on each patient and for unobserved differences in response between patients.

Immunosuppressive drug regimen. The primary immunosuppressive protocol used in Papworth Hospital consists of CYA, azathioprine, and corticosteroids. Methyl-prednisolone (500 mg) is administered i.v. at induction and reperfusion followed by three further doses of 125 mg in the immediate postoperative period. CYA is given daily in two divided oral doses to maintain the total CYA concentration at 300–400 $\mu\text{g/liter}$ in the first 3 postoperative months, 200–300 $\mu\text{g/liter}$ from 3 to 12 months posttransplant and 100–200 $\mu\text{g/liter}$ thereafter. The maximum daily dose of azathioprine is 2 mg/kg as a single oral dose in the evening and the doses adjusted to maintain the white blood cell count between $4\text{--}6 \times 10^9/\text{liter}$. The oral corticosteroid regimen comprises 1 mg/kg/day prednisolone in two divided doses reducing by 5 to 0.2 mg/kg/day as a maintenance dose. The decision to wean patients off maintenance prednisolone is based on consideration of individual patient's clinical status including the occurrence of acute rejection episodes, degree of renal dysfunction, and corticosteroid related side effects. Allograft rejections are treated with 3 daily doses of 500 or 1000 mg i.v. methylprednisolone followed by augmentation of oral prednisolone back to 1 mg/kg/day, tapering again to 0.2 mg/kg/day over 2 weeks. Patients who experience two or more episodes of treated allograft rejection are generally switched from CYA to TAC or from azathioprine to mycophenolate mofetil. None of the patients included in the study received rapamycin or its derivative SDZ-RAD.

Other medications. The influence of lipid lowering, β -adrenoceptor blocking, calcium channel blocking, and diuretic agents of serum lipids were also investigated. HMG-CoA reductase inhibitors were the only type of lipid lowering agents administered. This included pravastatin (87 patients, 10–40 mg/day), simvastatin (24 patients, 10–40 mg/day), and atorvastatin (15 patients, 10–80 mg/day). HMG-CoA reductase inhibitors were generally started between 3 and 6 months posttransplant and the dose increased at clinic visits with the aim lower total cholesterol less than 5 and LDL-C less than 3 mmol/liter or until maximal recommended doses of drugs were reached. Pravastatin was generally the first drug used and patients

were changed to simvastatin and latterly to atorvastatin if lipid levels were still high on 40 mg a day of pravastatin.

In total, 13 patients received β -blocking agents atenolol (10 patients, 50–100 mg/day), propranolol (2 patients, 240 mg/day), and metoprolol (1 patient, 50 mg/day). The calcium channel blocking agents administered were nifedipine (72 patients, 10–80 mg/day), amlodipine (19 patients, 5–10 mg/day), diltiazem (6 patients, 90–1200 mg/day), lacidipine (2 patients, 12 and 16 mg/day), and verapamil (2 patients, 160 mg/day). The most frequently administered diuretic agent was the loop diuretic, frusemide (157 patients, at doses of 5–300 mg daily) although 12 patients received frusemide in combination with the potassium sparing agent, amiloride (5 mg). Diuretic agents other than frusemide included bumetanide (1–4 mg daily, 12 patients), and metolazone (2.5–7.5 mg daily, 16 patients).

RESULTS

The demographic characteristics of heart transplant recipients included in the study are shown in Table 1 and the dosages of immunosuppressive agents administered at various time intervals post transplant are shown in Table 2. In summary, the majority of patients were male (81.3%) and ischemic heart disease (IHD) was the most common primary diagnosis for heart transplantation (49%). In addition, Table 3 present a summary of the various factors that increase or decrease the concentration of serum lipids in the patients included in this study.

