

Dyslipidemia and nephrotic syndrome

History:

A previously healthy 5-year-old boy was noticed by his mother to have generalized edema. Over the next 2 weeks, the swelling seemed to get worse. When examined, he was otherwise asymptomatic and playful, and he has maintained a normal appetite. There was no reported use of medications within the past 6 months.

Physical findings:

Height was 103 cm, weight 18 kg, BMI 17 (86.7 %) and blood pressure 98/50 mm Hg. Temperature 98.7 °F, HR 82 and RR 18 bpm. Pertinent findings included moderate periorbital edema. Heart sounds were normal and the lungs were well aerated, with no crackles or rhonchi. The abdomen was soft, non-tender and mildly distended but without masses or hepatosplenomegaly. The genitalia were normal with no scrotal edema. Mild pitting edema of the hands and feet was noted.

Clinical course:

The patient was diagnosed with nephrotic syndrome and started on oral prednisone.

Medications:

Prednisone 30 mg BID.

Laboratory studies:

Urinalysis

- Protein 4+
- Blood none
- Specific gravity of 1.030

Chemistry panel

- Total protein 2.0 g/dL
- Serum albumin 1.4 g/dL

Renal function studies

- BUN 12 mg/dL
- Creatinine 0.6 mg/dL

Liver function studies

- ALT 12 mg/dL
- AST 14 mg/dL
- Total bilirubin 0.4 mg/dL

Thyroid profile

- Free T4 1.2 ng/mL
- TSH 2.0 mIU/mL

Lipid profile

- Total cholesterol 364 mg/dL
 - Triglycerides 450 mg/dL
 - HDL-C 2 mg/dL
 - LDL-C 180 mg/dL

Questions:

1. In considering this child's lipid abnormalities, which of the following best characterizes the dyslipidemia generally present in nephrotic syndrome?

- a. Elevated total and LDL-c, normal triglycerides and normal HDL-c.
- b. Elevated total and LDL-c, elevated triglycerides and normal HDL-c.
- c. Elevated total and LDL-c, normal triglycerides and low HDL-c.
- d. Normal total and LDL-c, normal triglycerides and low HDL-c.

Answer: b. Elevated total and LDL-c, elevated triglycerides and normal HDL-c.

Discussion: Nephrotic syndrome is characterized by glomerular dysfunction that results in proteinuria. Affected individuals exhibit generalized edema, hypoalbuminemia and hyperlipidemia. The hyperlipidemia in nephrotic syndrome is characterized by elevated total and LDL cholesterol and elevated triglycerides, but little or no change in HDL-c.

2. Which of the following best describes the mechanism for the lipid abnormalities in nephrotic syndrome?

- a. Insulin resistance along with a high fat, high caloric diet.
- b. Decreased lipoprotein lipase activity, increased triglyceride production and increased apolipoprotein C-III.
- c. Renal loss of HDL-c.
- d. Decreased lipoprotein lipase activity, increased triglyceride production and decreased triglyceride catabolism.

Answer: d. Decreased lipoprotein lipase activity, increased triglyceride production and decreased triglyceride catabolism.

Discussion: The hypoproteinemia in nephrotic syndrome is thought to stimulate protein synthesis in the liver, including overproduction of lipoproteins. In addition, lipid catabolism is decreased due to lower levels of lipoprotein lipase.

3. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, a fasting lipid panel is recommended for which of the following?

- a. All adults and post-pubertal children with chronic kidney disease (CKD).
- b. Only individuals with CKD 18 years of age or older.
- c. All individuals with CKD, regardless of age.
- d. All individuals with CKD, regardless of age, with 2 or more CVD risk factors.

Answer: c. All individuals with CKD, regardless of age.

Discussion: KDOQI guidelines recommend a fasting lipid panel (total cholesterol, triglycerides, HDL and LDL) for all individuals with CKD. The pattern of dyslipidemia in CKD varies by etiology and treatment. Key factors that contribute to dyslipidemia in CKD include the primary disease process and its rate of progression, degree of renal function and response to treatment, medication use, nutrition, transplantation and genetics. In addition to nephrotic syndrome, hyperlipidemia is commonly found in children with chronic renal disease and those who are recipients of a renal transplant. The pattern of dyslipidemia varies depending on the type of renal disease, type of treatment and the presence of insulin resistance.

