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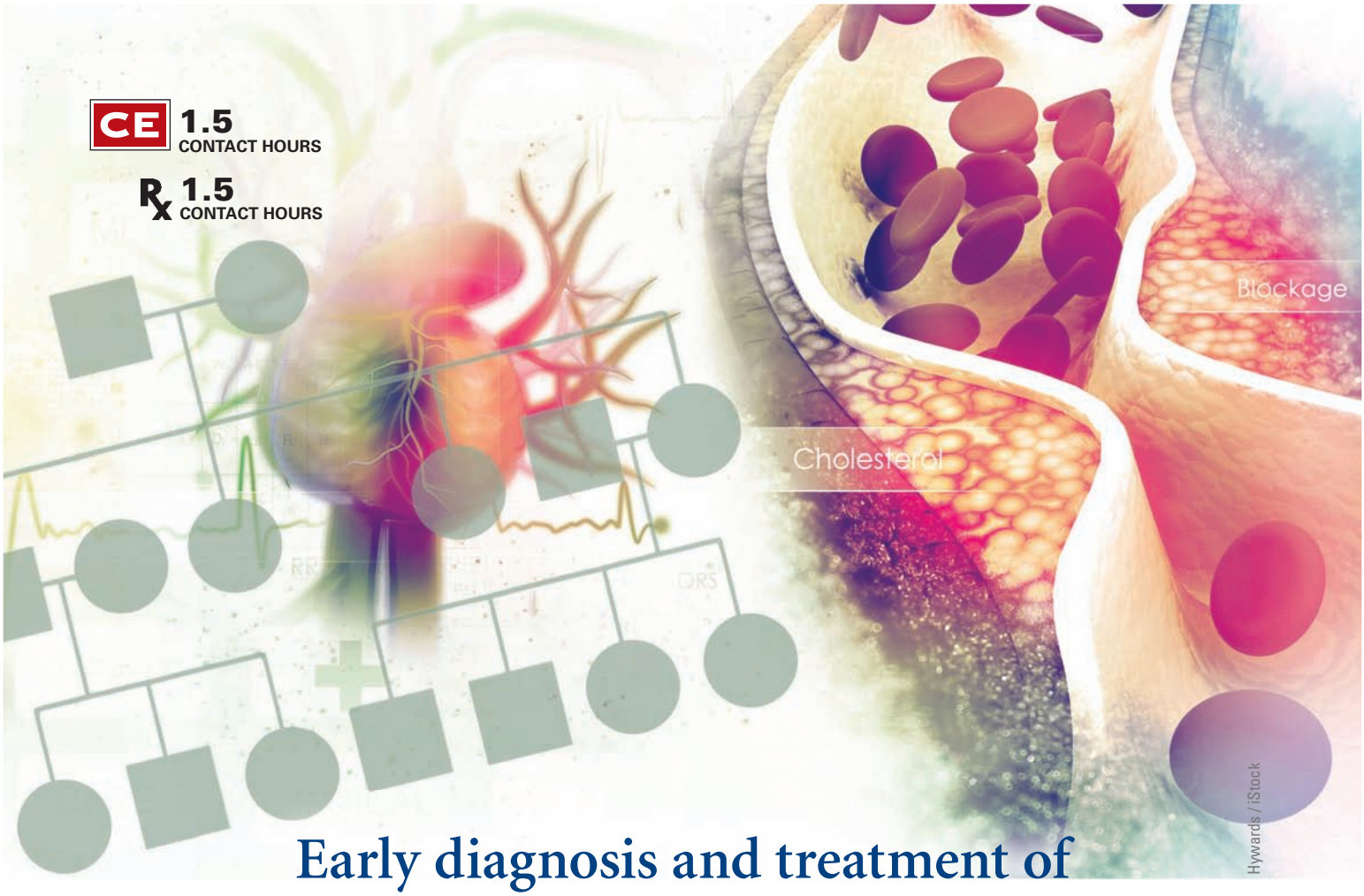

Early diagnosis and treatment of familial hypercholesterolemia

Abstract: If undiagnosed and untreated, familial hypercholesterolemia can lead to serious cardiac complications, such as premature atherosclerotic cardiovascular disease. NPs should be familiar with the clinical presentation of this inherited metabolic disease to diagnose patients as early as possible and promptly begin treatment that may include lifestyle changes, statin therapy, and/or nonstatin therapy.

