CHAPTER 8.5 Dyslipidaemia

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1 Introduction

The prevalence of dyslipidaemia in paediatric kidney transplant recipients is 10–60% [1]. In addition to immunosuppressive therapy, other comorbidities such as impaired graft function, obesity, proteinuria and diabetes mellitus contribute to its development. Dyslipidaemia causes atherosclerosis and is a classic risk factor for cardiovascular disease (CVD). Cardiovascular mortality is increased up to 1,000-fold in paediatric patients with chronic kidney disease compared to healthy controls [2]. In paediatric kidney transplant patients, CVD remains the second leading cause of mortality [3], although kidney transplantation substantially reduces several risk factors for CVD and consecutively cardiac mortality 10- to 100-fold [2]. The American Heart Association (AHA) has therefore stratified transplant recipients into the highest risk group for development of CVD [2].

2 Determination of CVD risk

(i) Identification of risk factors for CVD: family history of hyperlipidaemia, smoking status, level of physical activity, blood pressure, body mass index (BMI), fasting glucose, HbA_1C, dysregulation of the calcium/phosphate metabolism, anaemia, chronic inflammation, hyperhomocysteinaemia, albuminuria, hypothyroidism.

A positive family history of dyslipidaemia and cardiovascular disease requires a more intensive diagnostic and therapeutic approach for risk reduction.

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(ii) Monitoring of blood lipids (non-fasting: triglycerides (TG), total cholesterol (TC), LDL-C (low-density-lipoprotein cholesterol), HDL-C (high-density-lipoprotein cholesterol)

- At 2–3 months post-transplant
- At 2–3 months after any change in therapy or condition that could cause dyslipidaemia
- At least 1 x per year
- Repeat lipid panel in fasting state in case of abnormal values

Table 1 Target ranges

LDL-cholesterol	≤ 130 mg/dL preferably ≤ 100 mg/dL	≤ 3.36 mmol/L ≤ 2.59 mmol/L
Total cholesterol (TC)	< 250 mg/dL	< 6.47 mmol/L
Non-HDL cholesterol	< 160 mg/dL	< 4.17 mmol/L
Triglycerides (TG)	< 400 mg/dL	< 4.56 mmol/L

(iii) Sonographic diagnosis: non-invasive measurement of carotid intima-media thickness (cIMT) as a surrogate for cardiovascular damage (reference values [6]).

3 Prophylactic options:

Therapeutic lifestyle changes (TLC) [7]:

- Dietary advice (e.g., rapeseed or olive oils, trans-fat-free margarines)
- Physical activity advice: Children: ≥ 60 minutes of active play daily; Adolescents: 3 to 4 times a week moderate physical activity (e.g., 20–30 minutes of walking, swimming, supervised activity within ability) and resistance exercise training (i.e., exercises that cause muscle contraction against an external resistance)
- Limit screen time (computer + video games and TV) to ≤ 2 hours per day as recommended by the WHO
- Weight loss

- Stop smoking
- Optimal treatment of hypothyroidism and diabetes, if present

4 Therapeutic options

Step 1:
(i) Therapeutic lifestyle changes (TLC) [7]
- Physical activity guidance: see above
- Diet with < 30% of calories from fat, < 7% of calories from saturated fat, 10% from polyunsaturated fat, cholesterol < 200 mg/d, avoidance of trans-fatty acids according to prescription of registered paediatric dietitian, used judiciously in case of failure to thrive
- Diet with whole grains, high fibre foods, legumes, fruits and vegetables
- Reduce obesity (refer to obesity clinic)

(ii) Adjustment of immunosuppressive therapy (balance with risk of rejection) [8]:
- Steroid withdrawal/minimisation
- Cyclosporin A withdrawal/minimisation/change to tacrolimus
- mTOR inhibitor withdrawal/minimisation

Step 2:
Start statin therapy in children aged > 8–10 years (> 6 years for rosuvastatin) if LDL-C target is not achieved within 6 months with therapeutic lifestyle changes.

General recommendations
- Start with the lowest recommended dose and increase in small increments, no more than every 4 weeks.
- In general, be aware of the frequent drug interactions of statins – *check if combined with any drug.*
- Monitor serum CK (especially if muscle pain occurs) and liver enzymes; caution: rhabdomyolysis; interrupt treatment if severely ill, avoid intensive sun exposure.
- Effectiveness: Statin therapy reduces LDL-C by about 30% (+ 15% additional reduction with ezetimibe)

Preferred statins depend on concomitant immunosuppressive regimen:

- No interaction between statins and mycophenolate mofetil and methylprednisolone
- Cyclosporin A: In general, strongest interactions between statins and cyclosporin A (see chapter 4.3); simvastatin and rosuvastatin are contraindicated, strong interaction with pravastatin, and atorvastatin.
- Tacrolimus: Potentially clinically relevant, moderate interaction between tacrolimus and pravastatin/simvastatin.
- Everolimus: No interaction with pravastatin or atorvastatin.

Table 2 HMG-CoA reductase inhibitor (statin) dosing in paediatrics

Medication name	Lowest available tablet strength	Approved at the earliest from	Noteworthy
Fluvastatin	20 mg	9 years	• No relevant interaction with tacrolimus • Potentially clinically relevant moderate interaction with cyclosporin A
Pravastatin	10 mg	8 years	• No relevant interaction with everolimus • Potentially clinically relevant moderate interaction with tacrolimus • Clinically serious interaction with cyclosporin A – avoid combination
Rosuvastatin	5 mg	6 years	• Contraindicated in comedication with cyclosporin A or if CCR <30 ml/min/1.73 m^2 BSA
Atorvastatin	10 mg	10 years	• No relevant interaction with tacrolimus • No relevant interaction with everolimus • Clinically serious interaction with cyclosporin A – avoid combination
Simvastatin	5 mg	♂ > Tanner II ♀ 1 year post menarche	• Potentially clinically relevant moderate interaction with tacrolimus • Contraindicated in comedication with cyclosporin A

Information adapted from manufactures' prescribing information; prescribing is at your own responsibility.

