April 2018

Spotlight on Health

Quest Diagnostics™

Family Heart Health

Approximately 370,000 people in the United States die from coronary heart disease (CHD) each year.[1] And over 700,000 have a myocardial infarction (MI).[1] Familial hypercholesterolemia (FH) causes greatly increased low-density lipoprotein cholesterol (LDL-C) levels and increased risk of MI.[2]

The buildup of plaque in coronary arteries is influenced by cholesterol and fat intake. Diet and lifestyle changes can reduce blood cholesterol and triglyceride levels. This reduces the risk of CHD and MI.

This newsletter reviews atherosclerosis, CHD, and FH, a relatively common yet underdiagnosed cause of elevated cholesterol. It also discusses the limitations of current methods of cholesterol testing and reviews the management of elevated cholesterol.

Atherosclerosis and CHD

The buildup of fatty deposits in the walls of arteries, including coronary arteries, is called atherosclerosis. The fatty deposits, called plaques, reduce blood flow. Atherosclerosis starts with damage to the arterial endothelium. White blood cells move into the wall of the injured artery. They then change into foam cells, which collect cholesterol and other fatty materials. Foam cells, filled with fat, accumulate over time to form plaques.[3] Calcium also accumulates in the plaques.[3] Plaques grow and restrict blood flow. They can also rupture and cause a blood clot.[3]

Familial Hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant disorder associated with very high levels of LDL-C (adults ≥190 mg/dL; children ≥160 mg/dL).[4] About 1 in 200 to 1 in 500 persons in the United States has heterozygous FH, and over 90% are undiagnosed.[4] Untreated individuals have a 30% to 50% increased risk of having an MI by age 50 to 60.[4] FH is often caused by variants in the *LDLR, APOB,* and/or *PCSK9* genes.[5]

FH is diagnosed on the basis of clinical criteria or a positive genetic test result.[5] In families with known or suspected FH, guidelines recommend that children have cholesterol and/or genetic testing as young as 2 years of age.[4,5] If diagnosed, the condition is treated with aggressive cholesterol-lowering drugs and lifestyle modifications.

Limitations of Cholesterol and Triglyceride Measurement

Lipid testing is a cornerstone of CHD risk assessment.[6] The diagnosis of elevated blood cholesterol and triglycerides is typically performed by measuring fasting levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides.[7] The LDL-C level is then calculated.[7]

The Friedewald formula for calculating LDL-C was developed because direct measurement is costly and time-consuming. However, the formula is less accurate when cholesterol levels are very low (as recommended for high-risk patients) and when triglycerides are high.[7-10] This inaccuracy can result in undertreatment of high-risk patients.[7]

Desirable Lipid Levels[6]

- HDL-C ≥40 mg/dL (men), ≥50 mg (women)
- Triglycerides <150 mg/dL
- LDL-C <100 mg/dL
- non-HDL-C <130 mg/dL (ie, 30 mg/dL above the LDL-C goal)

Clinical investigators at the Johns Hopkins University School of Medicine developed a novel method of calculating LDL-C (Martin-Hopkins Calculation). The Martin-Hopkins calculation is based on an individual's unique lipid profile.[7] The method is more accurate than the Friedewald formula for calculating LDL-C level.[7,8] Importantly, non-fasting blood samples can be used, making it convenient for patients.

Management of Elevated Blood Cholesterol

Modifiable risk factors for CHD include tobacco use, hypertension, diabetes, obesity, physical inactivity, low consumption of fruits and vegetables, and high blood levels of cholesterol and triglycerides. The most recent guidelines from the American College of Cardiology and the American Heart Association use LDL-C and other patient characteristics to determine which at-risk individuals are likely to benefit from statin therapy.[10] For high-risk individuals without a diagnosis of FH, the recommended intensity of statin therapy is determined by the degree of risk. It is also determined by the desired percent reduction in LDL-C concentration, rather than a predefined target as previously used.[10]

How the Laboratory Can Help

Quest Diagnostics uses the Martin-Hopkins calculation for determining LDL-C concentration. The Quest Diagnostics lipid panel (Test Code 7600) can be performed on non-fasting blood samples, making it convenient for patients to have cholesterol testing. Quest also offers direct LDL-C measurement (Test Codes 8293 and 91723) for when triglyceride levels are very high, or when LDL-C values are very low (10 mg/dL to 40 mg/dL), and calculation is less accurate.[8]

For diagnosis of FH, Quest Diagnostics offers the Familial Hypercholesterolemia Panel (Test Code 94877), which tests for variants in the *LDLR, APOB,* and *PCSK9* genes. The Familial Hypercholesterolemia Single-Site test (Test Code 94878) is useful when 1 or 2 familial pathogenic variants are known.

References

1. Heart disease facts. Centers for Disease Control and Prevention website. https://www.cdc.gov/heartdisease/facts.htm. Accessed December 12, 2017.
2. Marks D, Thorogood M, Neil HA, et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis.* 2003;168:1-14.
3. Zmysłowski A, Szterk A. Current knowledge on the mechanism of atherosclerosis and pro-atherosclerotic properties of oxysterols. *Lipids HealthDis.* 2017;16:188. doi: 10.1186/s12944-017-0579-2
4. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation.* 2015;132:2167-2192.
5. Henderson R, O'Kane M, McGilligan V, et al. The genetics and screening of familial hypercholesterolaemia. *J Biomed Sci.* 2016;23:39. doi: 10.1186/s12929-12016-10256-12921
6. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. *J Clin Lipidol.* 2015;9:129-169.
7. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald Equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA.* 2013;310:2061-2068.
8. Quispe R, Hendrani A, Elshazly MB, et al. Accuracy of low-density lipoprotein cholesterol estimation at very low levels. *BMC Med.* 2017;15:83. doi:10.1186/s12916-017-0852-2
9. Sathiyakumar V, Park J, Golozar A, et al. Fasting versus nonfasting and low-density lipoprotein cholesterol accuracy. *Circulation.* 2018;137:10-19.
10. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 129(25 suppl 2):S1-S45.