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Familial hypercholesterolemia (FH)—the most common inherited metabolic disease—causes lifelong elevated low-density lipoprotein cholesterol (LDL-C).[1] It is critical that healthcare providers promptly diagnose and treat FH to prevent cardiac complications. Untreated FH is related to premature atherosclerotic cardiovascular disease (ASCVD), acute myocardial infarction, and sudden cardiac death.[1] FH is not rare, but it is severely underdiagnosed and undertreated; less than 1% of the population is diagnosed with FH in most countries, and only 20% of diagnosed patients achieve their LDL-C goals.[2,3] Early diagnosis and treatment mitigate the risk of premature ASCVD.

Pathophysiology

Patients with heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) have two times higher and four times higher LDL-C levels than the general population, respectively.[1] Known genetic mutations in the

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low-density lipoprotein receptors (LDLRs), apolipoprotein B (Apo B), proprotein convertase subtilisin/kexin 9 (PCSK9), and low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) are found in over 80% of patients with FH.[3-6] Although there are over 2,000 identified genetic mutations that cause FH, approximately 30% to 40% of FH cases cannot be attributed to a genetic mutation.[7] These contributing genetic mutations primarily inhibit the LDLRs' capacity to clear LDL-C from circulation.

The LDLR, discovered by Joseph L. Goldstein, MD, and Michael S. Brown, MD, is primarily expressed in the hepatocytes, acts like a scavenger for LDL-C, is the primary pathway for LDL-C reduction, and is the mechanism by which most lipid-lowering therapy (LLT) works.[8] LDLRs on the hepatocyte bind LDL-C through ApoB-100. Then, LDL-C dissociates and is metabolized in the endosome. Finally, the LDLR is recycled into the cell surface.[8] LDLRs can be recycled to the hepatocyte surface up to 150 different times. An increase in the number of functional LDLRs results in increased clearance of LDL-C and lower serum levels of LDL-C.

HeFH occurs when a mutation is inherited from only one parent, whereas HoFH arises when the same mutated gene is inherited from both parents. Compound HeFH occurs when a different mutated gene is inherited from each parent. The phenotype of compound HeFH presents very similarly to that of HoFH and should be treated as such.

Epidemiology

Although the historical prevalence of HeFH in North America and Europe was thought to be 1 in 500, recent genetic studies suggest a higher prevalence of approximately 1 in 200 to 300.[3,5,9,10] Based on these estimates, there should be between 600,000 and 1,500,000 individuals with FH in the US.[6,10] Some subpopulations with gene founder effects have a much higher prevalence; for example, South African Ashkenazi Jews have a rate of 1 in 67, and Christian Lebanese have a rate of 1 in 85.[2] In individuals from French Canada, South Africa, India, Finland, and Denmark, the prevalence of FH may be as high as 1 in 100.[4,6,10]

HoFH and compound HeFH—two genetically different disorders that present in the same clinical manner—are extremely rare, with a frequency of 1 in 1,000,000 worldwide; however, specific populations experience HoFH much more frequently (1 in 100,000 in Lebanon).[2,5] More recent estimates suggest the actual prevalence is now considered 1 in 160,000 to 300,000.[3,9,10] Although FH remains underdiagnosed in most countries, the Netherlands has an estimated diagnosis rate of 71% secondary to an aggressive national screening program.[2]

Clinical approach to FH[2]

Consider FH in patients who exhibit the following:
- presence of premature ASCVD
- fasting LDL-C ≥190 mg/dL
- presence of xanthomas or xanthelasmas
- presence of corneal arcus before age 45
- family history of premature ASCVD
- family history of high cholesterol levels.

Clinical presentation

Clinical presentation of FH includes tendon xanthomas, xanthelasmas, and premature corneal arcus, although sometimes no clinical findings are present (see *Clinical approach to FH*).[2] Often, the initial presentation of a patient with FH is at the time of the initial ASCVD event.[5] Patients with FH predominantly present with significant coronary heart disease rather than peripheral arterial disease or cerebral disease.[6] As a result of chronic lifelong exposure to elevated LDL-C, there is a 20-fold increase in the risk of premature ASCVD in patients with HeFH; untreated young men have the highest risk.[5,6] Patients with HoFH typically develop ASCVD by the second decade of life; however, ASCVD deaths have been reported in the first decade of life.[6] In patients with HoFH, cases of valvular or supravalvular aortic stenosis have been reported due to lipid deposition; this is not seen frequently in patients with HeFH.[6] The variation in clinical presentation is frequently related to the amount of LDLR activity.

