Etiology and management of dyslipidemia in children with chronic kidney disease and end-stage renal disease

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Abstract Lipids are essential components of cell membranes, contributing to cell fuel, myelin formation, subcellular organelle function, and steroid hormone synthesis. Children with chronic kidney disease (CKD) and end-stage renal disease (ESRD) exhibit various co-morbidities, including dyslipidemia. The prevalence of dyslipidemias in children with CKD and ESRD is high, being present in 39–65 % of patients. Elevated lipid levels in children without renal disease are a risk factor for cardiovascular disease (CVD), while the risk for CVD in pediatric CKD/ESRD is unclear. The pathogenesis of dyslipidemia in CKD features various factors, including increased levels of triglycerides, triglyceride-rich lipoproteins, apolipoprotein C3 (ApoC-III), decreased levels of cholesteryl ester transfer protein and high-density lipoproteins, and aberrations in serum very low-density and intermediate-density lipoproteins. If initial risk assessment indicates that a child with advanced CKD has 2 or more co-morbidities for CVD, first-line treatment should consist of non-pharmacologic management such as therapeutic lifestyle changes and dietary counseling. Pharmacologic treatment of dyslipidemia may reduce the incidence of CVD in children with CKD/ESRD, but randomized trials are lacking. Statins are the only class of lipid-lowering drugs currently approved

by the U.S. Food and Drug Administration (FDA) for use in the pediatric population. FDA-approved pediatric labeling for these drugs is based on results from placebo-controlled trial results, showing 30–50 % reductions in baseline low-density lipoprotein cholesterol. Although statins are generally well tolerated in adults, a spectrum of adverse events has been reported with their use in both the clinical trial and post-marketing settings.

Keywords Dyslipidemia · Chronic kidney disease · Cardiovascular disease · Lifestyle change · Dietary counseling · Statin therapy · Adverse events

Lipid abnormalities in CKD-ESRD

Lipid metabolism and function

Lipids are essential components of cell membranes, contributing to cell fuel, myelin formation, subcellular organelle function, and steroid hormone synthesis. Lipids are generally categorized by their density and other physical characteristics [1]. Since lipids such as cholesterol and triglycerides (TG) are insoluble in plasma, lipoproteins are required to transport all sources (e.g., diet) of lipids to areas in which the lipids can either be stored for future use or used immediately [2], although it should be noted that short- and medium-chain fatty acids also flow via the portal system as fatty acids. Specifically, low-density lipoproteins (LDL) carry the majority of cholesterol (forming LDL-C), while very low-density lipoproteins (VLDL) carry the majority of triglycerides.

The broad categories of lipoproteins are chylomicrons, VLDL, LDL, and high-density lipoproteins (HDL). The major sites of lipoprotein synthesis are the liver and intestine [3].

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Prevalence and sub-types of dyslipidemia in pediatric chronic kidney disease (CKD) and end-stage renal disease (ESRD)

Children with CKD/ESRD exhibit various co-morbidities, including dyslipidemia. The prevalence of dyslipidemias in children with CKD and ESRD is high (39–65 %), but is significantly dependent on the cause and vintage of CKD (e.g., usually more common and severe with glomerular disease and proteinuria) and the stage of the disease [4, 5]. The Chronic Kidney Disease in Children (CKiD) study included an assessment of the relationship between renal function and serum lipid levels. The most common type of dyslipidemia was hypertriglyceridemia. They found an inverse relationship between renal function (measured glomerular filtration rate, or GFR) and serum TG and total cholesterol (TC) levels; that is, as GFR declines, TG and TC levels generally increase. Conversely, there is a direct relationship between GFR and HDL-C [4].

The dyslipidemia profile characteristic of pediatric CKD/ESRD does not include an elevated LDL-C as a prominent or consistent finding. This is noteworthy given that epidemiology studies suggest that LDL are the lipoproteins most relevant to atherosclerosis [1, 2]. Specifically, children with CKD/ESRD display aberrations in serum VLDL, intermediate-density lipoproteins (IDL), and HDL-C. While some of the abnormalities in these indices may recede after renal transplantation, others may persist [6]. In addition, serum TC levels are near normal, while LDL-C levels are variable [7–14].

Impact of dyslipidemia on cardiovascular morbidity and mortality in renal disease

The potential impact of dyslipidemia is profound. Indeed, elevated lipid levels in children without renal disease are a risk factor for hyperlipidemia in adult life and for cardiovascular disease (CVD) [15]. For example, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study showed that children with normal renal function may develop fatty streaks during adolescence, which can progress to atheromatous plaques during early adult life [16], and, there is other evidence that children with hypercholesterolemia and diabetes exhibit increased aorta intima-medial thickness and early atherosclerosis [17].

