Screening, Diagnosis, Therapeutic Lifestyle Changes and Pharmacological Treatment in the Management of Heterozygous Familial Hypercholesterolemia in Children and Adolescents Ages 2-18

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Heterozygous familial hypercholesterolemia (heFH) is a dominantly inherited genetic disorder, resulting in transmission of the disease to 50% of the offspring of the parent with heFH (Descamps et al., 2011). Occurring more commonly than cystic fibrosis, congenital hypothyroidism, Type 1 diabetes mellitus, Parkinson’s and many other disorders, it affects 1 in 500 persons in the United States (O’Gorman, 2008). Children with heFH exhibit levels of low-density cholesterol from birth onwards; 2-3 times higher than in the general population. HeFH is associated with a high risk for premature coronary heart disease (>50% risk in men by age 50 and >30% in women by age 60) and shorter life expectancy (Goldberg et al., 2011). Numerous research studies indicate that atherosclerotic process is reversible at its early stages with proper lifestyle changes and medication regimen. However, only approximately 20% of children and adolescents who have heFH are actually diagnosed with this disorder and, of those, “only a small minority receive appropriate treatment” (Goldberg et al., 2011, p. S2). While the benefits, screening, diagnosis, and treatment are well defined in adults, until recently, a clear consensus did not exist for the management of children and adolescents with heFH. The purpose of this paper is to review and summarize the most current evidence-based research findings and guidelines on screening, diagnosis, and management of children and adolescents (ages 2-18) with heFH.
Key Words: heterozygous familial hypercholesterolemia, lipid screening, children, adolescents, low-density lipoprotein cholesterol, dyslipidemia, atherosclerosis
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Problem Statement

Heterozygous familial hypercholesterolemia (heFH) is one of the most common, yet among the most underdiagnosed and undertreated genetic abnormalities. This congenital metabolic disorder affects 1 in 500 Americans (O’Gorman, 2008), suggesting that there are approximately 148,363 afflicted children in the United States under the age of 18 (U.S. Census Bureau, 2010). HeFH is more prevalent in certain populations: the South Afrikaners (1 in 70), the Christian Lebanese (1 in 170), and the French Canadians (1 in 270) (Bender et al., 2011). This disorder is present from birth and has a co-dominant transmission, meaning that first-degree relatives of a person with heFH have a 50% probability of inheriting it. Children with two heFH carrier parents have a 25% chance of inheriting both defective genes and, therefore, developing the rare (1 in 1,000,000), but most severe form of hypercholesterolemia - homozygous FH. Affected individuals present with low density lipoprotein cholesterol (LDL-C) levels ranging from 650 mg/dL to 1,000 mg/dL, thus carrying a significant risk for developing cardiovascular disease (CVD) by the second decade of life, or even earlier in severe cases (Goldberg et al., 2011).

HeFH is primarily caused by one of more than 1,700 identified mutations (Fahed & Nemer, 2011) of the low-density lipoprotein receptor (LDLR) gene, and less frequently by the mutations in genes for familial defective apolipoprotein B-100 (ApoB-100), as well as the most recently identified proprotein convertase subtilin/kexin type 9 (PCSK9) and low density lipoprotein adaptor protein 1 (LDLRAP1). As a consequence of these mutations, LDL cannot be catabolized by cells, especially by hepatocytes, leading to abnormally elevated concentrations of LDL-C in the blood, strongly predisposing to early development of atherosclerosis.

HeFH is characterized by a 2- to 3-fold elevation in levels of total cholesterol (TC) and LDL-C from birth. The results of the Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) showed that for every 30mg/dL increase in non-HDL cholesterol, the coronary vasculature develops the
equivalent of 2-3 years of accumulation of atherosclerosis (Gidding, 2010). “Vascular age” is advanced in 73% of children with heFH, independently of the presence of other atherosclerosis-promoting risk factors (Iughetti, Bruzzi, & Predieri, 2010). Researchers discovered that without treatment, individuals under age 40 with heFH are about 100 times more prone to develop coronary artery disease (CAD) than the general population (Nicholls, Cather, Byrne, Graham, & Young, 2008). Furthermore, without treatment, more than 50% of men and 30% of women with heFH are expected to have a myocardial infarction before 60 years of age (National Lipid Association [NLA] Expert Panel, 2011). About 50% of myocardial infarctions are fatal (National Heart, Lung, and Blood Institute [NHLBI], 2011).