Progression of hyperlipidemia over time. In the first 3 months posttransplant, the cholesterol concentration increased significantly from its pretransplant value but gradually decreased thereafter (Fig. 1). In this period, the concentration of both cholesterol and triglyceride increased by an average of 0.63 and 0.33 mmol/liter, respectively (Table 4). The increase in the concentration of total cholesterol was associated with an increase in the concentration of both LDL-C [mean (95% CI), 0.347 (0.18, 0.514) mmol/liter] and HDL-C [0.171 (0.117, 0.225) mmol/liter] whereas LDL-C/HDL-C decreased by an average of -0.36 (95% CI, -0.57 , -0.15) in this period. Over the subsequent months, the concentrations of total cholesterol, triglyceride, and LDL-C/HDL-C decreased slightly (Table 4). To evaluate the influence of periodical variations in routine clinical practices on hyperlipidemia, we have modeled the overall effect of the year that patients received their organ transplant on lipid concentrations (years after 1993). The analysis showed that, although the total cholesterol and triglyceride concentrations were not influenced by the transplant year, the LDL-C/HDL-C was significantly decreased reflecting both a decrease in LDL-C [-0.169 (-0.259 , -0.079) mmol/liter] and an increase in HDL-C [0.118 (0.080, 0.154) mmol/liter]. This ob-

TABLE 1. Demographic characteristics of patients

No of patients	194
Gender	
Male	157(81.3%)
Female	36(18.7%)
Age in years (range)	20–65
Weight (kg)	75.9 \pm 11.8
Mean \pm SD	
Primary diagnosis	
IHD	95(49%)
Dilated cardiomyopathy	84(43.3%)
Others	15(7.7%)

IHD, Ischemic heart disease.

TABLE 2. Dosage of immunosuppressive agents

Months posttransplant	Cyclosporine (mg/kg/day)	Azathioprine (mg/kg/day)	Prednisolone (mg/kg/day)
1	6.79 ± 2.57	1.61 ± 0.52	0.47 ± 0.94
6	4.68 ± 2.04	1.19 ± 0.89	0.39 ± 1.27
12	4.18 ± 2.01	0.87 ± 0.77	0.36 ± 1.28
24	2.66 ± 2.05	0.80 ± 0.79	0.12 ± 0.64

Data are mean ± SD.

servation is likely to be related to the increasing use of lipid lowering agents soon after transplantation in the latter years of this study.

Effect of demographic characteristics. The pretransplant concentration of HDL-C was lower [0.82 ± 0.28 (SD) vs. 1.01 ± 0.68 mmol/liter; $P < 0.01$] and the LDL-C/HDL-C was higher (4.96 ± 2.03 vs. 3.90 ± 1.58 ; $P < 0.001$) in patients with a history of IHD as compared with other primary diagnosis although total cholesterol and triglyceride concentration did not differ (Table 5). After transplantation, total cholesterol and the LDL-C/HDL-C were also significantly greater in patients with a primary diagnosis of IHD whereas the triglyceride concentration was not different from that in patients with other diagnosis (Table 5).

In female transplant recipients, the postoperative increase in total cholesterol was more pronounced than that in male patients. However, because the concentration of LDL-C and HDL-C were equally increased, the change in the LDL-C/HDL-C remained nonsignificant. Moreover the average number of treated rejections was 2.5 vs. 2.0 episodes for female and male transplant recipients respectively. In addition, neither age at transplant nor increase in BMI influenced the concentration of serum lipids (Table 5).

Effect of immunosuppressive agents

Every episode of treated rejection increased the concentrations of total cholesterol and triglyceride by an average of 0.306 and 0.164 mmol/liter, respectively, whereas rejection did not influence the LDL-C/HDL-C. In addition CYA dose had a minimal effect on the serum lipids although the daily dose of maintenance prednisolone and azathioprine had no significant effect on the serum concentration of lipids (Table 6).

Maintenance oral prednisolone was discontinued in 66 patients at an average time of 415 days posttransplant and it had a beneficial effect on the lipid profile (total cholesterol concentration was 6.8 ± 1.3 vs. 5.6 ± 1.3 mmol/liter, $P < 0.0001$; total triglyceride: 2.4 ± 1.0 vs. 2.1 ± 1.1 mmol/liter, $P < 0.01$; HDL-C: 1.1 ± 0.4 vs. 1.1 ± 0.3 , $P = 0.23$ and LDL-C: 4.5 ± 1.2 vs. 3.5 ± 1.0 , $P < 0.0001$, before and after prednisolone discontinuation, respectively).