The relative risk for CVD from dyslipidemia in children with CKD and ESRD compared to the general pediatric population is not known due to the short time frame of follow-up and the existence of other CVD risk factors (e.g., inflammation). However, the American Heart Association Expert Panel on Population and Prevention Science has concluded that prevention of CVD in high-risk pediatric patients is warranted due to the higher risk of developing disease as adults [18].

While it is known that children with advanced CKD or ESRD develop atherosclerosis and CVD, it is not clear that

clinically relevant CVD occurs in Stage 1 or 2 CKD. Pennisi et al. [19] showed that children with ESRD reveal intimal damage of the coronary arteries. The direct relationship between dyslipidemia and vascular disease is difficult to ascertain due to the small number of patients, concurrent risk factors for vascular disease, the relatively brief period of follow-up, and the shorter period of CKD.

The mortality rate due to CVD in adults with ESRD is about 10–20-fold higher than the general population [20–22]. However, a definitive role for dyslipidemia in the development of CVD in patients with CKD or on dialysis remains controversial. In a meta-analysis of patients with pre-dialysis CKD, Strippoli et al. studied more than 6,500 patients with CKD and showed that statins significantly reduced serum lipid levels and the incidence of CVD [23]. Similarly, a Cochrane database meta-analysis demonstrated that statins reduced the relative all-cause mortality, and reduced death from CVD by 20 % in more than 18,000 patients with pre-dialysis CKD, with or without CVD [24]. However, a randomized control trial (statins versus control) showed that statins did not decrease all-cause mortality or stroke in patients with CKD due to diabetes [25].

A direct benefit for statins on CVD in patients with ESRD is also unproven. In one placebo, randomized controlled trial (RCT; 4D study) of 1,255 patients (460 evaluable patients who reached the primary endpoint) with ESRD secondary to diabetes, atorvastatin had no effect on CVD events [26]. The study of Heart and Renal Protection (SHARP) trial was a RCT of 9,270 patients with pre-dialysis CKD and ESRD without prior myocardial infarction or coronary revascularization. Patients received a combination of simvastatin plus ezetimibe, or placebo. The follow-up period was 4.9 years, and it showed a significant reduction in major atherosclerotic events, stroke, and arterial revascularization procedures in the treatment group. However, this effect was not observed in ESRD patients alone [27]. The AURORA trial [28] was a RCT that included more than 2,700 patients receiving hemodialysis. Patients received either rosuvastatin or placebo. While rosuvastatin therapy lowered LDL-C, it neither reduced CVD endpoints nor all-cause mortality.

Specific factors involved in the pathogenesis of dyslipidemia in CKD/ESRD

The pathogenesis of dyslipidemia in CKD involves various factors. These factors have been elegantly and thoroughly discussed in three reviews: [5, 29, 30].

Triglyceride-rich lipoproteins (TRL)

In general, the accumulation of triglycerides and TRL in CKD/ESRD is due to increased production and impaired catabolism [31]. Indeed, there is strong evidence of reduced

lipolysis of TRL due to the decreased activity of the major lipases, lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL), that are mainly responsible for breaking down TG into free fatty acids [32]. Increased production of TRL may also be secondary to reduced carbohydrate tolerance and enhanced hepatic VLDL synthesis [33]. The reduced fractional catabolic rate is likely due to the decreased activity of two endothelium-associated lipases, LPL and HTGL.

Apolipoprotein C3 (ApoC-III)

The levels of apoC-III are increased in patients with CKD [34, 35]. Since ApoC-III induces an increase in plasma TG levels [36], this may be an additional factor contributing to dyslipidemia in CKD.

Cholesterylester transfer protein (CETP)

CETP, also called plasma lipid transfer protein, is expressed in the liver, small intestine, adipose tissue, and spleen [37]. CETP is a substance that binds lipids and transfers them between the lipoproteins. There is evidence that CETP levels are decreased in patients with ESRD [8, 38]. The impact of decreased CETP levels in ESRD remains controversial.

HDL-C

A reduction in HDL-C levels is due to several factors. First, the relative distribution of HDL subfractions is altered in CKD-ESRD, due mainly to diminished conversion of HDL₃ to HDL₂. In turn, this results in a reduced capacity of HDL to carry cholesterol into the liver, leading to elevated serum TC levels [39]. The activity of plasma paraoxonase, an enzyme that inhibits the oxidation of LDL, is reduced in patients with CKD, potentially resulting in increased oxidation and reduced activity of HDL-C [40]. In addition, elevated TRL stimulates the conversion of accumulated TG into HDL, whereupon HDL is vulnerable to breakdown by hepatic lipase. Other mechanisms that may play a role in the decline in HDL include reduced lecithin-cholesterol acyltransferase activity [41, 42].

