Lipid Disorders, Screening

Basic Information

Terminology

- The term dyslipidemia refers to disturbances leading to excess or reduction in levels of plasma lipoproteins. This term is associated with disease states leading to development of atherosclerotic cardiovascular disease or pancreatitis
- Hyperlipidemia is defined as excess of lipoproteins leading to hypercholesterolemia, hypertriglyceridemia, or excess lipoprotein (a) in plasma
- Hypolipidemia is defined as low levels of lipoproteins that lead to reduced values of cholesterol or triglycerides in plasma
- The term *total cholesterol* reflects cholesterol carried by all circulating lipoproteins in fasting (LDL-C; VLDL-C; and its remnants, mainly intermediate-density lipoprotein; HDL-C; and lipoprotein [a]). In postprandial states, total cholesterol includes all the before-mentioned lipoproteins, in addition to chylomicrons and their remnants
- Hypercholesterolemia (total cholesterol 200 mg/dL or higher) usually results from excess accumulation of LDL-C (LDL-C level 130 mg/dL or higher)
- Hypercholesterolemia may rarely occur due to excess accumulation of HDL-C[1]
- Hypertriglyceridemia (triglyceride level 150 mg/dL or higher) is characterized by excess accumulation of triglyceride-rich lipoproteins (VLDL-C; intermediate-density lipoprotein; and/or chylomicrons and remnants)[1]
- Low HDL-C level (hypoalphalipoproteinemia, HDL-C below 40 mg/dL) may occur in an isolated manner but usually occurs with hypertriglyceridemia
- Mixed dyslipidemia is characterized by elevation in both total cholesterol and triglycerides
- Elevation in lipoprotein (a) (50 mg/dL or higher) may occur in an isolated manner or in association with other forms of dyslipidemia,[2] and may also cause hypercholesterolemia

Epidemiology

- Between 2011 and 2016, 38% and 11.7% of the adult population in the United States had total cholesterol levels 200 mg/dL or higher and 240 mg/dL or higher, respectively [1]
- LDL-C level 130 mg/dL or higher in US adults was encountered 28.9% and HDL-C level below 40 mg/dL was found in 19.2%[1]
- Severe hypercholesterolemia (LDL-C level 190 mg/dL or higher) is present in approximately 6% of the US population[3]

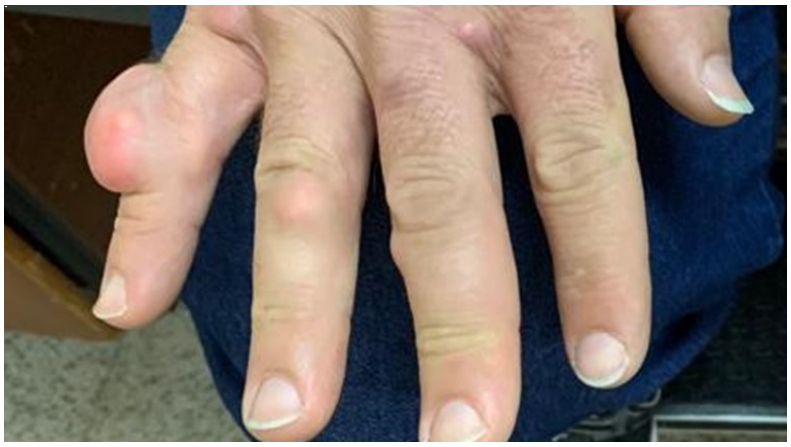
- The familial hypercholesterolemia phenotype is encountered in approximately 1 in 313 people in the general population[4]
- The familial hypercholesterolemia phenotype characterized by severe elevations in LDL-C is encountered in 1 in 31, 1 in 25, and 1 in 14, in people with ischemic heart disease, premature ischemic heart disease, and severe hypercholesterolemia, respectively [4]
- High LDL-C was the fifth leading cause of mortality worldwide between 1990 and 2017, according to the Global Burden of Disease study[5]
- Triglyceride levels are elevated (150 mg/dL or higher) in 22.2% of US adults[1]
- Severe forms of hypertriglyceridemia (triglyceride level 1000 mg/dL or higher) are encountered in roughly 0.4% of the US population[6]
- Lipoprotein (a) level varies according to ethnicity, being higher in Black and South Asian populations than in White and Chinese groups[7]
- Around 20% of White people have lipoprotein (a) above 50 mg/dL ~~or 107 nmol/L~~[2]