Administration of TAC in place of CYA also had beneficial effects on the serum cholesterol concentration. The total cholesterol and LDL-C concentrations were significantly lower and the HDL-C concentration was higher in patients after switching to TAC whereas the concentration of triglyceride did not differ from baseline (Fig. 2). In addition the daily dose of prednisolone was not significantly different before and after switch to TAC (1.25 ± 0.39 vs. 1.12 ± 0.44 mg/kg/day, respectively, $P = 0.2$).

Lipid lowering therapy

The administration of HMG-CoA reductase inhibitors was associated with a significant reduction in total cholesterol [-0.39 (-0.54 , -0.24) mmol/liter] and LDL-C [-0.51 (-0.66 , -0.36) mmol/liter] concentrations as well as a reduction in LDL-C/HDL-C [-0.56 (-0.75 , -0.37)]. Figure 3 compares the effect of pravastatin and simvastatin administration on the concentration of serum lipids indicating that the magnitude of change in total cholesterol concentration was similar for both statins although pravastatin lowered the LDL-C to a greater extent than simvastatin ($P < 0.05$).

Diuretic agents

Frusemide significantly increased total [0.20 (0.08, 0.32) mmol/liter] and LDL [0.17 (0.05, 0.28) mmol/liter] cholesterol concentrations but did not influence HDL-C and triglyceride concentrations. Additionally, administration of bumetanide or metolazone significantly increased the concentration of serum triglyceride [0.365 mmol/liter (0.135, 0.595)] (Fig. 4).

Administration of β -blockers and calcium channel blockers. Univariate analyses revealed that administration of the antihypertensive agents, β -blockers, or calcium channel blockers did not have a significant effect on serum lipid concentrations.

Serum glucose and creatinine. Diabetic patients had significantly higher total cholesterol [0.175 (0.0087, 0.343) mmol/liter] and triglyceride [0.313 (0.159, 0.467) mmol/liter] concentrations whereas the multivariate analysis revealed that an increase of 1 mmol/liter in the serum concentration of glucose was associated with a slight but significant increase in the concentration of cholesterol and an average of 0.106 mmol/liter increase in the concentration of serum triglyceride (Table 7).

Significant associations were found between total cholesterol, triglyceride, and LDL-C/HDL-C and the reciprocal of creatinine concentration (Table 7). This indicates that for an average patient with a creatinine concentration of 100 μ mol/liter, an increase of 11 μ mol/liter in creatinine concentration was associated with a 0.07 mmol/liter (CI; 0.037, 0.103) increase in total cholesterol, 0.127 mmol/liter (0.0957, 0.158) increase in triglyceride and 0.103 (0.0651, 0.142) increase in LDL-C/HDL-C.

DISCUSSION

In this study we have used uni- and multivariate linear regression analyses to identify the risk factors for the development and progression of hyperlipidemia after heart transplantation. In this way, we have avoided the commonly used approach that assigns patients to two groups of normo- or hyperlipidemics by the use of clinically relevant cut-off values for cholesterol or triglyceride.

The steepest increase in the concentrations of cholesterol and triglyceride occurred in the first 90 days posttransplant although the concentrations of both lipids gradually declined after this time period. The explanation for this phenomenon may lie with both physiological changes in lipid concentration associated with recovery from advanced heart failure and the impact of pharmacological agents used posttransplantation. In the first few postoperative months heart transplant recipients are prone to a significant weight gain. The dosage of immunosuppressive and diuretic agents is also

TABLE 3. Summary of contribution of various factors on the concentration of serum lipids

