Lipid Profile Changes During the First Year After Kidney Transplantation: Risk Factors and Influence of the Immunosuppressive Drug Regimen

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ABSTRACT

Aim. This study analyzed the incidence, time course, and risk factors associated with dyslipidemia during the first year after kidney transplantation among patients receiving various immunosuppressive regimens.

Methods. The analysis included 474 kidney transplant recipients receiving cyclosporine (CSA) combined with sirolimus (SRL; $n = 137$) or mycophenolate (MMF, $n = 58$) or everolimus (EVR, $n = 47$); or SRL combined with MMF ($n = 32$); or tacrolimus (TAC) combined with SRL ($n = 86$) or MMF ($n = 114$). All patients received prednisone. We evaluated the influence of demographic features, clinical outcomes, and statin use on lipid profiles during the first year after transplantation. total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, TC:HDL-C, LDL-C:HDL-C, TG:HDL-C.

Results. Lipid profiles were within the recommended ranges in 28% of patients pretransplantation and in 10% at 1 year; 27% of them received statins. At 1 year, LDL-C <100 mg/dL was observed in 31.8% of patients but more than 35% of these patients still showed other lipid fractions or ratios outside recommended target concentrations. Among all patients with LDL-C > 100 mg/dL, almost 70% to 80% had other lipid fractions or ratios within target ranges. A logistic regression analysis showed age, gender, time on dialysis, diabetes, type of calcineurin inhibitor (CSA vs TAC), adjunctive therapy (SRL/EVR vs MMF) and prednisone dose to be associated with dyslipidemia.

Conclusion. Dyslipidemia is frequent at 1 year after transplantation. The lack of agreement among changes observed in lipid fractions and ratios suggests that more studies are necessary to guide therapy besides targeting LDL-C concentrations as recommended by current guidelines.

DYSLIPIDEMIA, which shows a high prevalence in all stages of renal disease, has been associated with increased cardiovascular morbidity and mortality[1] as well as possibly late graft failure.[2] In addition to all of the risk factors of the general population, the presence of impaired allograft function, proteinuria, an acute rejection episode and its treatment with corticosteroids, new-onset diabetes mellitus after transplantation and various types and doses of immunosuppressive agents also contribute as risk factors among the kidney transplant population.[3,4]

Several guidelines defining the type, severity, and targets for therapeutic interventions of dyslipidemia have been implemented. They focus on total cholesterol (TC) and/or low-density lipoprotein cholesterol (LDL-C) concentrations. Evidence supporting the importance of lowering LDL-C concentrations to decrease the risk of cardiovascular events. Nevertheless, a significant number of cardiovascular events occured[5] even in trials that achieved substantial

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reductions in LDL-C. Targeting LDL-C concentrations may miss other lipid abnormalities, underestimate cardiovascular risk, and hamper adequate treatment. Current prevention guidelines also support optimal high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations to further reduce the incidence of cardiovascular events.[6] Furthermore, reduction in the atherogenic non- non-HDL-C lipid fraction[7] may be superior to LDL-C to predict cardiovascular events.[8]

There is no consensus regarding the utility of TC:HDL-C, LDL:HDL-C, or TG:HDL-C ratios to predict coronary heart disease risk. TC:HDL-C ratio is a useful summary of the joint contribution of TC and HDL-C to coronary heart disease risk.[9] An high LDL-C:HDL-C ratio combined with hypertriglyceridemia (lipid triad) has been described as atherogenic dyslipidemia, which was associated with highest coronary heart disease risk.[8,10] Finally, TG:HDL-C ratios, a marker for the presence of highly atherogenic small-dense LDL, are also an important lipid ratio to assess atherogenic potential mainly with the presence of insulin resistant metabolic syndrome.[11] Our study analyzed the effect of demographic characteristics, clinical outcomes, and maintenance immunosuppressive regimens on temporal changes in lipid profiles during the first year after kidney transplantation.

METHODS

This retrospective single-center study compared the incidence, time course, and severity of dyslipidemia among renal transplant patients treated with six different immunosuppressive regimens for up to 12 months. Data were captured from individual files of patients who had previously participated in prospective randomized clinical trials conducted in accordance with the International Conference of Harmonization and good clinical practice. All study protocols had been approved by an independent local Ethics Committee.

Population

For this analysis, we selected first living related or deceased kidney transplant recipients performed between March 6, 1999, and December 5, 2006, who were older than 13 years with pretransplant total white blood cell count $\leq 4.0 \times 10^3/mm^3$, platelet count $\leq 100.0 \times 10^3/mm^3$, fasting cholesterol ≥ 300 mg/dL, and fasting TG ≥ 400 mg/dL.