Physical exam

Physical signs for diagnosing FH are not always present in patients; however, the presence of tendon xanthomas at any age and corneal arcus in patients younger than age 45 should prompt a further workup for FH.[6] Xanthomas, or cholesterol deposits in the skin, frequently occur around the eyelids (xanthelasma) and on the tendons of the feet, hands, and elbows.[6] Patients with HoFH may develop triglyceride-rich lipoprotein remnant accumulation called tuberous xanthomas, which is rare in patients with HeFH. Xanthomas may be missed on physical exam or mistaken for warts or

other skin conditions. Further, xanthomas are only present in less than 30% of patients with genetically diagnosed FH, suggesting a relationship with phenotype and genotype severity.[11]

Diagnostic screening

Screening for elevated cholesterol levels should occur universally between ages 9 and 11 and should begin at age 2 for those with a family history of elevated cholesterol or premature ASCVD.[6] Screening before age 2 is not recommended because lipoprotein levels increase until age 2 when they become more stable.[6] Early screening offers the most significant benefits because patients can implement specific measures and treatment to prevent lifelong exposure to elevated cholesterol levels.[6] However, routine screening is not recommended during adolescence because LDL-C levels fluctuate with the onset of puberty.[12] In males, LDL-C levels fall during puberty and rise as adulthood approaches, whereas in females, LDL-C levels tend to rise during puberty.[12]

Fasting LDL-C or nonfasting non-high-density lipoprotein cholesterol (non-HDL-C) can be used for screening.[6] FH should be strongly suspected in children or young adults with non-HDL-C levels of at least 190 mg/dL or LDL-C levels of at least 160 mg/dL. In adults, FH should be strongly suspected when non-HDL-C levels reach at least 220 mg/dL or LDL-C levels reach at least 190 mg/dL.[6]

It is important to rule out secondary causes of elevated cholesterol, including hypothyroidism, nephrotic syndrome, and hepatic dysfunction. Thus, it is necessary to obtain lab work that includes a thyroid-stimulating hormone, comprehensive metabolic panel, complete blood cell count, and a lipid panel. Other genetic conditions, such as sitosterolemia, lysosomal acid lipase A deficiency, familial combined hyperlipidemia, and apolipoprotein E deficiency, can cause significant elevations in total cholesterol and LDL-C and should be considered differential diagnoses.

Diagnosis

An FH diagnosis is based on lipid levels, family history, genetic analysis, and/or physical exam findings. Average untreated LDL-C and total cholesterol levels in HeFH are higher than 220 mg/dL and 350 mg/dL, respectively.[6] In HoFH, untreated LDL-C and total cholesterol levels are higher than 500 mg/dL and 650 mg/dL, respectively. Note that recent data suggest wide variation in LDL-C levels; in some patients, untreated LDL-C has been as low as 155 mg/dL.[10] Classically, patients with FH present with only marked elevations in total cholesterol and LDL-C; however, the presence of hypertriglyceridemia does not preclude the diagnosis of FH.[6] Triglyceride levels higher than 400 mg/dL prevent accurate estimation of LDL-C using the Friedewald equation (LDL-C = [total cholesterol]−[HDL-C]−[triglyceride/5]), preventing clinicians from making an accurate diagnosis.[6]

Evidence-based diagnostic tools

Three evidence-based tools exist to aid in the clinical diagnosis of FH: the Simon Broome register, Dutch Lipid Clinic Network criteria, and Make Early Diagnosis to Prevent Early Death (MedPed) program (see *Diagnostic tools*). In the US, the Dutch Lipid Clinic Network criteria are most commonly used for diagnosing FH. However, the Dutch Lipid Clinic Network criteria are generally not useful in children, and alternative methods should be employed when considering an FH diagnosis.

