

## CLINICAL MANAGEMENT OF DYSLIPIDEMIA IN YOUTH WITH CHRONIC KIDNEY DISEASE

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### ABSTRACT

Chronic kidney disease (CKD) is commonly associated with abnormal lipid metabolism which may contribute to the morbidity and premature mortality associated with impaired renal function. Dyslipidemia often occurs in the early phases and becomes progressively worse with disease severity and progression to end stage renal disease (ESRD). In this review, we discuss the clinical features, diagnosis, and management of dyslipidemia in children with renal disease, focusing primarily on nephrotic syndrome (NS) and ESRD. There are limited data on treatment of dyslipidemia, outcomes, and prevention of CVD in youth with these conditions to help inform clinical decision-making and define best practices.

### INTRODUCTION

Chronic kidney disease (CKD) is characterized by a progressive decrease in renal function, divided into five stages (Table 1). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) defines CKD as a glomerular filtration rate (GFR) persistently < 60 mL/min (1). Further decline in kidney function results in ESRD, with permanent and complete loss of renal function, necessitating either dialysis or renal transplantation. Due to a wide variety of common causes, including diabetes and hypertension, the prevalence of CKD is increasing (2). In individuals with CKD, CVD is the leading cause of death and dyslipidemia is recognized as a major risk factor (3). Mortality in up to half of individuals with CKD is the result of CVD (4).

Table 1. CKD Stages		
Stage	GFR	
1	> 90	mL/min
2	60-90	mL/min
3A	45-59	mL/min
3B	30-44	mL/min
4	15-29	mL/min
5	< 15	mL/min

Modified from Table 1 Hager et al (1).

Nephrotic Syndrome (NS), clinically characterized by proteinuria, hypoalbuminemia, and edema, is one of the most common kidney diseases affecting youth. Injury to podocytes and glomeruli in NS is well described. Complications include acute injury of the kidney, systemic infection, and thromboembolism. Dyslipidemia is common and corresponds to the severity of proteinuria with or without CKD. In adults, risk of fatal and non-fatal MI is based upon the degree of proteinuria and the GFR. Despite the presence of dyslipidemia similar to that in adults, youth with CKD are often undertreated. This, in part, may reflect a lack of data regarding CVD risk in this population (5).

In addition to traditional risk factors, CVD disease in youth with ESRD appears to be directly related to the effects of renal impairment, exacerbated, in part, by medications necessary for treatment. Because mono and polygenic disorders affecting lipid and lipoprotein metabolism are common, some youth may also have an underlying predisposition to atherosclerosis in addition to the risk associated with renal failure – the impact of these on the risk of coronary artery disease and of congestive heart failure may well be substantially larger among younger patients (6,7).

Early onset of risk factors in children with kidney disease provides a longer period of exposure,

significantly increasing risk of premature CVD. Although unproven, it is likely that optimum management of risk factors, such as elevated cholesterol and blood pressure, especially when implemented at an early age, may result in substantial reduction in subsequent incidence of CVD-related events. It is important, therefore, that youth with ESRD undergo global risk factor assessment and that all risk factors be optimally managed. Based on randomized trials, data suggests that reduction of LDL-C concentrations may decrease the risk of CVD among individuals with renal failure who have average (or even below average) LDL-C concentrations (8-11).

## ETIOLOGY AND PATHOGENESIS OF DYSLIPIDEMIA IN KIDNEY DISEASE

The pattern of dyslipidemia seen in CKD is typically characterized by hypertriglyceridemia (HTG), decreased HDL-C, variable changes in LDL-C, increase in non-HDL-C, and an increase in small dense LDL-C (12), as well as an increase in the apoB to apoA-I ratio. Elevations in Lp (a) are also common in CKD. However, elevations in Lp (a) generally occur in subgroups of individuals who express larger Lp (a) isoforms (13). HTG is present in early stages of renal disease and its origin is multifactorial, including impaired catabolism of VLDL and chylomicrons

secondary to decreased lipoprotein lipase (LPL) activity. With the onset of uremia, inhibitors of LPL are increased, including apoC-III and pre-beta-HDL. A decrease in lecithin cholesterol ester transfer protein (LCAT), important for the maturation of HDL, and reduced expression of the apoA-I gene *APOA1*, the main apolipoprotein of HDL, have also been reported. These changes in gene expression and protein availability lead to alterations in two key HDL functions: 1) reverse cholesterol transport; and 2) anti-oxidation (1).

