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ORIGINAL ARTICLE

Dyslipidaemia in children on renal replacement therapy

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ABSTRACT

Background. Information on lipid abnormalities in end-stage renal disease (ESRD) mainly originates from adult patients and small paediatric studies. We describe the prevalence of dyslipidaemia, and potential determinants associated with lipid measures in a large cohort of paediatric ESRD patients.
Methods. In the ESPN/ERA-EDTA registry, lipid measurements were available for 976 patients aged 2–17 years from 19 different countries from the year 2000 onwards. Dyslipidaemia was defined as triglycerides >100 mg/dL (2–9 years) or >130 mg/dL (9–17 years), high-density lipoprotein (HDL) cholesterol <40 mg/dL or non-HDL cholesterol >145 mg/dL. Missing data were supplemented using multiple imputation.
Results. The prevalence of dyslipidaemia was 85.1% in peritoneal dialysis (PD) patients, 76.1% in haemodialysis (HD) patients and 55.5% among renal allograft recipients. Both low and high body mass index (BMI) were associated with a less favourable lipid profile. Younger age was associated with a worse lipid profile among PD patients. HDL levels significantly improved after transplantation, whereas no significant improvements were found for triglyceride and non-HDL levels. In transplant recipients, use of cyclosporin was associated with significantly higher non-HDL and HDL levels than tacrolimus usage ($P < 0.01$). In transplant patients with eGFR < 29 mL/min/1.73 m^2, the mean triglyceride level was 137 mg/dL (99% confidence interval (CI): 119–159) compared with 102 mg/dL among those with eGFR > 90 mL/min/1.73 m^2 ($P < 0.0001$).
Conclusions. Dyslipidaemia is common among paediatric ESRD patients in Europe. Young age and PD treatment are associated with worse lipid profiles. Although lipid levels generally improve after transplantation, dyslipidaemia may persist due to decreased graft function, high BMI or to the use of certain immunosuppressants.

Keywords: children, dialysis, dyslipidaemia, renal replacement therapy, transplantation

INTRODUCTION

Cardiovascular disease is a major cause of morbidity and mortality in children with end-stage renal disease (ESRD) [1]. Paediatric dialysis patients are estimated to have an up to 1000-fold increased cardiovascular mortality risk compared with age-

related peers [2]. Dyslipidaemia has been reported in over 50% of paediatric ESRD patients [1, 3]. Insulin resistance, increased Apo lipoprotein C-III and impaired lipolysis [4, 5] are involved in the inappropriate clearance of lipoproteins, contributing to lipid abnormalities in the uraemic environment [4]. Whereas neither peritoneal dialysis (PD) nor haemodialysis (HD) fully correct the lipoprotein abnormalities, these treatment modalities appear to have differential effects on lipid levels, with PD generally causing a less favourable lipid profile than HD [6]. Although transplantation corrects the uraemic environment, transplanted patients still display a high rate of dyslipidaemia [1], mainly due to the chronic use of immunosuppressive medications [7].

Since dyslipidaemia is a potentially modifiable risk factor, and in the general population, childhood lipid levels were found to persist into adulthood and predict cardiovascular disease in later life [8], it is important to identify the factors associated with dyslipidaemia in paediatric ESRD. Most data regarding dyslipidaemia in paediatric ESRD originate from cross-sectional single-centre studies [3, 9–11], and information about the change of lipid levels over time is scarce [12]. Therefore, the objective of this study is to describe the prevalence and evolution of dyslipidaemia and its potential determinants in a large cohort of paediatric ESRD patients.

MATERIALS AND METHODS

Subjects

The ESPN/ERA-EDTA registry collects annual data of paediatric patients undergoing renal replacement therapy (RRT) in Europe. Within the registry, individual patient data are collected regarding date of birth, gender, primary renal diagnosis, the initial and any subsequent RRT treatment modalities, as well as a variable set of anthropometric, biochemical and medication-related data. For the present study, only those countries providing data on total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels from the year 2000 onwards were included. This included information for the following countries and periods: Belarus (2008–10), Czech Republic (2007–11), Denmark (2008), Estonia (2008–10), Finland (2000–10), Greece (2009–12), Croatia (2009), Hungary (2005–11), Iceland (2005–11), Lithuania (2008–12), FYR Macedonia (2008–12), Norway (2008–10), Poland (2007–12), Portugal (2007–11), Serbia (2007–12), Slovakia (2005–10), Slovenia (2007–10), Switzerland (2009) and the Netherlands (2007–12). Missing data for total cholesterol (3.4%), HDL (31.6%), triglycerides (14.3%), serum creatinine (16.7%), height (8.3%) and weight (7.9%) were imputed using a multiple imputation method as recommended by the STROBE guidelines [13, 14]. To test whether associations were similar in patients with complete information we performed sensitivity analyses among complete cases only, these analyses did not reveal different associations compared with the associations found in patients in whom missing data were imputed.