Etiology and Risk Factors

Etiology

- Most dyslipidemias are primary and occur due to a mix of polygenic effects with inadequate dietary habits, lifestyle habits, or both[8]
- Severe dyslipidemias (eg, familial hypercholestrerolemia,[9] familial chylomicronemia syndrome) are usually caused by rare large-effect monogenic defects[8,10]
- Familial hypercholesterolemia has an autosomal co-dominant etiology involving the LDL receptor, apolipoprotein B, and *PCSK9* genes[9]
- Autosomal recessive variants in the LDL receptor-related protein (*LDLRAP1*) gene may also cause a phenotype similar to homozygous familial hypercholesterolemia (autosomal recessive hypercholesterolemia)[9] (**Figure 1**)

Figure 1. Interdigital and cutaneous planar xanthomas in a child with homozygous familial hypercholesterolemia.



- Rarely, variants in apolipoprotein E may cause the familial hypercholesterolemia phenotype[9]
- Familial chylomicronemia syndrome is caused mostly by loss of function variants in the lipoprotein lipase gene or in genes modulating its activity[10]
- Lipoprotein (a) levels are highly genetically determined, with elevated family heritability in White and Black populations[11]
- Dyslipidemias may also occur due to secondary causes (**Table 1**)
- Dyslipidemias may be caused by some medications (**Table 2**)

Table 1. Secondary causes of dyslipidemias.[12,13]

Condition	Type of dyslipidemia
Abdominal obesity and insulin resistance	Mixed dyslipidemia, hypertriglyceridemia, and low HDL-C level
Diabetes mellitus	Hypertriglyceridemia, mixed dyslipidemia, and low HDL-C level
Polycystic ovary syndrome	Hypertriglyceridemia, mixed dyslipidemia, and low HDL-C level
Albuminuria	Mixed dyslipidemia
Hypothyroidism	Hypercholesterolemia or mixed dyslipidemia
Obstructive jaundice	Hypercholesterolemia
Excess alcohol consumption	Hypertriglyceridemia

Smoking	Low HDL-C level
Cushing syndrome	Hypertriglyceridemia and mixed dyslipidemia
Pregnancy	Hypercholesterolemia, hypertriglyceridemia or mixed dyslipidemia

Adapted from Vodnala D et al. Secondary causes of dyslipidemia. *Am J Cardiol*. 2012. 110:823-825, and Yanai H et al. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med*. 2021;3(1):15-23.

Table 2. Effects of medications on lipid profile.[13]

	LDL-C level	**Triglyceride level**	**HDL-C level**
High-dose diuretics	↑	→	-
Nonselective β-blockers	-	↑	↓
Estrogens	↓	↑	↑
Progestins	-	→↑	→↓
Tibolone	-	-	↓↓
Danazol	↑	-	↓↓
Corticosteroids	↑	↑	-
Anabolic steroids	↑	-	↓
HIV protease inhibitors	↑	↑↑↑	-
Retinoids	↑	↑↑	-
Cyclosporine and tacrolimus	↑	↑↑	↑
First generation antipsychotic drugs	-	↑	↓
Atypical (second generation) antipsychotic drugs	↑	↑↑	-

Data from Yanai H et al. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med* 2021;3(1):15-23.