Immunosuppressive Regimens

We evaluated six immunosuppressive regimens: cyclosporine (CsA) with sirolimus (SRL) or mycophenolate mofetil (MMF), or everolimus (CSA/EVR); sirolimus plus mycophenolate mofetil (MMF); tacrolimus (TAC) plus sirolimus (SRL) or MMF. All patients received 1 g methylprednisolone administered before graft revascularization, followed by daily initial prednisone doses of 0.5 mg/kg/d (maximum of 30 mg) for 30 days. Steroid mean daily doses and taper regimens were similar among the groups, reaching 10 mg between 90 and 120 days. No patient underwent steroid withdrawal during the first year. The initial drug combination was maintained until the end of the first year after transplantation unless complicated by adverse events or a lack of efficacy.

Study Visits and Evaluations

Fasting TC, TG, and HDL-C, determinations used enzymatic assays in an Hitachi 912 auto analyzer (Roche Diagnostics, Lewes, UK). Lipid-lowering drug uses were collected pretransplant as well as 30, 90, 180, 270, and 365 days these after these. LDL-C was estimated by Friedewald's formula.[12] The non-HDL-C was calculated by subtracting HDL-C from TC.[13] Biochemistry and hematology assessments were also obtained at all study visits. Creatinine clearance was calculated using the Cockcroft-Gault formula.[14] Proteinuria was not systematically evaluated in these patients.

Definitions

Dyslipidemia was diagnosed in patients showing (1) TC $>$ 200 mg/dL[15]; (2) LDL-C $>$ 100 mg/dL[15]; (3) non-HDL-C $>$ 130 mg/dL[15]; (4) TG $>$ 150 mg/dL[15]; (5) HDL-C $<$ 40 mg/dL (males) or $<$50 mg/dL (females)[8]; (6) LDL-C:HDL-L ratio $>$ 3.3 (males) or $>$ 2.9 (females); (7) TC:HDL ratio $>$ 5.1 (males) or $>$ 4.4 (females)[16]; (8) TG:HDL-C ratio $>$ 4.0.[17] At the time of the diagnosis of dyslipidemia, patients sequentially received dietary and activity instructions followed by statin therapy at the discretion of the attending physicians. New-onset diabetes after transplantation (NODAT) was defined according to the American Diabetes Association guidelines.[18]

Statistical Analysis

Descriptive data and results are reported as mean values and standard deviations for continuous variables and as frequency distributions for categorical variables. Demographic features, transplant outcomes, lipid profiles, and the proportions of patients outside recommended target ranges were compared using analysis of variance or chi-square test. Student *t* test was used to compare immunosuppressive drug doses and concentrations as well as lipid fractions and ratios. Logistic regression analysis was employed to assess adjusted odds ratio (AOR) for the development of dyslipidemia at 1 year using median values of TC, TG, LDL-C, and HDL-C as dependent variables. Covariates included recipient age, gender, body mass index, ethnicity (black and intermediate vs others), end-stage renal disease (diabetes vs others), time on dialysis, donor source (living vs deceased), renal function at 30 days, NODAT, biopsy-proven acute rejection (BPAR), type of calcineurin inhibitor (CSA vs TAC), type of adjunctive agent (SRL or EVR vs MMF), and mean weight-normalized prednisone dose at 30 days after transplantation. Statistical analysis was performed using a computer statistics package (SPSS v 7.5).

RESULTS

Demographics, Immunosuppressive Regimens, and Transplant Outcomes

Among the 474 subjects included in this analysis, patients receiving SRL/MMF were older than those receiving CSA/SRL or TAC/SRL (Table 1). The proportion of white patients was lower in the CSA/SRL group. Mean time on dialysis was longer among patients receiving TAC/MMF. Calculated creatinine clearance at 12 months was higher in patients receiving TAC/MMF and lower in those receiving CSA/EVR. The incidence of first BPAR ranged from 8% (CSA/EVR) to 34% (SRL/MMF). The incidence of NO-