Individuals with NS often have elevated triglycerides (TG) and other atherogenic apoB-containing lipoproteins, including VLDL, IDL, LDL, and lipoprotein(a). A decrease in oncotic pressure may be contributory to increased production of lipoproteins by stimulating the synthesis of apoB. However, the

mechanisms are not well understood. HDL-C levels are similar to those of healthy individuals. Despite normal levels, however, it is likely the efficiency of the HDL-related reverse cholesterol transport in NS is decreased. The elevation in TG is likely due to decreased LPL activity. There is also downregulation of glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), which serves to anchor LPL to heparin sulfate proteoglycans on endothelial cells. The increased levels of LDL-C seen in NS is believed to be the result of increased production through increased acyl-CoA cholesterol acyltransferase (ACAT) and HMG-CoA reductase activity and decreased clearance through decreased LDL-receptor activity. Increased activity of proprotein convertase subtilisin/kexin type 9 (PCSK9) has also been reported, leading to a decrease in the number of LDL receptors and a reduction in hepatic uptake (5).

**Table 2- Lipid Patterns in Kidney Disease**

Lipid / Lipoprotein	CKD 1-5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total Cholesterol	Progressive increase	↑↑	↔ ↓	↑
TG	Progressive increase	↑↑	↑	↑
HDL-C	↓	↓	↓	↓
LDL-C	Progressive increase	↑↑	↔ ↓	↑
Non-HDL cholesterol	Progressive increase	↑↑	↔ ↓	↑
Lipoprotein (a)	Progressive increase	↑↑	↑	↑↑

Modified from Mikolasevic et al (14).

## CLINICAL FEATURES

### Nephrotic Syndrome

Elevated fractions of apoB-containing particles in NS can increase the risk for formation of atherosclerotic plaque, leading to CVD-related events, such as MI and stroke, and may contribute to the increased risk for thrombosis and other adverse events (Table 3). Progressive loss of renal function and development of CKD further increases the risk of morbidity (5).

Dyslipidemia may also contribute to glomerulosclerosis (15), further damaging the kidney (i.e., the lipid nephrotoxicity hypothesis). Excess accumulation of lipids, particularly in the interstitium and glomeruli (16), is accompanied by a pronounced inflammatory response, which appears to injure glomerular podocytes and mesangial cells. Such changes contribute to renal injury and impaired function.

**Table 3. Nephrotic Syndrome and CKD Estimates of Clinical Consequences of Dyslipidemia**

	NS	CKD	NS and CKD
<b>CVD</b>			
• Atherosclerosis	++	+	+++
• Myocardial infarction	++	+	+++
• Stroke	++	+	+++
<b>Progressive Kidney Disease</b>			
• Glomerulosclerosis	++	+	+++
• Mesangial Proliferation	+	+/-	+
• Podocyte injury	+	+	++
• Tubulointerstitial disease	++	+	+++
• Proximal tubular cell injury	+	+	++

NS=nephrotic syndrome; CKD=chronic kidney disease.

Adapted from Table 2 Agrawal, et al (5).

### Chronic Kidney Disease

Dyslipidemia in CKD is characterized by increased serum levels of TG, decreased HDL-C, variable levels of LDL-C and an increase in apoB to apoA-I ratio. HTG is often present even in the early stages of CKD and is one of the most common lipid abnormalities encountered in this population. A large cross-sectional analysis of 391 children ((236 male, 154 female aged 1-16 years (median age 12 years), 71% Caucasian) with moderate CKD (median GFR 43 mL/min/1.73m<sup>2</sup>) enrolled in the Chronic Kidney Disease in Children (CKiD) Study noted 32% of children with HTG, 21%

low HDL-C and 16% elevated non-HDL-C (17). Overall, 45% children with CKD had dyslipidemia, and of those 179 children, 45% had two or more lipid abnormalities.

There was a higher prevalence of HTG in children with nephrotic-range proteinuria (61%), as compared to 21%, 30%, and 24% in children with normal, mild, and moderate proteinuria, respectively. Twenty-one percent (21%) had a total cholesterol (TC) >200 mg/dL. However, no relationship was observed between TC and GFR. Twenty-one percent (21%) had HDL-C <40 mg/d, and obese children had an average HDL-C 14%

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lower than children with normal BMI. Changes in LDL-C levels were not discussed in this study (17).

