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Statins in the Management of Pediatric Dyslipidemia

Joyce L. Ross MSN, ANP, CS, CRNP, FNLA, FPCNA*

University of Pennsylvania, Philadelphia, PA

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Hypercholesterolemia is a major concern in the USA, with studies identifying children as young as 2 years old with early-stage atherosclerosis. Genetics play a major role in the dyslipidemia of children, but other factors, such as diet and lack of physical activity, confound the problem. Familial hypercholesterolemia (FH) is a genetic condition that causes lifelong elevations in low-density lipoprotein cholesterol (LDL-C). The heterozygous form of the disease affects around 1 in 200 people, and the homozygous form of the disease affects around 1 in 160,000–300,000 people. Early identification and appropriate management of patients with FH are essential to reduce cardiovascular disease morbidity and mortality. Consequently, US dyslipidemia guidelines recommend routine screening of all children aged 9–11 years, and that LDL-C levels should be <110 mg/dL in children and adolescents. The primary management strategy in all children with dyslipidemia is diet and lifestyle; a healthy diet (including fruits, vegetables, fish, and whole grains) and increased physical activity should be encouraged. Most patients with FH will also require pharmacotherapy to reduce LDL-C levels to ≤130 mg/dL. Statins are recommended as first-line therapy due to their proven efficacy in reducing LDL-C and improving other lipid parameters in children. They have also been shown to have a positive effect on atherosclerosis. Safety is of particular concern with children; however, studies have so far shown that the side-effect profile of statins in children is similar to that in adults. Despite improvements in disease management, FH remains underdiagnosed and undertreated, highlighting the need for greater awareness and understanding.

CARDIOVASCULAR DISEASE (CVD) is a serious health concern in the USA, and increasing evidence suggests that risk factors for CVD, such as elevated low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), low high-density lipoprotein cholesterol (HDL-C) (Box 1), diabetes mellitus, and elevated blood pressure may already be present in children and adolescents (Berenson et al., 1998; McGill, McMahan, Malcom, Oalmann, & Strong, 1997; McGill et al., 2001; Newman et al., 1986; Webber et al., 1995). Furthermore, atherosclerosis is detectable in children from 8 years old (Wiegman et al., 2015), and fatty streaks (the precursors of atherosclerosis) have been detected in children as young as 2 years old (Berenson et al., 1998).

Dyslipidemia in children has a major genetic component, but environmental factors such as diet and lack of physical activity can also influence the lipid profile. Familial hypercholesterolemia (FH) is a genetic condition that causes lifelong elevations in LDL-C; the heterozygous form of FH (HeFH) can produce total cholesterol (TC) levels in the region of 310–580 mg/dL (Nordestgaard et al., 2013; Wiegman et al., 2015). These elevated TC levels result in a considerably increased risk of premature coronary heart disease (CHD) from the age of 20 years, and usually before age 55 years in men and 60 years in women (Nordestgaard et al., 2013; Wiegman et al., 2015). The homozygous form of FH (HoFH) is rarer but results in more severe elevations in cholesterol, producing TC levels in the region of 460–1160 mg/dL, with CHD or CVD events occurring as early as childhood or early adolescence (Nordestgaard et al., 2013; Wiegman et al.,

* Corresponding author: Joyce L. Ross, MSN, CRNP, FNLA, FPCNA.
E-mail address: jlr@joycerossnp.com.

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Box 1 Cholesterol.

Cholesterol is a waxy substance that is a primary component of cell membranes and is a key substrate in the synthesis of bile acids, which aid fat digestion, steroid hormone production, and vitamin D.

The majority of cholesterol circulating the body is produced by the liver through conversion of saturated fats. Cholesterol is transported in the blood by lipoproteins. Low-density lipoprotein (LDL) carries cholesterol to the cells, but if too much cholesterol is produced, it builds up in the arteries and contributes to atherosclerosis. LDL-C is therefore often called "bad" cholesterol. HDL-C, also called "good" cholesterol, helps remove excess cholesterol from the arteries to the liver, where it is destroyed.

Triglycerides are used to store excess energy from diet. High levels of triglycerides in the blood are also associated with atherosclerosis.