Apolipoprotein A-IV (Apo A-IV)

Apo-A-IV might protect against atherosclerosis by removing cholesterol from peripheral cells and directing it to the liver and other organs. ApoA-IV plasma levels are considered markers of progression of nondiabetic kidney disease [43]. ApoA-IV levels are reduced in patients with significant proteinuria [44], but increased in dialysis patients [45]. Therefore, Apo-A IV may be protective against dyslipidemia, but this feature may be impaired in patients with glomerular disease in CKD.

LDL-C

As mentioned above, plasma LDL-C levels vary in CKD: they are often elevated in patients with CKD and nephrotic syndrome but normal in patients with CKD due to other causes and in patients with ESRD. However, there may be functional abnormalities in LDL-C in CKD and ESRD. Small dense LDL (sdLDL) is a type of LDL that stimulates the atherosclerotic process. Intermediate-density lipoprotein (IDL) is a metabolite of VLDL that is usually degraded to LDL by HTGL. As mentioned above, there is reduced HTGL activity in CKD, resulting in reduced conversion of IDL to LDL [46]. Taken together, there is accumulation of both sdLDL and IDL in CKD. There is preliminary evidence that sdLDL and IDL may contribute to the development of atherosclerotic plaques [47].

Lipoprotein(a) [Lp(a)]

Lp(a) consists of Apo(a) covalently bound to an LDL particle. Apo(a) competes with plasminogen for the binding of the pro-atherosclerotic factors plasminogen receptors, fibrinogen, and fibrin [44]. The Apo(a) gene determines plasma Lp(a) levels. In addition, there is an inverse relationship between the molecular weight or size of Apo(a) isoforms and plasma Lp(a) levels. In CKD, plasma Lp(a) levels are also influenced by GFR. In some patients, plasma Lp(a) levels increase early in CKD [48] or in patients without CKD but active nephrotic syndrome [49]. Most people with CKD also exhibit increased or normal levels of ApoB [50].

Nephrotic syndrome

Nephrotic syndrome (NS) is a common feature of many glomerular diseases affecting children, many of which may progress to CKD. Active NS results in significant proteinuria and hyperlipidemia, the latter featuring elevated TC with or without elevated TG [51, 52]. Specifically, patients with NS exhibit elevated levels of all Apo-B containing lipoproteins, due to reduced catabolism, including VLDL, IDL, LDL-C, and Lp(a); conversely, HDL-C levels are usually normal [53–57]. The pathogenesis includes increased production together with reduced clearance of lipoproteins [54, 58–63]. Specifically, elevation of plasma LDL in NS is thought to be due to increased LDL synthesis and depressed LDL catabolism [52]. Other important changes in NS include elevation of hepatic HMG-CoA reductase and reduction of Ch 7 α -hydroxylase, the rate-limiting enzyme in cholesterol catabolism [64]. Finally, there is recent evidence of an increase in circulating angiopoietin-like 4 as a compensatory mechanism in patients with nephrotic-range proteinuria in an attempt to reduce the pathology associated with proteinuria, with the unfortunate result of causing hypertriglyceridemia [65].

Other specific factors

Insulin resistance, common in CKD and ESRD [66], has been shown to induce abnormalities in lipid metabolism [67] in CKD and ESRD. There are various medications that contribute to dyslipidemia in CKD/ESRD, including corticosteroids and cyclosporine. Singh et al. measured fasting serum lipid profiles in 73 children, including 21 controls, 25 patients treated with cyclosporine and/or prednisone for glomerular diseases, and 25 patients receiving chronic dialysis. Children receiving combination therapy with cyclosporine and prednisone had higher TC, TG, LDL-C, and VLDL compared to the control group. Similarly, children receiving dialysis had higher TG and VLDL levels than the controls [1]. Finally, intestinal lipoproteins distribute dietary lipid in the postprandial state. In addition, several apolipoproteins are produced by the intestine [68]. The impact of CKD/ESRD on postprandial lipoprotein metabolism is still under study. In studies of patients with CKD, there is a greater rise and an abnormally prolonged increase in circulating triglycerides postprandially [20, 69].

Summary

In summary, the hallmarks of uremic dyslipidemia are hypertriglyceridemia; increased remnant lipoproteins (chylomicron remnants and IDL); reduced HDL cholesterol; and increased sdLDL, Lp(a), and ApoA-IV. Elevated plasma LDL cholesterol level is not typical but can mostly be observed in patients with nephrotic syndrome and peritoneal dialysis (PD) patients.