Definition of variables

Non-HDL cholesterol was calculated as total cholesterol-HDL cholesterol. We defined dyslipidaemia by the presence of at least one of the following: hypertriglyceridaemia (triglycerides >100 mg/dL (>1.1 mmol/L) (2–9 years of age) or triglycerides >130 mg/dL (>1.5 mmol/L) (10–17 years of age)), low HDL cholesterol (<40 mg/dL or <1.0 mmol/L) or high non-HDL cholesterol (>145 mg/dL or >3.7 mmol/L) according to the guidelines for cardiovascular health and risk reduction in children and adolescents [15]. The eGFR was calculated using the new Schwartz formula [16]. To reflect changes in body size and adiposity during childhood, the body mass index (BMI) is expressed in age and sex specific values. However, as paediatric ESRD patients usually suffer from growth retardation, it has been suggested to express their BMI according to height age (age at which a child's height will be at the 50th percentile) [17]. Therefore, BMI was calculated as weight/height^2 and expressed to height age. We used cut-off values of the International Obesity Task Force [18, 19] to categorize BMI. To study the effects of a continuous measure for BMI on lipid levels, we modelled BMI as the percent difference from the median BMI (BMI %) [20] according to WHO growth charts [21]. Associations between BMI and lipid measures did not differ when BMI was expressed relative to chronological age instead of according to a patient's height age.

Statistical analyses

The number of lipid measurements recorded in the registry differed largely per patient. To correct for the correlations of measurements within the same patient, we used multinomial generalized estimating equations models [22] to estimate prevalence estimates of dyslipidaemia. In this way, a patient who had an elevated triglyceride level at one measurement and a normal triglyceride level at the second measurement, this patient contributed as ½ of a patient to the group of patients with elevated triglyceride levels and ½ to the group with normal triglyceride levels. To study factors associated with different lipid levels, lipid concentrations were log transformed and analysed with linear mixed models with both a random intercept and a random slope to account for the time between successive measurements within a patient, and adjustments were made for possible confounders. We adjusted the P-value for multiple testing by using a more conservative cut-off value for significance. P-values of <0.01 were considered statistically significant, and results are presented with 99% CIs. All statistical analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

For a total of 976 patients, information on lipid levels was available from 3293 measurements (median 5, range of 1–27 measurements per patient). Patient characteristics are listed in Table 1. At the time of lipid measurement, most patients (54.7%) were between 12 and 17 years of age, 58.2% of the patients were male, 52.7% had a functioning graft and the most common cause of renal failure was CAKUT (38.1%).

Prevalence of dyslipidaemia

The prevalence of dyslipidaemia in the total cohort was 68.0%. No significant country differences were found, except

Table 1. Patient characteristics of prevalent patients

	Patients ($N = 976$)
Age at start of RRT (years)	*N* (%)
0–1	224 (23.0)
2–5	182 (18.7)
6–11	296 (30.3)
12–17	274 (28.0)
Age at lipid measurement (years)	
2–5	176 (18.0)
6–11	266 (27.3)
12–17	534 (54.7)
Gender (%)	
Male	568 (58.2)
Female	408 (41.8)
Treatment modality at start of RRT	
HD	281 (28.8)
PD	604 (61.9)
Tx	84 (8.6)
Unknown/missing	7 (0.7)
Treatment modality at lipid measurement	
HD	178 (18.2)
PD	284 (29.1)
Tx	514 (52.7)
Primary renal disease	
CAKUT	372 (38.1)
Glomerulonephritis	146 (15.0)
Cystic kidneys	121 (12.4)
Hereditary nephropathy	132 (13.5)
Ischaemic renal failure	20 (2.0)
HUS	35 (3.6)
Metabolic disorders	23 (2.4)
Vasculitis	7 (0.7)
Miscellaneous	78 (8.0)
Unknown/missing	42 (4.3)

RRT, renal replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; Tx, renal transplant; CAKUT, congenital anomalies of the kidney and the urinary tract; HUS, haemolytic-uraemic syndrome.

for PD patients from Portugal who displayed a significantly lower prevalence of dyslipidaemia. In Figure 1, the prevalence of dyslipidaemia is shown stratified by lipid marker and treatment modality. The prevalence of dyslipidaemia was highest among PD patients (85.1%) and lowest among transplant recipients (55.5%), while 76.1% of the HD patients suffered from dyslipidaemia ($P < 0.0001$). Of the different lipid measures, triglyceride levels were most frequently abnormal; hypertriglyceridaemia was found among 73.9% of PD, 60.7% of HD and 45.3% of the patients with a functioning graft ($P < 0.0001$). Low HDL cholesterol levels were found in 23.8% of PD, 38.2% of HD patients and 12.9% of transplant patients, whereas elevated non-HDL levels were found in 54.6% of PD patients, 24.1% of HD patients and 22.5% of the transplant recipients. Among the patients with dyslipidaemia, 33.7% displayed combined dyslipidaemia (i.e. more than one lipid abnormality) and combined dyslipidaemia was more common among dialysis patients (39.1% in HD and 55.4% in PD) as compared with transplant recipients (23.4%) ($P < 0.0001$).