Cardiovascular risk assessment tools, such as the Framingham Risk Score, Reynolds Risk Score, or the Pooled Cohort Risk Assessment Equations, should not be used to assess ASCVD risk in patients with FH. These risk assessment tools do not adequately

Diagnostic tools

Simon Broome register
www.ncbi.nlm.nih.gov/pmc/articles/PMC1671226/pdf/bmj00148-0031.pdf
www.atherosclerosis-journal.com/article/S0021-9150(98)00200-7/fulltext

Dutch Lipid Clinic Network criteria
http://apps.who.int/iris/bitstream/handle/10665/66346/WHO_HGN_FH_CONS_99.2.pdf

MedPed program
www.sciencedirect.com/science/article/pii/0002914993901556

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predict risk in patients with FH and underestimate risk because of exposure to high levels of cholesterol from birth.

Genetic testing

Although clinical phenotypes appear more important in diagnosing and treating patients with FH, genetic testing can also be beneficial. Several factors preclude routine genetic testing in the US, namely the high cost associated with testing, lack of coverage by third-party payors, and limited information gained to influence ASCVD risk.[6] Genetic testing may be a valuable tool for diagnosis in specific individuals and families. However, it is important to remember that genetic testing does not exclude the diagnosis of FH, as over 20% of genetic mutations that may cause FH have not been identified and thus will not be detected with this testing.[6] Patients with a phenotypic presentation of FH should still be treated as clinically appropriate.

Treatment

A multifaceted approach to treating FH is required. In addition to a goal of at least 50% LDL-C reduction in patients with FH, LDL-C goals are less than 100 mg/dL or less than 70 mg/dL for those with known coronary disease or diabetes mellitus.[7,13] Early instituted lifelong management of patients with FH is essential.

Lifestyle changes. Patients with FH should be aggressively counseled and coached to implement lifestyle changes, including smoking cessation; getting regular moderate-intensity exercise; and consuming a diet low in trans and saturated fats, refined sugars, cholesterol, and calories and high in fiber and plant sterols and stanols. (See *Lifestyle changes for patients with FH*.)

Statin therapy. Statins, or 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the most effective class of drugs for lowering LDL-C and should be the initial pharmacotherapeutic intervention for adults and children with FH.[10] Statins increase LDLR expression by reducing HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.[10] Because of mechanisms of action of statin drugs and reliance on the LDLR, patients with FH often do not have the expected LDL-C reduction from LLT. High-intensity statin LDL-C reduction (see *Statin therapy intensity*), typically 55% to 60%, may be reduced to 20% to 25%.[7] So, statins are still beneficial for patients who maintain even a small degree of LDLR activity. Statins increase PCSK9 levels through negative feedback, which promotes LDLR degradation.[15]

High-intensity statins should be used as first-line treatment for adults with FH; low- and moderate-potency statins generally provide insufficient LDL-C reduction. If patients are not initially placed on maximum-dose high-intensity statin therapy and inadequate LDL-C reduction is attained, doubling the statin dose will only result in an additional 6% LDL-C reduction.

Statin adverse reactions, particularly muscle symptoms, tend to limit optimal dose therapy. Muscle symptoms are the most common cause for statin discontinuation and are typically dose-dependent.

Lifestyle changes for patients with FH[14]

- Modify diet to improve lipid profiles:
  - Aim for saturated fat intake <7% of total calories.
  - Avoid trans fats.
  - Eat a heart-healthy diet high in vegetables, fruits, beans, tree nuts, and lean meats.
  - Eat plant sterols/stanols (2 g/day).
  - Eat insoluble fiber (10-20 g/day).
  - Limit alcohol intake to moderate consumption (if choosing to consume alcohol) and avoid alcohol intake if TG levels are ≥500 mg/dL.
  - Consult a dietitian.
- Complete 200-300 minutes per week of moderate- or high-intensity physical activity.
- Lose weight, if overweight, and maintain a healthy weight after weight loss.
- Stop smoking.
- Avoid passive smoke exposure.
- Manage diabetes mellitus and hypertension.
- Consult with primary care provider and consider low-dose aspirin.

