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Serum lipids in children 3 to 5 years after kidney, liver, and heart transplantation

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Abstract Although dyslipidaemia is common after solid organ transplantation (Tx), there are few long-term studies in children. We investigated the prevalence of dyslipidaemia up to 5 years after Tx in 125 children on triple immunosuppression with one of three different well-functioning grafts, kidney, liver, and heart, and 181 controls. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations were measured annually. Low-density lipoprotein cholesterol concentrations were also calculated. The risk factors for dyslipidaemia were determined at 3 years. There was a high prevalence of hypertriglyceridaemia in all three groups, 50% in the kidney transplantation (KTx) and heart transplantation (HTx) groups and 30% in the liver transplantation (LTx) group. In addition, 50% of KTx patients had high TC. In the Tx groups taken together, the following independent associations were observed: KTx and high pre-Tx TC were associated with high TC, high trough concentration of blood cyclosporine with low HDL-C, and older age at Tx accounted for higher TG. Dyslipidaemia, especially hypertriglyceridaemia, was common 3–5 years after Tx. The aetiology is multifactorial and depends on the transplanted organ.

Keywords Transplantation · Cholesterol · Triglyceride · Paediatric · Cyclosporine · Methylprednisolone

Introduction

In adults, atherosclerotic vascular disease is the most important cause of death and graft loss after kidney transplantation (KTx) [1] and heart transplantation (HTx) [2]. The incidence of symptomatic arterial disease after KTx is three to four times that of the background population [3, 4]. In the general population, high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and low high-density cho-

lesterol (HDL-C) concentration are well-known risk factors for atherosclerosis [5] and are also believed to promote atherosclerosis after Tx [3]. The reported prevalence of hyperlipidaemia in adults after KTx varies widely, from 16 to 70% [6]. After liver transplantation (LTx), 16–50% of patients have elevated serum TC and approximately 40% have hypertriglyceridaemia [7]. LDL-C and TG remain high at 6 months, despite postoperative dietary recommendations in 64% and 41% of HTx patients, respectively [8]. Similarly, dyslipidaemia seems to complicate paediatric solid organ Tx [9, 10, 11], though there are few prospective long-term data regarding its permanence.

Dyslipidaemias have been considered to be the most significant non-immunological risk factors for transplant vascular disease [12]. Hypertriglyceridaemia in particular has been considered a strong predictor of graft loss and chronic rejection [13, 14]. The role of dyslipidaemia in promoting post-transplantation atherosclerotic vascular disease has also been doubted, as there are few data on the effect of lipid-lowering therapy in the prevention of cardiovascular disease and chronic allograft rejection in the long term. However, lipid-lowering therapy improves lipid values, without considerable adverse effects in the short term [15, 16]. In November 2002, the US FDA approved atorvastatin and pravastatin for treatment of familial hypercholesterolaemia in children older than 8 years. Preliminary results of atorvastatin and pravastatin in reducing cholesterol levels in paediatric heart transplant recipients have also been published [17, 18].

Pre-transplantation disease and lipid levels, weight gain after Tx, age, gender, the presence of diabetes, reduced kidney function, proteinuria, unfavourable diet, and the use of cyclosporine A (CyA), corticosteroids, and antihypertensives (β-blockers and diuretics) have all been associated with dyslipidaemia after Tx [9, 16, 19, 20]. Although these risk factors are common, their relative importance has been difficult to determine.

The aim of the present study was to characterize the serum lipid profile and to determine the prevalence and permanence of dyslipidaemias in children 1–5 years after KTx, LTx, or HTx and to compare the values with controls. A further aim was to assess the determinants of dyslipidaemia 3 years after Tx in children with stable graft function.

Patients and methods

Subjects

A total of 125 children who had received a kidney, liver, or heart transplant between October 1987 and October 1997 was followed for 3–5 years after Tx. There were 71, 34, and 20 children in the KTx, LTx, and HTx groups, respectively. Correspondingly, 57, 31, and 13 of the children were followed for 5 years. The study group was selected from all 130 children who had survived for at least 3 years after Tx. Four KTx patients were excluded because of lacking data and one HTx patient because lipid-lowering medication was started at 1.5 years. The clinical characteristics are presented in Table 1. All the subjects volunteered for the study, which had been approved by the Ethical Committee of Tampere and Helsinki University Hospital.

All children with end-stage kidney disease were on peritoneal dialysis before KTx. Pre-Tx diagnoses were: congenital nephrosis ($n=38$), urethral valve ($n=10$), nephronophthisis ($n=5$), polycystic kidney disease ($n=3$), prune-belly syndrome ($n=2$), vesico-ureteral reflux ($n=2$), glomerulonephritis ($n=2$), Alport's syndrome ($n=1$), mega-ureter ($n=1$), neuroblastoma ($n=1$), dysplastic kidney ($n=1$), vaginal cancer ($n=1$), bilateral multicystic kidneys ($n=1$), Denys-Drash syndrome ($n=1$), renal insufficiency due to a complication of prematurity ($n=1$), and congenital nephropathy (juvenile nephronophthisis) ($n=1$). Bilateral nephrectomy was

Table 1 Clinical characteristics of 125 children studied for dyslipidaemia after kidney, liver or heart transplantation and controls. P values of statistically significant differences are displayed in abbreviations

Characteristic	Kidney		Liver		Heart		Controls
Gender, male/female (n)[a]	50/21		16/18		9/11		112/69
Median age at Tx (years)[b]	3.8		3.6		12.3		9.1
(range)	(1.1–15.9)		(0.4–16.3)		(1.0–16.8)		(3.2–18.7)
Percentage of patients with acute rejections (n)	62.0 (44)		73.5 (25)		60.0 (12)		
Timepoints	1 year	3 year	1 year	3 year	1 year	3 year	
Height SDS (mean)[c]	−1.7	−1.5	−2.0	−2.0	−1.4	−1.5	0.2
(95% CI)	(−2.0; −1.5)	(−1.7; −1.2)	(−2.6; −1.5)	(−2.5; −1.5)	(−2.2; −0.7)	(−2.1; −0.8)	(0.0; 0.3)
BMI SDS (mean)	0.5	0.5	0.4	0.8	0.1	0.0	0.3
(95% CI)	(0.2; 0.8)	(0.2; 0.8)	(−0.3; 1.2)	(0.3; 1.3)	(−0.7; 0.9)	(−0.8; 0.9)	(0.1; 0.5)
HOMA (median)[d]	1.6	1.8	0.8	1.7	2.5	1.8	
(Q_1, Q_3)	(0.7; 2.7)	(1.1; 3.1)	(0.6; 1.8)	(1.0; 3.0)	(1.5; 3.4)	(1.2; 3.1)	