Modelled association between body mass index and lipid levels

Both a low and a high BMI were associated with a less favourable lipid profile (Figure 2). After adjustment for age, sex and treatment modality, we found a U-shaped association between BMI and triglyceride and non-HDL levels, whereas BMI and HDL cholesterol were associated in an inverted-U-shaped manner. Due to a limited number of dialysis patients in the overweight group and transplant patients in the underweight group, the increased risk of dyslipidaemia in underweight patients was mainly seen in dialysis patients and the association between being overweight and dyslipidaemia was most apparent in the transplant recipients.

Mean lipid levels in HD patients

All mean lipid levels were lower in patients on HD ($N = 236$) (triglycerides: 139 mg/dL (124–155), non-HDL: 111 mg/dL (103–121) and HDL: 43.8 mg/dL (40.9–46.8)) (Table 2), as compared with patients on PD (triglycerides: 174 mg/dL, non-HDL: 144 mg/dL, HDL: 48.8 mg/dL) (Table 3). There were no age and gender differences between the lipid levels of HD patients, and HD vintage was not associated with any of the lipid measures (Table 2). Furthermore, hypoalbuminaemic HD patients tended to have higher triglyceride (152 mg/dL, 99% CI: 128–180 mg/dL) and non-HDL levels (119 mg/dL, 99% CI: 107–132 mg/dL) compared with patients with normal albumin levels, for whom triglyceride and non-HDL levels were 134 and 108 mg/dL, respectively, but these results did not differ significantly.

Mean lipid levels in PD patients

Mean lipid levels differed according to subgroups of PD patients ($N = 365$) (Table 3). Triglyceride and non-HDL levels were inversely associated with age: younger patients displayed significantly higher triglyceride and non-HDL levels. Gender, time on PD and hypoalbuminaemia were not associated with any of the lipid levels in PD patients.

Mean lipid levels in transplant recipients

Among transplant recipients ($N = 564$), average triglyceride, non-HDL and HDL levels were 116, 115 and 54.6 mg/dL, respectively. Associations of potential risk factors and lipid levels among transplanted patients are listed in Table 4. The use of cyclosporin instead of tacrolimus resulted in significantly higher triglyceride, non-HDL and HDL levels. Steroid use tended to be associated with higher triglyceride and non-HDL levels. The use of mycophenolate mofetil (MMF) instead of azathioprine was associated with significantly lower HDL levels, while triglyceride levels were significantly higher when using MMF compared with using azathioprine. Sirolimus use was associated with higher triglyceride, non-HDL and HDL levels, but only the latter two were significantly higher. Based on our modelling, we attempted to identify an immunosuppressive protocol which would result in the most favourable lipid profile. Patients treated with a hypothetical combination of tacrolimus and azathioprine seemed to have the most favourable lipid profile which would result in a lower prevalence of dyslipidaemia (48.6%) compared with transplant patients on other immunosuppressive protocols (57.4%).

Finally, we found an inverse association between eGFR and triglyceride levels. Triglyceride levels of patients with an eGFR < 29 mL/min/1.73 m^2 were on average 137 mg/dL (99% CI: 119–159) compared with 102 mg/dL in patients with an eGFR

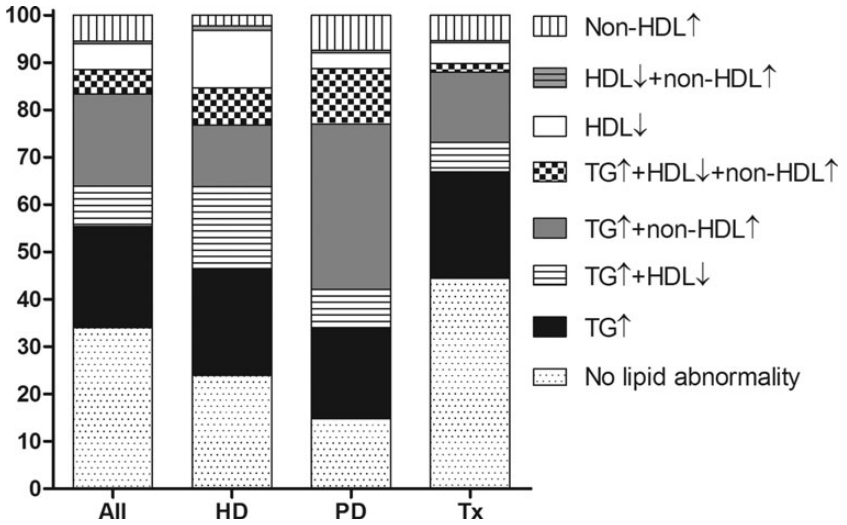

FIGURE 1: Prevalence of dyslipidaemia by lipid marker stratified by treatment modality (TG, triglycerides; HDL, HDL cholesterol; non-HDL, non-HDL cholesterol).