Etiology of dyslipidemia in renal transplantation

Many of the risk factors for dyslipidemia mentioned above exist in patients with functioning allografts since CKD naturally occurs in this patient population. Compared to the general population, the rates of CVD are also markedly elevated in renal transplant recipients [70]. The most likely reason for this continued risk is the presence of a degree of CKD in almost all transplant recipients. Indeed, studies in adult renal transplant recipients have revealed that the prevalence of hyperlipidemia initially increases and subsequently decreases, with a prevalence rate of about 30 % up to 5 years after transplantation [71]. In pediatric renal transplant recipients, the prevalence of hypercholesterolemia is about 70 % 1 year after transplant, but thereafter declines to 15 % (for TG) and 35 % for TC [72]. The most common pattern of dyslipidemia is an increase in LDL-C and Lp(a) [73].

Other than gradual decline in GFR, there are other factors contributing to dyslipidemia in this patient population. The major culprit is medication use, particularly corticosteroids [74]. Cyclosporine is also associated with dyslipidemia,

particularly elevated TC and LDL-C [75]. Interestingly, another calcineurin inhibitor, tacrolimus, is less likely to be associated with dyslipidemia than cyclosporine [76]. Finally, sirolimus is also a risk factor for the development of hyperlipidemia [77].

Targets

As summarized in the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) [78], the National Institutes of Health (NIH) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents in 2011 discussed specific questions of screening for dyslipidemias in children and adolescents and also treatment of dyslipidemias [79]. Serum lipid levels vary depending on age, puberty, and gender. Indeed, serum lipid levels are very low at birth and increase during the first year of life [mean TC of 3.9 mmol/l (150 mg/dl), LDL-C 2.6 mmol/l (100 mg/dl), and HDL-C 1.4 mmol/l (55 mg/dl)] where they remain fairly constant until age 12 and are slightly lower in girls than boys. During puberty, there is a decrease in TC, LDL-C, and a slight decrease in HDL-C in boys. After puberty, TC and LDL-C increase to adult levels in boys and girls. Boys continue to have a slightly lower HDL-C than girls [80]. The NIH Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents in 2011 published a table displaying acceptable, borderline high and high lipid levels for children and adolescents.

Frequency of measurements

There are no accepted standard guidelines for the measurement of serum lipids in children with CKD or ESRD. It seems logical to assess the levels in any patient with nephrotic syndrome that is unresponsive or only partially responsive to dietary and/or medical therapy, or in any patient with a glomerular disease receiving medications associated with dyslipidemia. If the expected duration of disease or medication exposure is brief, it seems reasonable to defer measurement until a steady level is established. For children and adolescents with established CKD, with or without NS, KDIGO recommends annual measurement of fasting lipids. KDIGO adds that the frequency of annual measurements may require alteration if the clinical circumstances suggest lower or higher risk, or if changes in therapy for dyslipidemia warrant measurement [78].

Management of dyslipidemia in pediatric CKD-ESRD

Non-pharmacologic management

Initial management in all children with dyslipidemia, regardless of whether they have CKD, should consist of therapeutic

lifestyle changes (TLC). These changes are intended to ensure growing children receive an adequate amount of nutrients while avoiding excessive dietary fat, increasing physical activities, and limiting sedentary activities. Excess dietary fat restriction as part of a heart-healthy dietary plan such as the Cardiovascular Health Integrated Lifestyle Diet [81] has been shown to reduce total cholesterol and LDL-C, lower the risk of obesity, and decrease insulin resistance in otherwise healthy children without causing adverse effects on growth, development, or nutrition [18]. Evidence that TLC is beneficial in improving clinical outcomes in pediatric CKD is weak, but such measures are unlikely to cause harm and may promote better health. Certain aspects of TLC such as a heart-healthy diet focused on consumption of fat-free milk and water as primary beverages and dietary fat restrictions to 25–30 % of total calories may be possible in otherwise healthy children but not practical in children with CKD who must restrict dietary calcium, phosphorus, or fluid intake or are malnourished. Similarly, increased physical activity may not be feasible if serious metabolic complications of CKD are present. In such cases, disease-specific management becomes particularly important [82], and secondary causes of dyslipidemia should be sought and treated [81, 83]. Sedentary activities should also be minimized by limiting leisure screen time to less than 2 h per day in children older than age 2 years and encouraging children older than age 5 years to participate in at least 1 h of moderate-to-vigorous activity (jogging, baseball) every day and vigorous activity (running, soccer) 3 days per week [18].