According to the NLA Expert Panel on heFH, approximately 20% of children and adolescents who have heFH are actually diagnosed with this disorder and, of those, “only a small minority receive appropriate treatment” (Goldberg et al., 2011, p. S2). One of the reasons behind this is the fact that a lot of variation and inconsistency exists in the current clinical guidelines related to screening, diagnosis, and management of primary hypercholesterolemia, including heFH. Yet, early interventions are essential in slowing the progression of this potentially deadly disorder. The challenge to the practitioner is to decide (a) when to begin screening for heFH, (b) how to properly diagnose heFH, and (c) what type of treatment (pharmacological and/or non-pharmacological) to initiate in the pediatric population diagnosed with heFH.

The purpose of this paper is to review and summarize the most current evidence-based research findings and guidelines on screening, diagnosis, and management of children and adolescents (ages 2-18) with heFH. Management is defined as a set of activities (therapeutic lifestyle changes and pharmacological treatment) aimed at improving the health and clinical outcomes of children and adolescents (ages 2-18) characterized by each having a chronic medical condition (heFH) (American Academy of Family Physicians, 2006).

**Literature Search Strategies**

The literature search began by utilizing the WSU online library. The initial key words that were used during the cross search of multiple health science databases such as: PubMed, American Medical
Association, CINAHL (EBSCO), and Cochrane Library (Wiley), were “heterozygous familial hypercholesterolemia,” “dyslipidemia,” “pediatric population,” “premature atherosclerosis,” “screening,” “diagnosis,” and “management.” Over 174 articles were then narrowed down by using “peer reviewed” and “published within the past 5 years” limits. Thus, 62 journal articles were reviewed, and 34 were selected and organized into the following conceptual framework: screening (8 articles), diagnosis (7 articles), therapeutic lifestyle changes (11 articles), and pharmacological treatment (8 articles). The National Heart, Lung, and Blood Institute (NHLBI) 2011 clinical practice guidelines on Pediatric Cardiovascular Risk Reduction and Clinical Guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia (2011) were incorporated into each of these sections.

**Theoretical Framework**

The Natural History of a Disease Theory (Leavell & Clark, 1965) is a biomedical science theory that suggests that the natural history of any disease exists on a continuum, with health at one end and advanced disease at the other. By utilizing this model, one can clarify the need for identification and treatment of children and adolescents with heFH. Understanding the natural history can also tell roughly the time frame within which one has to intervene to alter the clinical course of a particular disease, thus preventing the development of more serious consequences. Because heFH is due to a genetic defect, hypercholesterolemia (2-3-fold elevations in plasma LDL-C concentrations) is present from birth predisposing affected individuals to early atherosclerosis (observed as increased carotid intima-media thickness and endothelial dysfunction) starting from childhood. Over the years excess cholesterol may be deposited in peripheral tissues, often leading to yellow-orange tuberous xanthomas or xanthelasma in a patient aged 20 to 25 years, thickening of the Achilles, finger extensor, patellar and/or triceps tendons (at any age), and the presence of corneal arcus senilis in mid-adulthood (Hopkins, Toth, Ballantyne, & Rader, 2011). More importantly, elevated plasma LDL levels result in accumulation of lipid-filled macrophages within the arterial intima (a “fatty streak”) which, together with smooth muscle cell proliferation, can eventually progress to an atherosclerotic lesion or fibrous plaque. Blockage of the arterial lumen by the
fibrous plaque or its rupture leads to the clinical outcomes seen in the CVD: myocardial infarction and stroke, occurring at a much earlier age than in the general population.

Leavell and Clark (1965) outlined three levels of prevention – primary, secondary, and tertiary. Secondary prevention is concerned with early detection and includes any screening activities (e.g., cholesterol screening, gathering accurate family history of high cholesterol and heart disease in first-degree relatives, genetic testing for specific LDLR gene mutations) and subsequent efforts to limit disease progression of those identified with a health condition, e.g., therapeutic lifestyle changes: low fat and cholesterol diet, quitting smoking, weight control, and exercise; HMG-CoA reductase inhibitors administration. Early interventions are usually more cost effective than intervening once symptoms appear. More importantly, detection and treatment of pathological processes at an earlier stage usually results in more effective disease management. In fact, failure to diagnose and treat heFH in a timely manner leads to increased morbidity and mortality from premature CVD.