Risk Factors

- Lifestyle: sedentarism,[14] smoking[13]
- Dietary patterns rich in saturated and *trans*–fatty acids, simple carbohydrates, and sugars, as well as excess alcohol consumption (more than 30 g/day),[15-17] may suggest presence of dyslipidemias
- Disease states: obesity, type 1 or 2 diabetes, albuminuria, or acute pancreatitis may suggest presence of dyslipidemias[13]
- Heritability: family history of early atherosclerotic cardiovascular disease (diagnosis younger than age 55 years and age 65 years respectively, in male and female first-degree relatives) and family history of dyslipidemia may suggest presence of dyslipidemias[9,16]

Screening and Prevention

Screening

- Goal of screening is to identify dyslipidemias predisposing to increased atherosclerotic cardiovascular disease risk that may by ameliorated by lipid-lowering therapy or lifestyle modifications
- Screen all adults who are aged 20 years or older with a fasting or nonfasting lipid profile to determine LDL-C level and estimate atherosclerotic cardiovascular disease risk[16]
- In adults aged older than 20 years without previous atherosclerotic cardiovascular disease, repeat screening every 4 to 6 years[13]
- Obtain a fasting lipid profile in adults who are 20 years or older to determine LDL-C level and estimate atherosclerotic cardiovascular disease risk if triglyceride levels are 400 mg/dL or higher on initial nonfasting lipid profile[16]
- Obtain a fasting lipid profile in adults with a family history of premature atherosclerotic cardiovascular disease (diagnosis younger than age 55 years and age 65 years for males and females, respectively) or genetic hyperlipidemia to screen for familial lipid disorders like familial hypercholesterolemia[16]
- Obtain a lipid profile for all patients with diabetes at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients under the age of 40 years[18]
- Consider screening for high lipoprotein (a) level at least once in a lifetime for everyone,[19,20] mainly in people with a personal history or family history of premature atherosclerotic

cardiovascular disease, and/or recurrent or progressive atherosclerotic cardiovascular disease despite optimal lipid lowering[2,20]

- Screen for high lipoprotein (a) in patients with severe hypercholesterolemia (LDL-C level 190 mg/dL or higher) or suspected familial hypercholesterolemia, and when there is a parent or sibling with elevated lipoprotein (a) level [2,20]

Prevention

- Regular physical activity, an adequate dietary pattern, limitation of alcohol consumption, nonsmoking, and weight loss in obesity may help prevent the onset of dyslipidemias[16,17]
- Evaluate presence of atherosclerotic cardiovascular disease or its risk factors (eg, smoking, hypertension, diabetes) to stratify risk and prevent complications of dyslipidemias[16]

Special Considerations

Patients with Diabetes

- Patients with diabetes are prone to development of mixed dyslipidemia, hypertriglyceridemia, and low HDL-C level[13]
- Dyslipidemia is a risk factor for atherosclerotic cardiovascular disease in diabetes[18]
- Obtain a lipid profile for all patients with diabetes at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients under age 40 years[18]

Patients with Severe Hypercholesterolemia (LDL-C 190 mg/dL or higher)

- Suspect genetic forms of dyslipidemia—mainly familial hypercholesterolemia—in patients with severe hypercholesterolemia, especially those with family history of dyslipidemia or early atherosclerotic cardiovascular disease[21]
- Perform an adequate evaluation using either clinical scores or genetic diagnosis[19,21]
- If familial hypercholesterolemia is diagnosed, perform cholesterol or genetic cascade screening to identify affected relatives[21]
- Screen for high lipoprotein (a) level in patients with severe hypercholesterolemia (LDL-C level 190 mg/dL or higher), those with suspected familial hypercholesterolemia, and those who have a parent or sibling with elevated lipoprotein (a)[2,20]

Diagnostic Considerations and Implications

- All lipoproteins are composed of cholesterol and triglycerides; mixed dyslipidemia may occur due to accumulation of VLDL and/or chylomicrons or accumulation of LDL-C and VLDL-C