Pharmacologic management

Five classes of lipid-lowering drugs exist and include bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, 3-hydroxy-3-methyl-glutaryl-CoA

(HMG-CoA) reductase inhibitors or statins, and nicotinic acid (see Table 1). Drugs from only three classes are currently approved by the U.S. Food and Drug Administration (FDA) for use in the pediatric population. The FDA-approved pediatric indications for statins are limited to children and adolescents ages 8–18 years with familial hypercholesterolemia to lower TC, LDL-C, and Apo-B levels in conjunction with diet and lifestyle modifications (see Table 2). FDA-approved pediatric labeling for statins was based on results from placebo-controlled trial results showing 30–50 % reductions in baseline LDL-C regardless of the statin used. The short-term safety of statin therapy in children is based on clinical trials conducted for durations of 2 years or less [84]. These trials have reported asymptomatic elevations in liver transaminases in 1–5 % of children treated with a statin that reversed upon discontinuation of statin therapy. Ezetimibe is currently the only FDA-approved cholesterol absorption inhibitor indicated to reduce TC and LDL-C in the same pediatric population as statins. This approval was based on a 6-week trial of ezetimibe co-administered with simvastatin using simvastatin monotherapy as the active comparator followed by a 27-week open-label phase. Results at both week 6 and week 33 showed a mean 12 % reduction in TC and 15 % reduction in LDL-C. Colesevelam hydrochloride is a bile acid sequestrant also recently FDA approved for use in boys and post-menarchal girls, age 10–17 years, with heterozygous familial hypercholesterolemia on the basis of a randomized, double-blind, placebo-controlled trial that showed mean reductions in baseline TC by 12 %, in LDL-C by 13 %, and in Apo-B by 8 %. These trials ranged in duration from 24 weeks to up to 2 years, so the long-term efficacy of using these drugs in children to prevent cardiovascular morbidity and mortality in adulthood has

Table 1 Five classes of lipid-lowering drugs [4]

Lipid-lowering class	Mechanism of action	Effect
Bile acid sequestrants (cholestyramine, colestipol, colesevelam)	Bind intestinal bile acids to prevent bile acid reuptake in terminal ileum to lower intrahepatic cholesterol which upregulates LDL receptor expression and LDL-C clearance	↓ TC ↓ LDL-C
Cholesterol absorption inhibitors (ezetimibe)	Prevent absorption of dietary and biliary cholesterol at intestinal brush border via apparent inhibition of Niemann-Pick C1-like 1 protein which lowers intrahepatic cholesterol and upregulates LDL receptor expression and LDL-C clearance	↓ LDL-C
Fibric acid derivatives	Unclear mechanism but possible ↓ hepatic TG production	↓ TG ↑ HDL-C
Statins	Inhibit 3-hydroxy-3-methyl-glutaryl rate-limiting coenzyme for de novo cholesterol synthesis	↓ LDL-C
Nicotinic acid (niacin)	Inhibits hepatic VLDL and, therefore, LDL production Reduces lipid transfer of cholesterol from HDL to VLDL and delays HDL clearance	↓ TG ↑ HDL-C ↓ LDL-C

LDL low-density lipoproteins, TG triglycerides, VLDL very low-density lipoproteins, HDL high-density lipoproteins

Table 2 FDA-approved lipid-lowering agents for use in children

Drug	Pediatric indication	Approval year	Pediatric age group
Statins			
Atorvastatin	HFH	2002	10–17 years
Lovastatin	HFH	2002	10–17 years; ≥ 1 year post-menarchal females
Pravastatin	HFH	2002	8–13 years 14–18 years
Simvastatin	HFH	2002	10–17 years; ≥ 1 year post-menarchal females
Fluvastatin	HFH	2006	10–16 years; ≥ 1 year post-menarchal females
Rosuvastatin	HFH	2009	10–17 years; ≥ 1 year post-menarchal females
Cholesterol absorption inhibitors			
Ezetimibe	HFH	2002	10–17 years; > 1 year post-menarchal females
Ezetimibe/simvastatin	HFH	2004	10–17 years; > 1 year post-menarchal females
Bile Acid Sequestrants			
Colesevelam	HFH	2009	10–17 years; > 1 year post-menarchal females

HFH heterozygous familial hypercholesterolemia, LDL low-density lipoproteins, CVD cardiovascular disease

FDA-approved pediatric indications for statin use:

HFH with LDL-C > 190 mg/dl OR HFH with LDL-C > 160 mg/dl with a positive family history of premature CVD or two or more other CVD risk factors

not been established. Additionally, the long-term safety of these drugs on growth, development, and sexual maturation in children is not known.

When considering the utility of treating dyslipidemia with lipid-lowering drugs in adults or children with CKD or ESRD, it is important to first note that the pathogenesis of vascular endothelial injury in these populations is multi-factorial and may be increasingly governed by non-traditional risk factors, particularly as renal function deteriorates, to which such drugs may not have the same impact as in the non-CKD population. Those with CKD or ESRD develop intimal atherosclerosis similar to the general population for whom the traditional risk factors of hypertension, dyslipidemia, insulin resistance, and obesity play major roles. However, unlike the general population, the CKD/ESRD population also develops arteriosclerotic disease with medial calcifications in which non-traditional risk factors unique to the uremic milieu may play a more important role, particularly as CKD progresses [85–87].