[a]Within Tx groups, gender distribution differed, $P=0.024$
[b]Difference between Tx groups, $P=0.004$ and all groups at 3 years, $P=0.001$
[c]Difference between groups at 1 and 3 years, $P<0.001$ (ANOVA)
[d]Log transformation normalized the distribution. Approximation of HOMA is based on assumption that normal-weight healthy subjects aged <35 years have an insulin resistance of 1 [28]. Mean + 2 SDS for healthy adults is approximately 2.6 [56]. Change in HOMA between time points: $P=0.029$, difference between groups: $P=0.048$, interaction between time and group: not significant (ANOVA for repeated measures)

undertaken prior to Tx in all patients with congenital nephrosis (NPHS1) except one, and unilateral or bilateral nephrectomy in eight patients with other diagnoses.

Indications for LTx were biliary atresia ($n=12$), tyrosinaemia ($n=7$), hepatitis (one neonatal) ($n=5$), hepatoblastoma ($n=4$), Wilson's disease ($n=2$), hepatocellular carcinoma ($n=1$), homozygous familial hypercholesterolaemia ($n=1$), hepatic adenoma ($n=1$), and α_1-antitrypsin deficiency ($n=1$). The high number with malignant liver disease is explained by our active policy of accepting children with hepatoblastoma, without extrahepatic disease, for liver transplantation after chemotherapy [21]. Indications for HTx were a congenital heart defect ($n=9$) and restrictive or dilative cardiomyopathy ($n=11$).

Living-related donor grafts were transplanted only in the KTx group in 25 (35%) patients. Seven had a second graft, three in the KTx and four in the LTx group. None of the patients was hypothyroid or diabetic, and all were on a common Finnish diet. If there was marked weight gain after Tx, caloric restriction and a diet low in saturated fat was advised.

The control group was recruited between November 1997 and August 1999 and comprised 181 first-visit paediatric clinic outpatients or minor paediatric or oto-rhino-laryngological surgery patients without regular medication, acute inflammation, or metabolic disease.

Immunosuppression

The immunosuppressive protocols have been described elsewhere [22, 23, 24]; they included triple therapy with azathioprine (AZA), CyA, and methylprednisolone (MP), in addition to anti-thymocyte globulin after HTx. The CyA whole-blood (B-CyA) trough level was maintained between 80 and 120 μg/l after the first year in the KTx group and between 100 and 200 μg/l in the LTx and HTx groups. The CyA dose was individually adjusted according to trough levels and renal function tests to maintain sufficient immunosuppression and to avoid nephrotoxicity. Preschool children took CyA in three daily doses because of their faster metabolism, and older children in two. In 1994, CyA was introduced in a microemulsion composition. In the KTx group, one boy was on triple therapy with tacrolimus from 2 years on and two boys received cyclophosphamide instead of AZA at 3 years as treatment for renephrosis [25]. MP was given on alternate days beyond the first 3–6 months after Tx. One girl was switched to tacrolimus and MP during the first year, as were two children during the second year after LTx. One especially steroid-sensitive boy was taken off MP during the first year after LTx. Antihypertensive therapy was instituted if ambulatory-measured blood pressure exceeded age-specific reference values. Calcium-channel blockers were mostly used. Two children in the KTx group were on warfarin as thrombosis prophylaxis subsequent to Tx. In one, warfarin was replaced with acetosalicylic acid (ASA) between 1 and 2 years. All HTx, six KTx, and two LTx patients received ASA after Tx. Acute rejection during the first 3 months after Tx was treated with MP at 1.5 mg/kg orally, followed by 3 mg/kg per day, for 5 days or until the blast cell reaction in a fine-needle aspirate subsided.

Methods

The following clinical data were collected: gender, age at Tx, preceding nephrectomy (KTx), indication for Tx, living-related donor vs cadaveric graft, first or second graft, doses of AZA, CyA, MP, and cumulative dose of CyA and MP at 3 years; the use of antihypertensives (nifedipin, β-blocker or diuretics), anti-epileptics, hydrocortisone (HC) substitution, and growth hormone (GH); the occurrence and number of acute rejections, height, weight, kidney function [glomerular filtration rate (GFR), creatinine, daily urinary protein excretion (dU-prot)], liver function [serum alanine aminotransferase (ALT), plasma thromboplastin time (TT), serum total bilirubin], fasting blood glucose and insulin, coronary narrowing in angiography (HTx), and heart function (clinical echocardiography). Data on dyslipidaemia or early-onset cardiovascular disease (men < 55 years, women < 65 years) in first-degree or second-degree relatives were collected by questionnaire in a subgroup of 80 patients and 180 controls.

Anthropometry

Height was measured with a Harpenden stadiometer (Holtain, Crymych, Dyfed, UK) and weight on electronic scales at noon. Body mass index (BMI) was calculated according to the formula: weight (kg)/height^2 (m^2). Body mass index standard deviation score (BMI SDS) was calculated according to the following equation: (individual BMI−mean BMI for age)/SD, and height standard deviation score (HSDS) according to the following equation: (observed height−mean height for age)/SD. SD represents the standard deviation for a general Finnish population of the same chronological age and gender [26, 27]. Growth velocity was defined as the rate of change in HSDS during follow-up (ΔHSDS). A positive value indicates catch-up growth, a negative value deceleration of growth.

Laboratory analyses

Blood samples for lipid, B-CyA trough levels, glucose and insulin were taken after overnight fasting, while blood samples for other laboratory tests were taken the previous day. A 24-h urine sample was collected within a week from the fasting blood sample. B-CyA was determined by specific monoclonal radioimmunoassay. GFR was determined by ^{51}Cr-EDTA clearance [22]. If the distribution space deviated more than 10% from the expected extracellular fluid volume, the result was ignored. dU-prot, determined from 24-h urine output, creatinine, ALT, TT (expressed as percentage of normal mean), total bilirubin, insulin and glucose were determined by routine laboratory methods. A result above the age-specific and gender-specific reference value of the laboratory was considered abnormal. Insulin resistance index as homeostasis model assessment of insulin resistance (HOMA) was calculated according to the equation: resistance = insulin/($22.5e^{-\ln \text{glucose}}$) [28].

