Lipoproteins are complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides, and fat-soluble vitamins. Until recently, lipoprotein disorders were the purview of lipidologists, but the demonstration that lipid-lowering therapy significantly reduces the clinical complications of atherosclerotic cardiovascular disease (ASCVD) has brought the diagnosis and treatment of these disorders into the domain of the general internist. The metabolic consequences associated with changes in diet and lifestyle have increased the number of hyperlipidemic individuals who could benefit from lipid-lowering therapy. The development of safe, effective, and well-tolerated pharmacologic agents has greatly expanded the therapeutic armamentarium available to the physician to treat disorders of lipid metabolism. Therefore, the appropriate diagnosis and management of lipid disorders is critically important to the practice of medicine. This chapter reviews normal lipoprotein physiology, the pathophysiology of the known single-gene disorders of lipoprotein metabolism, the environmental factors that influence lipoprotein metabolism, and the practical approaches to their diagnosis and management.

**LIPOPROTEIN METABOLISM**

**LIPOPROTEIN CLASSIFICATION AND COMPOSITION**

Lipoproteins are large, mostly spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. Lipoproteins play an essential role in the absorption of dietary cholesterol, long-chain fatty acids, and fat-soluble vitamins; the transport of triglycerides, cholesterol, and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver.

Lipoproteins contain a core of hydrophobic lipids (triglycerides and cholesteryl esters) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids. The plasma lipoproteins are divided into five major classes based on their relative densities (Fig. 18-1 and Table 18-1): chylomicrons, very low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Each lipoprotein class comprises a family of
particles that vary slightly in density, size, migration during electrophoresis, and protein composition. The density of a lipoprotein is determined by the amount of lipid and protein per particle. HDL is the smallest and most dense lipoprotein, whereas chylomicrons and VLDL are the largest and least dense lipoprotein particles. Most triglyceride is transported in chylomicrons or VLDL, and most cholesterol is carried as cholesteryl esters in LDL and HDL.

The apolipoproteins are required for the assembly and structure of lipoproteins (Table 18-2). Apolipoproteins also serve to activate enzymes important in lipoprotein metabolism and to mediate the binding of lipoproteins to cell-surface receptors. ApoA-I, which is synthesized in the liver and intestine, is found on virtually all HDL particles. ApoA-II is the second most abundant HDL apolipoprotein and is found on approximately two-thirds of all HDL particles. ApoB is the major structural protein of chylomicrons, VLDL, IDL, and LDL; one molecule of apoB, either apoB-48 (chylomicrons) or apoB-100 (VLDL, IDL, or LDL), is present on each lipoprotein particle. The human liver makes only apoB-100, and the intestine makes apoB-48, which is derived from the same gene by mRNA editing. ApoE is present in multiple copies on chylomicrons, VLDL, and IDL and plays a critical role in the metabolism and clearance of triglyceride-rich particles. Three apolipoproteins of the C-series (apoC-I, -II, and -III) also participate in the metabolism of triglyceride-rich lipoproteins. The other apolipoproteins are listed in Table 18-2.

**TRANSPORT OF DIETARY LIPIDS (EXOGENOUS PATHWAY)**

The exogenous pathway of lipoprotein metabolism permits efficient transport of dietary lipids (Fig. 18-2). Dietary triglycerides are hydrolyzed by pancreatic lipases within the intestinal lumen and are emulsified with bile acids to form micelles. Dietary cholesterol and retinol are esterified (by the addition of a fatty acid) in the enterocyte to form cholesteryl esters and

**FIGURE 18-1**
The density and size distribution of the major classes of lipoprotein particles. Lipoproteins are classified by density and size, which are inversely related. VLDL, very low density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; HDL, high-density lipoproteins.

**TABLE 18-1**

<table>
<thead>
<tr>
<th>LIPOPROTEIN</th>
<th>DENSITY, G/ML</th>
<th>SIZE NM</th>
<th>ELECTROPHORETIC MOBILITY</th>
<th>APOLIPOPROTEINS</th>
<th>OTHER CONSTITUENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>0.930</td>
<td>75–1200</td>
<td>Origin</td>
<td>ApoB-48</td>
<td>A-I, A-IV, C-I, C-II, C-III Retinyl esters</td>
</tr>
<tr>
<td>Chylomicron remnants</td>
<td>0.930–1.006</td>
<td>30–80</td>
<td>Slow pre-β</td>
<td>ApoB-48</td>
<td>E, A-I, A-IV, C-I, C-II, C-III Retinyl esters</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.906–1.006</td>
<td>30–80</td>
<td>Pre-β</td>
<td>ApoB-100</td>
<td>E, A-I, A-IV, E, C-I, C-II, C-III Vitamin E</td>
</tr>
<tr>
<td>IDL</td>
<td>1.006–1.019</td>
<td>30–80</td>
<td>Slow pre-β</td>
<td>ApoB-100</td>
<td>E, C-I, C-II, C-III Vitamin E</td>
</tr>
<tr>
<td>LDL</td>
<td>1.019–1.063</td>
<td>25–35</td>
<td>β</td>
<td>ApoB-100</td>
<td>Vitamin E</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>1.050–1.120</td>
<td>25</td>
<td>Pre-β</td>
<td>ApoB-100</td>
<td>Apo(a)</td>
</tr>
</tbody>
</table>

*All of the lipoprotein classes contain phospholipids, esterified and unesterified cholesterol, and triglycerides to varying degrees.

The density of the particle is determined by ultracentrifugation.

The size of the particle is measured using gel electrophoresis.

The electrophoretic mobility of the particle on agarose gel electrophoresis reflects the size and surface charge of the particle, with β being the position of LDL and α the position of HDL.

**Note:** VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein A; LCAT, lecithin-cholesterol acyltransferase; CETP, cholesteryl ester transfer protein.
retinyl esters, respectively. Longer-chain fatty acids (>12 carbons) are incorporated into triglycerides and packaged with apoB-48, cholesteryl esters, retinyl esters, phospholipids, and cholesterol to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered directly to the systemic circulation, where they are extensively processed by peripheral tissues before reaching the liver. The particles encounter lipoprotein lipase (LPL), which is anchored to proteoglycans that decorate the capillary endothelial surfaces of adipose tissue, heart, and skeletal muscle (Fig. 18-2). The triglycerides of chylomicrons are hydrolyzed by LPL, and free fatty acids are released; apoC-II, which is transferred to circulating chylomicrons, acts as a cofactor for LPL in this reaction. The released free fatty acids are taken up by adjacent myocytes or adipocytes and either oxidized or reesterified and stored as triglyceride. Some free fatty acids bind albumin and are transported to other tissues, especially the liver. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids (cholesterol and phospholipids) on the particle surface are transferred to HDL. The resultant smaller, more cholesterol ester–rich particles are referred to as chylomicron remnants. The remnant particles are rapidly removed from the circulation by the liver in a process that requires apoE. Consequently, few, if any, chylomicrons are present in the blood after a 12-h fast, except in individuals with disorders of chylomicron metabolism.