Historically, developing a consensus on dyslipidemia management in the CKD population has been challenging, given the unique metabolic complications of CKD, the potentially greater role of non-traditional risk factors in contributing to cardiovascular (CV) disease, and the lack of randomized controlled clinical trials of dyslipidemia treatment in CKD. Extrapolation of results from dyslipidemia trials conducted in the general adult population to children with CKD is not appropriate because the majority of these trials, which showed treatment benefits and prompted recommendations for more aggressive lipid reduction in moderate- to high-risk adults, were secondary prevention trials and do not apply to children and adolescents in whom

primary prevention is the treatment goal [84]. Traditionally, primary prevention trials in adults have not definitively shown the benefits of dyslipidemia treatment in reducing the risk of both coronary and total mortality. A more recently conducted primary prevention placebo-controlled trial in 17,802 adults with C-reactive protein levels > 2 mg/dl and LDL-C less than 130 mg/dl (the Justification for the Use of Statins in Primary Prevention [JUPITER] trial) showed clear benefit in the statin-treated group for the primary endpoints of nonfatal myocardial infarction, nonfatal stroke, arterial vascularization, hospitalization for unstable angina, and all-cause mortality [88]. However, the study population did not have dyslipidemia, and adults with a serum creatinine higher than 2.0 mg/dl or other established CKD risk factors such as diabetes and uncontrolled hypertension were excluded from trial entry.

The U.S.-based National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) work group published Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease in 2003 and classified CKD as a coronary heart disease (CHD) risk equivalent given the increased risk of CV disease in the CKD population compared to the general population. In the absence of randomized controlled clinical trials of dyslipidemia in CKD patients, these guidelines recommended following the 1992 National Cholesterol Education Program guidelines [89] for dyslipidemia goals in adults and adolescents with estimated glomerular filtration rates (eGFR) values of 15 ml/min/1.73 m² or greater (formerly known as CKD stages 1 to 4) and also recommended treatment in dyslipidemic adults and adolescents with eGFR values below 15 ml/min/1.73 m² (formerly known as stage 5 CKD) [90].

Recognizing that CKD is associated with pathological and/or clinical evidence of coronary disease before the age of 30 years and that multiple prospective studies show childhood lipid and lipoprotein profiles are predictive of future adult lipoprotein profiles with the strongest statistical correlation occurring between late childhood and the third and fourth decades of life [18, 83], two expert pediatric panels published evidence-based guidelines for intensive cardiovascular risk reduction in children with CKD after the 2003 publication of the KDOQI guidelines [18, 78]. In general, the cardiovascular risk mitigation strategies outlined in these guidelines rely on expert consensus rather than efficacy data, are largely based on the premise that plasma lipid levels in otherwise healthy children are predictive of future plasma lipid levels and subsequent CV events in adulthood [91–94], and include recommendations for the non-pharmacologic and pharmacologic management of dyslipidemia.

The 2006 Scientific Statement from the American Heart Association (AHA) Expert Panel, endorsed by the American Academy of Pediatrics, states CV risk mitigation strategies are warranted in certain chronic pediatric conditions, including CKD, given the high risk of development of adult-onset CVD. This panel recommended that children with eGFR less than 15 ml/1.73 m², on dialysis, or renal transplant recipients should undergo modification of traditional CV risk factors and be monitored for end organ injury with an emphasis on chronic CV risk factor reduction [78]. In addition to disease-specific management, this panel recommended rigorous age-appropriate TLC and smoking cessation as well as optimization of blood pressure, LDL-C, blood glucose, and glycosylated hemoglobin with use of statin therapy in children older than age 10 years to reach the LDL-C goal.

The 2011 National Heart, Blood, Lung Institute (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular, Health Risk Reduction in Children and Adolescents focused on the promotion of CV health in all children from birth through young adulthood with an emphasis on preventing risk factor development and prevention of future CV disease by effective risk factor management [18]. These guidelines identified CKD, ESRD, and post-renal transplant as high-risk conditions for future CV disease and recommended TLC as a first-line treatment if the initial risk assessment indicates that a child with advanced CKD has two or more comorbidities for CVD. The panel did not recommend statin therapy in children under age 10 years with CKD but stated that the potential prevention of adverse CV events may outweigh the risk of statin-related adverse events in males age 10 years or older and post-menarchal females

with severely elevated LDL-C and CKD, particularly if they have one or more of the following additional risk factors for CVD [95]:

- Family history of premature coronary disease
- Diabetes
- Hypertension
- Smoking
- ESRD