Statin therapy intensity

- High-intensity statins: reduce LDL-C ≥50%
- Atorvastatin, 40-80 mg
- Rosuvastatin, 20-40 mg
- Moderate-intensity statins: reduce LDL-C 30% to <50%
- Atorvastatin, 10-20 mg
- Fluvastatin, 40 mg bid
- Fluvastatin XL, 80 mg
- Lovastatin, 40 mg
- Pitavastatin, 2-4 mg
- Pravastatin, 40-80 mg
- Rosuvastatin, 5-10 mg
- Simvastatin, 20-40 mg

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Symptoms occur more frequently with increased age and number of medications and decreased kidney function and body size.[10]

Although statin-associated hepatic toxicity is often a concern for patients and providers, it is not common and serious complications are extremely rare.[10] Hepatic transaminase elevation is often mild and only requires statin discontinuation if hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) rise to greater than three times the upper limit of normal.[10] Only about 1% of patients experience transaminase elevations more than three times the upper limit of normal and the elevation decreases even if the statin is continued.[10] If hepatic transaminases remain more than three times the upper limit of normal, clinicians should identify contributing conditions or medications and consider changing to a different statin.

Statins can be used cautiously in the presence of hepatic disease if it is not decompensated.[10] Specifically, nonalcoholic fatty liver disease is not a contraindication to statin therapy.[10] Hepatic transaminases should be measured before starting statin therapy and during treatment only if there is a clinical indication. Routine monitoring of hepatic transaminases has been removed from package labeling since 2012.

Nonstatin therapy. Lifestyle modifications and statin therapy frequently do not provide sufficient LDL-C reduction in patients with FH, and combination therapy must be considered. This results in patients often requiring combination therapy to achieve LDL-C goals (see *Drugs affecting lipoprotein metabolism*). In patients with FH who have an LDL-C of at least 100 mg/dL, established ASCVD with LDL-C of at least 70 mg/dL, or who are intolerant to statin therapy, nonstatin therapy should be added to other LLT to attain LDL-C goals. Intensification of LLT should be considered for those who do not attain lipid goals.

Drugs affecting lipoprotein metabolism

Drug class	LDL-C reduction (%)
Statins	18-55%
Cholesterol absorption inhibitor	13-20%
Bile acid sequestrants	15-30%
Nicotinic acid	5-25%
PCSK9	40-60%
Lomitapide	50%

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Ezetimibe. Ezetimibe, a cholesterol absorption inhibitor, is localized to the brush border of the small intestines and is frequently the initial nonstatin therapy used in combination with statins in patients with FH.[10] It reduces LDL-C by approximately 20% and has very few drug interactions.[10]

Niacin. Niacin, a water soluble B vitamin, lowers LDL-C and raises HDL-C and has been used for over 50 years to treat dyslipidemia.[16] It is available over-the-counter in immediate and slow-release forms, with a prescription in extended-release form, and has been used effectively in those intolerant to statins. The clinical utility of niacin has been significantly limited by adverse reactions.[16] The most common adverse reaction, flushing, is experienced by 70% of patients and is caused by prostaglandin D_2. Flushing can be mediated by pretreatment aspirin.[16] It should be noted that "flush-free" niacin does not have any lipid-lowering benefits.[17] Niacin has also demonstrated the ability to decrease insulin sensitivity, increase uric acid levels, and worsen peptic ulcer disease.[16] Further, in 2016, the FDA withdrew the approved indication of niacin extended-release to be used in combination with statins, citing lack of cardiovascular benefit.[18]

Bile acid sequestrants. Bile acid sequestrants decrease LDL-C by preventing reabsorption of bile acids in the terminal ileum. They are considered safer than other LLT because they are not systemically absorbed.[10] However, gastrointestinal (GI) adverse reactions, multiple medication interactions, and the large number of pills or suspensions required for use limit patient adherence and use. Colesevelam is the recommended bile acid sequestrant in patients with FH because it has fewer GI adverse reactions, medication interactions, and it is approved in the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to help achieve glycemic goals.[10] However, bile acid sequestrant should be used with caution in patients with hypertriglyceridemia and is contraindicated in patients with triglyceride levels greater than 500 mg/dL.

PCSK9 inhibitors. PCSK9 was discovered in 2003 by researchers in Paris and Montreal who found a gain of function mutation in patients with FH. This finding prompted researchers to elucidate PCSK9 biology and in the quest to develop PCSK9 targeted therapeutic options.[19] PCSK9 increases degradation of LDLR and

prevents LDLR recycling for continued catabolism of LDL-C, leading to elevated LDL-C levels.