### TRANSPORT OF HEPATIC LIPIDS (ENDOGENOUS PATHWAY)

The endogenous pathway of lipoprotein metabolism refers to the hepatic secretion and metabolism of VLDL to IDL and LDL (Fig. 18-2). VLDL particles resemble chylomicrons in protein composition but contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to triglyceride (~1 mg of cholesterol for every 5 mg of triglyceride). The triglycerides of VLDL are derived predominantly from the esterification of long-chain fatty acids. The packaging of hepatic triglycerides with the other major components of the nascent VLDL particle (apoB-100, cholesteryl esters, phospholipids, and vitamin E) requires the action of the enzyme microsomal transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series. The triglycerides of VLDL are hydrolyzed by LPL, especially in muscle and adipose tissue. As VLDL remnants undergo further hydrolysis, they continue to shrink in size and become

---

**TABLE 18-2**

<table>
<thead>
<tr>
<th>APOLIPOPROTEIN</th>
<th>PRIMARY SOURCE</th>
<th>LIPOPROTEIN ASSOCIATION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>Intestine, liver</td>
<td>HDL, chylomicrons</td>
<td>Structural protein for HDL, activates LCAT</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>Liver</td>
<td>HDL, chylomicrons</td>
<td>Structural protein for HDL</td>
</tr>
<tr>
<td>ApoA-IV</td>
<td>Intestine</td>
<td>HDL, chylomicrons</td>
<td>Unknown</td>
</tr>
<tr>
<td>ApoA-V</td>
<td>Liver</td>
<td>VLDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>ApoB-48</td>
<td>Intestine</td>
<td>Chylomicrons</td>
<td>Structural protein for chylomicrons</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>Liver</td>
<td>VLDL, IDL, LDL, LP(a)</td>
<td>Structural protein for VLDL, LDL, IDL, LP(a); ligand for binding to LDL, receptor</td>
</tr>
<tr>
<td>ApoC-I</td>
<td>Liver</td>
<td>Chylomicrons VLDL, HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>ApoC-II</td>
<td>Liver</td>
<td>Chylomicrons VLDL, HDL</td>
<td>Cofactor for LPL</td>
</tr>
<tr>
<td>ApoC-III</td>
<td>Liver</td>
<td>Chylomicrons VLDL, HDL</td>
<td>Inhibits lipoprotein binding to receptors</td>
</tr>
<tr>
<td>ApoD</td>
<td>Spleen, brain, testes, adrenals</td>
<td>HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>ApoE</td>
<td>Liver</td>
<td>Chylomicron remnants, IDL, HDL</td>
<td>Ligand for binding to LDL receptor</td>
</tr>
<tr>
<td>ApoH</td>
<td>Liver</td>
<td>Chylomicrons VLDL, LDL, HDL</td>
<td>B2 glycoprotein I</td>
</tr>
<tr>
<td>ApoJ</td>
<td>Liver</td>
<td>HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>ApoL</td>
<td>Unknown</td>
<td>HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>Liver</td>
<td>Lp(a)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Note:** HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; LPL, lipoprotein lipase.
IDL, which contain similar amounts of cholesterol and triglyceride. The liver removes ~40 to 60% of VLDL remnants and IDL by LDL receptor–mediated endocytosis via binding to apoE. The remainder of IDL is remodeled by hepatic lipase (HL) to form LDL; during this process, most of the triglyceride in the particle is hydrolyzed and all apolipoproteins except apoB-100 are transferred to other lipoproteins. The cholesterol in LDL accounts for ~70% of the plasma cholesterol in most individuals. Approximately 70% of circulating LDLs are cleared by LDL receptor–mediated endocytosis in the liver. Lipoprotein(a) [Lp(a)] is a lipoprotein similar to LDL in lipid and protein composition, but it contains an additional protein called apolipoprotein(a) [apo(a)]. Apo(a) is synthesized in the liver and is attached to apoB-100 by a disulfide linkage. The mechanism by which Lp(a) is removed from the circulation is not known.

HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT

All nucleated cells synthesize cholesterol but only hepatocytes can efficiently metabolize and excrete cholesterol from the body. The predominant route of cholesterol elimination is by excretion into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported from the plasma membranes of peripheral cells to the liver by an HDL-mediated process termed reverse cholesterol transport (Fig. 18-3).

Nascent HDL particles are synthesized by the intestine and the liver. The newly formed discoidal HDL particles contain apoA-I and phospholipids (mainly lecithin) but rapidly acquire unesterified cholesterol and additional phospholipids from peripheral tissues via transport by the membrane protein ATP-binding...
cassette protein A1 (ABCA1). Once incorporated in the HDL particle, cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT), a plasma enzyme associated with HDL. As HDL acquires more cholesterol ester it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDL during lipolysis.

HDL cholesterol is transported to hepatocytes by both an indirect and a direct pathway. HDL cholesteryl ester is transferred to apoB-containing lipoproteins in exchange for triglyceride by the cholesteryl ester transfer protein (CETP). The cholesteryl esters are then removed from the circulation by LDL receptor-mediated endocytosis. HDL cholesterol can also be taken up directly by hepatocytes via the scavenger receptor class B1 (SR-B1), a cell-surface receptor that mediates the selective transfer of lipids to cells.

HDL particles undergo extensive remodeling within the plasma compartment as they transfer lipids and proteins to lipoproteins and cells. For example, after CETP-mediated lipid exchange, the triglyceride-enriched HDL becomes a substrate for HL, which hydrolyzes the triglycerides and phospholipids to generate smaller HDL particles.

**FIGURE 18-3**

**HDL metabolism and reverse cholesterol transport.** This pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDL. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by LCAT, forming mature HDL. HDL cholesterol can be selectively taken up by the liver via SR-B1. Alternatively, HDL cholesteryl ester can be transferred by CETP from HDL to VLDL and chylomicrons, which can then be taken up by the liver. LCAT, lecithin-cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; VLDL, very low density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; HDL, high-density lipoproteins; LDLR, low-density lipoprotein receptor; TG, triglycerides; SR-B1, scavenger receptor class B1.