Longitudinal data of 508 children (76% non-glomerular CKD, 24% glomerular CKD) from the CKiD study, representing 1,514 person-visits and a median follow-up of 4 years (interquartile range, 2.1–6.0), showed that non-HDL-C and TG worsened in proportion to declining GFR, increasing BMI and worsening proteinuria (18). A waist to height ratio of >0.49 has also been shown to be associated with lower HDL-C, higher left ventricular mass index, TGs, and non-HDL cholesterol compared to lean controls (19).

The prevalence of dyslipidemia was 61.5% among 356 East Asian pediatric patients < 20 years of age (median age 10.8 years; 246 males, 110 females) with CKD who participated in the **KoreaN** cohort study for **Outcomes in patients With Pediatric Chronic Kidney Disease** (KNOW-PedCKD) (20). Twenty-five percent (25%) had elevated TC, 19% elevated LDL-C, 15.2% low HDL-C, and 15.2% elevated TG. The authors demonstrated that children with glomerulonephropathy and nephrotic range proteinuria exhibited increased risk for high TC; whereas increased BMI z-score, elevated proteinuria, hypocalcemia, and 1,25-dihydroxyvitamin D deficiency were associated with low HDL-C. Glomerular filtration rate stage 3b or higher and hyperphosphatemia were associated with increased the risk for HTG (20).

## Dialysis

While dyslipidemia is common in ESRD, the need for chronic dialysis, either hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD), often results in further alteration in lipids and lipoproteins (21,22). Some studies demonstrate no significant differences in TC, LDL-C, HDL-C, TG, ApoA, ApoB, or Lp(a) serum levels between individuals receiving HD when compared to PD (23). However other studies reported important differences

in lipoprotein concentrations and their composition in adults undergoing HD and CAPD. A more atherogenic profile was observed in the latter group, consisting mainly of lower concentrations of HDL-C with higher levels of TC, TG, LDL-C, ApoB and ApoE. CAPD patients showed significantly higher TG and LDL-C levels, with a different pattern of apoprotein profile characterized by lower ApoA-I levels and higher ApoE levels than controls. Similar differences in ApoA-I and ApoE were also seen between controls and HD patients, whereas in the hemodialysis group a significant increase in ApoB was also observed (24).

There have been studies demonstrating different lipid patterns in children receiving dialysis. Children (aged 12.6 +/- 4.7 years) undergoing treatment with continuous ambulatory peritoneal dialysis/continuous cycling peritoneal dialysis (CAPD/CCPD) were found to have fasting mean levels of TGs (90%) and cholesterol (69%) above the 95<sup>th</sup> percentile of published normal values prior to the start of dialysis. The authors found a high prevalence of hyperlipidemia at baseline with no significant change of serum lipid levels during 2 years of treatment with CAPD/CCPD. (25).

## Renal Transplantation

Second only to infection, cardiovascular disease is a significant cause of mortality in pediatric renal transplant patients (26). Analysis of retrospective data from the CERTAIN registry (386-transplant recipients aged 0.5-25 years) showed the prevalence of dyslipidemia to be 95% before engraftment and 88% at 1-year following transplant (27). TC and LDL-C levels are considerably higher post-renal transplant compared to children undergoing hemodialysis (27). Risk factors include elevated pre-transplant serum cholesterol, years since renal transplant (28), and use of certain immunosuppressive medications (28).

Immunosuppressive drugs, including prednisone, cyclosporine, and sirolimus, have been shown to be

associated with dyslipidemia, whereas the use of tacrolimus and mycophenolic acid is associated with lower lipid parameters (27,28,29). TC and LDL-C in these children have not been shown to have direct association with age, sex, ethnicity, duration of ESRD, stage of chronic kidney disease, diabetes mellitus, or BMI (27,28). Reduced GFR is a risk factor for elevated TGs in this population (27,30).

DIAGNOSIS

Dyslipidemia in children with renal disease is the result of complex interactions of a variety of factors, including the primary disease process, use of medications such as corticosteroids, the presence of malnutrition or obesity, diet, and genetics. When present in NS or those who have undergone renal transplantation, dyslipidemia it is easily recognized; while often less obvious in those with chronic renal insufficiency or ESRD. Detection of dyslipidemia in the latter requires more careful analysis and knowledge of normal laboratory ranges for children. Current KDIGO clinical practice guidelines recommend an initial lipid profile in all newly

diagnosed children with CKD, including those who require chronic dialysis therapy or kidney transplant therapy. After the initial lipid profile, annual testing is recommended (31).