Since publication of the KDOQI, AHA, and NHLBI guidelines, results from more than a dozen randomized controlled trials, including three landmark trials [88–90], have better informed dyslipidemia management in the adult CKD population and resulted in publication of the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in CKD [78]. This guideline focuses on lipid management for adults and children with CKD and contains substantial changes in dyslipidemia management in adult CKD from the KDOQI guidelines including the following:

- Treatment escalation with lipid-lowering agents to achieve specific LDL-C targets is not recommended given that LDL-C does not reliably discriminate between those at low versus high CV risk.
- Higher CV risk rather than elevated LDL-C should be the primary indication to initiate or adjust lipid-lowering treatment.
- The risk of CHD is sufficiently high in adults age 50 years or older with non-dialysis dependent CKD or renal transplant to justify the use of statin or statin/ezetimibe combination.
- Statins or statin/ezetimibe combination should not be initiated in adults with dialysis-dependent CKD due to the uncertain clinical benefits of LDL-C reduction in this population.

Unlike their recommendations for pharmacologic treatment in adults with CKD, the 2013 KDIGO guidelines do not recommend initiation of statins or a statin/ezetimibe combination in children under 18 years with CKD due to their lack of clear benefit compounded by safety concerns associated with their long-term use in children. Extrapolating results from the recent landmark trials in adults with CKD to children with CKD is not appropriate for several reasons. First, the etiology of CKD in adults is different from that in children. Second, adults with CKD often have co-morbidities that contribute to the dyslipidemia, making them potentially more likely than children to benefit from lipid-lowering treatment. Third, the atherosclerotic lesions targeted by lipid-lowering agents are more likely to be in advanced stages of pathogenesis in adults than in children [85].

Sarnak and colleagues recently published (95; online version available only) the KDOQI US Commentary on the 2013 KDIGO Clinical Practice Guideline for Lipid Management in CKD. They note that KDIGO and other (e.g., AHA) guidelines do not recommend using LDL-C as a guide for treatment. Regarding the KDIGO guidelines, the authors state: “The KDIGO guideline did not compare or harmonize their recommendations to other lipid guidelines, which may lead to some confusion among practitioners”, and therefore recommended reconciling the various published guidelines. While the majority of the commentary pertains to the treatment of adult patients with CKD, the commentary does highlight the various discrepancies among guidelines for treating children with hyperlipidemia. Specifically, KDIGO does not provide any specific recommendations to treat children with CKD and hyperlipidemia while AHA recommends lifestyle therapy for all patients, with the addition of a statin in those older than ten years of age with LDL-C > 100 mg/dl and AACE guidelines recommend pharmacotherapy for children older than age 8 years unresponsive to lifestyle changes. In addition, KDOQI suggests further research to better understand the relationship between hyperlipidemia and CVD and developing risk calculators for CVD in children with CKD. They also recommend developing short-term pharmacodynamics and drug safety data in children with CKD, proteinuria or renal transplants. KDOQI agrees with various guidelines that recommend a screening lipid profile in children with recently diagnosed CKD and for those with other conditions such as NS, with annual follow-up assessments. Finally, in children under age 18 years with CKD, KDOQI agrees that there is insufficient evidence to recommend initiation of statins or a combination of statin/ezetimibe; rather, lifestyle changes should be employed for children with CKD and LDL-C > 130 mg/dl. However, KDOQI recommends that consideration of underlying renal disease duration and age of onset be considered in the decision of therapy.

Available trials evaluating the efficacy of lipid-lowering drugs in children with CKD are limited to those evaluating the use of statins in children with steroid-resistant nephrotic syndrome (SRNS) [96–98]. Dyslipidemia is a characteristic feature of NS and generally resolves with spontaneous or steroid-induced remission of the disease. However, dyslipidemia can be persistent and severe in steroid-resistant forms where complete remission is not achieved. Given the long-standing nature of childhood SRNS, persistent dyslipidemia in this setting is potentially associated with atherosclerotic complications. At least two autopsy studies have shown evidence of accelerated coronary [99] and renal artery [100] atherosclerosis in dyslipidemic children with NS. These trials showed significant reductions in baseline serum lipid levels

after statin treatment, but the results have limited utility for several reasons. The trials were small and uncontrolled. The use of concomitant medications such as angiotensin-converting enzyme inhibitors or corticosteroids, which may have confounded assessment of serum lipid levels, was not consistently specified. Despite their purported pleiotropic effects, the statins had no effect on delaying renal functional deterioration or ameliorating proteinuria. It is also important to note that, despite the significant reduction in baseline serum lipid levels, the mean post-treatment values were not in the normal reference range for the majority of treated children. Surrogate measures of cardiovascular outcomes were not measured in these trials, which were too short in duration to reliably detect such outcomes. Probucol has also been shown to have effects similar to statins for dyslipidemia treatment in childhood SRNS [101], but this drug was removed from the U.S. market in 1995 for safety reasons.