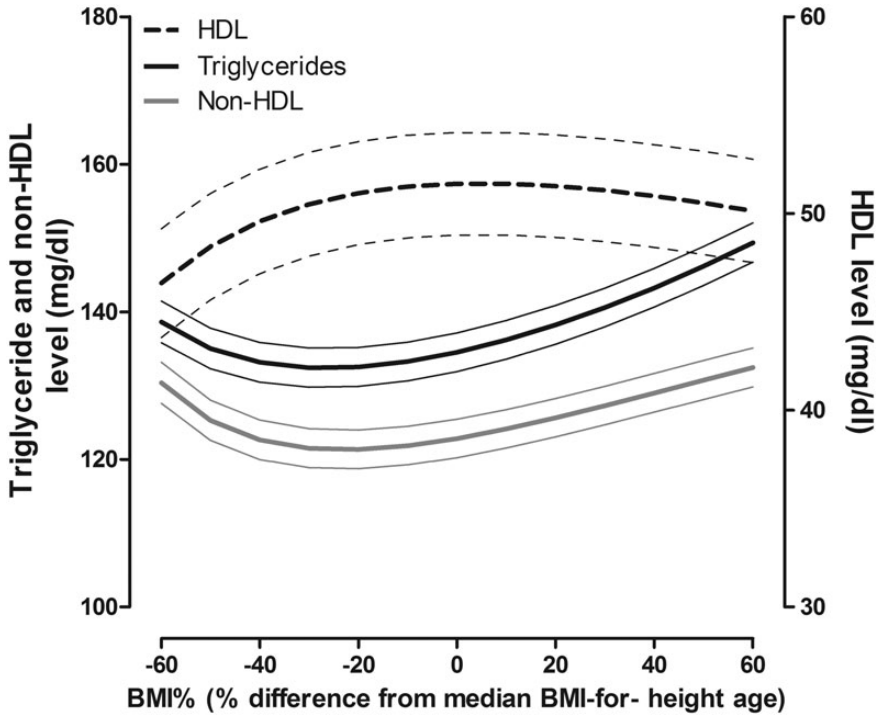

FIGURE 2: Modelled association between BMI% and lipid levels. Adjustments were made for age, sex and treatment modality. BMI% was calculated as the percentage difference from the median BMI-for-age based on BMI curves from the World Health Organization [21].

> 90 mL/min/1.73 m^2 ($P < 0.0001$). However, no such association was found for non-HDL or HDL cholesterol (Figure 3).

Intra-individual changes in lipid levels

For a total number of 126 patients lipid levels were available while changing from dialysis (mean time before transplantation: 5.2 months) to transplantation (mean follow-up time post-transplant: 4.9 months). Following renal transplantation, mean triglyceride levels showed a non-significant decrease of 23 mg/dL (99% CI: −56 to 9 mg/dL, P = 0.06), while average HDL levels significantly increased by 8.6 mg/dL (99% CI: 4.4–12.8 mg/dL, $P < 0.0001$). The mean change in non-HDL level following transplantation was +7 mg/dL (99% CI: −8 to 22 mg/dL, P = 0.24).

To put these post-transplant changes into perspective, information on normal within-subject variation in serum lipid levels is needed. Therefore, we selected subsequent lipid measurements of patients who did not switch RRT treatment. The average time between these subsequent lipid determinations was 314 days. We found a large intra-individual variation between subsequent triglyceride measurements. In PD patients ($N = 180$), 59% of the total variance in triglyceride

Table 2. Factors associated with mean lipid levels in HD patients

	Triglycerides (mg/dL) Mean (99% CI)	Non-HDL (mg/dL) Mean (99% CI)	HDL (mg/dL) Mean (99% CI)
All HD patients ($N = 236$)	138.8 (124.1–155.1)	111.4 (102.8–120.7)	43.8 (40.9–46.8)
Age (years)[a]			
2–5	146.9 (114.5–188.5)	124.8 (105.7–147.4)	43.2 (37.3–49.9)
6–11	148.2 (124.6–176.2)	110.6 (98.8–124.0)	46.9 (42.3–51.9)
12–17[b]	134.4	109.5	42.9
Gender			
Male[b]	141.1	113.0	43.6
Female	136.1 (116.8–158.5)	109.2 (97.6–122.1)	43.9 (40.0–48.2)
HD vintage (years)[c]			
<0.5	145.3 (121.5–173.8)	117.8 (104.0–133.4)	40.0 (38.9–49.2)
0.5 < 1	128.8 (85.9–193.0)	103.9 (80.2–134.6)	51.0 (40.3–64.6)
1 < 2	116.3 (87.5–154.4)	91.5 (76.1–110.0)	39.8 (33.5–47.2)
≥2[b]	135.9	106.5	44.7
Primary renal disease[c]			
FSGS with nephrotic syndrome	146.1 (114.7–186.0)	127.8 (106.4–153.4)	41.8 (35.4–49.4)
Other cause[b]	145.1	115.0	44.7
BMI-for-height age[c]			
Underweight	171.3 (124.8–235.2)	123.9 (103.7–148.0)	41.4 (34.3–50.1)
Normal weight[b]	136.6	109.5	45.0
Overweight	133.3 (108.5–164.0)	106.4 (94.3–120.1)	44.6 (39.1–50.8)
Obese	140.0 (104.0–188.6)	113.0 (93.5–136.4)	39.9 (33.6–47.4)
Albumin[c]			
Low (albumin <35 g/L)	152.1 (127.9–180.8)	118.8 (107.1–131.9)	41.7 (37.8–46.1)
Normal (albumin ≥35 g/L)[b]	133.9	107.6	44.5