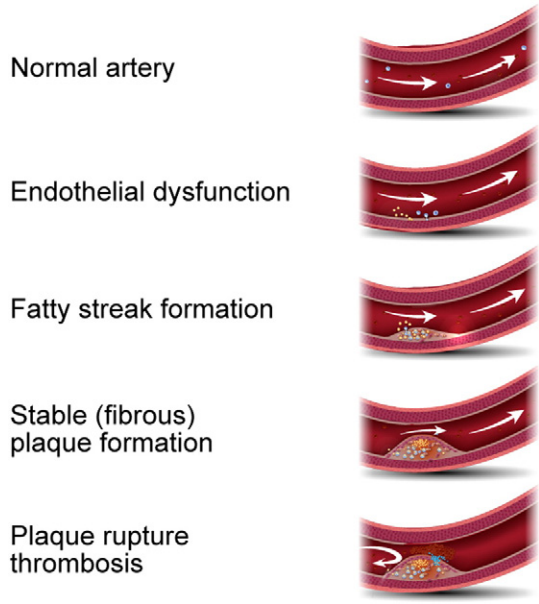

Figure 1 Development of atherosclerosis.

2015). Early identification of children with FH, followed by initiation of an appropriate management plan, is essential to reduce CVD morbidity and mortality (Jacobson et al., 2015).

This article provides an overview of hypercholesterolemia in children, including its prevalence and etiology, and recommendations for managing the disease, with a focus on the use of statins in children with hypercholesterolemia.

Epidemiology

FH is one of the most common genetic disorders (Wiegman et al., 2015). It is estimated that HeFH currently affects 1 in 200 of the general population, 20%–25% of whom are children and adolescents. HoFH is much less common and affects around 1 in 160,000–300,000 people worldwide (Wiegman et al., 2015).

At birth, TC levels are usually low but increase during childhood, with a peak in levels just before the onset of puberty in both boys and girls, at which point they decrease. As sex hormone levels increase during puberty, TC levels generally decrease, before increasing again in late adolescence (around 17 years old). During puberty/sexual maturation, TC and LDL-C levels can decrease by as much as 10%–20%, reflecting rapid changes in growth and sexual maturation (Berenson, Srinivasan, Cresanta, Foster, & Webber, 1981; Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. National Heart Lung and Blood Institute, 2011). The changes in TC levels seen during adolescence vary with gender and race. Normally, Black children transition from adolescence to young adulthood with higher levels of cardioprotective HDL-C and lower levels of triglycerides than their White counterparts. Higher levels of HDL-C observed in females in adulthood are also observed in the adolescent to young adulthood transition (Berenson et al., 1981).

It is currently estimated that around 8% of children and adolescents aged 8–17 years have TC levels ≥200 mg/dL, 13% have HDL-C levels <40 mg/dL, and 8% have non-HDL-C levels ≥145 mg/dL (Kit et al., 2015). More girls than boys tend to have TC levels ≥200 mg/dL (9.0% versus 6.6%, respectively) and non-HDL-C levels ≥145 mg/dL (9.2% versus 7.5%, respectively). However, the proportion of girls and boys with HDL-C levels <40 mg/dL appears to be similar (12.9% versus 12.6%, respectively). More older children (13–17 years) than younger children (8–12 years) have TC ≥200 mg/dL (8.5% versus 7.0%, respectively), HDL-C <40 mg/dL (14.7% vs 10.5%, respectively), and non-HDL-C ≥145 mg/dL (9.6% versus 6.9%, respectively) (Jacobson et al., 2015; Kit et al., 2015). Between 1999–2000 and 2011–2012, lipid levels appeared to improve slightly; however, 20% of children in the USA are still at risk of CVD due to adverse lipid levels (Kit et al., 2015).

Etiology

FH is usually caused by mutations in the gene encoding the LDL receptor (the *LDLR* gene). LDL receptors are present on the surface of many cell types, and are particularly abundant in the liver. Their role is to remove cholesterol-carrying LDL particles from the bloodstream and transport them into cells, where they are broken down to release cholesterol. The cholesterol is then either stored or removed from the body. Loss-of-function mutations in the *LDLR* gene can lead to either reduced numbers of LDL receptors or decreased functioning of the LDL receptors. To date, around 1300 different *LDLR* mutations have been reported (Daniels, Gidding, & de Ferranti, 2011; Goldberg et al., 2011; Jacobson et al., 2015; Usifo et al., 2012).