Table 1. Demographic Characteristics, Immunosuppression, and Transplant Outcomes

	CSA/SRL (*n* = 137)	CSA/MMF (*n* = 58)	CSA/EVR (*n* = 47)	SRL/MMF (*n* = 32)	TAC/SRL (*n* = 86)	TAC/MMF (*n* = 114)	Total (*n* = 474)
Age (y)*	36 ± 11	39 ± 11	39 ± 12	44 ± 14	36 ± 11	42 ± 13	39 ± 12
BMI (kg/m^2)	23.4 ± 4.1	23.3 ± 3.6	24.2 ± 4.8	24.0 ± 4.5	23.7 ± 3.7	24.2 ± 3.8	23.7 ± 4.0
Gender, *n* (%)							
Male	93 (68)	33 (57)	27 (57)	19 (59)	52 (60)	83 (73)	307 (65)
Female	44 (32)	25 (43)	20 (43)	13 (41)	34 (40)	31 (27)	167 (35)
Ethnicity, *n* (%)*							
White	44 (32)	29 (50)	26 (55)	20 (63)	43 (50)	64 (56)	226 (48)
Black	36 (26)	08 (14)	03 (06)	01 (03)	18 (21)	12 (11)	78 (16)
Mulatto	55 (40)	15 (26)	06 (13)	02 (06)	18 (21)	25 (22)	121 (26)
Other	02 (02)	06 (10)	12 (26)	09 (28)	07 (08)	13 (11)	49 (10)
Cause of ESRD, *n* (%)							
Hypertension	28 (20)	10 (17)	07 (15)	03 (09)	12 (14)	19 (17)	79 (17)
Chronic glomerulonephritis	22 (16)	05 (09)	06 (13)	06 (19)	10 (12)	15 (13)	64 (13)
Diabetes mellitus	07 (05)	06 (10)	01 (02)	01 (03)	07 (08)	11 (10)	33 (07)
Other	80 (59)	37 (64)	33 (70)	22 (69)	57 (66)	69 (60)	298 (63)
Time on dialysis (mo)*	26.3 ± 21.3	33.7 ± 24.2	25.7 ± 21.7	23.5 ± 23.6	28.2 ± 32.6	39.4 ± 31.0	30.4 ± 27.1
Donor source, *n* (%)†							
Living	122 (89)	37 (64)	44 (94)	32 (100)	74 (86)	71 (62)	380 (80)
Deceased	15 (11)	21 (36)	03 (06)	0 (0)	12 (14)	43 (38)	94 (20)
Renal function							
Serum creatinine (mg/dL)	1.6 ± 0.5	1.5 ± 0.4	2.0 ± 1.6	1.6 ± 0.8	1.6 ± 0.9	1.5 ± 1.1	1.6 ± 0.9
CrCl (min/mL/1.73 m^2)*	64 ± 19	64 ± 18	55 ± 20	60 ± 20	64 ± 17	67 ± 19	64 ± 19
NODAT (%)	18 (13)	05 (09)	08 (17)	02 (06)	12 (14)	12 (10)	57 (12)
BPAR, *n* (%)†	24 (17)	14 (24)	04 (08)	11 (34)	09 (10)	13 (11)	75 (16)
On therapy at 12 mo, *n* (%)†	121 (88)	52 (90)	46 (98)	27 (84)	77 (89)	114 (100)	437 (92)
Immunosuppression at 12 mo							
CSA concentration (ng/mL)	54 ± 42	124 ± 66	76 ± 36	—	—	—	
TAC concentration (ng/mL)	—	—	—	—	6.4 ± 2.6	6.6 ± 2.9	
SRL concentration (ng/mL)	13.3 ± 5.4	—	—	8.1 ± 4.0	9.6 ± 5.3	—	
EVR concentration (ng/mL)	—	—	7.0 ± 2.2	—	—	—	
MMF dose (mg/d)	—	2.1 ± 0.5	—	1.8 ± 0.5	—	1.8 ± 0.5	
PRED dose (mg/d)	9.1 ± 4.3	9.4 ± 4.3	9.6 ± 2.1	9.7 ± 1.0	9.1 ± 5.3	6.9 ± 2.3	

CsA, cyclosporine; SRL, sirolimus; MMF, mycophenolate mofetil; TAC, tacrolimus; ESRD, end-stage renal disease; Crcl, creatinine clearance; NODAT, new-onset diabetes after transplantation; BPAR, biopsy-proven acute rejection; PRED, prednisone.

*$P < .05$, analysis of variance comparing all groups.

†$P < .05$ chi-square test among all groups.

DAT ranged from 6% (SRL/MMF) to 14% (TAC/SRL). Overall more than 92% of patients were still receiving the initial immunosuppressive regimen at 1 year. At 12 months, CSA concentrations were significantly lower when associated with SRL or EVR compared with MMF. No differences were observed in TAC concentrations comparing patients receiving SRL or MMF. Higher SRL concentrations were observed when this drug was combined with CSA compared with TAC or MMF. MMF doses were higher in patients receiving CSA compared with those patients receiving SRL or TAC. Prednisone doses were lower among patients receiving the TAC/MMF combination compared with the other regimens.