To convert values for triglycerides to mmol/L multiply by 0.0113, to convert non-HDL and HDL cholesterol to mmol/L multiply by 0.0258.
BMI, body mass index.
[a]Adjusted for country and sex.
[b]Reference category.
[c]Adjusted for country, age and sex.

levels could be attributed to the variance within the same patient, whereas this was 51% in HD ($N = 106$) and 42% in transplant patients ($N = 358$). For HDL and non-HDL cholesterol levels the intra-individual variation was slightly lower, but still 34–53% of the total variance in HDL and 27–39% of the total variance in non-HDL cholesterol was intra-individual variation. There were no significant trends in the variations of serum lipids over time.

DISCUSSION

Over 60% of the European children with ESRD suffer from dyslipidaemia. Its prevalence varies by treatment modality, with the highest prevalence observed in PD patients, but even after transplantation 50% of patients display dyslipidaemia. Our estimates were similar to those reported previously in children with chronic renal failure: 45% in children with chronic kidney disease (CKD) [23, 24], 56–93% in dialysis patients [25, 26] and 15–67% among transplant recipients [3, 9, 11, 25, 27]. All these figures are much higher than those reported in healthy children, which vary between ∼10% and over 20% [28–31].

Although hypertriglyceridaemia was most frequently observed in our cohort (ranging from 45.3% among transplanted patients to 73.9% among PD patients), elevated non-HDL cholesterol levels seemed to be most important for cardiovascular disease [32, 33]. This was observed in 30.8% of the patients.

We found that both a low and a high BMI were associated with a less favourable lipid profile for all parameters. A high BMI has been identified as a distinct risk factor for dyslipidaemia in the paediatric CKD population [23, 24], the general paediatric population [30], as well as adult renal graft recipients [34]. Moreover, a low BMI could be a marker of severity of disease, and a reason for calorie supplementation, thereby resulting in a less favourable lipid profile.

The observed U-shaped association of BMI with dyslipidaemia resembles the previously reported relationship of BMI and mortality risk in children with ESRD [35] and contrasts with observations in adult dialysis patients [36]. Nevertheless, although data from the Bogalusa heart study show that in the general childhood population lipid levels persist into adulthood and predict cardiovascular disease in later life [8], it is not known to what extent abnormal lipid levels are associated with adverse outcomes in children. This would be an interesting topic for future studies.

Another predictor for an abnormal lipid profile in dialysis patients was receiving PD treatment, especially among those of young age. The high glucose load from the dialysis fluid might contribute to this high dyslipidaemia prevalence [26]. Although it has been suggested that considerable protein losses in the dialysate also contribute to the disturbed lipid profile, we did not find higher lipid levels among hypoalbuminaemic PD patients, which is consistent with data from a Turkish study [37]. As we did not have sufficient data on C-reactive protein levels, it was not possible to study the effect of inflammation (C-reactive protein) on serum lipid levels. Besides lower cut-off values for hypertriglyceridaemia in children younger than 9 years of age, the absolute triglyceride, as well as the non-HDL levels, were higher among

Table 3. Factors associated with mean lipid levels in PD patients

	Triglycerides (mg/dL) Mean (99% CI)	Non-HDL (mg/dL) Mean (99% CI)	HDL (mg/dL) Mean (99% CI)
All PD patients ($N = 365$)	173.6 (158.6–190.0)	144.3 (135.0–154.2)	48.8 (45.5–52.3)
Age (years)[a]			
2–5	**218.2 (187.3–254.2)**	**162.0 (148.8–176.3)**	48.6 (44.4–53.2)
6–11	**179.2 (156.7–205.0)**	**146.5 (135.4–158.5)**	48.7 (44.9–52.8)
12–17[b]	140.1	129.5	49.0
Gender			
Male[b]	173.9	144.0	48.6
Female	173.9 (151.1–200.1)	145.7 (135.0–157.3)	49.0 (45.5–52.8)
Peritoneal dialysis vintage (years)[c]			
<0.5	177.1 (146.0–215.0)	146.2 (131.0–163.1)	48.9 (43.5–54.9)
0.5 < 1	155.7 (106.9–226.7)	130.4 (106.7–159.2)	49.2 (39.5–61.3)
1 < 2	145.5 (108.4–195.3)	142.2 (121.1–167.1)	48.8 (40.8–58.4)
≥2[b]	152.8	136.0	47.9
Primary renal disease[c]			
FSGS with nephrotic syndrome	203.9 (162.8–255.4)	156.4 (142.0–173.3)	45.6 (39.8–52.4)
Other cause[b]	169.5	146.0	49.6
BMI-for-height age[c]			
Underweight	187.9 (155.4–227.2)	151.4 (135.2–169.6)	47.7 (42.2–53.9)
Normal weight[b]	178.8	147.5	49.4
Overweight	183.5 (157.8–213.3)	139.9 (127.6–153.3)	46.2 (41.9–50.9)
Obese	185.3 (152.7–224.8)	141.3 (125.6–159.0)	50.3 (44.5–56.9)
Albumin[c]			
Low (albumin <35 g/L)	172.3 (156.2–190.1)	146.8 (140.4–153.5)	48.5 (45.5–51.7)
Normal (albumin ≥35 g/L)[b]	174.9	142.8	49.0