**DISORDERS OF LIPOPROTEIN METABOLISM**

The identification and characterization of genes responsible for the genetic forms of hyperlipidemia have provided important molecular insight into the critical roles of apolipoproteins, enzymes, and receptors in lipid metabolism.

**PRIMARY DISORDERS OF ApoB-CONTAINING LIPOPROTEIN BIOSYNTHESIS CAUSING LOW PLASMA CHOLESTEROL LEVELS (KNOWN ETIOLOGY)**

The synthesis and secretion of apoB-containing lipoproteins in the enterocytes of the proximal small bowel and in the hepatocytes of the liver involve a complex series of events that coordinate the coupling of various lipids with apoB-48 and apoB-100, respectively.

**Abetalipoproteinemia**

Abetalipoproteinemia is a rare autosomal recessive disease caused by mutations in the gene encoding MTP, which transfers lipids to nascent chylomicrons.
and VLDL in the intestine and liver, respectively. Plasma cholesterol and triglyceride levels are extremely low in this disorder, and no chylomicrons, VLDL, LDL, or apoB are detectable. The parents of patients with abetalipoproteinemia (who are obligate heterozygotes) have normal plasma lipid and apoB levels. Abetalipoproteinemia usually presents in early childhood with diarrhea and failure to thrive and is characterized clinically by fat malabsorption, spinocerebellar degeneration, pigmented retinopathy, and acanthocytosis. The initial neurologic manifestations are loss of deep-tendon reflexes, followed by decreased distal lower extremity vibratory and proprioceptive sense, dysmetria, ataxia, and the development of a spastic gait, often by the third or fourth decade. Patients with abetalipoproteinemia also develop a progressive pigmented retinopathy presenting with decreased night and color vision, followed by reductions in daytime visual acuity and ultimately progressing to near blindness. The presence of spinocerebellar degeneration and pigmented retinopathy in this disease has resulted in misdiagnosis of Friedreich’s ataxia. Rarely, patients with abetalipoproteinemia develop a cardiomyopathy with associated life-threatening arrhythmias.

Most clinical manifestations of abetalipoproteinemia result from defects in the absorption and transport of fat-soluble vitamins. Vitamin E and retinyl esters are normally transported from enterocytes to the liver by chylomicrons, and vitamin E is dependent on VLDL for transport out of the liver and into the circulation. Patients with abetalipoproteinemia are markedly deficient in vitamin E and are also mildly to moderately deficient in vitamin A and vitamin K. Treatment of abetalipoproteinemia consists of a low-fat, high-caloric, vitamin-enriched diet accompanied by large supplemental doses of vitamin E. It is imperative for treatment to be initiated as soon as possible to obviate the development of neurologic sequelae.

**Familial Hypobetalipoproteinemia**

Familial homozygous hypobetalipoproteinemia has a clinical picture similar to abetalipoproteinemia but is autosomal codominant in inheritance pattern. The disease can be differentiated from abetalipoproteinemia since the parents of the probands with this disorder have levels of plasma LDL-C and apoB that are less than half of the normal levels. Mutations in the gene encoding apoB-100 that interfere with protein synthesis are common causes of this disorder. These patients, like those with abetalipoproteinemia, should be referred to specialized centers for confirmation of the diagnosis and appropriate therapy.

**PRIMARY DISORDERS OF ApoB-CONTAINING LIPOPROTEIN CATABOLISM CAUSING ELEVATED PLASMA CHOLESTEROL LEVELS (KNOWN ETIOLOGY)**

Single-gene defects can result in the accumulation of specific classes of lipoprotein particles. Mutations in genes encoding key proteins in the metabolism and clearance of apoB-containing lipoproteins cause type I (chylomicronemia), type II (elevations in LDL) and type III (elevations in IDL) hyperlipoproteinemias (Table 18-3).

**Lipoprotein Lipase and ApoC-II Deficiency (Familial Chylomicronemia Syndrome; Type I Hyperlipoproteinemia)**

LPL is required for the hydrolysis of triglycerides in chylomicrons and VLDL. ApoC-II is a cofactor for LPL (Fig. 18-2). Genetic deficiency of either LPL or apoC-II results in impaired lipolysis and profound elevations in plasma chylomicrons. These patients also have elevations in plasma VLDL, but chylomicronemia predominates. Normally chylomicrons are delipidated and removed from the circulation within 12 h of the last meal, but in LPL-deficient patients, the triglyceride-rich chylomicrons persist in the circulation for days. The fasting plasma is turbid, and if left at 4°C for a few hours, the chylomicrons float to the top and form a creamy supernatant. In these disorders, called familial chylomicronemia syndrome, fasting triglyceride levels are almost invariably >11.3 μmol/L (1000 mg/dL). Fasting cholesterol levels are also usually elevated, but to a much less severe degree.

LPL deficiency is autosomal recessive and has a population frequency of ~1 in 1 million. ApoC-II deficiency is also recessive in inheritance pattern and is even less common than LPL deficiency. Multiple mutations in the LPL and apoC-II genes cause these diseases. Obligate LPL heterozygotes have normal or mild to moderate elevations in plasma triglyceride levels, whereas individuals heterozygous for mutation in apoC-II are not hypertriglyceridemic.

Both LPL and apoC-II deficiency usually present in childhood with recurrent episodes of severe abdominal pain caused by acute pancreatitis. On fundoscopic examination the retinal blood vessels are opalescent (lipemia retinalis). Eruptive xanthomas, which are small yellowish-white papules, often appear in clusters on the back, buttocks, and extensor surfaces of the arms and legs. These typically painless skin lesions may become pruritic as they regress. Hepatosplenomegaly results from the uptake of circulating chylomicrons by reticuloendothelial cells in the liver and spleen. For reasons unknown, some patients with persistent and pronounced chylomicronemia never develop pancreatitis, eruptive xanthomas, or hepatosplenomegaly. Premature...
ASCVD has not been consistently demonstrated to be a feature of familial chylomicronemia syndromes. The diagnoses of LPL and apoC-II deficiency are established enzymatically by assaying triglyceride lipolytic activity in post-heparin plasma. Blood is sampled after an intravenous heparin injection to release the endothelial-bound lipases. LPL activity is profoundly reduced in both LPL and apoC-II deficiency; in patients with apoC-II deficiency, the addition of normal pre-heparin plasma (a source of apoC-II) normalizes LPL activity, but this correction does not occur in patients with LPL deficiency.