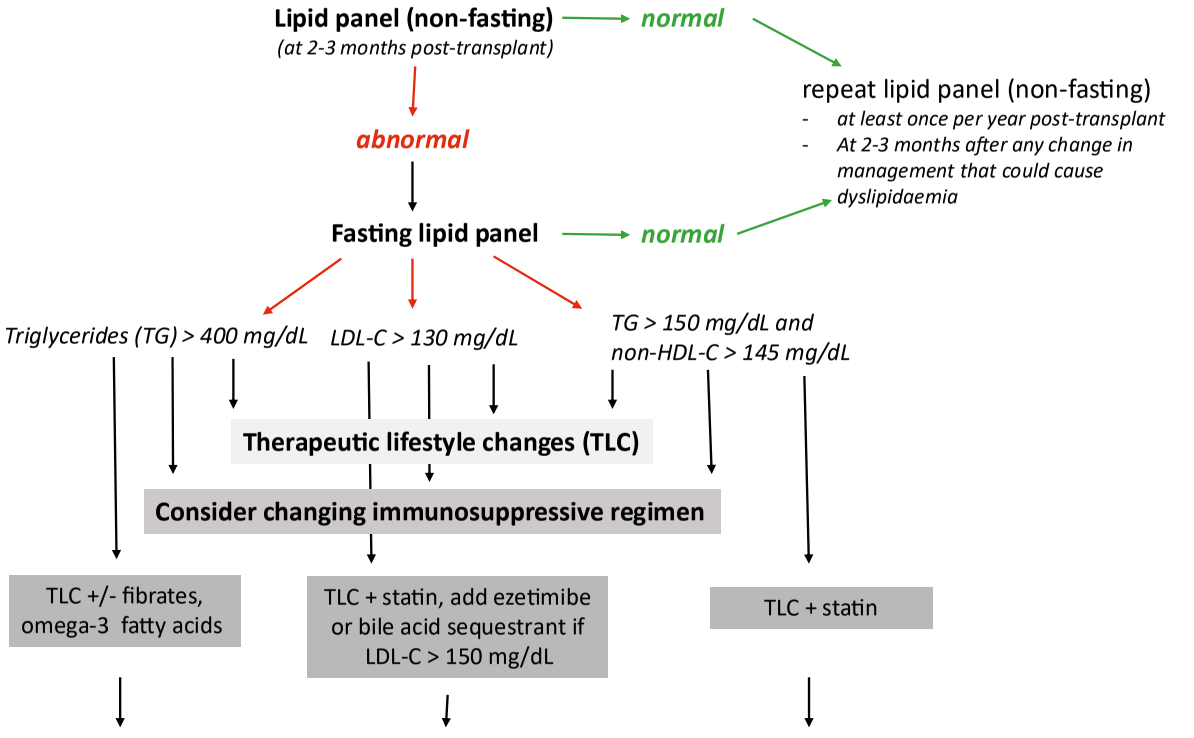
Fluvastatin might therefore be a good choice for combination therapy with calcineurin inhibitors. Fluvastatin is approved in Germany for the treatment of heterozygous familial hypercholesterolaemia from the age of 9 years.

Alternative treatment options:

- Ezetimibe (blocks intestinal absorption of cholesterol; combination with statins possible): 10 mg/day in patients >10 years: safe, well tolerated and effective. Most common adverse events: diarrhoea, myopathy. Cautiousness in cases of elevated transaminases/hepatic disease; caution: eGFR < 30 mL/min/1.73 m^2 increases exposure to ezetimibe. Caution against the combination with cyclosporin A (interaction).
- Omega-3 fatty acids (fish oil capsules + vitamin E; if triglycerides > 400 mg/dL (> 4.56 mmol/L); initial dose 1 g/day, which can be increased after a few weeks, if necessary; well tolerated.
- Bile acid sequestrants (e.g., cholestyramine): May be used in combination with statins. Caution: May reduce absorption of fat-soluble vitamins and mycophenolate mofetil.
- Use of sevelamer (lowers LDL-C) as a prophylactic or therapeutic option in hyperphosphatemia [9] (caution: reduces exposure to mycophenolic acid).

Newer agents: Evolocumab: human monoclonal antibody that inhibits PSCK9 and thus LDL receptor degradation → enhances removal of circulating LDL cholesterol; approved for children ≥10 years of age with homozygous familial hypercholesterolaemia (HFH). No effect on CYP450, P-glycoprotein or OATP pathways, so limited potential for drug-drug interactions. Monthly injection. Limited but encouraging experience to date: safe and effective in one randomised trial, 104 children aged 10–17 years with HFH received evolocumab, follow-up 24 weeks [10]; 1 study in 13 adult kidney transplant recipients, follow-up 6 months: effective, stable kidney function, proteinuria and immunosuppression, no other safety concerns reported [11]. Most common adverse events: nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%).

Figure 1 Screening and management of paediatric kidney transplant recipients aged ≥ 8 years, adapted from [7]



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