MANAGEMENT

Since publication of the 2003 National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) clinical guidelines for management of dyslipidemia in CKD, data from randomized controlled trials on statin therapy in adults with CKD KDIGO (Kidney Disease: Improving Global Outcomes or KDIGO) have helped inform management guidelines. Recommendations for treatment (Table 4 and Table 5) are based on risk for coronary heart disease (32, 33, 34). It should be recognized, however, that clinical recommendations (Table 5) differ for adults as well as children. While all guidelines target CVD prevention, none specifically address treatment of lipid abnormalities to prevent deterioration of kidney function, especially in youth with NS (15,16).

**Table 4. Assessment of lipid status and treatment in children (< 18 years-of-age) with chronic kidney disease (CKD)**

Clinical Scenario	Lipid Profile	Statins ± Ezetimibe	Management of HTG
CKD, including those treated with chronic dialysis or kidney transplantation.	Recommended at initial diagnosis and repeated annually.	Not recommended.	Therapeutic lifestyle changes are recommended.

Lipid profile=TC, TG, HDL-C and LDL-C. Modified from: Wanner (32).

**Table 5. Lipid management guidelines for CKD in Children < 18 years-of-age**

<b>KDIGO</b>	<b>ACC/AHA</b>	<b>2014 ADA</b>	<b>AACE</b>
Do not initiate.	Prior AHA statement for high-risk patients (including CKD) recommends therapeutic lifestyle intervention; if >10 years-of-age and LDL-C remains >100 mg/dL despite therapeutic lifestyle recommendations, treat with statin.	If patient has DM, consider statin use ≥10 years-of-age if, following changes in diet and lifestyle, LDL-C >160 or >130 mg/dL with multiple risk factors.	Recommend pharmacotherapy for > 8 years-of-age if no response to therapeutic lifestyle, especially if LDL-C ≥ 190 or ≥ 160 mg/dL with additional risk factors.

Adapted from Table 1; Sarnak (33). ACC/AHA, 2014 ADA, and AACE guidelines not CKD specific.

### **Nephrotic Syndrome**

Treatment options for dyslipidemia in children with NS include lifestyle changes and pharmacologic agents. Little evidence exists on optimal lifestyle management in children with NS, and the majority of studies have included adult populations. Studies of soy-based vegetarian diets have shown promising results, but include limited subjects and these findings have not been confirmed (35,36). The addition of omega-3 fatty acids has demonstrated a small decrease in TG and postprandial chylomicron levels (37,38).

There is also very limited data on pharmacologic treatment in youth compared with the adult population. Medications commonly used in adults include statins, bile acid sequestrants, and fibric acid derivatives. Most of the studies in youth have been limited to statins. These studies have shown reductions in TG and LDL-C levels but tend to be small in number and often lack a control group (5).

The utility of lipid apheresis, a technique used to lower cholesterol in patients with homozygous familial hypercholesterolemia, has been assessed in youth

with NS. A study of children who underwent lipid apheresis in combination with prednisone found reductions in both cholesterol and TG. Of the study group, 7/11 youth achieved a partial or complete remission of NS; and all remained in remission at their 10-year follow-up (39). However, as discussed in other chapters of Endotext, lipid apheresis is currently not preformed specifically for lipid management. At present, apheresis is only FDA approved for new onset focal segmental glomerulosclerosis in pediatric patients who are resistant to standard forms of treatment (40).

### **Chronic Kidney Disease**

The American Heart Association (AHA) classifies youth with ESRD in the highest risk group and those with pre-dialysis CKD at moderate risk for development of CVD and its sequelae. It recommends therapeutic lifestyle changes (TLC) as the initial management strategy, with the goal of lowering LDL to ≤130 mg/dL and TG <400; with addition of pharmacological therapy if these goals are not met (41). In the SHARP trial, 9270 adult patients with CKD or ESRD were randomly divided into simvastatin plus



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ezetimibe, simvastatin, and placebo groups (42). The goal of the study was to look at primary prevention of a major atherosclerotic cardiac event. The patients were followed for a median of 4.9 years, and the simvastatin and ezetimibe group had significant risk reduction of a major atherosclerotic event.