**Literature Review**

The literature is organized into four sections: screening, diagnosis, therapeutic lifestyle changes, and pharmacological treatment. Each section is now reviewed.

**Screening**

Screening is defined as the examination of asymptomatic persons (specific target or general population) and classifying them as “probable” (positive) or “improbable” (negative) to have a certain disease or condition (heFH) (Cohen et al., 2010).

Up until November of 2011, the American Academy of Pediatrics (AAP), the American Heart Institute (AHA), as well as the NHLBI, all recommended a targeted approach (focused on “high risk” for CVD groups) for fasting cholesterol screening after 2 years of age and no later than age 10 - in children who have had a family history of premature CVD (<55 years of age for men and <65 years of age for women) with a parental history of hypercholesterolemia (a TC>240 mg/dL), or when family history has been unknown (AAP, 2008). Other risk factors that warranted screening in childhood included: obesity (BMI≥95th percentile), overweight (BMI ≥ 85th and < 95th percentiles), physical inactivity, hypertension
(blood pressure ≥95th percentile), diabetes mellitus (type 1 or type 2), tobacco use, or having a specific moderate- (e.g., chronic inflammatory disease, HIV, nephrotic syndrome) or high-risk (e.g., chronic renal disease, postorthotopic heart/renal transplant, Kawasaki disease) medical condition (Daniels & Greer, 2008).

When possible, medical providers are urged to obtain a comprehensive CVD family history (including premature events and hypercholesterolemia) which, when positive, would increase the probability that a child has heFH. One has to keep in mind that children with young or uninsured parents who are “free of CVD” may be simply unaware of their lipid profiles, leading to potentially inaccurate or incomplete family history of CVD – one of the main weaknesses of a targeted approach (McNeal et al., 2010). Up to one third of uninsured adults have never had their cholesterol levels tested (Ritchie et al., 2010).

Despite the fact that in March, 2011, a U.S. Preventive Services Task Force (USPSTF) came to the conclusion that “there was insufficient evidence to recommend for or against routine screening of lipids for any group of children and teenagers” (USPSTF, 2011, p. 206), on November 11, 2011, the NHLBI released new cholesterol screening guidelines, recommending the universal cholesterol screening in all children ages 9-11, followed by another screening at age 17-21. These guidelines were endorsed by the AAP. The main reasoning behind this major change was the fact that a method used to screen for a family history of elevated TC levels resulted in missing up to 60% of children with high TC levels (NHLBI, 2011). Fasting lipid profile (FLP) measurement is still recommended starting at age 2 for children at high risk for hypercholesterolemia. The averaging of two FLP measurements (after 2 weeks but within 3 months) is warranted for proper diagnosis. The NHLBI Expert Panel discourages a lipid screen at ages 12-16 because of significantly decreased specificity and sensitivity for predicting adult LDL-C levels, as well as significantly increased false-negative results in this age group.

Wald, Bestwick, and Wald (2007) performed a meta-analysis on total and LDL cholesterol in individuals (N=18,128) with and without FH according to age. The significant finding of this study was
that the screening sensitivity was greatest at 1-9 years (88% with TC and 85% for LDL-C) and reduced in newborns (31% with TC and 72% with LDL-C), as well as in young adults.

The results of the study above are consistent with the idea that lipid concentrations are age and maturation dependent. Namely, cholesterol levels increase slowly after the age of 2 years – lipid and lipoprotein levels are rather constant up to adolescence when a 10-20% or more drop in plasma cholesterol levels is usually observed during puberty, thus increasing the risk of false negative results (Cohen et al., 2010). Specificity and sensitivity of cholesterol screening are considerably higher from age 2 and up until adolescence, making this age interval an excellent time for screening.

HeFH is an autosomal dominant disorder meaning that a child with the disorder will have an affected parent. The early identification of children with heFH would allow for cascade (family members) screening, leading to the prevention of premature cardiac events in adults that may have otherwise gone undiagnosed (Ritchie et al., 2010). Genetic screening can be invaluable for the entire extended family. This approach has been successfully adopted and considered as “cost-effective” by countries such as Scotland, England, Wales, the Netherlands, as well as other European countries (Finnie, 2010).