Lipid Profiles

The concentrations of all lipid fractions increased from pretransplant to 1 year posttransplantation (Table 2). The time course of changes in TC and TG are shown in Fig 1. The mean TC concentration increased 39% and the proportion of patients with a TC value above 200 mg/dL increased from 18% to 64%. Similar trends were observed with LDL-C and non-HDL-C fractions. In 20% of patients, LDL-C concentrations were not calculated at 12 months because TG concentrations were above 400 mg/dL,[12] particularly among patients receiving SRL (28%) or EVR (38%). The mean TG concentration increased 55% and the proportion of patients with TG above 150 mg/dL increased from 41% to 69%. The magnitude of changes in TC and TG at 12 months was higher among patients receiving CSA/SRL or CSA/EVR compared with those prescribed TAC/MMF. Mean HDL-C concentration increased 14% in males and 22% in females resulting in a reduction (46% for males and 52% females) in the proportion of patients with HDL-C below recommended target at 1 year after the transplant.

No uniform trends were observed among all calculated lipid ratios from pretransplant to 1 year. The proportion of patients with TC:HDL-C ratios above the recommended target concentrations increased 95% for males and 32% for females. Similarly, the proportion of patients with an LDL-

Table 2. Lipid Profiles Pretransplant and 12 Months Posttransplant

Lipid fraction	Day	CSA/SRL	CSA/MMF	CSA/EVR	SRL/MMF	TAC/SRL	TAC/MMF	Total
TC	0	159 ± 40 (15)	170 ± 47 (29)	172 ± 49 (21)	167 ± 43 (16)	159 ± 41 (13)	165 ± 42 (20)	164 ± 43 (18)
	365[ab]	247 ± 58[c] (76)[d]	230 ± 59[c] (65)[d]	278 ± 52[c] (98)[d]	236 ± 61[c] (74)[d]	218 ± 65[c] (60)[d]	191 ± 47[c] (36)[d]	228 ± 62[c] (64)[d]
TG	0	162 ± 116 (39)	153 ± 82 (50)	184 ± 155 (38)	150 ± 167 (53)	160 ± 117 (35)	160 ± 97 (43)	161 ± 110 (41)
	365[ab]	298 ± 203[c] (82)[d]	214 ± 155[c] (60)	331 ± 225[c] (80)[d]	256 ± 143[c] (81)[d]	233 ± 165[c] (65)[d]	193 ± 142[c] (53)	250 ± 181[c] (69)[d]
LDL-C	0[b]	85 ± 34 (28)	94 ± 38 (39)	98 ± 36 (35)	90 ± 37 (28)	79 ± 33 (18)	90 ± 35 (34)	88 ± 35 (30)
	365[ab]	136 ± 46[c] (78)[d]	135 ± 46[c] (74)[d]	166 ± 39[c] (97)[d]	133 ± 56[c] (70)[d]	118 ± 49[c] (69)[d]	104 ± 35[c] (46)[d]	126 ± 47[c] (68)[d]
	Missing[b]	39 (28)	7 (12)	18 (38)	5 (15)	9 (10)	15 (13)	93 (20)
Non-HDL-C	0[b]	116 ± 40 (33)	124 ± 45 (45)	133 ± 46 (43)	119 ± 42 (34)	112 ± 41 (28)	122 ± 41 (39)	120 ± 42 (36)
	365[ab]	192 ± 56[c] (88)	176 ± 55[c] (80)	228 ± 53[c] (100)	180 ± 61[c] (81)	164 ± 60[c] (73)	142 ± 44[c] (53)	175 ± 59[c] (76)
HDL-C								
Male	0	41 ± 12 (55)	44 ± 12 (48)	39 ± 16 (64)	43 ± 19 (53)	44 ± 11 (40)	41 ± 10 (52)	42 ± 12 (52)