Lipid analyses were performed on fresh samples according to laboratory routine. TC, HDL-C and TG concentrations were analysed enzymatically (Reagena, Roche). LDL-C was calculated according to Friedewald's formula though not if TG values exceeded 4.0 mmol/l [29]. HDL-C was determined after precipitation of other lipoproteins by dextran sulphate and $MgCl_2$ between 1987 and February 1997 and directly, without precipitation of other lipoproteins, from February 1997 on. During follow-up, the calibrator for TC and TG analyses was changed. The effect of changes in calibrators and methods was corrected by a regression equation.

Statistical analysis

The values are presented as mean and 95% confidence interval (CI) and/or range or SD or median and lower (Q1 = 25th percentile) and upper (Q3 = 75th percentile) quartile or number (n) and percentages of subjects. MP dose is presented as daily dose, which equals the dose on alternate days divided by 2. The normality of the distribution of the variables was tested by one-sample Kolmogorov–Smirnov goodness-of-fit test. If the distribution was skewed, we tried parameters to normalize by log transformation. As distribution of TG was skewed, the mean of TG distribution was displayed

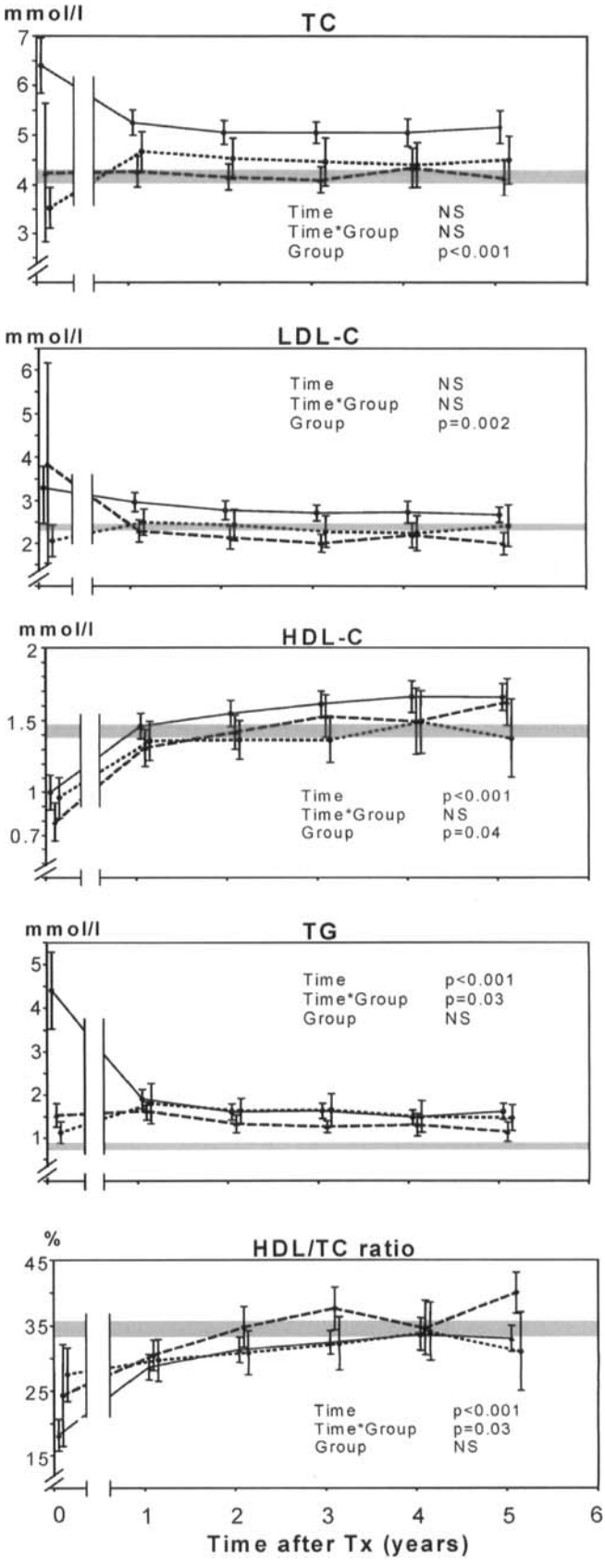

Fig. 1 Serial changes in lipid values of 125 children 1 to 5 years after kidney, liver and heart transplantation. Mean and 95% CI for the mean are displayed. *Solid line* KTx, *dashed line* LTx, *dotted line* HTx, *shadowed area* control group. *Textboxes* represent results of ANOVA for repeated measures

as geometric mean (the antilogarithm of the mean of the log-transformed distribution) instead of arithmetic mean (Fig. 1). Arithmetic means are shown for TC and LDL-C distributions, since the distribution was skewed only before Tx.

Differences in means between groups were tested with the analysis of variance (ANOVA) for normally distributed continuous variables or Kruskal–Wallis test for skewed or discrete variables. To evaluate whether changes in variables within time were statistically significant, we used ANOVA for repeated measures (normal distribution) or the Wilcoxon test (skewed or discrete distribution). When making group comparisons in each time point separately, we multiplied P values by the number of tests performed to avoid a multiple comparison problem. The significance of differences in the categorical variables was tested by the χ^2 test. In cases where the frequencies in the cells were low, Fisher's exact test was used instead. We used the McNemar test to evaluate the significance of changes within time in categorical variables. The association with the pre-Tx and subsequent lipid values to 3rd-year values was evaluated by univariate linear regression, and coefficients of determination are reported.

Determinants of dyslipidaemia were analysed by univariate and multivariate forward stepwise logistic regression at 3 years, as all patients were followed for at least 3 years. Altogether, 120 children, who were treated with CyA and MP, were included in the logistic regression analysis at 3 years so that we could determine the independent significance of the variables associated with dyslipidaemia. We dichotomized lipid variables (TC, HDL-C, LDL-C, TG and HDL/TC), using the most markedly dyslipidaemic quartile as an indicator of dyslipidaemia. Analyses were done for all groups together and separately for each Tx group. Possible risk factors are described in Table 2. Variables were divided into three blocks, each of the blocks including transplanted organ or pre-Tx diagnosis and respective pre-Tx lipid data (Table 2). Univariate associations between lipid variable and each possible risk factor were first separately analysed by logistic regression. Then, we carried out multivariate logistic regression analysis, using each block of variables separately in the model. Variables significant in the first multivariate blocks were included in the final model. The variables in the model did not correlate significantly (based on the correlation coefficient or cross-tabulation). A variable was included in the multivariate model if its significance was less than 0.05 and was removed if the significance was >0.1. Otherwise, a P value less than 0.05 was considered statistically significant. Computations were carried out with SPSS for Windows version 10.1 (SPSS, Chicago, Ill, USA).