	Nephrotic syndrome	Chronic renal insufficiency (CRI)	End-stage renal disease (ESRD)	Renal transplantation
Plasma triglyceride	↑ ↑	↑	↑	↑
Plasma cholesterol	↑ ↑	↔	↔	↑
Plasma HDL	↔	↓	↓	↔
Plasma LDL	↑ ↑	↔	↔	↑
Major associations	↓Plasma lipase activity ↑TRL synthesis ↓TRL catabolism Disordered interactions among lipoprotein's, vascular endothelial, and lipoprotein lipase	↓Plasma lipase activity Insulin resistance ↑Apolipoprotein C-III	↓Plasma lipase activity Insulin resistance ↑Apolipoprotein C-III Heparin usage	Medication usage: Corticosteroids Cyclosporin Rapamycin Recurrent or de novo renal disease

4. Which of the following would be considered an appropriate intervention for individuals with CKD- associated dyslipidemia?

- a. A diet with <30 percent fat, <10 percent saturated fat and <10 percent trans fats.
- b. Statins to lower LDL-c and apo B-containing lipoproteins.
- c. Fish oil to reduce hypertriglyceridemia.
- d. All of the above.

Answer: d. All of the above.

Discussion: After successful treatment, many children with nephrotic syndrome will remain asymptomatic with a normal lipid profile. Lipid profiles should be tested since some children may have a concomitant primary or secondary dyslipidemia, made worse with the onset of the nephrotic syndrome. Those with persistent dyslipidemia and chronic manifestations of nephrotic syndrome may be candidates for lipid-lowering therapy. Although there are no long-term outcome studies in children demonstrating the efficacy and safety of lipid-lowering therapy, it is well known that dyslipidemia increases the risk of cardiovascular events among adults with renal disease.

It is also well recognized that the process of atherosclerosis begins during childhood and progresses with age. Children with CKD, therefore, have a number of CV risk factors from an early age, factors likely to accelerate the atherosclerotic process as these children mature. The American Academy of Pediatrics has issued recommendations for children and adolescents with CKD or end-stage renal disease. These recommendations include the following: Optimization of renal failure management with dialysis or transplantation. Assess BMI, BP, lipids, FG: step 1 management for 6 months. If goals not achieved, proceed to step 2; statin prescription if 10 years old or older to achieve tier I treatment goals.

5. Which of the following statements about the potential benefits of treating dyslipidemia in CKD is NOT true?

- a. Chronic renal disease, even in renal transplant recipients, is strongly associated with atherosclerosis-related diseases.
- b. Although only one of several risk factors (such as age, smoking or blood pressure), hyperlipidemia can be effectively controlled with diet and lipid-lowering medications.
- c. Dyslipidemia does not appear to have a role in the progression of renal disease.
- d. Statins, fibrates and other treatments have been safe and effective in short-term studies.

Answer: c. Dyslipidemia does not appear to have a role in the progression of renal disease.

Discussion: In addition to contributing to the risk for CVD, dyslipidemia seems to play a role in progression of renal disease. Although conclusive evidence of the benefits and safety of treatment are lacking in children with CKD, CV events are the number one cause of death in adults with CKD. Children with CKD that is optimally controlled should be considered for lipid lowering interventions.

Except in patients with extreme hypertriglyceridemia, treatment strategies focus initially on reducing LDL-cholesterol, then reducing non-HDL cholesterol. The potential benefits of lipid-lowering therapy must be weighed against the short- and long-term risks. However, avoiding progression of renal disease and the other options listed (a, b and d) makes timely intervention compelling.

Key points:

1. Disturbances in lipoprotein metabolism are common in both adults and children with chronic renal disease.
2. The lipoprotein pattern in CKD is variable and influenced by the primary disease process, renal function, medication use, nutrition and genetics as well as the type of intervention utilized (i.e., dialysis or transplantation).
3. Although long-term studies in children with CKD are limited, most studies in adults suggest a potential benefit from treatment of dyslipidemia.
4. In addition to contributing to premature cardiovascular disease in individuals with CKD, dyslipidemia may contribute to the progression of renal disease.
5. Diet, non-pharmacologic therapies (e.g., plant stanols) and standard lipid-lowering agents (e.g., statins, fibrates and bile acid sequestrants) have shown short-term safety and efficacy.

References/suggested reading:

1. Saland JM, Ginberg H, and Fisher EA. Dyslipidemia in pediatric renal disease: epidemiology, pathophysiology and management, *Cun Opin Pediatr.* 2002:197-204.
2. American Academy of Pediatrics Endorsed Policy Statement. Cardiovascular Risk Reduction in High-Risk Pediatric Populations *Circulation.* 2006; 114:2710–2738.
3. Wheeler D. Lipid abnormalities in the nephrotic syndrome: the therapeutic role of statins. *J Nephrol.* 2001; 14 (suppl. 4): S70-75.
4. KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Diseases. *American Journal of Kidney Disease.* Vol 41, No 4, Suppl 3, April 2003.