	365	51 ± 16[c] (24)[d]	50 ± 11[c] (19)[d]	47 ± 12 (26)[d]	52 ± 10 (10)[d]	50 ± 17 (32)	47 ± 12[c] (40)	49 ± 14[c] (28)[d]
Female	0[a]	46 ± 16 (65)	50 ± 11 (56)	40 ± 10 (89)	53 ± 19 (54)	52 ± 15 (56)	47 ± 12 (61)	48 ± 14 (63)
	365	65 ± 16[c] (14)[d]	60 ± 13[c] (30)	54 ± 14[c] (44)[d]	64 ± 18 (17)	59 ± 16 (30)	56 ± 11[c] (36)	60 ± 15[c] (30)
TC:HDL-C								
Male	0[a]	4.0 ± 1.5 (17)	3.8 ± 1.3 (12)	4.9 ± 2.3 (32)	4.0 ± 1.3 (21)	3.8 ± 1.3 (17)	4.1 ± 1.2 (19)	4.0 ± 1.5 (19)
	365[ab]	5.0 ± 1.5[c] (44)[d]	4.3 ± 1.1 (28)	6.4 ± 1.9[c] (87)[d]	4.5 ± 1.3 (47)	4.6 ± 1.4[c] (26)	4.3 ± 1.1 (22)	4.7 ± 1.5[c] (37)
Female	0[a]	4.3 ± 1.9 (39)	3.9 ± 1.2 (24)	4.7 ± 2.1 (32)	3.6 ± 1.4 (23)	3.3 ± 1.2 (18)	3.8 ± 1.3 (29)	3.9 ± 1.6 (28)
	365[ab]	4.2 ± 1.2 (42)	4.4 ± 1.1 (43)	5.2 ± 1.6 (67)[d]	4.3 ± 1.9 (42)	3.9 ± 1.2[c] (30)	3.4 ± 0.8 (14)	4.1 ± 1.3 (37)
LDL-C:HDL-C								
Male	0	2.1 ± 1.1 (10)	2.1 ± 1.0 (6)	2.6 ± 0.9 (23)	2.2 ± 1.1 (10)	1.9 ± 1.0 (10)	2.2 ± 0.9 (14)	2.1 ± 1.0 (12)
	365[ab]	2.8 ± 1.3[c] (27)[d]	2.6 ± 08 (17)	3.6 ± 0.9[c] (80)[d]	2.4 ± 1.1 (20)	2.5 ± 1.0[c] (16)	2.3 ± 0.7 (8)	2.6 ± 1.1[c] (21)
Female	0	2.4 ± 1.3 (29)	2.2 ± 1.0 (16)	2.4 ± 0.9 (23)	2.0 ± 1.0 (15)	1.6 ± 0.8 (9)	2.2 ± 1.1 (19)	2.1 ± 1.1 (18)
	365[a]	2.2 ± 0.9 (21)	2.5 ± 0.8 (24)	2.7 ± 0.7 (29)	2.4 ± 1.4 (25)	2.1 ± 0.9[c] (16)	1.8 ± 0.6 (4)	2.2 ± 0.9 (18)
TG:HDL-C								
	0[a]	4.4 ± 4.3 (36)	3.5 ± 2.1 (31)	6.2 ± 8.4 (45)	3.8 ± 2.2 (47)	3.8 ± 3.2 (27)	4.1 ± 3.1 (38)	4.3 ± 4.2 (36)
	365[ab]	5.9 ± 4.2[c] (44)[d]	4.2 ± 3.3 (41)	7.7 ± 6.6 (25)	5.1 ± 3.7 (59)	5.1 ± 5.0 (55)[d]	4.3 ± 3.6 (55)	5.2 ± 4.5[c] (47)
Normal lipid profile (%)	0[b]	25	24	21	34	42	25	28
	365[b]	05[d]	11[d]	0[d]	10[d]	10[d]	20	10[d]
Statin use (%)	365[b]	40	11	32	19	40	09	27

Mean ± standard deviation. In parenthesis is the proportion of patients with lipid fraction outside recommended target range [TC > 200 mg/dL; TG > 150 mg/dL; LDL-C > 100 mg/dL; non-HDL-C > 130 mg/dL; HDL-C < 40 mg/dL (male) and < 50 mg/dL (female); TC/HDL-C > 5.1 (male) and > 4.4 (female); LDL-C/HDL-C > 3.3 (male) and >2.9 (female); TG/HDL-C > 4.0]. LDL-C missing values were due to high (>400 mg/dL) TG concentrations.

CSA, cyclosporine; SRL, sirolimus; MMF, mycophenolate mofetil; EVR, everolimus; SRL, sirolimus; TAC, tacrolimus; TC, total cholesterol; TG, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

[a] $P < .05$ comparing mean lipid fraction concentrations among all groups.

[b] $P < .05$ comparing proportion of patients with lipid fraction concentration outside recommended target ranges among all groups.

[c] $P < .05$ comparing pre- vs posttransplant mean lipid fraction concentrations.

[d] $P < .05$ comparing pre- vs posttransplant proportion of patients with lipid fraction concentration outside recommended target ranges.