- Elevations in lipoprotein (a) may cause hypercholesterolemia since lipoprotein (a) is cholesterol rich; in mass assays, lipoprotein (a) cholesterol may be counted as part of total and LDL-C levels[22]
- Dyslipidemias may cause atherosclerotic cardiovascular disease (hypercholesterolemia due to high LDL-C and/or lipoprotein (a) levels, moderate hypertriglyceridemia, or mixed dyslipidemia)[16]
- Moderate or severe hypertriglyceridemia (mainly) may cause acute pancreatitis[10,23]
- There is controversy whether low HDL-C level per se causes atherosclerosis[24]
- Presence of early atherosclerotic cardiovascular disease in an individual or a family may indicate presence of dyslipidemias, especially monogenic forms (eg, familial hypercholesterolemia, high lipoprotein [a] level)[9,16]
- Severe hypercholesterolemia (LDL-C level 190 mg/dL or higher) or high lipoprotein (a) level especially when there is history of early family history of atherosclerotic cardiovascular disease implicate in family screening for dyslipidemias[2,16]
- Corneal arcus (**Figures 2** and **4**) in individuals younger than age of 45 years, cutaneous or tendinous xanthomas (**Figures 1** and **3**), palpebral xanthelasmas (**Figure 4**), and aortic valve murmurs (usually systolic) may indicate severe hypercholesterolemia (eg, familial hypercholesterolemia)[9]
- Eruptive xanthomas, hepatosplenomegaly, and lipemia retinalis may occur in the presence of severe hypertriglyceridemia and in familial chylomicronemia syndrome[25]
- Patients with repetitive episodes of acute pancreatitis may suffer from severe hypertriglyceridemia and chylomicronemia syndrome, and therefore lipid profile is indicated in this situation[8,26]

Figure 2. Corneal arcus (*white arrow*) in a patient with familial hypercholesterolemia.

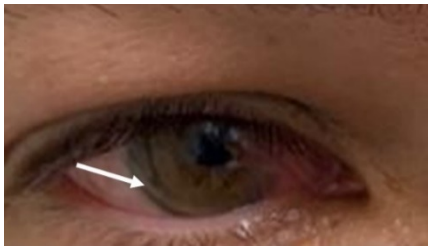


Figure 3. Tendinous xanthomas in a patient with familial hypercholesterolemia.

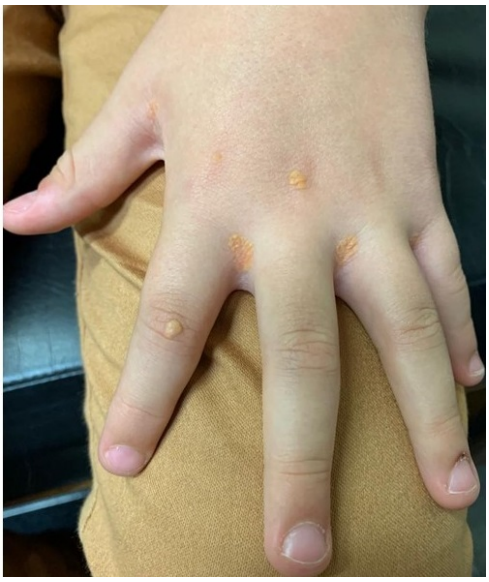
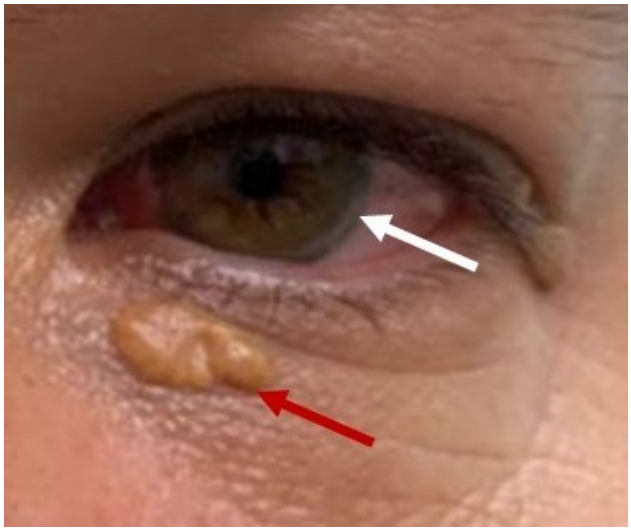


Figure 4. Xanthelasmas (*red arrow*) and corneal arcus (*white arrow*) in a patient with familial hypercholesterolemia.