The major therapeutic intervention in familial chylomicronemia syndromes is dietary fat restriction (to as little as 15 g/d) with fat-soluble vitamin supplementation. Consultation with a registered dietician familiar with this disorder is essential. Caloric supplementation with medium-chain triglycerides, which are absorbed directly into the portal circulation, can be useful but may be associated with hepatic fibrosis if used for prolonged periods. If dietary fat restriction alone is not successful in resolving the chylomicronemia, fish oils have been effective in some patients. In patients with apoC-II deficiency, apoC-II can be provided by infusing fresh-frozen plasma to resolve the chylomicronemia. Management of patients with familial chylomicronemia syndrome is particularly challenging during pregnancy when VLDL production is increased. Plasmapheresis may be required if pancreatitis develops and the chylomicronemia is not responsive to diet therapy.

**Hepatic Lipase Deficiency**

HL is a member of the same gene family as LPL and hydrolyzes triglycerides and phospholipids in remnant lipoproteins and HDL. HL deficiency is a very rare autosomal recessive disorder characterized by elevated plasma cholesterol and triglycerides (mixed hyperlipidemia) due to the accumulation of lipoprotein remnants. HDL-C is normal or elevated. The diagnosis is confirmed by measuring HL activity in post-heparin plasma. Due to the small number of patients with HL deficiency, the association of this genetic defect with ASCVD is not known, but lipid-lowering therapy is recommended.

**Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)**

Like HL deficiency, familial dysbetalipoproteinemia (FDBL) (also known as type III hyperlipoproteinemia or familial broad β disease) is characterized by a mixed hyperlipidemia due to the accumulation of remnant lipoprotein particles. ApoE is present in multiple copies on

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**TABLE 18-3**

<table>
<thead>
<tr>
<th>GENETIC DISORDER</th>
<th>GENE DEFECT</th>
<th>LIPOPROTEINS ELEVATED</th>
<th>CLINICAL FINDINGS</th>
<th>GENETIC TRANSMISSION</th>
<th>ESTIMATED INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein lipase deficiency</td>
<td>LPL(LPL)</td>
<td>Chylomicrons</td>
<td>Eruptive xanthomas, hepatosplenomegaly pancraetitis</td>
<td>AR</td>
<td>1/1,000,000</td>
</tr>
<tr>
<td>Familial apolipoprotein C-II deficiency</td>
<td>ApoC-II (APOC2)</td>
<td>Chylomicrons</td>
<td>Eruptive xanthomas, hepatosplenomegaly pancraetitis</td>
<td>AR</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>Familial hepatic lipase deficiency</td>
<td>Hepatic lipase (LIPC)</td>
<td>VLDL remnants</td>
<td>Premature atherosclerosis</td>
<td>AR</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>ApoE(APOE)</td>
<td>Chylomicron and VLDL remnants</td>
<td>Palmar and tuberoeruptive xanthomas, CHD, PVD</td>
<td>AR/AD</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDL receptor (LDLR)</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AD</td>
<td>1/500</td>
</tr>
<tr>
<td>Familial defective apoB-100</td>
<td>ApoB-100 (APOB) (Arg950 → Gln)</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AD</td>
<td>1/1000</td>
</tr>
<tr>
<td>Autosomal recessive hypercholesterolemia</td>
<td>ARH (ARH)</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AR</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>Sitosterolemia</td>
<td>ABCG5 or ABCG8</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
<td>AR</td>
<td>&lt;1/1,000,000</td>
</tr>
</tbody>
</table>

**Note:** AR, autosomal recessive; AD, autosomal dominant; VLDL, very low density lipoprotein; CHD, coronary heart disease; PVD, peripheral vascular disease; LDL, low-density lipoprotein.
apoE2/2 genotype does not rule out the diagnosis of mozygosity for apoE2. However, absence of the apoE genotyping can be performed to confirm homozygosity for apoE2, either by elevated plasma LDL-C levels and increased coronary heart disease (CHD) risk, the apoE4 allele is not associated with FDBL. Patients with apoE4 have an increased incidence of late-onset Alzheimer disease. ApoE2 has a lower affinity for the LDL receptor. Therefore, chylomicron and VLDL remnants containing apoE2 are removed from plasma at a slower rate. Individuals who are homozygous for the E2 allele (the E2/E2 genotype) comprise the most common subset of patients with FDBL.

Approximately 1% of the general population are apoE2/E2 homozygotes but only a small minority of these individuals develop FDBL. In most cases an additional, identifiable factor precipitates the development of hyperlipoproteinemia. The most common precipitating factors are a high-caloric, high-fat diet, diabetes mellitus, obesity, hypothyroidism, renal disease, estrogen deficiency, alcohol use, or the presence of another genetic condition. The disease seldom presents in women before menopause. Two distinctive types of xanthomas are seen in FDBL patients: tuberoeruptive and palmar xanthomas. Tuberoeruptive xanthomas begin as clusters of small papules on the elbows, knees, or buttocks and can grow to the size of small grapes. Palmar xanthoma (alternatively called xanthomata striata palmars) are orange-yellow discolorations of the creases in the palms. In FDBL, the plasma cholesterol and triglyceride are elevated to a relatively similar degree until the triglyceride levels reach ~5.6 mmol/L (~500 mg/dL), and then the triglycerides tend to be greater than cholesterol.

The traditional approach to diagnose this disorder is to use lipoprotein electrophoresis; in FDBL, the remnant lipoproteins accumulate in a broad β band. The preferred method to confirm the diagnosis of FDBL is to measure VLDL-C by ultracentrifugation and determine the ratio of VLDL-C to total plasma triglyceride; a ratio >0.30 is consistent with the diagnosis of FDBL. Protein methods (apoE phenotyping) or DNA-based methods (apoE genotyping) can be performed to confirm homozygosity for apoE2. However, absence of the apoE2/2 genotype does not rule out the diagnosis of FDBL, since other mutations in apoE can cause this condition.

Because FDBL is associated with increased risk of premature ASCVD, it should be treated aggressively. Other metabolic conditions that can worsen the hyperlipidemia (see above) should be actively treated. Patients with FDBL are typically very diet responsive and can respond dramatically to weight reduction and to low-cholesterol, low-fat diets. Alcohol intake should be curtailed. In postmenopausal women with FDBL, the dyslipidemia responds to estrogen-replacement therapy. HMG-CoA reductase inhibitors, fibrates, and niacin are all generally effective in the treatment of FDBL, and combination drug therapy is sometimes required.