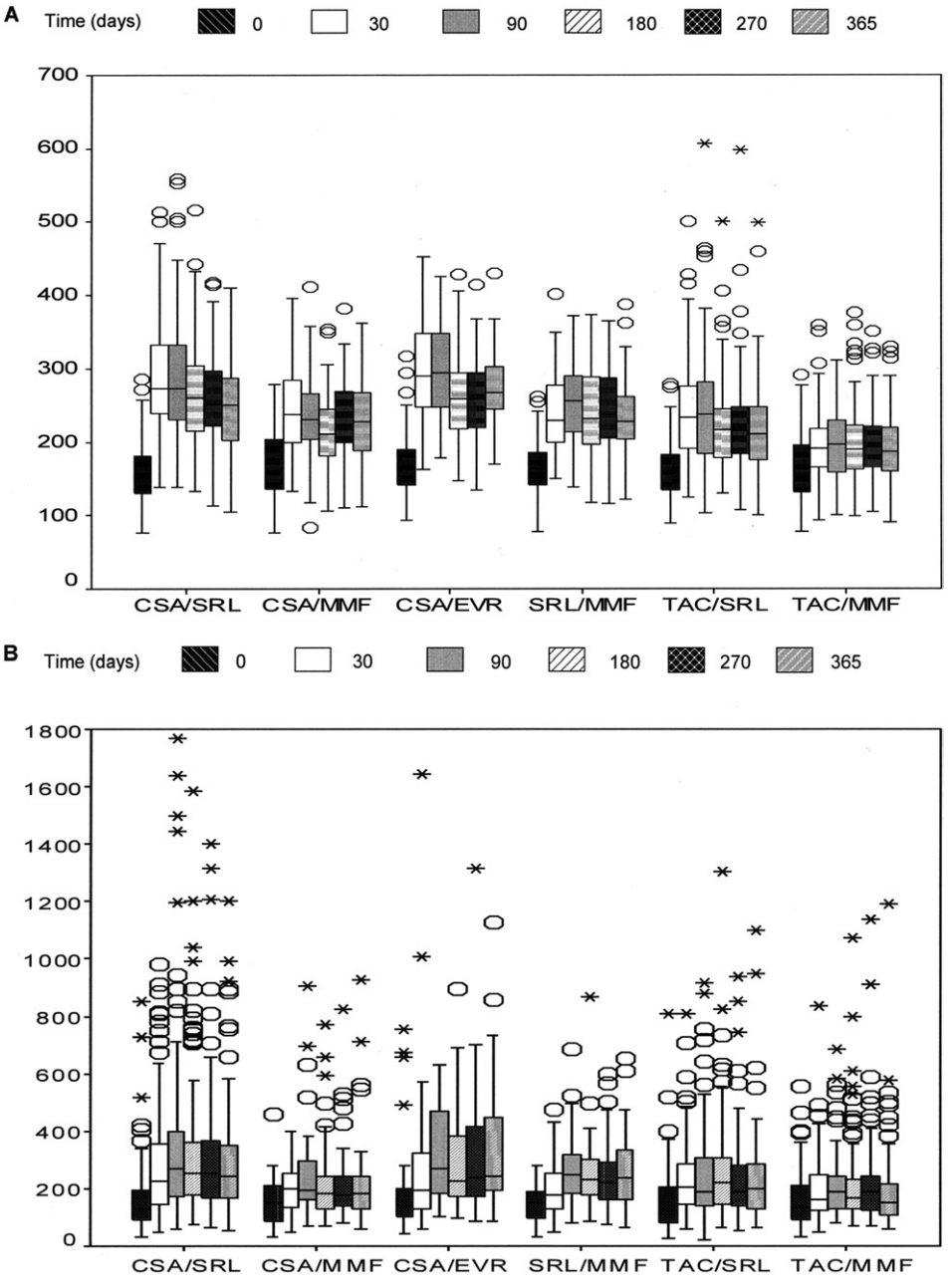

Fig 1. Box plot distribution of time-dependent changes in total cholesterol (**A**) and triglycerides (**B**) concentration according to immunosuppressive regimen. The boxes show the lower, median, and upper quartiles (25th, 50th, and 75th percentiles). *Outlier* (°) was defined as a value 1.5 times lower (or higher) than box length. *Extreme value* (*) was defined as a value 3 times lower (or higher) than box length. CSA, cyclosporine; SRL, sirolimus; MMF, mycophenolate mofetil; EVR, everolimus; SRL, sirolimus; TAC, tacrolimus.

C:HDL-C ratio above the recommended target increased 75% for males but did not change for females. For the TG:HDL-C ratio, a 31% increase was observed at 12 months after transplantation.