Follow-up

Referral

- Refer patients with severe genetic forms of dyslipidemia (eg, familial chylomicronemia syndrome, homozygous familial hypercholesterolemia) to a lipid specialist

Summary

Key Points

- The term dyslipidemia applies to disturbances leading to excess or reduction in levels of plasma lipoproteins
- Hypercholesterolemia, hypertriglyceridemia, and low HDL-C levels are encountered in 28.9%, 22.2%, and in 19.2% of US adults, respectively[1]
- High lipoprotein (a) levels affect around 1 in 5 White people, with variable levels in other ethnicities[2]
- Dyslipidemias may predispose to atherosclerotic cardiovascular disease (high LDL-C level, moderate hypertriglyceridemia, high lipoprotein [a] level) or pancreatitis (moderate but mostly severe hypertriglyceridemias)
- Low HDL-C level is a marker of greater atherosclerotic cardiovascular disease risk; however, there are controversies about its causal role[16]
- Most dyslipidemias occur due to a mix of genetic, dietary, and lifestyle factors but can be secondary to other conditions or use of some medications
- Familial hypercholesterolemia is an autosomal-dominant disorder frequently found in individuals and families with early atherosclerotic cardiovascular disease[9]
- Family screening for hypercholesterolemia is mandatory when the diagnosis of familial hypercholesterolemia is confirmed
- Most dyslipidemias are asymptomatic and universal screening is recommended for all adults[16]
- Evaluate presence of atherosclerotic cardiovascular disease or its risk factors (eg, smoking, hypertension, diabetes) to stratify risk and prevent complications of dyslipidemias[16]

References

1. Virani SS et al. Heart disease and stroke statistics--2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596.

2. Wilson DP et al. Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come. A Scientific Statement from the National Lipid Association. *J Clin Lipidol*. 2019;13(3):374-392.

3. Bucholz EM et al. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia (1999-2014). *Circulation*. 2018;137(21):2218-2230.

4. Beheshti SO et al. Worldwide relevance of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol*. 2020;75(20):2553-2566.

5. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923-1994.

6. Ford ES et al. Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med*. 2009;169(6):572-578.

7. Patel AP et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41:465-474.

8. Garg A et al. Practical definitions of severe versus familial hypercholesterolaemia and hypertriglyceridaemia for adult clinical practice. *Lancet Diabetes Endocrinol*. 2019;7(11):880-886.

9. Defesche JC et al. Familial hypercholesterolaemia. *Nat Rev Dis Primers*. 2017;3:17093.

10. Hegele RA et al. Clinical and biochemical features of different molecular etiologies of familial chylomicronemia. *J Clin Lipidol*. 2018;12(4):920-927e4.

11. Kronenberg F. Human genetics and the causal role of lipoprotein(a) for various diseases. *Cardiovasc Drugs Ther*. 2016;30(1):87-100.

12. Vodnala D et al. Secondary causes of dyslipidemia. *Am J Cardiol*. 2012;110(6):823-825.

13. Yanai H et al. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med*. 2021;3(1):15-23.

14. Grundy SM et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol*. 2004;24(2):e13-e18.

15. Klop B et al. Alcohol and plasma triglycerides. *Curr Opin Lipidol*. 2013;24(4):321-326.

16. Grundy SM et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

17. Van Horn L et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134(22):e505-e529.

18. American Diabetes A. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1): S125-S150.

19. Mach F et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. *Eur Heart J*. 2020;41(1):111-188.

20. Pearson GJ et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol*. 2021;37(8):1129-1150.

21. Gidding SS et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation*. 2015;132(22):2167-2192.

22. Santos RD. Familial hypercholesterolaemia: beware of lipoprotein(a). *Lancet Diabetes Endocrinol.* 2016;4(7):553-555.

23. Pedersen SB et al. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med*. 2016;176(12):1834-1842.

24. Barter PJ et al. HDL cholesterol concentration or HDL function: which matters? *Eur Heart J*. 2017;38(32): 2487-2489.

25. Blom DJ et al. Characterizing familial chylomicronemia syndrome: baseline data of the APPROACH study. *J Clin Lipidol*. 2018;12(5):1234-1243e5.

26. Hegele RA et al. Rare Dyslipidaemias, From Phenotype to Genotype to Management: A European Atherosclerosis Society Task Force Consensus Statement. *Lancet Diabetes Endocrinol*. 2020;8(1):50-67.

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