**Familial Hypercholesterolemia**

FH is an autosomal codominant disorder characterized by elevated plasma LDL-C with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. FH is caused by >750 mutations in the LDL receptor gene and has a higher incidence in certain populations, such as Afrikaners, Christian Lebanese, and French Canadians, due to the founder effect. The elevated levels of LDL-C in FH are due to delayed catabolism of LDL and its precursor particles from the blood, resulting in increased rates of LDL production. There is a major gene dose effect, in that individuals with two mutated LDL receptor alleles (FH homozygotes) are much more affected than those with one mutant allele (FH heterozygotes).

Homozygous FH occurs in approximately 1 in 1 million persons worldwide. Patients with homozygous FH can be classified into one of two groups based on the amount of LDL receptor activity measured in their skin fibroblasts: those patients with <2% of normal LDL receptor activity (receptor negative) and those patients with 2 to 25% of normal LDL receptor activity (receptor defective). Most patients with homozygous FH present in childhood with cutaneous xanthomas on the hands, wrists, elbows, knees, heels, or buttocks. Arcus cornea is usually present and some patients have xanthelasmas. Total cholesterol levels are usually >12.93 mmol/L (500 mg/dL) and can be >25.86 mmol/L (1000 mg/dL). Accelerated atherosclerosis is a devastating complication of homozygous FH and can result in disability and death in childhood. Atherosclerosis often develops first in the aortic root and can cause aortic valve incompetence and valvular aortic valve stenosis and typically extends into the coronary ostia. Children with homozygous FH often develop symptomatic vascular disease before puberty, when symptoms can be atypical and sudden death is common. Untreated, receptor-negative patients with homozygous FH rarely survive beyond the second...
decade; patients with receptor-defective LDL receptor defects have a better prognosis but almost invariably develop clinically apparent atherosclerotic vascular disease by age 30, and often much sooner. Carotid and femoral disease develop later in life and are usually not clinically significant.

A careful family history should be taken, and plasma lipid levels should be measured in the parents and other first-degree relatives of patients with homozygous FH. The diagnosis can be confirmed by obtaining a skin biopsy and measuring LDL receptor activity in cultured skin fibroblasts or by quantifying the number of LDL receptors on the surfaces of lymphocytes using cell-sorting technology.

Combination therapy with an HMG-CoA reductase inhibitor and a bile acid sequestrant sometimes results in modest reductions in plasma LDL-C in the FH homozygote. Patients with homozygous FH invariably require additional lipid-lowering therapy. Since the liver is quantitatively the most important tissue for removing circulating LDL via the LDL receptor, liver transplantation is effective in decreasing plasma LDL-C levels in this disorder. Liver transplantation is, however, associated with substantial risks, including the requirement for long-term immunosuppression. The current treatment of choice for homozygous FH is LDL apheresis (a process where the LDL particles are selectively removed from the circulation), which can promote regression of xanthomas and may slow the progression of atherosclerosis. Initiation of LDL apheresis should be delayed until ~5 years of age except when evidence of atherosclerotic vascular disease is present.

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele and occurs in ~1 in 500 persons worldwide, making it one of the most common single-gene disorders. It is characterized by elevated plasma LDL-C [usually 5.17 to 10.34 μmol/L (200 to 400 mg/dL)] and normal triglyceride levels. Patients with heterozygous FH have hypercholesterolemia from birth, although the disease is often not detected until adulthood, usually due to the detection of hypercholesterolemia on routine screening, the appearance of tendon xanthomas, or the premature development of symptomatic coronary atherosclerotic disease. Since the disease is codominant in inheritance and has a high penetrance (>90%), one parent and ~50% of the patient’s siblings are usually hypercholesterolemic. The family history is frequently positive for premature ASCVD. FH patients inevitably require lipid-lowering drug therapy. HMG-CoA reductase inhibitors are especially effective in heterozygous FH, inducing upregulation of the normal LDL receptor allele in the liver. Many heterozygous FH patients can achieve desired LDL-C levels with HMG-CoA reductase inhibitor therapy alone, but combination drug therapy with the addition of a bile acid sequestrant or nicotinic acid is frequently required. Heterozygous FH patients who cannot be adequately controlled on combination drug therapy are candidates for LDL apheresis.

**Familial Defective ApoB-100**

Familial defective apoB-100 (FDB) is a dominantly inherited disorder that clinically resembles heterozygous FH. FDB occurs with a frequency of ~1 in 1000 in western populations. The disease is characterized by elevated plasma LDL-C levels with normal triglycerides, tendon xanthomas, and an increased incidence of premature ASCVD. FDB is caused by mutations in the LDL receptor–binding domain of apoB-100. Almost all patients with FDB have a substitution of glutamine for arginine at position 3500 in apoB-100, although other rarer mutations have been reported to cause this disease. As a consequence of the mutation in apoB-100, LDL binds the LDL receptor with reduced affinity and LDL is removed from the circulation at a reduced rate. Patients with FDB cannot be clinically distinguished from patients with heterozygous FH, although patients with FDB tend to have lower plasma LDL-C than FH heterozygotes. The apoB-100 gene mutation can be detected directly, but currently genetic diagnosis is not encouraged since the recommended management of FDB and heterozygous FH is identical.
Autosomal Recessive Hypercholesterolemia

Autosomal recessive hypercholesterolemia (ARH) is a rare disorder (except in Sardinia) due to mutations in a protein (ARH) involved in LDL receptor–mediated endocytosis in the liver. ARH clinically resembles homozygous FH and is characterized by hypercholesterolemia, tendon xanthomas, and premature coronary artery disease. The hypercholesterolemia tends to be intermediate between the levels seen in FH homozygotes and FH heterozygotes. LDL receptor function in cultured fibroblasts is normal or only modestly reduced in ARH, whereas LDL receptor function in lymphocytes and the liver is negligible. Unlike FH homozygotes, the hyperlipidemia responds partially to treatment with HMG-CoA reductase inhibitors, but these patients usually require LDL apheresis to lower plasma LDL-C to recommended levels.