Variable	Total cholesterol	LDL-C/HDL-C	Triglyceride
Time posttransplant			
1st 3 months	↑	↓	↑
Subsequent months	↓	↓	↓
Transplant year	—	↓	—
Demographic characteristics			
Primary diagnosis of IHD	↑	↑	—
Gender: female	↑	—	—
Age	—	—	—
BMI	—	—	—
Immunosuppressive agents			
Rejection episodes	↑	—	↑
CYA dose	↑	↓ (slightly)	—
Prednisolone (maintenance dose)	—	—	—
Tacrolimus dose	↓	↓	—
Other medications			
HMG-CoA reductase inhibitors	↓	↓	—
Diuretics			
Frusemide ^a	↑	↑	—
Others ^b	—	—	↑
β Blockers	—	—	—
Calcium Channel Blockers	—	—	—
Serum biochemistry			
Glucose	↑ (slightly)	—	↑
Serum Creatinine	↑	↑	↑

^a Frusemide or in combination with Amiloride.

^b Bumetanide or Metolazone.

↑, Increase; ↓, decrease, — no effects; IHD, ischemic heart disease; BMI, body mass index; CYA, cyclosporine; TAC, tacrolimus.

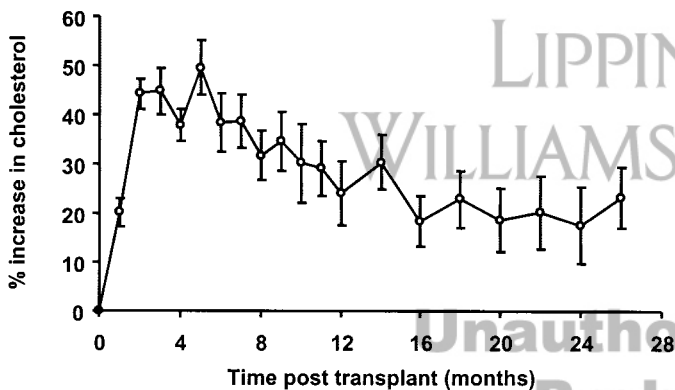


FIGURE 1. Percent increase in total cholesterol concentration from pretransplant baseline over time posttransplant.

higher in this period as is the risk of allograft rejection, which both factors collectively contribute to the development of hyperlipidemia.

Despite the increase in the total cholesterol concentration, the LDL-C/HDL-C is significantly reduced in the first 90 days posttransplant as well as in subsequent 90-day periods. This was due to a proportionately greater increase in the HDL-C to the LDL-C that may support the notion that chronic administration of corticosteroids increases the HDL-C (12, 13).

The effect of transplant year on serum lipids, was another significant finding of this study. Because this study extended over a 5-year period, we included this factor in the multivariate model to account for periodical variations in routine clinical practices. The influence of transplant year on the LDL-C/

HDL-C was most probably a reflection of the growing recognition that hyperlipidemia as an important comorbidity factor after transplantation and the consequent ever-increasing use of HMG-CoA reductase inhibitors in the later years of this study.

We observed that the postoperative increase in the total concentration of cholesterol was more pronounced in female than male transplant recipients although a similar observation was made in the liver transplant population (14). One probable explanation may be that female transplant recipients are more prone to allograft rejection and therefore require high-dose corticosteroid treatment more often. We have also observed that the clearance of oral prednisolone was significantly lower in female than in male transplant recipients (unpublished observation) which may expose female patients to more steroid-related side effects.

The use of immunosuppressive agents CYA and corticosteroids are frequently attributed to the development of post-transplant hyperlipidemia. It is believed that these agents increase production and/or reduce catabolism of lipoproteins (7, 8). CYA has also been shown to increase the oxidizability of LDL in vitro, which may in turn increase the risk of coronary artery disease (15). Indeed, in this study we demonstrated that every episode of organ rejection was associated with a significant increase in the concentration of total cholesterol and triglyceride but not in the LDL-C/HDL-C. Treatment of rejection episodes involves administration of high doses of methylprednisolone (usually 1000 mg/day for 3 days) followed by an increase in the oral prednisolone dose. Despite the adverse effects on total cholesterol and triglyceride, this regimen does not seem to significantly elevate LDL-C/HDL-C, possibly because corticosteroids increase the concentrations of both LDL and HDL cholesterol (16).