Bold values are statistically significant at the 0.01 level.
To convert values for triglycerides to mmol/L multiply by 0.0113, to convert non-HDL and HDL cholesterol to mmol/L multiply by 0.0258.
BMI, body mass index.
[a]Adjusted for country and sex.
[b]Reference category.
[c]Adjusted for country, age and sex.

younger children. This may in part reflect a puberty-related decrease in non-HDL levels [38]. Furthermore, many young patients (especially those on PD) might receive supplemental feeding [39, 40] possibly leading to higher lipid levels. Indeed, increased (dietary) energy intake of PD patients has been associated with higher triglyceride and cholesterol levels [41].

In transplant recipients, both the use of cyclosporin and glucocorticoids as immunosuppressive therapy was positively associated with an adverse lipid profile. Several other studies have suggested that combined steroid and cyclosporin use increases the risk of dyslipidaemia [9, 12, 25, 42]. The use of tacrolimus instead of cyclosporin has been associated with better graft function in paediatric [42] and adult renal graft recipients [43, 44]. A significantly improved lipid profile was found after late steroid withdrawal [45], and with reducing the use of steroids to very low doses [46]. One of the most notable side effects of sirolimus use is a marked increase in serum lipid levels [47]. Indeed, we found a significant increase in non-HDL and HDL levels associated with sirolimus use, which was more pronounced than the effect of cyclosporine. Modification of immunosuppressive protocols might play a role in reducing lipid abnormalities among graft recipients. Modelling the conditions associated with the most favourable lipid profile, we found that an immunosuppressive protocol consisting of tacrolimus and azathioprine would interfere least with lipid metabolism. Furthermore, we found an inverse association between graft function and triglyceride levels. Surprisingly, we did not find a positive association between graft function and HDL cholesterol levels. This might partly be explained by the low prevalence of abnormal HDL levels among graft recipients in our population or by the use of different immunosuppressive medications. Previous studies among adult graft recipients reported an independent association between dyslipidaemia and graft loss [48, 49], leading to the assumption that dyslipidaemia might be involved in the atherosclerotic process of graft arteries. However, a lower GFR was associated with dyslipidaemia in children with CKD [23] and is a frequent complication among renal transplant patients [1]. Dyslipidaemia is therefore, most likely a consequence rather than cause of deteriorating graft function.

Similar to others [50] we found a large intra-individual variation in serum lipid levels. Porkka *et al.* reported a correlation coefficient of only 0.49 between triglyceride levels when measured 7 days apart, with similar findings for total, HDL and LDL cholesterol [50]. As the average time between repeated lipid measurements in our registry was much longer than 7 days, the large intra-individual variation would mainly result from biological variation in serum lipid levels, therefore explaining limited changes over time. The large intra-individual variation might also have resulted in the marginal post-transplant improvements in the lipid profile of patients changing from dialysis to transplantation. Given the lower prevalence of dyslipidaemia as well as a more favourable lipid profile in transplant compared with dialysis patients, we believe that there was a true, albeit modest, improvement in lipid levels post-transplant.