Alirocumab and evolocumab, the currently available PCSK9 inhibitors, are fully human monoclonal antibodies, delivered subcutaneously every 2 weeks or monthly. When added to maximally tolerated statin therapy, these drugs can further decrease LDL-C by up to 60%.[19,20] Safety data regarding PCSK9 inhibitors revealed low injection site reactions, no increase in the incidence of adverse reactions in those attaining very low LDL-C levels (less than 25 mg/dL), and a relatively favorable safety profile.[18] PCSK9 monoclonal antibodies are large molecules and do not normally cross the blood-brain barrier.

Lomitapide. Lomitapide is a microsomal triglyceride transfer protein inhibitor approved by the FDA, in December 2012, as adjunct to a low-fat diet and other LLT, including apheresis, to reduce LDL-C, total cholesterol, Apo B, and non-HDL-C in patients with HoFH.[5] Lomitapide has enabled some HoFH patients to reduce the frequency of or discontinue apheresis by reducing LDL-C by up to 50%.[10,14] Because of the significant concerns of hepatotoxicity, prescribers are required to complete an FDA-approved Risk Evaluation and Mitigation Strategy program before prescribing lomitapide.

Apheresis. When patients cannot tolerate intensive LLT or have an insufficient LDL-C reduction, lipoprotein apheresis offers a costly but efficacious option.[7] For a patient with HoFH or a patient with HeFH with LDL-C greater than 300 mg/dL (greater than 200 mg/dL for those with ASCVD), lipoprotein apheresis can be performed on a weekly or bimonthly basis.[7] Currently approved lipoprotein apheresis methods decrease LDL-C and Lp(a) by approximately 60% to 70% immediately and lead to a 72% reduction in total coronary event rate.[7]

Surgical therapy. Patients who do not achieve appropriate lipid goals with the above-mentioned modalities may be candidates for surgical therapy, including partial ileal bypass or liver transplantation. Partial ileal bypass is rarely used and works by interrupting enterohepatic bile acid circulation.[10] Liver transplantation provides significant LDL-C reduction by the introduction of normal LDLRs. It is used primarily in HoFH children when apheresis is not an option or with concurrent heart transplantation.[10] Liver transplantation is limited by the number of available organ donors and risks associated with transplant surgery.

Patient education

Cascade screening. Although the ASCVD manifestations of FH occur later in life, the clinical effects begin in the first decade of life. Early screening mechanisms can prevent complications if diagnosis and treatment strategies are employed early. Cascade screening, or the systematic testing the first-degree and higher-order relatives, of all patients with identified FH (index patients), is recommended to increase diagnosis of those affected by FH and improve treatment options for patients who may have been unaware of their diagnosis.[6] Cascade screening can be accomplished clinically, with the use of LDL-C, physical exam, and other diagnostic tools, such as the Simon Broome register, Dutch Lipid Clinic Network criteria, and MedPed, or with genetic testing if the causal mutation is known. If new patients are diagnosed with FH through cascade screening, they become an index patient, and the cascade screening should begin again through that patient's first-degree and higher-order relatives. Cascade screening is cost effective.[7] A family-centric screening approach promotes disease prevention and early diagnosis of FH. The probability of FH is 50% in first-degree relatives, 25% in second-degree relatives, and 12.5% in third-degree relatives. Cascade screening can be lifesaving, especially in young patients who may otherwise not undergo screening lipid measurement.

Key patient-teaching points. NPs should counsel patients to limit saturated fat and avoid transfat intake, increase fiber intake, and consume a diet high in vegetables, fruits, beans, and lean meats.[14] Smoking cessation counseling and patient-specific options to increase physical activity to 200 to 300 minutes per week of moderate- or high-intensity physical activity should also be offered.[14] Further, patients and family members should participate in recommended screening efforts to increase diagnosis and treatment.

Follow-up. Uncomplicated and well-controlled FH can easily be managed in the primary care setting. Patients should be referred to and managed by a lipid specialist if they are complex FH patients with multiple ASCVD risk factors, severely elevated LDL-C levels, complications from pharmacotherapy, and/or HoFH.

Conclusion

FH begins early in life, well before clinical signs of the disease are present, and promotes premature ASCVD. There is a significant opportunity to improve the diagnosis and management of FH, decrease the progression

of atherosclerosis, and mitigate ASCVD risk. Primary care providers manage the most patients with hypercholesterolemia and are exceptionally positioned to implement cascade screening and begin the diagnosis and management process in the many undiscovered patients with FH. NP

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