In contrast, the KDIGO 2013 clinical practice guidelines recommend assessment of fasting lipids annually, while discouraging the use of statin or statin/ezetimibe combination in youth <18 years with CKD (33,43). Boys >10 years-of-age and post-menarche girls with severely elevated LDL-C in the setting of a family history of premature coronary disease, diabetes, hypertension, smoking, and ESRD might be candidates for low dose statin use. However multi-drug regimens, even in youth with severely elevated LDL-C (43), is not recommended.

In youth with fasting TG >500 mg/dL, KDIGO recommends a very low-fat diet (<15% total calories), use of medium-chain triglycerides, and fish oil. Pharmacologic treatment can be considered in those with TG >1000 mg/dL, however, the safety or efficacy of fibric acid or niacin for this population is unknown (44).

In 2011, the NHLBI, although focused primarily on youth with FH, recommended pharmacologic management for children >10 years-of-age with LDL-C >190 mg/dL alone, >160 mg/dL with one high-risk condition, or >130 mg/dL with two high-risk conditions despite lifestyle modifications. High-risk conditions include high blood pressure (treated with

antihypertensive medication), BMI >97<sup>th</sup> percentile, smoking, and chronic kidney disease (45).

## Dialysis

CVD-related events are the leading cause of death among adults with ESRD receiving maintenance dialysis. It accounts for 45% of deaths, a rate 10-30 times higher than that in the general population (46-50).

The relationship between serum cholesterol and CVD is more complex in individuals with CKD, particularly those receiving maintenance hemodialysis. A history of coronary heart disease, coronary artery bypass surgery, coronary angioplasty or an abnormal coronary angiogram was present in 36% (peritoneal dialysis) and 42% (hemodialysis) (51).

In contrast, comparable data in youth receiving maintenance dialysis are limited in regards to the prevalence of CVD-related risk factors, clinical management of modifiable risk factors, and the incidence of morbidity and mortality. Despite the common occurrence of hyperlipidemia in youth with ESRD, monitoring is rarely performed (52,53). The relative risk of CVD, however, appears to be even greater in younger dialysis patients (8).

A study by Blanche and colleagues suggests CVD is also common amongst children who require chronic dialysis. (Table 6) The type of cardiac-related events differed significantly among ethnic groups, being highest among Black youth (54).



**Table 6. Adjusted annual cardiac events/1000 patient-years in children receiving chronic dialysis**

Event	1991	1992	1993	1994	1995	1996	Trend
Arrhythmia	90.9	115	138.9	145.0	141.3	128.6	P= NS
Cardiac Arrest	19.1	18.0	10.0	19.5	11.6	22.0	P= NS
Valvular disease	59.3	66.3	55.4	91.2	79.6	68.1	P= NS
Cardiomyopathy	42.0	44.9	50.9	60.7	73.8	84.8	P= 0.003
All-cause death	56.9	30.7	31.1	48.1	32.2	31.4	P=NS
Cardiac death	14.4	10.4	12.6	18.1	12.4	4.5	P=NS

Adapted from Table 2, Chavers (54).

Despite the increased prevalence of CVD, randomized controlled trials have not shown definitive evidence that lipid-lowering therapies are effective in reducing risk in adults with ESRD who require chronic dialysis. This lack of benefit may be the result of 1) a significant difference in the pathophysiology and spectrum of CVD in adults who require chronic dialysis compared to the general population; and 2) although affected by atherosclerosis, the majority of deaths in dialysis patients are not related to coronary artery disease and, therefore, would not be expected to respond favorably to lipid-lowering therapy.

As noted in the Table 6, coronary disease in youth with ESRD receiving chronic dialysis is also rare. Most of the CVD involves cardiomyopathy and/or dysrhythmia. Therefore, as in adults, lipid-lowering therapy may be of limited benefit in this population.