Table 4. Factors associated with mean lipid levels in transplant patients

	Triglycerides (mg/dL) Mean (99% CI)	Non-HDL (mg/dL) Mean (99% CI)	HDL (mg/dL) Mean (99% CI)
All transplanted patients ($N = 564$)	116.0 (108.6–123.8)	114.7 (109.4–120.2)	54.6 (52.5–56.8)
Age (years)[a]			
2–5	**128.4 (115.9–142.3)**	119.2 (110.9–128.2)	54.3 (51.2–57.6)
6–11	112.2 (104.6–120.5)	116.7 (111.1–122.6)	**56.2 (54.0–58.5)**
12–17[b]	114.8	112.8	54.0
Gender			
Male	115.8	113.4	53.8
Female	116.0 (105.8–127.1)	117.1 (109.7–125.0)	55.9 (52.8–59.3)
Time on current treatment (years)[c]			
<0.5	**109.3 (97.3–122.8)**	111.3 (102.4–121.0)	54.2 (50.5–58.1)
0.5 < 1	118.6 (104.1–135.2)	116.5 (106.1–128.0)	54.6 (50.5–59.0)
1 < 2	112.1 (98.2–128.0)	112.5 (102.3–123.6)	55.0 (50.8–59.5)
≥2[b]	123.4	118.0	52.7
Pre-emptive transplantation[c]			
Yes[b]	113.3	106.5	51.6
No	116.5 (101.7–133.4)	115.9 (105.2–127.6)	54.2 (49.9–58.9)
Primary renal disease[c]			
FSGS with nephrotic syndrome	132.2 (106.2–164.6)	134.6 (111.4–162.6)	53.8 (46.8–61.8)
Other cause[b]	115.2	114.6	54.6
Calcineurin inhibitors[d]			
Tacrolimus[b]	111.6	103.0	52.0
None	112.3 (93.0–135.7)	113.9 (100.5–129.0)	53.5 (48.4–59.2)
Cyclosporin	**129.4 (118.4–141.4)**	**125.6 (118.3–133.3)**	**58.4 (55.7–61.2)**
Steroids[d]			
Yes	122.3 (109.1–137.0)	115.8 (106.4–123.8)	55.8 (52.3–59.1)
No[b]	110.2	110.7	53.0
mTOR inhibitor[d]			
No[b]	119.7	113.2	54.8
Sirolimus	130.9 (93.3–183.4)	**152.7 (122.1–191.0)**	**67.4 (56.0–81.3)**
Antimetabolites[d]			
AZA[b]	111.6	112.5	57.7
MMF	**123.6 (113.3–134.7)**	115.5 (109.0–122.4)	**53.2 (50.9–55.6)**
None	124.7 (110.8–140.4)	112.7 (104.2–121.8)	56.0 (52.6–59.6)
BMI-for-height age[e]			
Underweight	101.4 (73.6–139.6)	112.5 (89.6–141.2)	54.7 (45.8–65.2)
Normal weight[b]	114.1	111.2	56.5
Overweight	120.4 (109.3–132.6)	116.8 (109.4–124.8)	55.6 (52.9–58.5)
Obese	**132.1 (116.5–149.8)**	**124.0 (113.8–135.1)**	55.3 (51.7–59.3)

Bold values are statistically significant at the 0.01 level.
To convert values for triglycerides to mmol/L multiply by 0.0113, to convert non-HDL and HDL cholesterol to mmol/L multiply by 0.0258.
FSGS, focal segmental glomerulosclerosis; mTOR, mammalian target of rapamycin; AZA, azathioprine; MMF, mycophenolate mofetil; BMI, body mass index.
[a]Adjusted for country and sex.
[b]Reference category.
[c]Adjusted for country, age, sex and year of transplantation.
[d]Adjusted for country, age, sex, time since transplantation, year of transplantation and eGFR.
[e]Adjusted for country, age, sex, year of transplantation and immunosuppressive medication.

Transplantation could thus be an important step towards a better cardiovascular risk profile in paediatric ESRD patients. Further improvement in lipid profiles might occur through a diet restricted in (saturated) fat, which was found to decrease total and LDL cholesterol levels by 11 and 14%, respectively [51]. Statin or fibrate use was not reported in our registry, but if statins or fibrates were actually applied to lower lipid levels our findings would even underestimate the true prevalence of dyslipidaemia. However, no studies have been performed on statin safety and efficacy in children undergoing dialysis [52], and studies in adult dialysis patients yielded conflicting results [53–56].

A limitation of our study might be the measurement of serum lipids under non-fasting conditions.

Although it is common practice to measure blood specimens after an overnight fast, this information was not reported in our registry. Total and HDL cholesterol (and thus non-HDL levels) can be accurately measured in plasma from non-fasting patients [38], but considerable variation between fasting and non-fasting lipid levels has been reported [57]. Furthermore, the use of different analytical methods for lipid determination across participating centres might also have introduced variability in the measurements [58]. However, the potential error in lipid measurements is likely to be unrelated to the presence of dyslipidaemia (non-differential misclassification), and will therefore, mainly have resulted in a underestimation of the associations, resulting in wider CIs and less significant associations between lipid levels and the factors studied. HDL cholesterol, and therefore non-HDL cholesterol, was missing for 31.6% of patients. As patients with complete data might have different characteristics than patients with missing data, excluding patients with missing