Finally, the proportion of patients with normal lipid profiles, including all lipid fractions and ratios, decreased from 28% before transplantation to 10% at 1 year there after. Overall, 27% of patients were prescribed a lipid-lowering agent at 12 months, a proportion that was higher among recipients treated with calcineurin inhibitors in combination with SRL or EVR. No significant differences in overall results were observed when analyzing only those patients who did not receive any lipid-lowering agent during the 12-month period of observation (data not shown).

LDL-C Versus Other Lipid Fractions and Ratios

In patients with LDL-C below 100 mg/dL (31.8%), over 60% of other lipid fractions and ratios were also within target ranges. Interestingly, among patients with LDL-C above 100 mg/dL (68.2%), over 57% of other lipid fractions and ratios were within target ranges (Table 3).

Table 3. Proportion of Patients With Lipid Fractions or Ratios Within Recommended Targets According to LDL-C Concentrations 1 Year After Kidney Transplantation

Lipid fraction or ratio (%)	LDL-C > 100 mg/dL (n = 260, 68.2%)	LDL-C < 100 mg/dL (n = 121, 31.8%)
Non-HDL-C < 130 mg/dL	3	78
HDL-C > 50 mg/dL female	77	66
HDL-C > 40 mg/dL male	79	61
Total	78	63
COL:HDL-C < 4.4 female	58	93
COL:HDL-C < 5.1 male	61	92
Total	60	92.6
LDL-C:HDL-C < 2.9 female	74	100
LDL-C:HDL-C < 3.3 male	69	99
Total	71	99.2
TG:HDL < 4.0	57	67

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Risk Factors Associated With Dyslipidemia

Using logistic regression analysis, we identified age, gender, time on dialysis, NODAT, type of calcineurin inhibitor, class of immunosuppressive agent, and prednisone dose to be associated with dyslipidemia (Table 4). Risk factors associated with higher TC concentration included age, gender, time on dialysis, CSA use, and EVR or SRL use, with AOR ranging from 1.6 to 3.5. Risk factors associated with higher LDL-C excluded gender but also included prednisone dose 30 days after transplantation (AOR of 1.6). Higher non-HDL-C concentrations were associated with CSA use, EVR or SRL use, and development of NODAT; the AOR ranged from 2.2 to 3.1. Finally, higher TG concentrations were associated with age, development of NODAT, and use of EVR or SRL with AOR ranging from 1.8 to 2.8. No risk factor was associated with lower HDL-C concentrations when the analysis was performed according to gender.

DISCUSSION

Baseline demographic characteristics of our study population showed relatively few risk factors associated with the development of dyslipidemia after transplantation. The population was relatively young and nonobese. It included only a small proportion of patients with chronic kidney disease due to diabetes (7%). Nevertheless, only 28% of these patients showed lipid profiles within normal laboratory ranges before the transplant surgery, as is typically seen among hemodialysis patients with chronic kidney disease.[19] Despite differences in age, ethnicity, and dialysis time, no significant differences were observed comparing lipid profiles of patients according to the immunosuppressive drug use after transplantation.

Our study confirmed that after kidney transplantation, there is a universal increase in all lipid fractions. At 1 year, the proportion of patients with a normal lipid profile was reduced to only 10%. Generally, increases in TC and TG were observed as early as 30 days after transplant surgery, peaking at 6 months with a trend to stabilization toward the end of first year, regardless of the immunosuppressive regimen (Fig 1). The overall use of statins (27%) was low.[20,21]

Generally, patients receiving CSA as opposed to TAC or SRL or EVR as opposed to MMF show worse lipid profiles despite a higher proportion of SRL or EVR patients prescribed statins at 1 year.[22] Compared with CSA, patients

Table 4. Risk Factors Associated With Dyslipidemia 1 Year After Kidney Transplantation