While the 2013 KDIGO guidelines do not recommend statin treatment in children under age 10 years with CKD, the work group acknowledges that statin initiation may be a consideration on a case-by-case basis for boys older than age 10 years and post-menarchal girls with severe LDL-C elevation. This approach is consistent with the 2011 NHBLI guidelines. In such cases, the KDIGO guidelines state the starting dose should be the lowest available dose but caution that no dose escalation trials have been done in children with CKD to confirm the safety of higher statin doses even over the short term and there are no data regarding what the appropriate target for LDL-C should be in children with or without CKD [78]. In addition, clinicians should be aware of several unique concerns to prescribing statin therapy in adolescents. An adolescent who begins statin therapy will receive a higher cumulative dose over the course of their lifetime than most adults, but the safety of such long-term statin exposure beginning in adolescence has not yet been established [84]. Clinical trials in adolescents have not observed adverse effects of statin therapy on growth parameters, hormone synthesis, pubertal development, myopathy, and rhabdomyolysis. However, these trials may have been too short in duration and underpowered to detect such effects. Because statins are potent teratogens, adolescents who are prescribed statin therapy must be educated about effective birth control.

The KDIGO guidelines do not recommend pharmacologic treatment of hypertriglyceridemia to prevent pancreatitis or reduce CV risk in children with CKD given the lack of strong evidence that use of drugs such as fibric acid derivatives, niacin, and fish oil are safe and effective. Given the lack of evidence that combination therapy with bile acid sequestrants, colestipol, and ezetimibe in pediatric CKD is safe or effective, the guidelines recommend these multi-drug regimens should be avoided even in children with very elevated LDL-C.

It is not clear whether pharmacologic treatment of dyslipidemia in children less than age 10 years or those with less advanced CKD may be as safe or effective in reducing the incidence of atherosclerotic CV disease as in other pediatric populations, and clinicians should carefully consider the risk benefit profile of the short- and long-term use of lipid-lowering drugs in these cases [102].

QUESTIONS (answers are provided following the reference list)

Option	<i>Serum triglycerides</i>	<i>LDL-C</i>	<i>HDL-C</i>	<i>Apolipoprotein C3</i>	<i>Lipoprotein(a)</i>
A	Increased	Normal	Decreased	Increased	Increased
B	Normal	Normal	Decreased	Normal	Decreased
C	Increased	Decreased	Increased	Increased	Normal
D	Increased	Increased	Increased	Decreased	Increased
E	Decreased	Decreased	Increased	Normal	Normal

2. The MOST accurate statement regarding cardiovascular disease (CVD) in children with CKD/ESRD who have dyslipidemia is:

- A) There is significant evidence that cardiovascular disease is common
- B) Atherosclerosis develops early (Stage 1 and 2 CKD) in the course of renal disease
- C) Evidence is either lacking or inconclusive regarding the relationship between dyslipidemia and CVD
- D) Studies show that children with ESRD have damage limited to the media of the coronary arteries
- E) Coronary artery disease is more commonly observed in children versus adults with CKD/ESRD

3. The MOST accurate statement about dyslipidemia in pediatric renal transplant patients is:

- A) Dyslipidemia typically is limited to elevated serum cholesterol
- B) The rates of dyslipidemia generally decline in the first year after transplantation
- C) There is a proven relationship between dyslipidemia and graft dysfunction
- D) The role of medications in the pathogenesis of dyslipidemia is unproven
- E) Dyslipidemia is a proven risk factor for cardiovascular disease

4. For a child with dyslipidemia, the INITIAL approach to therapy should include:

- A) Pharmacological therapy with a statin
- B) Discontinuation of all medications that may be contributing to dyslipidemia
- C) Specific lipid-lowering therapy targeting the specific lipid(s) levels that are abnormal

1. Among the following options, a child with chronic kidney disease (CKD) or end-stage renal disease (ESRD) would MOST likely a constellation of abnormalities in lipid profiles is:

- D) Lifestyle change and dietary counseling
- E) Referral to a cardiologist to tailor therapy based on cardiological status

5. Among the following, the MOST accurate statement regarding statin therapy for children with or without renal disease is:

- A) There are a multitude of randomized, controlled trials showing that the benefits of statin therapy outweigh the risks
- B) The most abundant evidence showing the efficacy and safety of statins in children with renal disease is for patients with nephrotic syndrome
- C) Several classes of statins have been approved by the Food and Drug Administration
- D) For children with CKD, statin therapy is approved for children age 5 years and older
- E) Adverse events uncommonly include elevations in liver transaminases

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Correct answers

- 1) A
- 2) C
- 3) B
- 4) D
- 5) B