JNP

Optimizing Diet, Weight, and Exercise in Adults With Familial Hypercholesterolemia

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ABSTRACT

Familial hypercholesterolemia results in severe elevation of low-density lipoprotein-cholesterol (LDL-c) and is estimated to affect up to 1 in 250 Americans. The rise in LDL-c has implications for the development of atherosclerotic disease and premature death. Treatment starts by its early identification, with careful attention to family history, physical exam, and laboratory analysis. By identifying this disorder, the nurse practitioner can assist the patient in implementing lifestyle changes involving exercise, weight loss, and diet, each impacting LDL-c. For those with familial hypercholesterolemia, each 1% reduction in LDL-c translates to a 3% risk reduction in the development of coronary artery disease.

Keywords: familial hypercholesterolemia, LDL-cholesterol, phytosterols, saturated and unsaturated and trans fatty acids, soluble and insoluble fiber

Familial hypercholesterolemia (FH) is a group of autosomal-dominant genetic disorders causing elevated levels of atherogenic low-density lipoprotein-cholesterol (LDL-c), advanced atherosclerosis, and premature death.[1-3] The level of rise in LDL-c is determined by one's genetic inheritance pattern—that is, inheriting 1 abnormal gene from 1 parent, 2 different abnormal genes from each parent, or 2 of the same abnormal genes from each parent—each resulting in a progressively steep rise in LDL-c.[1] These inheritance patterns are termed heterozygous, compound heterozygous, or homozygous FH, respectively.[1]

The prevalence of FH is estimated to be 1 in 500, is seen globally, and affects all racial and ethnic groups.[2] The prevalence in the United States was also once thought to be 1 in 500,[1] but recent data extracted from the 1999-2012 US National Health and Nutrition Examination Surveys suggest the prevalence is closer to 1 in 250.[4] Given these data, the adult nurse practitioner (NP) must be knowledgeable in identifying this condition, as well as the medication strategies and therapeutic lifestyle changes to optimize LDL-c. The focus of this article is on the therapeutic lifestyle changes for those with FH, with an emphasis on the contribution of dietary changes.

CLINICAL SIGNIFICANCE

Despite the relatively high prevalence of this autosomal-dominant genetic trait, FH remains largely unrecognized and, consequently, untreated,[5,6] with devastating clinical implications. Given the extreme elevation of LDL-c seen in homozygous FH, there is an accelerated rate of atherosclerosis, with clinical disease occurring within the first 1 or 2 decades of life[3,5] and, without advanced treatment, can result in death in the second or third decade of life.[7] Death from myocardial infarction associated with homozygous FH has been documented in a 4-year-old child.[5] Disease manifestation occurs later in those with heterozygous FH, with onset of fatal or nonfatal myocardial infarction typically occurring at age 50 in men[5,8] and about a decade later in affected women.[5,8,9] In addition to coronary artery disease, these individuals are also at risk for aortic valve stenosis,[5] and are 5-10 times more likely to develop peripheral artery disease.[9] The early identification and treatment of hypercholesterolemia, as well as other

cardiac risk factors, such as smoking, hypertension, obesity, and diabetes, can decrease the risk of development of cardiovascular disease.[3,5,9,10]

PATHOGENESIS: LDL-c METABOLISM AND DEFECTIVE LDL-c RECEPTORS

The genetic mutations in FH result in faulty LDL-c metabolism.[11] Most LDL-c is cleared from the plasma after binding to specialized LDL-c receptors (LDLRs) lining liver cells.[5] After binding to receptors on the liver cells, LDL-c is brought into the liver cells through a process of endocytosis, metabolized, thereby reducing the plasma LDL-c concentration.[5] Table 1 lists the 4 genes and genetic mutations responsible for impaired LDL-c clearance. The net effect of these genetic mutations is a deficiency in the number of LDLRs, or in the ability of LDLRs to bind LDL-c effectively,[5] and a sharp rise in LDL-c plasma concentration.[3] These genetic mutations do *not* affect triglyceride or high-density lipoprotein-cholesterol (HDL-c) levels.[5]

DIAGNOSIS

Family History

Early detection of FH starts with a good family history. The NP should assess for the presence of family members with high cholesterol levels or premature heart disease (occurring before the age of 55 in men and 65 in women),[12] particularly in first-degree relatives.[13,14]

Table 1. Genetic Mutations and FH

Gene	Genetic Mutation and Effects on LDLR
LDLR gene	Account for 85%-90% of cases of FH with 1,600 different genetic mutations.[1,13] Decreased number or function, or absence of receptor.[1,11,13]
ApoB gene	Decreased binding of LDL-c to receptor.[1,13]
PCSK9 gene	Increases the affinity for LDLR. Decreases recycling of LDLRs, and ultimately reduces the number of LDLRs on the hepatocyte.[5]
LDLRAP1 gene	*Autosomal-recessive* form of FH. Very rare cause of FH, resulting in the production of nonfunctional LDLR proteins.[1,5,7,11]

ApoB = apoliprotein B; FH = familial hypercholesterolemia; LDL-c = low-density lipoprotein-cholesterol; LDLR = low-density lipoprotein receptor; LDLRAP1 = LDLR adaptor protein 1; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Physical Exam

Physical exam may reveal signs of abnormal lipid deposit, although the signs are considered more specific than they are sensitive,[5] and may include tendon xanthomas, tuberous xanthomas, xanthelasma, and corneal arcus. Tendon xanthomas are nodules, or thickening of tendons, and are most likely observed or palpated over the Achilles tendon or extensor tendons of fingers.[5] Tuberous xanthomas are yellow-orange papules or nodules appearing over the extensor surface of knee or elbows.[15] Xanthelasma, yellow plaques on the upper, inner surface of eyelids, points to FH, particularly when seen in patients < 25 years old.[1,13] Corneal arcus is identified as a gray to white ring, partially or fully surrounding the cornea, and is particularly specific when seen in patients < 45 years old.[1,13] A systolic murmur can indicate the presence of aortic stenosis, which may be present in as many as 30%-40% of those with heterozygous FH by middle age.[9]

Cholesterol Screening

Cholesterol screening should ideally first occur in the pediatrician's office. It should be done initially at age 2 for those with a family history of elevated cholesterol or premature heart disease.[1,13] Universal pediatric cholesterol screening should occur between age 9 and 11[13] (a period of relative LDL-c stability), as relying on family history alone misses 30%-60% of childhood dyslipidemia.[10] Testing should be avoided during the adolescent growth spurt, when there is an approximate 10%-20% *decrease* in LDL-c.[10,16] In late adolescence and early adulthood there is a rise in LDC-c and, therefore, cholesterol testing should occur again at age 20, when, from a lipid perspective, one is considered an adult.[17] The adult NP is in an opportune position to detect FH as a patient transitions from a pediatric to an adult primary care practice.

The most current National Lipid Association (NLA) guidelines state it is acceptable to obtain a lipid profile in a nonfasting state as a first approach, although, if elevated, should then be repeated in a