Wolman Disease and Cholesteryl Ester Storage Disease

Wolman disease is an autosomal recessive disorder caused by complete deficiency of lysosomal acid lipase. After LDL is taken up from the cell surface by LDL receptor–mediated endocytosis, it is delivered from endosomes to lysosomes. In the acidic environment of the endosome, the particle dissociates from the receptor, which recycles to the cell surface. In the lysosome, apoB-100 is degraded and the cholesteryl esters and triglycerides of LDL are hydrolyzed by lysosomal acid lipase. Patients with Wolman disease fail to hydrolyze the neutral lipids, resulting in their accumulation within cells. The disease presents within the first weeks of life with hepatosplenomegaly, steatorrhea, adrenal calcification, and failure to thrive. The disease is usually fatal within the first year of life and can be diagnosed by measuring acid lipase activity in fibroblasts or liver tissue biopsy specimens. Cholesteryl ester storage disease is a less severe form of the same genetic disorder in which there is low, but detectable, acid lipase activity. Patients with this disorder sometimes present in childhood with hepatomegaly and mixed hyperlipidemia, due to elevations in the levels of plasma LDL and VLDL. Other patients present later in life with hepatic fibrosis, portal hypertension, or with premature atherosclerosis.

Sitosterolemia

Sitosterolemia is a rare autosomal recessive disease caused by mutations in one of two members of the adenosine triphosphate (ATP)–binding cassette transporter family, ABCG5 and ABCG8. These genes are expressed in the intestine and liver, where they form a functional complex to limit intestinal absorption and promote biliary excretion of plant- and animal-derived neutral sterols. In normal individuals, <5% of dietary plant sterols, of which sitosterol is the most plentiful, are absorbed by the proximal small intestine and delivered to the liver. Plant sterols in the liver are preferentially secreted into the bile, and plasma plant sterol levels are normally very low. In sitosterolemia, the intestinal absorption of plant sterols is increased and biliary excretion of the sterols is reduced, resulting in increased plasma levels of sitosterol and other plant sterols. The trafficking of cholesterol is also impaired. Patients with sitosterolemia can have either normal or elevated plasma levels of cholesterol. Irrespective of the plasma cholesterol level, these patients develop cutaneous and tendon xanthomas as well as premature atherosclerosis. Episodes of hemolysis, presumably secondary to the incorporation of plant sterols into the red blood cell membrane, are a distinctive clinical feature of this disease. The hypercholesterolemia in patients with sitosterolemia is unusually responsive to reductions in dietary cholesterol content. Sitosterolemia should be suspected when the plasma cholesterol level falls by >40% on a low-cholesterol diet (without associated weight loss).

Sitosterolemia is confirmed by demonstrating an elevated plasma sitosterol level. The hypercholesterolemia does not respond to HMG-CoA reductase inhibitors, but bile acid sequestrants and cholesterol–absorption inhibitors, such as ezetimibe, are effective in reducing plasma sterol levels in these patients.

PRIMARY DISORDERS OF ApoB-CONTAINING LIPOPROTEIN METABOLISM (UNKNOWN ETIOLOGY)

A large proportion of patients with elevated levels of apoB–containing lipoproteins have disorders in which the molecular defect has not been defined, largely because multiple other genetic and nongenetic factors contribute to the hyperlipidemia.

Familial Hypertriglyceridemia

Familial hypertriglyceridemia (FHTG) is a relatively common (1 in 500) autosomal dominant disorder of unknown etiology characterized by moderately elevated plasma triglycerides accompanied by more modest elevations in cholesterol. VLDL is the major class of lipoproteins elevated in this disorder, which is often referred to as type IV hyperlipoproteinemia (Frederickson classification, Table 18-4). The elevated plasma VLDL is due to increased VLDL production, impaired VLDL catabolism, or a combination of the two. Some patients with FHTG have a more severe form of hyperlipidemia in which both VLDL and chylomicrons are elevated (type V hyperlipidemia), as these two classes of lipopro-
teins compete for the same lipolytic pathway. Increased intake of simple carbohydrates, obesity, insulin resistance, alcohol use, or estrogen treatment, all of which increase VLDL synthesis, can precipitate the development of chylomicronemia. FHTG does not appear to be associated with increased risk of ASCVD in many families.

The diagnosis of FHTG is suggested by the triad of elevated plasma triglycerides [2.8 to 11.3 mmol/L (250 to 1000 mg/dL)], normal or only mildly increased cholesterol levels [<6.5 mmol/L (<250 mg/dL)], and reduced plasma HDL-C. Plasma LDL-C is generally not increased and is often reduced due to defective metabolism of the triglyceride-rich particles. The identification of other first-degree relatives with hypertriglyceridemia is useful in making the diagnosis. FDBL and FCHL should also be ruled out as these two conditions are associated with a significantly increased risk of ASCVD. The plasma apoB levels and the ratio of plasma cholesterol to triglyceride tend to be lower in FHTG than in either FDBL or FCHL.

It is important to exclude secondary causes of the hypertriglyceridemia before making the diagnosis of FHTG. Lipid-lowering drug therapy can frequently be avoided with appropriate dietary and lifestyle changes. Patients with plasma triglyceride levels >4.5 to 6.8 mmol/L (>400 to 600 mg/dL), after a trial of diet and exercise, should be considered for drug therapy to avoid the development of chylomicronemia and pancreatitis. A fibrate is a reasonable first-line drug for FHTG, and niacin can also be considered in this condition.

**Familial Combined Hyperlipidemia**

The molecular etiology of FCHL is unknown but is likely to involve defects in several different genes. FCHL is the most common primary lipid disorder, occurring in ~1 in 200 persons. Approximately 20% of patients who develop CHD before age 60 have FCHL.

FCHL is characterized by moderate elevation of plasma triglycerides and cholesterol and reduced plasma HDL-C. The disease is autosomal dominant, and affected family members typically have one of three possible phenotypes: (1) elevated plasma LDL-C, (2) elevated plasma triglycerides and VLDL-C, or (3) elevated plasma LDL-C and VLDL-C. A classic feature of FCHL is that the lipoprotein phenotype can switch among these phenotypes. FCHL can manifest in childhood but is sometimes not fully expressed until adulthood. Visceral obesity, glucose intolerance, insulin resistance, hypertension, and hyperuricemia are often present. These patients do not develop xanthomas.