Results

Clinical characteristics

Table 1 shows some clinical characteristics of the three Tx groups, and the controls. Gender distribution was similar in the LTx and HTx groups, whereas 70% of the KTx patients were boys ($P=0.024$). HTx patients were on average older ($P=0.004$). On average, growth velocity was delayed in all three patient groups during the first year after Tx [KTx: ΔHSDS $=-0.1\pm0.6$ SD (mean $\pm$ SD),

Table 2 Block division of the variables in multivariate logistic regression analysis. Variables were included categorized or continuous

Parameter	All ($n=115$)	Kidney group ($n=66$)	Liver group ($n=33$)	Heart group ($n=19$)
Block 1	Organ[a]	NPHS1 vs other	No pre-Tx liver failure vs other[b]	Cardiomyopathy vs other
Organ function	Respective pre-Tx lipid data (mmol/l)	Respective pre-Tx lipid data (mmol/l)	Respective pre-Tx lipid data (mmol/l)	Respective pre-Tx lipid data (mmol/l)
	Low GFR[c]	Low GFR[c]	Low GFR[c]	Low GFR[c]
	dU-prot >200 mg[d]	dU-prot >200 mg[d]		
	High TT[e]	High TT[e]	High TT[e]	High TT[e]
Block 2	Organ[a]	NPHS1 vs other	No pre-Tx liver failure vs other[b]	Cardiomyopathy vs other
Medication	Respective pre-Tx lipid data	Respective pre-Tx lipid data	Respective pre-Tx lipid data	Respective pre-Tx lipid data
	High MP[f]	High MP[f]	High MP[f]	High MP[f]
	B-CyA (μmol/l)	B-CyA (μmol/l)	B-CyA (μmol/l)	B-CyA (μmol/l)
	GH use[g]	GH use[g]	GH use[g]	GH use[g]
	β-blocker or diuretic use[h]	β-blocker or diuretic use[h]		
Block 3	Organ[a]	NPHS1 vs other	No pre-Tx liver failure vs other[b]	Cardiomyopathy vs other
Clinical characteristics	Respective pre-Tx lipid data	Respective pre-Tx lipid data	Respective pre-Tx lipid data	Respective pre-Tx lipid data
	Age at Tx	Age at Tx	Age at Tx	Age at Tx
	BMI SDS	BMI SDS	BMI SDS	BMI SDS
	Gender	Gender	Gender	Gender

[a]Transplanted organ (kidney vs liver vs heart)
[b]Hepatic cancer, familial hypercholesterolaemia, hepatic adenoma vs other
[c]Three highest quartiles = 0, lowest quartile = 1
[d]Absent = 0, present = 1
[e]Three highest quartiles = 0, lowest quartile = 1
[f]Dose at 3 years (three lowest quartiles = 0, highest quartile = 1)
[g]0 = No, 1 = yes
[h]0 = No, 1 = yes

Table 3 Medication at 1 and 3 years in 125 children studied for dyslipidaemia after kidney, liver or heart transplantation

Medication	Kidney		Liver		Heart	
	1 Year	3 Years	1 Year	3 Years	1 Year	3 Years
CyA, mg/kg per day, median (Q_1, Q_3)[a]	8.0 (5.6; 10.6)	5.4 (4.2; 6.8)	8.7 (5.3; 10.5)	5.3 (3.4; 6.6)	6.9 (5.0; 9.5)	5.7 (4.2; 6.6)
B-CyA, μg/l, median (Q_1, Q_3)[b]	110 (83; 147)	93 (77; 113)	184 (109; 225)	130 (80; 160)	194 (150; 244)	164 (137; 196)
MP, mg/kg per day, median (Q_1, Q_3)[a]	0.2 (0.1; 0.2)	0.1 (0.1; 0.1)	0.2 (0.1; 0.2)	0.1 (0.1; 0.1)	0.1 (0.1; 0.2)	0.1 (0.1; 0.1)
MP, mg/kg per year, median (Q_1, Q_3)[a,c]	87 (78; 101)	46 (35; 52)	99 (92; 115)	40 (31; 53)	90 (82; 97)	33 (29; 48)
AZA, mg/kg per day, median (Q_1, Q_3)	1.2 (1.2; 1.4)	1.3 (1.2; 1.4)	1.3 (1.2; 1.3)	1.3 (1.1; 1.4)	1.3 (1.2; 1.4)	1.3 (1.2; 1.5)
Antihypertensives, % (n)[d]	49.3 (35)	26.8 (19)	32.4 (11)	8.8 (3)	30.0 (6)	20.0 (4)
β-blockers or diuretics, % (n)	19.7 (14)	11.3 (8)	8.8 (3)	0 (0)	15.0 (3)	5.0 (1)
GH treatment, % (n)[e]	0 (0)	23.9 (17)	0 (0)	17.6 (6)	5.0 (1)	15.0 (3)
HC substitution, % (n)	25.4 (18)	15.5 (11)	38.2 (13)	47.1 (16)	75 (15)	50.0 (10)

[a]Change between 1 and 3 years: $P<0.001$ for kidney, liver and heart transplantation groups
[b]Change between 1 and 3 years: $P<0.01$ for kidney and liver patients, and difference between groups at 1 and 3 years, $P<0.001$
[c]Difference between the groups at 1 year: $P=0.003$
[d]Difference between 1 and 3 years, kidney transplantation group: $P<0.001$; liver transplantation group, $P=0.008$
[e]Difference between 1 and 3 years all groups together: $P<0.001$

LTx: ΔHSDS = -0.7 ± 0.5 SD, and HTx: ΔHSDS = -0.3 ± 0.5 SD]. Patients in the KTx group showed an average catch-up growth of 0.3 ± 0.6 SD between the first and third year, while patients in LTx and HTx groups did not show any catch-up growth (0.0 ± 0.7 SD and 0.0 ± 0.4 SD, respectively). Table 3 shows the medication used. The cumulative MP dose for the first year was highest for LTx patients ($P=0.003$) and decreased significantly in all three Tx groups ($P<0.001$) from the first to the third year. KTx patients needed more antihypertensive therapy, but the difference between groups was not statistically significant. The frequency of antihypertensive therapy decreased from 1 to 3 years within KTx and LTx groups. GH therapy was introduced until 3 years to 17 (23.9%), six (17.6%) and three (15.0%) children in the KTx, LTx and HTx groups, respectively. There was no difference in the prevalence of dyslipidaemia or early onset cardiovascular disease in first-degree or second-degree relatives between groups.