**Diagnosis**

Children and adolescents with heFH usually have a normal physical examination. Physical signs, such as tendon xanthomas and arcus cornea, begin to appear in the second decade of life (Friedrich, 2010). During the first decade of life, hypercholesterolemia is the only clinical finding. In fact, LDL-C levels are typically higher than 200 mg/dL beginning in infancy (NIHLB, 2011), placing the affected children for an increased risk of accelerated early atherosclerosis starting from birth. In general, children with heFH maintain normal triglyceride levels (Zappalla & G'idding, 2009). Yet, the presence of hypertriglycerideremia does not exclude the diagnosis of heFH (Hopkins et al., 2011).

The 2011 NHLBI Expert Panel adopted, endorsed by the AAP and the AHA, the 1992 National Cholesterol Education Program’s (NCEP) cutoff points for TC and LDL values in children ages 2-18 years. Thus, the acceptable cholesterol levels are: <75th percentile, TC <170mg/dL, and LDL <110 mg/dL. LDL concentrations greater than 95th percentile for age and gender are considered abnormal.
Recent research confirmed that approximately half of children with lipid levels above the 75th percentile in childhood will have elevated lipid levels as adults (NIHLB, 2011). If elevated, fasting lipid profile measurements are strongly recommended to be repeated (at least once) after 2 weeks but within 3 months following the initial screening, averaging the two results. Persistently elevated LDL-C levels >190 mg/dL (4.9 mmol/L) in children and adolescents are highly suggestive of heFH (Nemati & Astaneh, 2010). In families with known heFH, children with LDL-C levels above 160 mg/dL are likely to have heFH (NIHLB, 2011).

In general, genetic screening for heFH is neither required nor needed for diagnosis or clinical management but may be useful when the diagnosis is uncertain. It is important to remember that a negative genetic test result does not necessarily exclude heFH, since “approximately 20% of clinically definite heFH patients will not be found to have a mutation despite an exhaustive search using current methods” (Goldberg et al., 2011, p. S4). Deoxyribonucleic acid (DNA) testing is “the gold standard for diagnosis if, and only if, a mutation has already been identified for the family” (Hopkins et al., 2011, p. S14).

When hypercholesterolemia is initially detected, it is important to seek and exclude possible secondary causes of the disorder (e.g., autoimmune diseases, including systemic lupus erythematosus and Type 1 diabetes mellitus; Human Immunodeficiency Virus infection, Type 2 diabetes mellitus, hypothyroidism, hepatic disease, nephrotic syndrome, chronic kidney disease, as well as oral contraceptive intake).

**Therapeutic Lifestyle Changes (TLC)**

The initial mainstay treatment for children with heFH is the implementation of a healthy lifestyle, including a healthy diet, weight management where each kilogram of weight loss produces a reduction of about 0.8 mg/dL in the LDL-C concentration (Matthew, McGowan, & Moriarty, 2011), exercise (60 minutes of daily vigorous aerobic activity), and non-smoking. The NIHLB, AHA, and AAP guidelines endorse the original NCEP Pediatric Panel’s recommendation that all children over the age of 2 years with identified hypercholesterolemia and elevated LDL-C levels have to follow a more stringent low-fat
(saturated fat < 7% of total calories), low cholesterol (<200 mg/day) diet rich in fruits and vegetables (five or more daily servings), whole grains (six to 11 daily servings), fiber (age + 5g/day), and lean protein. Trans-unsaturated fatty acids or partially hydrogenated oils ideally should be eliminated from the diet or should compromise less than 1% of total calories. Sugar and salt intake should be minimized, as well. Children with heFH over 2 years of age should be encouraged to consume low-fat (1%) or nonfat milk and low-fat dairy products. However, total fat intake in children and adolescents should not be reduced to less than 20 percent of the daily caloric intake. The U.S. NCEP also recommends including 2g/day of phytosterols to the diet to enhance lowering of LDL-C (Kelly, 2010). Foods such as plant oils, legumes, nuts, and seeds have high concentrations of phytosterols, whereas cereal grains, fruits, and vegetables contain only modest amounts of phytosterols. Fortified foods (e.g., Promise Active and Benecol spreads) typically have 0.5 to 1 g of sterol per serving. Data from randomized clinical trials in children from 7 months of age and up revealed that these dietary recommendations are safe and do not interfere with normal development, growth, and sexual maturation (Daniels & Greer, 2008).

Restricted diets result only in modest falls in LDL-C levels. During the Dietary Intervention Study in Children (DISC) the researchers examined the efficacy and safety of lowering dietary intake of total fat and cholesterol to decrease LDL-C levels in those children followed through puberty. The children were placed on a low-fat diet (total fat intake was reduced to 28%) that limited dietary cholesterol to less than 200 mg/dL. The results of this 3-year study demonstrated that low fat diets can possibly lower LDL-C levels by 5 to 7 mg/dL. No differences were found at any data-collection point in height, BMI, or sexual maturation (Zappalla & Gidding, 2009).