Patients with FCHL almost always have significantly elevated plasma apoB. The levels of apoB are dispropor-

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**TABLE 18-4**  
**FREDERICKSON CLASSIFICATION OF HYPERLIPOPROTEINEMIAS**

<table>
<thead>
<tr>
<th>PHENOTYPE</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein elevated</td>
<td>Chylomicrons</td>
<td>LDL</td>
<td>LDL and VLDL</td>
<td>Chylomicron and VLDL remnants</td>
<td>VLDL</td>
<td>Chylomicron and VLDL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>++++</td>
<td>--</td>
<td>++</td>
<td>++ to +++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>+ to ++</td>
<td>+++</td>
<td>++ to +++</td>
<td>++ to +++</td>
<td>-- to +</td>
<td>++ to +++</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma appearance</td>
<td>Lactescent</td>
<td>Clear</td>
<td>Clear</td>
<td>Turbid</td>
<td>Turbid</td>
<td>Lactescent</td>
</tr>
<tr>
<td>Xanthomas</td>
<td>Eruptive</td>
<td>Tendon, tuberous</td>
<td>None</td>
<td>Palmar, tuberous</td>
<td>None</td>
<td>Eruptive</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Peripheral atherosclerosis</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Molecular defects</td>
<td>LPL and apoC-II</td>
<td>LDL receptor and apoB-100</td>
<td>Unknown</td>
<td>ApoE</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Genetic nomenclature</td>
<td>FCS</td>
<td>FH, FDB</td>
<td>FCHL</td>
<td>FDBL</td>
<td>FHTG</td>
<td>FHTG</td>
</tr>
</tbody>
</table>

**Note:** LPL, lipoprotein lipase; apo, apolipoprotein; FCS, familial chylomicronemia syndrome; FH, familial hypercholesterolemia; FDB, familial defective apoB; FCHL, familial combined hyperlipidemia; FDBL, familial dysbetalipoproteinemia; FHTG, familial hypertriglyceridemia.

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Polygenic Hypercholesterolemia

Polygenic hypercholesterolemia is characterized by hypercholesterolemia with a normal plasma triglyceride in the absence of secondary causes of hypercholesterolemia. Plasma LDL-C levels are not as elevated as they are in FH and FDB. Family studies are useful to differentiate polygenic hypercholesterolemia from the single-gene disorders described above; half of the first-degree relatives of patients with FH and FDB are hypercholesterolemic, whereas <10% of first-degree relatives of patients with polygenic hypercholesterolemia are hypercholesterolemic. Treatment of polygenic hypercholesterolemia is identical to that of other forms of hypercholesterolemia.

**GENETIC DISORDERS OF HDL METABOLISM (KNOWN ETIOLOGY)**

Mutations in certain genes encoding critical proteins in HDL synthesis and catabolism cause marked variations in plasma HDL-C levels. Unlike the genetic forms of hypercholesterolemia, which are invariably associated with premature coronary atherosclerosis, genetic forms of hypoalphalipoproteinemia (low HDL-C) are not always associated with accelerated atherosclerosis. Whereas high plasma LDL-C is invariably associated with increased atherosclerosis, the risk associated with low plasma levels of HDL-C depends on the underlying mechanism. Analysis of the genetic disorders of HDL metabolism has provided insights into the less well understood etiologic relationship between plasma HDL-C levels and atherosclerosis.

### ApoA-I Deficiency and ApoA-I Mutations

Complete genetic deficiency of apoA-I due to mutations in the apoA-I gene results in the virtual absence of HDL from the plasma. The genes encoding apoA-I, apoC-III, apoA-IV, and apoA-V are clustered together on chromosome 11, and some patients with complete absence of apoA-I have deletions that include more than one of these genes. Because apoA-I is required for LCAT function, plasma and tissue levels of free cholesterol are increased, resulting in the development of corneal opacities and planar xanthomas. Clinically apparent coronary atherosclerosis typically appears between the fourth and seventh decade in the apoA-I-deficient patient.

Although missense mutations in the apoA-I gene have been identified in selected patients with low plasma HDL [usually 0.39 to 0.78 mmol/L (15 to 30 mg/dL)], they are very rare causes of low HDL-C levels in the general population. Patients with apoA-I<sub>Minow</sub> have very low plasma levels of HDL due to the rapid catabolism of the apolipoprotein, but these patients do not have an increased risk of premature CHD. Other than corneal opacities, most individuals with low plasma HDL-C levels due to missense mutations in apoA-I have no clinical sequelae. A few specific mutations in apoA-I cause systemic amyloidosis, and the mutant apoA-I has been found as a component of the amyloid plaque.

### Tangier Disease

Tangier disease is a rare autosomal codominant form of low plasma HDL-C caused by mutations in the gene encoding ABCA1, a cellular transporter that facilitates efflux of unesterified cholesterol and phospholipids from cells to apoA-I (Fig. 18-3). ABCA1 plays a critical role in the generation and stabilization of the mature HDL particle. In its absence, HDL is rapidly cleared from the circulation. Patients with Tangier disease have plasma HDL-C levels <0.13 mmol/L (<5 mg/dL) and extremely low circulating levels of apoA-I. The disease is associated with cholesterol accumulation in the reticuloendothelial system,
resulting in hepatosplenomegal and pathognomonic enlarged, grayish yellow or orange tonsils. An intermittent peripheral neuropathy (mononeuritis multiplex) or a spondylopathy-like neurologic disorder can also be seen in this disorder. Tangier disease is associated with premature atherosclerotic disease, but the risk is not as high as might be anticipated given the markedly decreased plasma HDL-C and apoA-I. Plasma LDL-C is also low and this may attenuate the atherosclerotic risk. Obligate heterozygotes for ABCA1 mutations have moderately reduced plasma HDL-C levels and are also at increased risk of premature CHD.

**LCAT Deficiency**

LCAT deficiency is a rare disorder caused by mutations in lecithin-cholesterol acyltransferase (Fig. 18-3). LCAT is synthesized in the liver and secreted into the plasma, where it circulates associated with lipoproteins. Because the enzyme mediates the esterification of cholesterol, the proportion of free cholesterol in circulating lipoproteins is greatly increased (from ~25% to >70% of total plasma cholesterol). Lack of normal cholesterol esterification impairs the formation of mature HDL particles and leads to rapid catabolism of circulating lipoproteins.

CHD.

**Hypoalphalipoproteinemia**

The most common inherited cause of low plasma HDL-C is termed primary or familial hypoalphalipoproteinemia. Hypoalphalipoproteinemia is defined as a plasma HDL-C level below the 10th percentile in the setting of relatively normal cholesterol and triglyceride levels, no apparent secondary causes of low plasma HDL-C, and no clinical signs of LCAT deficiency or Tangier disease. This syndrome is often referred to as “isolated low HDL.” A family history of low HDL-C facilitates the diagnosis of an inherited condition, which usually follows an autosomal dominant pattern. The metabolic etiology of this disease appears to be primarily accelerated catabolism of HDL and its apolipoproteins. Several kindreds with primary hypoalphalipoproteinemia have been described in association with an increased incidence of premature ASCVD.