TABLE 4. Association between lipid concentration and time related variables

	Total cholesterol (mmol/liter)	LDL-C/HDL-C	Triglyceride (mmol/liter)
Pretransplant baseline	5.26 (5.06–5.46)	4.53 (4.26–4.81)	1.63 (1.53–1.73)
1st 90 days posttransplantation	0.63 (0.45, 0.80)	-0.36 (-0.57, -0.15)	0.33 (0.16, 0.50)
Subsequent days (for each 90 days)	-0.08 (-0.09, -0.06)	-0.11 (-0.13, -0.09)	-0.04 (-0.06, -0.03)
Transplant year	-0.08 (-0.19, 0.03)	-0.47 (-0.58, -0.36)	-0.04 (-0.12, 0.04)

Data are mean (95% confidence interval).

TABLE 5. Influence of demographic characteristics on serum lipids

	Total cholesterol (mmol/liter)	LDL-C/HDL-C	Triglyceride (mmol/liter)
Primary diagnosis IHD	0.55 (0.23, 0.88)	0.62 (0.30, 0.94)	0.10 (-0.14, 0.34)
Female gender	0.73 (0.34, 1.13)	0.09 (-0.30, 0.94)	0.18 (-0.12, 0.47)
Age at transplant (for every 10 yr increase)	0.088 (-0.087, 0.262)	0.12 (-0.05, 0.30)	0.034 (-0.096, 0.165)
BMI (for 1 kg/m ²)	-0.044 (-0.088, 0.0005)	0.002 (-0.042, 0.046)	0.0159 (-0.018, 0.050)

Data are mean (95% confidence interval).

LDL-C/HDL-C, Ratio of LDL to HDL cholesterol; IHD, ischemic heart disease; BMI, body mass index.

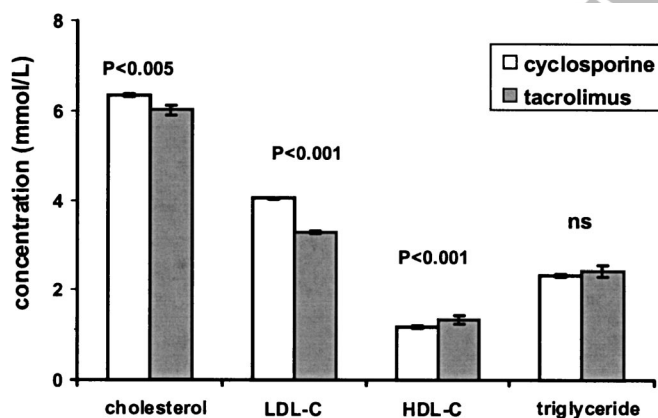


FIGURE 2. Effect switch from cyclosporine to tacrolimus on serum lipids (data are mean±SE of the mean).

Although the association between the maintenance dose of prednisolone or CYA and serum lipids was very weak, withdrawal from prednisolone or a switch from CYA to TAC had beneficial effects on serum lipids. Favourable effects of TAC on serum lipids have been noted by others (17, 18). We have also observed that the dosage of oral prednisolone before and after switching to TAC was not different indicating that the effects of TAC administration on lipid concentrations were independent of prednisolone dosage.

Secondary dyslipidemia induced by the administration of diuretic agents has previously been identified in non-transplant populations (8, 10, 11, 19). The exact mechanism of diuretic-induced dyslipidemia is not known. However, it has been speculated that it may be related to a reduction in vascular volume, a decrease in the catabolism of lipoproteins or the induction of hypocalcemia by these agents (11). The most likely mechanism of this effect, however, may be related to the induction of insulin non-responsiveness in the peripheral tissues frequently seen after treatment with diuretic agents (11). Our observation is consistent with earlier re-