Graft function

At 3 years, 35.2% of the KTx patients had a GFR below 60 ml/min per 1.73 m^2. The corresponding values in the LTx and HTx groups were 8.8% and 10.0%

(Table 4). Nephrotic syndrome (proteinuria >40 mg/m^2 per h with oedema and an albumin concentration <25 g/l) was diagnosed during the first 3 years in eight KTx subjects (six NPHS1, one urethral valve, one chronic glomerulonephritis). All except one of these eight patients were in remission at the time of the lipid tests. In the KTx group, mild proteinuria (>200 mg/day) occurred at least once in 14 children (19.7%), while in the LTx group the number was four (11.8%). At 3 years, a serum protein concentration below normal was seen in four (5.6%) children in KTx, two (5.9%) in LTx and four (20.0%) in HTx group. Reduced liver function (TT <70% of the normal mean) was rare in the KTx group (3%) and more common in the LTx (18%) and HTx (20%) groups. An abnormal ALT level was most common in the LTx group, 21% vs 0% in the KTx and HTx groups ($P<0.001$). Increased total bilirubin was seen in 0%, 9% and 7% in the KTx, LTx and HTx patients, respectively. Three children (15%) in the HTx group had angiographically visible coronary narrowing at 3 years. In echocardiography, the ejection fraction and fractional shortening were within normal limits.

Serum lipids

TG and associations

Figure 1 shows the mean serum lipid concentrations in our patients and controls. All three patient groups had higher mean TG level than the controls ($P<0.001$). However, the mean TG concentration decreased in all three groups from 1 to 3 years ($P<0.001$ Fig. 1). The prevalence of high TG (TG >1.5 mmol/l) varied from 17 to 61% in the three groups and was three- to seven-times higher than in the controls ($P<0.001$; Fig. 2). After KTx, the prevalence of high TG decreased from a pre-Tx prevalence of 94% and affected only 61% of the patients at 1 year and 45% at 3 years (prevalence prior to Tx vs 1 year, $P<0.001$). Mean TG concentration was slightly lower in LTx than in KTx and HTx patients from 1 to 3 years (Fig. 1). Pre-Tx TG did not statistically significantly predict the lipid values after Tx, but after Tx, preceding TG values explained 19 to 33% of the variation in TG in all groups.

Statistically significant explanatory variables from univariate and multivariate model lipid variables are given in Tables 5 and 6, respectively. As GH seemed to be associated with high TG in the LTx group, lipid values at 1 and 3 years were compared between children without GH and children who were introduced to GH after 1 year. In the KTx group, children who were introduced to GH had higher mean TG concentration levels before and during GH therapy than children without GH. TG decreased in all children, but no change in TG due to GH seemed to occur [TG in children without GH at 1 year after Tx: 2.17 mmol/l (geometric mean) vs1.60 mmol/l, respectively, and at 3 years with and without GH: 1.76 mmol/l vs 1.40 mmol/l; significance of change between time points: $P=0.007$, significance of difference between groups: $P=0.013$, and interaction between time and group: $P=0.51$, ANOVA for repeated measures]. In the LTx group, GH-treated children also had higher TG, though not statistically significantly, $P=0.082$. Kidney function was not independently associated with high TG. Patients in the highest quartile of TG were significantly older when all groups were analysed together (7.2 vs 3.3 years, median, $P=0.003$ and in the KTx group (6.3 vs 2.7 years, median, $P=0.011$).

Cholesterol and associations

Mean TC and LDL-C concentrations were stable after Tx, but HDL-C concentration as well as HDL/TC increased in all groups, $P<0.001$ (Fig. 1). A difference was observed in the magnitude of improvement of HDL/TC, $P=0.03$, as this was most obvious in the LTx group. During follow-up, 47% to 56% of the KTx, 6% to 26%

Table 4 Graft function in 125 children 1 and 3 years after kidney, liver or heart transplantation

Parameter	Kidney		Liver		Heart	
	1 Year	3 Years	1 Year	3 Years	1 Year	3 Years
GFR, ml/min per 1.73 m^2, mean (95% CI)[a]	76 (71; 82)	69 (63; 74)	104 (93; 115)	98 (88; 108)	104 (89; 120)	93 (81; 105)
(range)	(26–130)	(26–144)	(48–182)	(38–154)	(33–161)	(52–155)
dU-prot >500 mg, % (*n*)	4.2 (3)	5.6 (4)	0 (0)	5.9 (2)	0 (0)	0 (0)
dU-prot >200 mg, % (*n*)	11.3 (8)	11.3 (8)	2.9 (1)	8.8 (3)	5.0 (1)	0 (0)
ALT, U/l, median (Q_1, Q_3)[a]	15 (13; 20)	14 (10; 16)	29 (19; 56)	24 (18; 39)	17 (12; 29)	13 (11; 15)
Total bilirubin, μmol/l, median (Q_1, Q_3)[b]	7 (5; 10)	8 (5; 10)	10 (6; 15)	10 (8; 14)	8 (6; 13)	9 (6; 11)
TT, %, median (Q_1, Q_3)[c]	107 (95; 131)	109 (94; 124)	87 (75; 102)	89 (72; 108)	87 (65; 102)	81 (75; 106)

[a]Time, $P<0.001$; group, $P<0.001$; time × group, not significant (ANOVA for repeated measures)
[b]Change in total bilirubin between 1 and 3 years: $P=0.042$ for LTx group
[c]Difference between groups: $P<0.001$ at 1 and 3 years