In its 2014 clinical practice guidelines, the KDIGO Work Group noted that the magnitude of any relative risk reduction in individuals who require chronic dialysis appears to be substantially smaller than in earlier stages of CKD. Therefore, the KDIGO Work Group does not recommend initiation of statin treatment for most adults and children undergoing chronic dialysis. Previous guidelines in this population

suggested the use of targets for LDL-C, with treatment escalation to higher doses of statin when LDL-C targets are not achieved with lower dose therapy. Current recommendations, however, do not support this strategy since higher doses of statins have not been proven to be safe in the setting of CKD. Furthermore, since LDL-C levels do not necessarily suggest the need to increase statin doses, follow-up measurement of lipid levels is not recommended (55).

While there is little evidence that lifestyle changes will reduce serum TG levels and/or improve clinical outcomes in adults, the KDIGO Work Group recommend advising youth with high fasting levels of serum TGs ( $>5.65$  mmol/l or  $>500$  mg/dl) to adopt lifestyle changes (54). Dietary modification should be used judiciously, if at all, in youth who are malnourished. The safety and efficacy of fibric acid and niacin have not been established in youth nor FDA approved for use in this population. Prescription omega-3-fatty acids appear to lower serum TGs in adults. The benefits, harms, and tolerability of such treatment in children is unproven, nor are there data to suggest preferential use of EPA vs combination EPA/DHA products.

## Renal Transplantation

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TLC remains the first-line intervention for treatment of dyslipidemia in youth who undergo renal transplantation. The KDOQI clinical practice guidelines for nutrition in youth recommend that families receive intensive nutrition guidance to promote a heart-healthy diet and  $\geq 60$  minutes of active play time daily, along with limiting screen time (television + computer + video games) to  $\leq 2$  hours per day (56). KDIGO guidelines recommends against the use of statin or statin/ezetimibe combination in youth  $< 18$  years, although low dose statin should be considered in boys  $> 10$  years and post-menarche girls with severely elevated LDL-C in the setting of a family history of premature coronary disease, diabetes, hypertension, smoking, and ESRD (43).

NHLBI and AHA both recommended considering pharmacologic therapy if LDL-C goals are not met with TLC alone. If statins are considered, caution needs to be exercised and low doses given concomitantly with medications that utilize the CYP3A4 pathway, like cyclosporine, as they may increase serum concentration of the statin and risk of statin-induced rhabdomyolysis. There are no randomized trials for use of ezetimibe or bile acid sequestrants in pediatric renal transplant patients; and KDIGO does not recommend multi-drug regimens even in those with severely elevated LDL-C. The use of fibrates in adult renal transplant recipients with HTG has been accompanied by elevations in serum creatinine and also with reduced cyclosporine concentrations when used concomitantly (57). It should be noted that the effect of cyclosporine is more complex than CYP3A4 inhibition alone (see chapter 18 of Endotext on medications which states, in part, “Most statins are transported into the liver and other tissues by organic anion transporting polypeptides, particularly OATP1B1. Drugs, such as clarithromycin, ritonavir, indinavir, saquinavir, and cyclosporine that inhibit OATP1B1 can increase serum statin levels thereby increasing the risk of statin muscle toxicity. Fluvastatin is the statin that is least affected by OATP1B1

inhibitors. In fact, fluvastatin 40mg per day has been studied in adults receiving renal transplants concomitantly treated with cyclosporine and over a five year study period the risk of myopathy or rhabdomyolysis was not increased in the fluvastatin treated patients compared to those treated with placebo.”)

Several studies have shown an impact of cyclosporine mTOR inhibitor and prednisone immunosuppressive regimen on post-transplant dyslipidemia and this may contribute to CVD morbidity and mortality in pediatric renal transplant recipients (27,28,58). One study noted the prevalence of post-transplant dyslipidemia may be decreasing with the use of newer immunosuppressive regimens that include tacrolimus and lower doses of prednisone (28). Thus, improvement of the CVD risk profile may be accomplished by alteration of the immunosuppressive regimen.

## CONCLUSIONS

Chronic kidney disease and nephrotic syndrome are often accompanied by dyslipidemia, contributing to disease-related morbidity and increasing risk of premature CVD. Given the lack of randomized controlled trials in youth and long-term clinical outcomes, such as CVD-related events and mortality, optimum management is unknown. Further research is needed to demonstrate the benefit of strategies to improve health and wellbeing in this vulnerable population, including use of lipid-lowering medications, with the aim of decreasing CVD-related events. In addition, given the role of dyslipidemia in potentially contributing to deterioration of renal function in youth with NS, aggressive lipid-lowering therapy may be beneficial. Further studies, however, are needed.

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