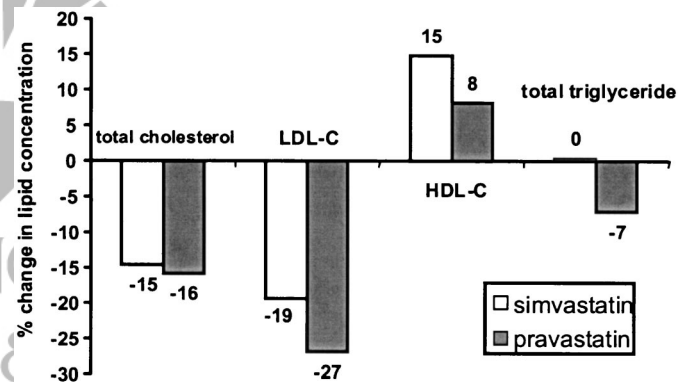


FIGURE 3. Effect of the HMG-CoA reductase inhibitors, simvastatin and pravastatin, on serum lipid concentrations.

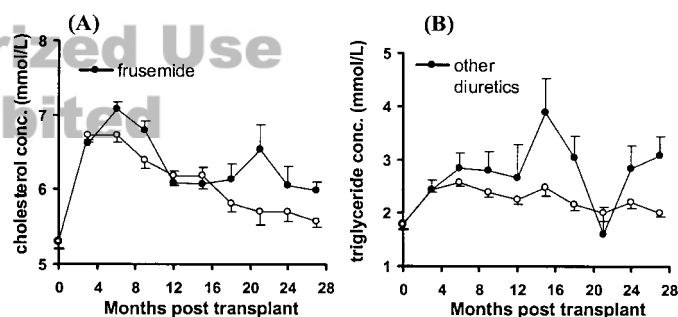


FIGURE 4. Effect of diuretic agents on serum lipids over time post transplant (A) frusemide and cholesterol concentration, (B) diuretics other than frusemide and triglyceride concentration. (Data are presented as mean and SEM.)

ports that administration of frusemide significantly increases the concentration of total cholesterol and LDL-C (20, 21).

We also noted that the administration of other diuretic agents, including bumetanide and metolazone, significantly

TABLE 6. Effect of rejection episodes and dosage of immunosuppressive agents on serum lipids

	Total cholesterol (mmol/liter)	LDL-C/HDL-C	Triglyceride (mmol/liter)
Each episode of treated rejections	0.306 (0.258, 0.355)	0.044 (-0.0125, 0.101)	0.164 (0.12, 0.209)
CYA dose (1 mg/kg/day)	0.0499 (0.0249, 0.075)	-0.0428 (-0.0703, -0.0152)	0.0138 (-0.00986, 0.0374)
Prednisolone dose (0.1 mg/kg/day)	8.12×10^{-5} (-0.00243, 0.00259)	0.0021 (-0.00082, 0.00502)	0.00035 (-0.00205, 0.00275)

TABLE 6. Association between serum lipids with glucose and creatinine concentration

Variable	Cholesterol (mmol/liter)	LDL-C/HDL-C	Triglyceride (mmol/liter)
Glucose (1 mmol/liter)	0.0228 (0.00895, 0.0365)	-0.0171 (-0.0358, 0.00167)	0.106 (0.093, 0.119)
Reciprocal creatinine (0.001 liter/mmol)	-0.0699 (-0.103, -0.0371)	-0.103 (-0.142, -0.0651)	-0.127 (-0.158, -0.0957)

increased the triglyceride concentration. Bumetanide is a loop diuretic that is used instead of frusemide because of its superior oral absorption. In a randomized placebo-controlled clinical trial in hypertensive population, administration of bumetanide resulted in 5 and 12% increase in the concentration of total cholesterol and triglyceride, respectively (21). Furthermore, anecdotal evidence indicates that the administration of metolazone may be associated with the development of diabetes mellitus or the aggravation of this condition (22) that in turn may produce hypertriglyceridemia. In our transplant recipients, frusemide is used either on its own or in combination with amiloride as the first line diuresis treatment to reduce edema. Patients are switched to bumetanide if they do not respond to oral frusemide administration or to metolazone if the edema persists. Another possible explanation for the observation is that patients requiring bumetanide or metazolone may have a more profound renal impairment and the hypertriglyceridemia is secondary to this condition (23).