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have also been evaluated as an option for dietary intervention. These essential fatty acids can be obtained directly through the consumption of certain marine foods, e.g., oily fish: salmon, tuna, halibut, trout, herring, sardines, and mackerel. Several research trials showed that consistently elevated plasma LDL-C levels associated with heFH are directly linked to inflammatory imbalances. High plasma cholesterol levels enhance the expression of cellular adhesion molecules (e.g.,
P-selectin), proinflammatory genes and cytokines (e.g., Interleukin-10, tumor necrosis factor, and C-reactive protein), thus promoting a low-grade systemic inflammatory status, which in turn exposes hypercholesterolemic patients to an additive risk of CVD (Guardamagna et al., 2009).

Dangardt et al. (2010) conducted a study on the effect of omega-3 fatty acid supplementation on vascular function and inflammation in adolescents. This was a small (N=31), but double-blinded, crossover designed study. The results of this study showed that omega-3 supplementation (1.2g of pure n-3 PUFAs/day for 3 months) can significantly decrease the levels of inflammatory factors (TNF-α, IL-1β, IL-6), potentially improving endothelial and vascular function. Several other trials have demonstrated improved flow-mediated arterial dilation, a measure of endothelial function and health, after n-3 PUFA supplementation (Mozaffarian & Wu, 2011). In 2004, the U.S. Food and Drug Administration (FDA) stated that “supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease” (FDA, 2004, p.1). Consumption of two to three servings of fatty fish per week has been recommended for children over the age of 2 years (Zapalla & Gidding, 2009). However, much needs to be clarified about omega-3 fatty acid supplementation with regard to the optimal effective and safe dose and the ratio of DHA and EPA which should be used in children and adolescents with heFH. The intake of older and larger fish (e.g., albacore tuna, tilefish, swordfish, shark, Gulf of Mexico King mackerel) should be limited in children due to potential harm from contaminants (methylmercury, dioxins, and polychlorinated biphenyls) present in these particular species.

A soya-substituted and a rapeseed oil substituting diets have been evaluated by researchers as possible effective and safe dietary interventions in lowering LDL-C levels in children and adolescents with heFH, as well. Even though these studies found promising results in lowering LDL-C levels, they all lacked control groups and had very small sample sizes (Gulessarian & Widhalm, 2002; Weghuber & Widhalm, 2008). Currently, there is very limited data on the safety of prolonged soya intake in children.

The NHLBI Expert Panel (2011) advocates that there is strong consistent evidence that increases in moderate (e.g., jogging, playing baseball) to vigorous physical activity (e.g., running, playing singles tennis, or soccer) are associated with lower TC, lower LDL-C, and higher HDL-C levels, resulting in
subclinical atherosclerosis improvement. A recently published report from the 5-year Muscatine Study demonstrated that “11% of the variance in the ratio of TC/HDL-C levels and 5% of the variance in LDL-C levels was due to aerobic fitness” (Iughetti, Predieri, Bruzzi, & Balli, 2008).

Meyer, Kundt, Lenschow, Schuff-Werner, and Kienast (2006) conducted a randomized controlled trial aimed to assess the effect of a 6-month exercise program in obese children (N=67) on flow-mediated vasodilation, carotid intima-media thickness (IMT), and cardiovascular risk factors. Exercises (swimming, aqua aerobic training, sports games, and walking) were performed 3 times/week and lasted from 60 to 90 minutes. The results of this study demonstrated that regular exercise can significantly improve endothelial-dependent vasodilation of the radial artery and IMT of the carotid artery. This improvement is consistent with a significant reduction of body weight, BP, insulin resistance, triglycerides, LDL/HDL ratio, fibrinogen, and CRP levels. Physical activity and fitness seem to be inversely associated with CVD risk factors.

It is important to keep in mind that low fat and cholesterol diets work synergistically with weight control and vigorous physical activity on lowering LDL-C levels. In fact, a low-saturated fat diet together with exercise can possibly lower LDL-C levels by up to 15 percent, while increasing high density lipoprotein (HDL) cholesterol levels by 5 to 14 percent (Kelly, 2010). There is strong evidence that exercise programs should be included into the treatment plan. A behavioral approach, delivered by a registered dietitian, that engages the child and family has been shown to be the most consistently effective approach for achieving dietary change (NHLBI, 2011).