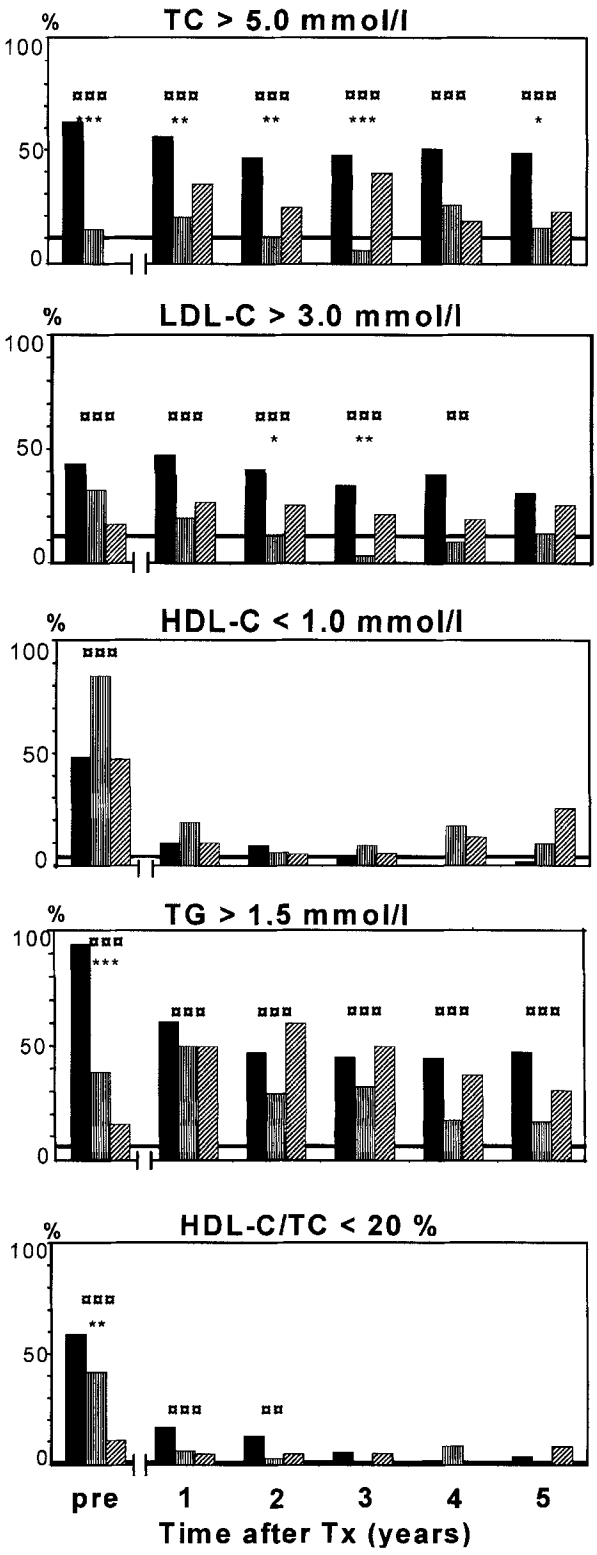

Fig. 2 Frequencies of dyslipidaemias in 125 children 1 to 5 years after kidney, liver and heart transplantation and controls. *Filled column* KTx, *hatched with vertical lines* LTx, *hatched with oblique lines* HTx, *horizontal line behind the columns* control group. ¤ $P<0.05$, ¤¤ $P<0.01$, ¤¤¤ $P<0.001$: significance of difference in frequencies of dyslipidaemia between the three Tx and control groups (cross-tabulation). * $P<0.05$, ** $P<0.01$, *** $P<0.001$: significance of difference in dyslipidaemia between the Tx groups (cross-tabulation)

of the LTx and 19% to 40% of the HTx children were hypercholesterolaemic (Fig. 2). At 3 years, 39%, 59% and 42% of the children in the KTx, LTx and HTx groups, respectively, had HDL-C, LDL-C and TG levels within the normal range. The KTx patients had a high mean TC and LDL-C but not a low HDL-C. Pre-Tx TC and HDL-C were of moderate predictive value, explaining a maximum of 10% of the variation in TC and HDL-C concentrations at 3 years in the KTx group. After Tx, the lipid values mostly predicted subsequent lipid values, $P<0.01$, explaining from 23% (TC in the LTx group) to 74% (HDL/TC in the HTx group) of the variation. In the final multivariate model for all Tx groups, a kidney graft together with a high pre-Tx TC level explained independently a high TC concentration at 3 years (Table 6). A high B-CyA concentration explained independently low HDL-C in all groups together, while a high MP dose explained low HDL-C in the KTx and HTx groups.

As LTx without pre-Tx liver failure ($n=7$) was an independent determinant of the highest quartile of TC (Table 6), the role of hepatic cancer ($n=5$) was tested against other indications for LTx in the multivariate model and was statistically significant; OR = 29.3 (95% CI 2.4–357.9), $P=0.008$. The patient with homozygous familial hypercholesterolaemia and no liver failure prior to Tx had a normal TC level of 4.2–4.9 mmol/l after LTx. Cumulative doses of CyA and MP did not add any new lipid associations.

Discussion

This is the first prospective, long-term study in which lipid profiles are followed in kidney, liver and heart transplanted children, all on triple immunosuppression and with acceptable graft function, to find determinants of dyslipidaemia. High TG levels were common in all three Tx patient categories and significantly more frequent than in controls, with a prevalence of 50% in the KTx and HTx patients and 30% in the LTx ones. However, during the first 3 years, in every Tx group, mean TG concentration decreased. Before KTx, our patients had severe hypertriglyceridaemia, typical of patients with end-stage kidney disease and on dialysis [30, 31]. After KTx, a high TG level was much less frequent. LTx patients had mild hypertriglyceridaemia before and after LTx, while HTx patients had a more severe hypertriglyceridaemia after HTx.