We found that an increase in the concentration of serum glucose was associated with an increase in the triglyceride concentration. The association between glucose metabolism and hypertriglyceridemia is well-established (24). Indeed, a positive correlation between hypertriglyceridemia and insulin concentration has been identified that raises the possibility that hypertriglyceridemic patients may be inherently resistant to insulin (24). Based on our study, however, we cannot identify the cause and effect relationship between serum glucose and triglyceride particularly when other confounding factors such as obesity may equally influence both variables.

We have also observed that dyslipidemia is strongly associated with the degree of renal failure. Patients with chronic renal failure are at greater risk of fatality from cardiovascular diseases (25) although elevated serum lipids are a well-established biochemical abnormality associated with end stage renal disease (23). In hemodialysis patients very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) are elevated whereas HDL is reduced (23) as is the case in renal allograft recipients with chronic graft dysfunction (26). The association between serum lipids and

creatinine found in this study is compatible with such observations.

In summary, we have shown that hyperlipidemia after heart transplantation is a complex condition influenced by a wide array of pre- and postoperative factors. Although many of the observations of our study had been described by others, this report is somewhat unique because it describes the varying degree of involvement of many risk factors that contribute to the development of posttransplant hyperlipidemia in the form of one coherent investigation.

In the context of prevention and treatment of hyperlipidemia, consideration of demographic and biochemical risk factors is essential to achieve desirable lipid concentrations in a given transplant recipient. At present, therapeutic interventions in the treatment of hyperlipidemia, in particular the administration of HMG-CoA reductase inhibitors, have been proving successful (27). The result of these interventions may be further improved if the risk factors identified in this study are considered. When possible we recommend the use of diuretic agents in moderation and greater attention to the treatment of renal impairment. Furthermore, in patients who are more susceptible to the development of lipid abnormalities, such as those with renal insufficiency or those with a history of IHD, administration of lipid friendly immunosuppressive agents, including tacrolimus, may prove useful in controlling the development of posttransplant hyperlipidemia. As a future direction, it may be warranted to study the incidence of atherosclerosis and the interplay of lipid concentrations on this condition in the context of a long-term investigation in heart transplant recipients.

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TRANSPLANTATION

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DECREASED SERUM AND BRONCHOALVEOLAR LAVAGE LEVELS OF CLARA CELL SECRETORY PROTEIN (CC16) IS ASSOCIATED WITH BRONCHIOLITIS OBLITERANS SYNDROME AND AIRWAY NEUTROPHILIA IN LUNG TRANSPLANT RECIPIENTS¹

MAGNUS NORD, KATJA SCHUBERT, TOBIAS N. CASSEL, OLOF ANDERSSON, AND GERDT C. RIISE²

Department of Medical Nutrition, Karolinska Institute, NOVUM, Huddinge University Hospital, Stockholm, Sweden

Background. The major hinderance for long-term survival after lung transplantation is chronic rejection in the form of bronchiolitis obliterans syndrome (BOS). BOS is a fibrosing process in the small airways causing irreversible airway obstruction. BOS is associated with increased oxidative burden and activation of inflamma-

tory and growth-stimulating mediators. The Clara cell secretory protein (CCSP or CC16) is a secreted differentiation marker for the bronchiolar epithelium with both antioxidative and antiinflammatory/immunomodulatory properties. We asked whether this molecule could have a role in the development of BOS.

Methods. Serum and bronchoalveolar lavage (BAL) fluid samples were collected from 22 consecutive lung transplant recipients, the majority (19) was followed for 2 years. Six patients developed BOS. CCSP in serum was measured in 162 samples from 19 patients with an ELISA method, and CCSP in 191 BAL samples from 22 patients with quantitative Western blot.

Results. CCSP in both serum and BAL was significantly lower in BOS compared with acute rejection or no rejection. After the first postoperative month, se-

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² Address correspondence to: Gerdt C. Riise, M.D., Ph.D. Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.