The treatment goal of LDL-lowering therapy in pediatric heFH patients is a ≥50% reduction in LDL-C or LDL-C <130 mg/dL (the 95th percentile). Even though lifestyle changes alone may not produce the desired results, they may allow for a temporary delay in the initiation of pharmacological treatment, as well as can lead to the use of a lower dose of lipid-lowering medications.

**Pharmacological Treatment**

The NHLBI recommends starting pharmacological therapy in children ages ≥ 10 with LDL-C ≥190 mg/dL after a 6-month trial of lifestyle management. Also, pharmacological therapy is indicated in
children \( \geq 10 \) years with LDL-C 160-189 mg/dL, after a 6-month trial of lifestyle/diet management, but only if these children have a positive family history of premature CVD in first-degree relatives or with other CVD risk factors. The NLA Expert Panel seems to be less conservative on this, recommending initiation of pharmacological therapy starting at the age of 8 years in cases where a 6-12-month TLC trial failed to bring the LDL-C levels down to the target levels of \( \geq 50\% \) reduction of LDL-C or LDL-C <130 mg/dL (Daniels, Gidding, & Ferranti, 2011). One should keep in mind the fact that up to now the long-term safety of lipid-lowering pharmacological treatment in children and adolescents has not yet been established. Furthermore, because the use of lipid lowering medications is not typically part of pediatric medical training, the primary care provider (PCP) is strongly encouraged to consult a lipid specialist for guidance and treatment or refer the child directly to a lipid specialist (Daniels, Gidding, & Ferranti, 2011).

Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the recommended first-line pharmacological therapy for children with heFH, in whom sufficient diet and lifestyle modifications have not significantly reduced cholesterol levels. Statins have been extensively studied in adults for the past 20+ years. This class of medications has the ability to decrease serum LDL-C levels by one third (Vuorio et al., 2011). Prior to initiating treatment with statins, a baseline lipid panel, creatine kinase (CK), and liver transaminases (ALT and AST) should be obtained and monitored closely thereafter. The medication should be initiated at the lowest recommended dose given once a day in the evening. The child and family should be advised to immediately report any adverse effects such as muscle cramps, weakness, asthenia, or more diffuse symptoms suggestive of myopathy to their PCP. Whenever potential myopathy symptoms present, the healthcare provider must stop the medication and assess CK. A CK level that is 10 times above the upper limit of reported normal is worrisome and should be further investigated. The impact of physical activity should be taken into the account. The threshold for worrisome levels of ALT and AST is \( \geq 3 \) times the upper limit of reported normal (NHLBI, 2011).

Medication can be restarted when laboratory abnormalities and symptoms have been resolved.

The laboratory tests initially performed are recommended to be rechecked at 4 weeks, 8 weeks, and 3 months. If the LDL-C levels are not achieved with at least 3 months of compliant use, then the dose
may be increased by one increment (NHLBI, 2011). The risk of rhabdomyolysis increases with the use of higher doses and interacting drugs. Drugs that potentially interact with statins include medications metabolized by the cytochrome P-450 system (e.g., fibrates, macrolides, antiarrhythmics, azol antifungals, and protease inhibitors). The growth and development of a child on statins should be closely monitored. At this point, the need for therapy and monitoring is lifelong. Females should be warned about statins’ teratogenic nature (Pregnancy Class X) and advised to seek medical advice prior to trying to conceive. The use of oral contraceptive in combination with statins is not contraindicated.

O’Gorman, Higgins, and O’Neil (2008) performed a systematic review and metaanalysis of statins for heFH in children ages 8-18 years. The primary outcome measure was a change in the lipid profile compared with the baseline profile. The results of this metaanalysis showed significant LDL reduction with statin treatment versus placebo. No significant differences in Tanner stages in the statin versus placebo-treated groups were noted. These findings have been consistent with the results of several other clinical trials that included children of both genders who were studied during puberty and have shown no impact on sexual maturation or height velocity (NHLBI, 2011). So far, the results of short-term studies have demonstrated a decrease or even regression in the rate of atherosclerosis development in children, showing improvement in endothelial function after 28-week treatment and a decrease in IMT after 2 years of statin treatment (Descamps et al., 2011).