Parameters	TC > 224 mg/dL		LDL-C > 121 mg/dL		non-HDL-C > 193 mg/dL		TG > 197 mg/dL	
	AOR (95% CI)*	P	AOR (95% CI)	P	AOR (95% CI)	P	AOR (95% CI)	P
Age (≥37 y)	2.2 (1.4–3.5)	.0011	2.1 (1.3–3.4)	.0026	2.9490	.0859	1.8 (1.2–2.8)	.0071
BMI (≥23 kg/m^2)	0.6847	.4080	0.2763	.5991	0.8846	.3470	1.5378	.2150
Gender (male/female)	1.6 (1.0–2.6)	.0422	0.7680	.3808	0.3597	.5486	0.2842	.5940
Race (others/black or mulatto)	0.3080	.5789	0.0180	.8932	0.7643	.3820	0.0417	.8382
ESRD (others/DM)	0.0292	.8644	1.0791	.2989	0.1376	.7107	0.5595	.4544
Time on dialysis (≥21 mo)	1.8 (1.2–2.9)	.0087	2.0 (1.2–3.2)	.0046	0.1886	.6641	0.9235	.3366
Donor source (living/deceased)	0.1469	.7015	0.0084	.9268	1.4248	.2326	1.8589	.1728
Creatinine at 30 d (≥1.5 mg/dL)	0.5133	.4737	0.0344	.8530	0.4044	.5248	0.2644	.6071
ClCr at 30 d (≤60 min/mL/1.73m^2)	0.0803	.7769	0.0397	.8422	0.7498	.3865	1.4267	.2323
NODAT	2.0097	.1563	1.5658	.2108	2.5 (1.3–4.8)	.0049	2.1 (1.1–4.1)	.0301
Acute rejection (yes/no)	0.2811	.5960	0.4754	.4905	0.0002	.9881	0.0327	.8564
CNI (CSA/TAC)	3.5 (2.2–5.6)	<.001	2.4 (1.5–3.8)	.0004	3.1 (1.9–5.0)	<.001	2.2688	.1320
Adjunctive agent (SRL or EVR/MMF)	2.9 (1.8–4.7)	<.001	2.2 (1.3–3.6)	.0023	2.2 (1.4–3.7)	.0015	2.8 (1.8–4.4)	<.001
Prednisone dose (day 30 ≥ 0.38 mg/kg)	1.2358	.2663	1.6 (1.0–2.6)	.0497	0.0433	.8351	0.0905	.7635

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; AOR, adjusted odds ratio; BMI, body mass index; ESRD, end-stage renal disease; ClCr, creatinine clearance; NODAT, new-onset diabetes after transplantation; CNI, calcineurin inhibitor; CSA, cyclosporine; TAC, tacrolimus; SRL, sirolimus EVR, everolimus; MMF, mycophenolate mofetil; DM, diabetes mellitus.

*AOR: obtained from logistic regression analysis and 95% confidence intervals.

receiving TAC showed less increase in TC but similar increases in TG concentrations. Conversion from CsA to TAC can result in a decrease of LDL-C and TG levels but no change in HDL-C levels.[23] Finally, chronic corticosteroid use is associated with increases in TC, TG, and HDL-C.[24]

Current guidelines suggest that treatment of dyslipidemia should aim at LDL-C concentrations below 100 mg/dL among the general population. It is also recommended that kidney transplant recipients be considered in the highest-risk category, equivalent to that of patients with known coronary heart disease. Nevertheless, only one robust prospective clinical trial in a low-risk kidney transplant population showed that treatment of dyslipidemia achieving a 32% reduction in LDL-C concentrations was associated with fewer cardiac deaths or nonfatal myocardial infarctions.[25] On the other hand, all lipid fractions and ratios have been shown to be predictors of coronary heart disease in the general population.[26] High TG concentrations are also an independent risk factor associated with coronary heart disease.[27] In epidemiological studies, non-HDL-C concentration was superior predictor of cardiovascular risk compared with LDL-C.[28] Among our cohort of patients, a high proportion of patients with LDL-C below 100 mg/dL also showed other lipid fractions and ratios within target ranges. More importantly, 57% to 79% of patients with LDL-C above 100 mg/dL also showed other lipid fractions and ratios within target ranges. Based on the recognized predictive value of all these lipid fractions and ratios for cardiovascular events, it is difficult to evaluate risk based on the changes observed among this patient cohort. This pattern of lipid changes and the direct or indirect effects of SRL/EVR and other immunosuppressive agents, including antiproliferative effects, may influence the development and progression of atherosclerotic cardiovascular disease in kidney transplant patients.[24]

The limitations of our study include its retrospective nature and the lack of information on proteinuria and on smoking. It was not our intention to associate lipid profiles with cardiovascular outcomes. This would require longer follow-up, taking into account the sample size of this population and the relatively low rate of cardiovascular events.

In summary, lipid profiles change significantly early and almost universally at 1 year after kidney transplantation, with significant influences of demographic characteristics, clinical events, and the type of immunosuppressive drug. Inconsistent changes in lipid fractions and ratios, comorbidities, deterioration of allograft function, the differential effects of immunosuppressive drugs on the development of atherosclerosis, and drug-drug interactions all affect these moieties, possibly reducing the predictive value of LDL-C to predict cardiovascular events among the kidney transplant population.

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