Table 5 Statistically significant associations from univariate logistic regression analysis between categorized lipid variables [most markedly dyslipidaemic lipid quartile (below 25th or above 75th percentile) vs other quartiles] and independent variables displayed in Table 2

Group	Lipid variable	Independent variable	OR	(CI 95%)	Significance
All ($n=120$)	High TC	TC before Tx (mmol/l)	1.22	(1.05–1.41)	0.009
		High TT (s)	0.26	(0.07–0.92)	0.040
		Organ			0.005
		Liver vs kidney	0.06	(0.01–0.43)	
		Heart vs kidney	0.28	(0.08–1.05)	
	High LDL-C	Organ			0.015
		Liver vs kidney	0.06	(0.01–0.45)	
		Heart vs kidney	0.45	(0.14–1.51)	
		dU-prot > 200 mg	4.04	(1.01–16.16)	0.048
	Low HDL-C	B-CyA (μmol/l)	1.02	(1.01–1.02)	0.001
		Organ			0.007
		Liver vs kidney	1.63	(0.56–4.73)	
		Heart vs kidney	5.96	(1.97–18.02)	
	High TG	Age at Tx (years)	1.12	(1.03–1.21)	0.009
		High TT (s)	0.17	(0.04–0.79)	0.023
		GH use	2.67	(1.04–6.86)	0.042
		dU-prot > 200 mg	4.53	(1.13–18.20)	0.033
	Low HDL-C/TC	β-blocker or diuretic use	7.17	(1.67–30.79)	0.008
Kidney Tx group ($n=70$)	High TC	B-CyA (μmol/l)	1.01	(1.00–1.02)	0.057
	Low HDL-C	B-CyA (μmol/l)	1.01	(1.00–1.02)	0.069
		High MP	5.63	(1.71–18.51)	0.004
	High TG	Age at Tx (years)	1.16	(1.04–1.30)	0.011
	Low HDL-C/TC	BMI SDS	2.24	(1.26–3.96)	0.006
		dU-prot > 200 mg	6.94	(1.45–33.18)	0.015
		β-blocker or diuretic use	10.29	(1.87–56.72)	0.007
Liver Tx group ($n=30$)	High TC	No pre-Tx liver failure	8.89	(1.29–61.06)	0.026
		Cancer vs other	29.33	(2.40–357.85)	0.008
	Low HDL-C	Low GFR	11.00	(1.27–95.18)	0.029
	High TG	BMI SDS	2.17	(1.00–4.72)	0.051
		GH use	17.25	(1.73–172.00)	0.015
Heart Tx group ($n=20$)	Low HDL-C	High MP	19.50	(1.30–292.67)	0.032

As risk factors for dyslipidaemia analysed for all Tx patients together, the risk for high TG at 3 years after Tx seemed to increase with increasing age at Tx. A kidney graft and a high concentration of TC before Tx were independent risk factors for hypercholesterolaemia after Tx. A high CyA trough level was associated with low HDL-C concentration, and the use of β-blockers or diuretic agents with a low HDL/TC. Associations of the risk factors within separate Tx groups are discussed below.

Mean TG concentration was reduced, though not normalized, in every Tx group during the first 3 years. This change in TG concentration coincided with a reduction in the median dosage of MP and CyA, as well as antihypertensive medication, whilst GH therapy was introduced in one-fifth of the children. Glucocorticoids may increase TG after Tx [32, 33, 34]. They may decrease their elimination, and increase hepatic synthesis of TG containing lipoproteins, through the action of lipoprotein lipase and fatty-acid synthase and acetyl-CoA carboxylase [35, 36]. However, in our patients, a high dose of MP did not show an independent association with high TG, although it has to be noted that our patients were on low-dose steroids, given every other day. In the LTx patients, the use of GH was associated with high TG, but further analysis showed that GH-treated children already had higher TG levels before introduction of GH. Thus, GH therapy did not cause an increase in TG in our patients, in line with previous observations [37]. In the literature, reduced kidney function and proteinuria have also been associated with high TG [32, 38]. In our patients high TG was not independently associated with reduced GFR or urinary protein concentration. This might be explained by the fairly good GFR seen in most of our patients, even in the KTx group. The mean GFR was 68.6 ml/min per 1.73 m^2 at 3 years after Tx.

After Tx, hypercholesterolaemia under triple immunosuppression with CyA is a frequent finding, and in adult patients mean TC, LDL-C and HDL-C concentrations remain stable from 1 year on [16, 19, 32, 38, 39, 40, 41, 42]. However, our patients showed significant improvement in HDL/TC, making HDL/TC comparable with the controls after 1 year. This reduces the significance of a high LDL-C, assuming that HDL-C would be functionally normal. Hypercholesterolaemia was most prevalent in KTx patients but less prevalent and less severe than in previous reports in adults [20, 42]. Low HDL/TC was most prevalent at 1 and 2 years after KTx and seen in 17 and 13% of the KTx patients, respectively. The prevalence of a reduced HDL/TC was much lower than in adult KTx patients treated with

Table 6 Results from multivariate logistic regression. Dependent variables were categorized lipid variables. Block division of the included independent variables is displayed in Table 2. Those variables significant in the first blocks were included in the final model

Group	Lipid variable	Independent variable	Significant in the first block			Significant in the final block		
			OR	(CI 95%)	Significance	OR	(CI 95%)	Significance
All	High TC	TC before Tx[a]	1.21	(1.02–1.45)	0.034	1.21	(1.02–1.45)	0.034
		Organ[a]			0.027			0.027
		Liver vs kidney	0.05	(0.01–0.52)		0.05	(0.01–0.52)	
		Heart vs kidney	0.54	(0.13–2.25)		0.54	(0.13–2.25)	
	Low HDL-C	Organ[b]			0.026			
		Liver vs kidney	1.58	(0.41–6.10)				
		Heart vs kidney	5.12	(1.55–16.92)				
		B-CyA (μmol/l)	1.02	(1.004–1.03)	0.006	1.02	(1.006–1.023)	0.001
	High TG	dU-prot >200 mg	4.88	(1.20–19.84)	0.027			
		TG before Tx (mmol/l)	1.15	(0.99–1.35)	0.072	1.15	(0.99–1.35)	0.072
		Age at Tx	1.16	(1.06–1.28)	0.002	1.16	(1.06–1.28)	0.002
	Low HDL-C/TC	β-blocker or diuretic use	5.33	(1.08–26.26)	0.040	7.17	(1.67–30.79)	0.008
		Age at Tx	1.10	(1.00–1.21)	0.052			
Kidney Tx group	High TC	B-CyA (μmol/l)	1.02	(1.001–1.03)	0.031	1.01	(1.00–1.02)	0.057
	High LDL-C	B-CyA (μmol/l)	1.03	(1.001–1.061)	0.042			
	Low HDL-C	dU-prot >200 mg	6.33	(0.92–43.68)	0.061			
		High MP	9.25	(2.00–42.77)	0.004	6.33	(1.88–21.30)	0.003
	High TG	Age at Tx (years)	1.18	(1.05–1.33)	0.007	1.16	(1.04–1.30)	0.011
	Low HDL-C/TC	BMI SDS	2.03	(1.15–3.59)	0.014	2.25	(1.25–4.05)	0.007
		β-blocker or diuretic use	5.71	(0.95–32.24)	0.056	6.24	(0.93–41.68)	0.059
		dU-prot >200 mg	8.79	(1.24–62.41)	0.030	9.73	(1.51–62.69)	0.017
Liver Tx group	High TC	No pre Tx liver failure[c]	10.22	(1.50–69.76)	0.018	8.889	(1.294–61.058)	0.026
	High LDL-C	BMI SDS	2.17	(0.99–4.72)	0.051			
	High TG	GH use	15.00	(1.50–150.39)	0.021	17.25	(1.730–172.00)	0.015
		Age at Tx	1.21	(1.00–1.46)	0.051			
		BMI SDS	2.87	(1.17–7.20)	0.022			
Heart Tx group	Low HDL-C	High MP	13.00	(0.77–219.05)	0.075	19.50	(1.30–292.67)	0.032