Rodenurg et al. (2007) conducted a follow-up placebo-controlled study on statin treatment in children with familial hypercholesterolemia. The subjects (N=214, ages 8-18 years) continued treatment with pravastatin 20 or 40 mg (depending on their age) for a mean of 4.5 years. The results of this study revealed that statin treatment implemented earlier resulted in smaller carotid IMT later in life.

When a pediatric patient is unable to tolerate any of the statins or to achieve the optimal LDL-C levels, a prescription of cholesterol absorption inhibitor such as ezetimibe can be an alternative or an add-on option. A recent randomized control trial of pediatric patients ages 10-17 years with heFH showed that co-administration of ezetimibe with simvastatin resulted in significantly greater reductions in LDL-C levels than did simvastatin alone. This combination was found to be safe and well tolerated for up to 53
weeks. The NHLBI Expert Panel suggests that “until more data are available on its safety, ezetimibe should be used only in consultation with a lipid specialist” (NHBLI, 2011, p. 248).

Bile acid sequestrants, the initial medication of choice recommended in the original NCEP Pediatric Guidelines, can also be tried but these have a poor compliance rate due to significant gastrointestinal side effects (Iughetti, Bruzzi, & Predieri, 2010). This class of medications can also lead to malabsorption of fat-soluble vitamins (A, D, E, and K), requiring a daily multivitamin and folate supplementation. Fasting lipid profiles, along with growth and maturation should be monitored every 6-12 months. Assessment of patient’s medication compliance, as well as assessment and counseling for risk factors such as weight gain, smoking, and inactivity should be performed at each patient-provider encounter.

**Discussion**

**Significance to Nursing**

HeFH is an autosomal-dominant trait, carrying a 50% inheritance factor. Because heFH is not only relatively common and associated with a high risk of early CAD but is easily manageable and treatable with therapeutic lifestyle changes and/or with LDL-C lowering agents, the early detection of this genetic disorder has the potential to save many people’s lives and prevent early morbidities associated with CAD. Nurse Practitioners should take a more active role in screening for CVD risk factors, detecting those children with heFH. Family education on a healthy diet and overall lifestyle should follow any positive LDL-C results. Pharmacological interventions to lower LDL-C levels should be reviewed and prescribed on an individual basis, considering age, sex, LDL-C levels, the presence of other risk factors, including family history of premature CVD. If statin therapy is initiated, practitioners should closely monitor the child’s growth and maturation, as well as frequently assess for possible side effects.

The Natural History of a Disease Theory assumes that an individual susceptible to a disease (a child with heFH) will progress to developing pathological clinical signs (e.g., tendon xanthomas) and the disease itself (premature CVDs) along its natural course, unless interventions to detect and control the disease’s progression previously were initiated. Thus, the early screening of children at high risk for heFH
will permit the disorder’s detection and will allow the initiation of treatment early enough to slow down or even reverse that disease’s progression. Disease progression may be limited by therapeutic lifestyle modifications (e.g., lipid lowering diet, weight management, exercise, and smoking cessation) and should not be discounted.

**Recommendations for Future Research**

Numerous research studies demonstrated that statins are an efficacious option for the management of heFH. However, concerns regarding long-term safety and efficacy have not been established. Today, there is a significant need in studying statins’ long-term effects and efficacy in the pediatric population.

Very few randomized controlled trials have been conducted on the effectiveness of lifestyle changes on cholesterol levels in children and adolescents with heFH. Therapeutic lifestyle changes are an essential and integral part in the management of pediatric population with heFH. Safety and effectiveness of dietary supplements and dietary adjuncts, as well as the effect of physical activity on cholesterol levels reduction in children and adolescents with heFH are thus should be addressed by researchers more extensively.

Finally, there is a need to evaluate the cost-effectiveness, as well as the emotional and ethico-legal burdens of the genetic testing. Once a mutation has been identified with a heFH index case by the means of a DNA testing, family members can be easily screened. Fifty percent of first-degree relatives would be expected to carry the mutation, making it much easier to identify other affected relatives. By comparison, when using a population screening approach, approximately 500 individuals would need to be screened to find one affected individual. Next, the potential for “labeling” children with a disease for which there may not be adverse health consequences for decades and the potential difficulties that these children may face when applying for health insurance when they reach adulthood because of their “pre-existing” cholesterol condition should be researched, as well (Lee, Gebremariam, Card-Higginson, Shaw, Thompson, & Davis, 2009).
References