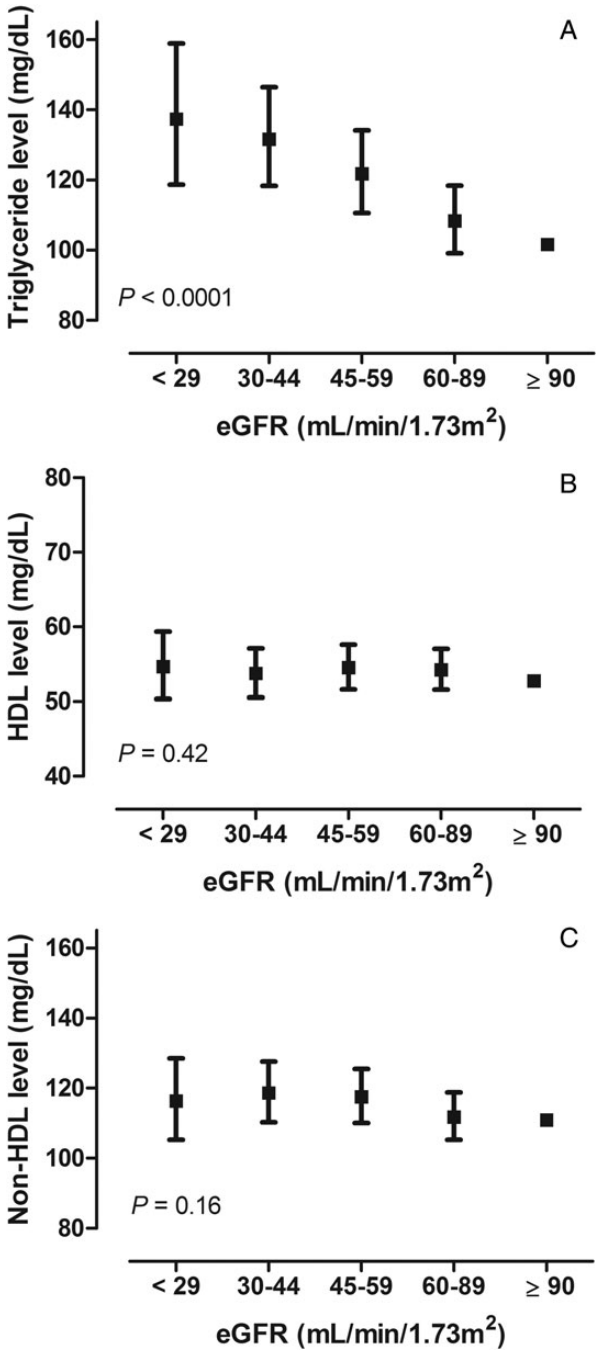

FIGURE 3: Association between eGFR and mean levels of triglycerides (**A**), non-HDL cholesterol (**B**) and HDL cholesterol (**C**). Adjustments were made for age, sex, time since transplantation and year of transplantation.

data might result in biased estimates. We approached this issue by supplementing missing data using multiple imputation, which has been shown to result in valid estimates [13]. Furthermore, sensitivity analyses comparing the original and imputed databases did not show any differences in associations.

Another limitation of our study is the lack of data regarding proteinuria in renal graft recipients and residual renal function in dialysis patients which could have affected the lipid levels [4, 7].

In summary, dyslipidaemia is present in more than half of paediatric ESRD patients in Europe. Lipid levels improve but do not normalize entirely after transplantation. The PD modality and young age are key factors associated with higher lipid levels among dialysis patients, while graft function, BMI and immunosuppressive medications are determinants of lipid levels among transplant patients. Considering its association with cardiovascular morbidity and mortality, dyslipidaemia should receive close attention in the treatment of children with ESRD.

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CONFLICT OF INTEREST STATEMENT

We have no conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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A clinical stratification tool for chronic kidney disease progression rate based on classification tree analysis

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ORIGINAL ARTICLE

ABSTRACT

Background. Registry-based studies have identified risk factors for chronic kidney disease (CKD) and for progression to end-stage renal disease. However, usually, these studies do not incorporate sequential measurements of kidney function and provide little information on the prognosis of individual patients. The aim of this study is to identify which combinations of demographic and clinical characteristics are useful to discriminate patients with a differential annual decline in glomerular filtration rate (GFR).

Methods. This observational retrospective study includes patients enlisted in the registry of the Prevention of Progressive Renal Insufficiency Project of Emilia-Romagna region (Italy) from July 2004 to June 2010, with at least four serum creatinine measurements. Classification tree analysis (CTA) was used to identify subgroups of patients with a different annual GFR decline using demographic and laboratory data collected at study entry.

Results. The CTA procedure generated seven mutually exclusive groups. Among patients with proteinuria, those with a baseline estimated GFR (eGFR) of >33 mL/min/1.73 m^2 exhibited the fastest illness progression in the study population (−3.655 mL/min/1.73 m^2), followed by patients with a baseline eGFR of <33 mL/min/1.73 m^2 and a baseline serum phosphorus of >4.3 mg/dL (−2.833 mL/min/1.73 m^2). Among patients without proteinuria, those aged <67 years exhibited a significantly faster progression, which was even faster for the subgroup with diabetes. Among patients aged >67 years, females had on average a stable eGFR over time, with a large variability.

Conclusions. It is possible to rely on a few variables typically accessible in routine clinical practice to stratify patients with a different CKD progression rate. Stratification can be used to guide decisions about the follow-up schedule, treatments to slow progression of kidney disease, prevent its complications and to begin planning for dialysis and transplantation.

Keywords: CKD progression, decision tree, prediction models