[a]Significant in all blocks. Results of the second and third block displayed in Table. First block: TC before Tx: OR = 1.20, 95% CI (1.01–1.43), $P = 0.044$; organ: liver vs kidney OR = 0.06, 95% CI (0.01–0.54) and heart vs kidney OR = 0.55, 95% CI (0.13–2.30); $P = 0.031$

[b]Significant in first and third block. Result of the first block displayed in Table. Third block: liver vs kidney OR = 1.73, 95% CI (0.45–6.67) and heart vs kidney OR = 5.62, 95% CI (1.71–18.51); $P = 0.017$

[c]Significant in all blocks. Result of the first and third block displayed. Second block: OR = 8.44, 95% CI (1.22–58.16), $P = 0.030$

CyA, where one-fifth to one-third have a significantly reduced HDL/TC [42, 43]. Of our LTx patients, 16% had a high TC, similar to controls. This is excellent, as high TC values have been reported in up to 50% after LTx in childhood [7, 9]. Children with heart failure prior to HTx were hypocholesterolaemic. Nutritional status and heart function improves after HTx, leading to an increase in TC, HDL-C and LDL-C [44, 45]. In 30% of our children, however, TC exceeded 5.0 mmol/l after HTx, and in 20% LDL-C exceeded 3.0 mmol/l. In adults, high TC is frequent in up to 40% of patients, though in children LDL-C has been within normal variation [11, 39, 46]. To conclude, the KTx patients differed from those with a liver transplant through their high mean TC and, to a lesser extent, LDL-C, but without a low HDL-C concentration. Possible explanations for this difference will be discussed below.

Kidney function, as well as nephrosis and proteinuria, have been related to high TC and low HDL/TC in kidney patients with or without Tx [19, 42, 47, 48]. In end-stage kidney disease with a GFR from 30 to 60 ml/min per 1.73 m^2, HDL-C values decline [47]. KTx patients with a GFR below 54 ml/min per 1.73 m^2 have had high TC values, but low HDL-C only with a GFR below 30 ml/min per 1.73 m^2 [42]. In our patients, low GFR was not independently associated with lipid values. In our KTx patients, proteinuria was associated with a low HDL/TC. Thus, even slight proteinuria is a risk factor of dyslipidaemia, though it might not be important in explaining the difference between the groups, as proteinuria and low serum protein were equally rare in all three groups. Liver dysfunction is accompanied by multiple changes in lipoprotein metabolism [49, 50]. Even though liver parameters in our patients were not related to the lipid values, the function of a transplanted liver might not be totally comparable to that of the native liver in KTx and HTx patients. As an indicator of slightly altered function, LTx patients had a higher mean ALT than the other patients. Despite of the inclusion of the kidney and liver function variables and

pre-Tx lipid data in the multivariate model, a kidney graft was an independent risk factor for hypercholesterolaemia.

In the present study, indications for LTx without liver failure were independently associated with high TC after LTx. Two of the five children that had undergone transplantation because of cancer had TC above the normal range, and, when included in the multivariate model, hepatic cancer compared with other indications for LTx was also an independent risk factor. This might reflect the consequences of cancer therapy agents on internal organs, or be a random association. Other indications for Tx, especially NPHS1, which is associated with a severe pathological condition prior to Tx [51], did not increase the risk of post-transplantation dyslipidaemia. Obesity after KTx and HTx has been considered a risk factor for dyslipidaemia [42, 46]. In the present study, BMI was associated with low HDL/TC in the KTx patients, possibly with high LDL-C in the LTx patients, and emphasizes the need for adequate weight control after Tx.

The use of CyA has often [40, 52, 53], though not invariably [19, 42, 54], been associated with increased TC and LDL-C, and an unfavourable HDL/TC [53]. In the present study, reduction of CyA and MP coincided with improvement of HDL/TC. However, in our KTx patients, B-CyA was independently associated with high TC at 3 years. Various mechanisms of CyA-induced hypercholesterolaemia have been proposed, including diminished LDL-receptor expression [15, 55]. Use of corticosteroids, in addition to CyA, has been associated with an increase in TC, though not with a decline in HDL/TC [32, 33, 34, 38, 39, 41, 52]. In our study, blood pressure therapy with β-blockers or diuretic agents was independently associated with a low HDL/TC within all groups. This might not be independent of the influence of blood pressure, though the association with β-blocker and diuretic use and dyslipidaemia has been previously reported [19]. Finally, the lipid values observed in our patients could reflect individual genetically determined lipid patterns modified by the influence of end-stage disease.

In conclusion, the most important lipid pathology in our kidney, liver and heart transplanted children was an elevated TG concentration without low HDL-C, seen in 40% of our patients, together with elevated TC and LDL-C, especially in KTx patients. Significant risk factors for dyslipidaemia were a kidney graft, high pre-Tx TC and a high CyA trough concentration, increasing age at Tx and β-blocker or diuretic use. Nevertheless, within the KTx group, obesity, high dosage of MP, and proteinuria were significant risk factors. Severe dyslipidaemia with an increased risk for atherosclerosis was less prevalent in our patients than in previous, mostly adult, studies, presumably due to our carefully monitored triple therapy and good graft function. However, some children are at an increased risk for future vascular complications, and we need to try to eliminate further even this relatively mild dyslipidaemia.

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