**Familial Hyperalphalipoproteinemia**

Familial hyperalphalipoproteinemia has a dominant inheritance pattern. Plasma HDL-C is usually >2.07 mmol/L (80 mg/dL) in affected women and >1.81 mmol/L (70 mg/dL) in affected men. The genetic basis of primary hyperalphalipoproteinemia is not known, and the condition may be associated with decreased risk of CHD and increased longevity in some cases.

**SECONDARY DISORDERS OF LIPOPROTEIN METABOLISM**

Significant changes in plasma levels of lipoproteins are seen in a variety of diseases. It is critical that secondary causes of hyperlipidemias (Table 18-5) are considered prior to initiation of lipid-lowering therapy.

**Obesity**

Obesity is frequently, though not invariably, accompanied by hyperlipidemia. The increase in adipocyte mass and accompanying decrease in insulin sensitivity associated with obesity have multiple effects on lipid metabolism.
More free fatty acids are delivered from the expanded adipose tissue to the liver where they are re-esterified in hepatocytes to form triglycerides, which are packaged into VLDL for secretion into the circulation. High dietary intake of simple carbohydrates also drives hepatic production of VLDL, leading to increases in VLDL and/or LDL in some obese individuals. Plasma HDL-C tends to be low in obesity. Weight loss is often associated with a reduction of plasma apoB-containing lipoproteins and an increase of plasma HDL-C.

**Diabetes Mellitus**

Patients with type 1 diabetes mellitus are generally not hyperlipidemic if they are under good glycemic control. Diabetic ketoacidosis is frequently accompanied by hypertriglyceridermia due to increased hepatic influx of free fatty acids from adipose tissue. The hypertriglyceridermia responds dramatically to administration of insulin in the insulinopenic diabetic.

Patients with type 2 diabetes mellitus are usually dyslipidemic, even if under relatively good glycemic control. The high levels of insulin and insulin resistance associated with type 2 diabetes have multiple effects on fat metabolism: (1) a decrease in LPL activity resulting in reduced catabolism of chylomicrons and VLDL, (2) an increase in the release of free fatty acid from the adipose tissue, (3) an increase in fatty acid synthesis in the liver, and (4) an increase in hepatic VLDL production. Patients with type 2 diabetes mellitus have several lipid abnormalities, including elevated plasma triglycerides (due to increased VLDL and lipoprotein remnants), elevated dense LDL, and decreased HDL-C. In some diabetic patients, especially those with a genetic defect in lipid metabolism, the triglycerides can be extremely elevated. Elevated plasma LDL-C levels are usually not a feature of diabetes mellitus and suggest the presence of an underlying lipoprotein abnormality or may indicate the development of diabetic nephropathy. Patients with lipodystrophy, who have profound insulin resistance, have markedly elevated VLDL and chylomicrons.

**Thyroid Disease**

Hypothyroidism is associated with elevated plasma LDL-C due primarily to a reduction in hepatic LDL receptor function and delayed clearance of LDL. Conversely, plasma LDL-C is often reduced in the hyperthyroid patient. Hypothyroid patients may have increased circulating IDL, and some are mildly hypertriglyceridermic [<3.4 μmol/L (<300 mg/dL)]. Because hypothyroidism is easily overlooked, all patients presenting

### TABLE 18-5

<table>
<thead>
<tr>
<th>SECONDARY FORMS OF HYPERLIPIDEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL</strong></td>
</tr>
<tr>
<td>ELEVATED</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Cholestasis</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Hepatoma</td>
</tr>
<tr>
<td>Drugs: thiazides, cyclosporine, tegretol</td>
</tr>
</tbody>
</table>

**Note:** LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low density lipoprotein; IDL, intermediate-density lipoprotein; LP(a), lipoprotein A; DM, diabetes mellitus.
with elevated plasma LDL-C or IDL should be screened for hypothyroidism. Thyroid replacement therapy usually ameliorates the hypercholesterolemia.

**Renal Disorders**

Nephrotic syndrome is associated with hyperlipoproteinemia, which is usually mixed but can manifest as hypercholesterolemia or hypertriglyceridemia alone. The hyperlipidemia of nephrotic syndrome appears to be due to a combination of increased hepatic production and decreased clearance of VLDL, with increased LDL production. Effective treatment of the underlying renal disease normalizes the lipid profile, but most patients with chronic nephrotic syndrome require lipid-lowering drug therapy.

ESRD is often associated with mild hypertriglyceridemia [<3.34 mmol/L (<300 mg/dL)] due to the accumulation of VLDL and remnant lipoproteins in the circulation. Triglyceride lipolysis and remnant clearance are both reduced in patients with renal failure. Because the risk of ASCVD is increased in hyperlipidemic patients with ESRD, they should be treated aggressively with lipid-lowering agents.

Patients with renal transplants are usually hyperlipidemic due to immunosuppression drugs (cyclosporine and glucocorticoids); they present a difficult management problem as HMG-CoA reductase inhibitors must be used cautiously in these patients.

**Liver Disorders**

Because the liver is the principal site of formation and clearance of lipoproteins, it is not surprising that liver diseases can profoundly affect plasma lipid levels in a variety of ways. Hepatitis due to infection, drugs, or alcohol is often associated with increased VLDL synthesis and mild to moderate hypertriglyceridemia. Severe hepatitis and liver failure are associated with dramatic reductions in plasma cholesterol and triglycerides due to reduced lipoprotein biosynthetic capacity. Cholestasis is associated with hypercholesterolemia, which sometimes can be very severe. The major pathway by which cholesterol is excreted is via secretion into bile, either directly or after conversion to bile acids. Cholestasis blocks this critical excretory pathway. In cholestasis, free cholesterol coupled with phospholipids are secreted into the plasma as constituents of a lamellar particle called Lp(X). These particles can deposit in skin folds, producing lesions resembling those seen in patients with FDBL (xanthomata strata palmatis). Planar and eruptive xanthomas can also be seen in patients with cholestasis.

**Alcohol**

Regular alcohol consumption has a variable effect on plasma lipid levels. The most common effect of alcohol is to increase plasma triglyceride levels. Alcohol consumption stimulates hepatic secretion of VLDL, possibly by inhibiting the hepatic oxidation of free fatty acids, which then promote hepatic triglyceride synthesis and VLDL secretion. The usual lipoprotein pattern seen with alcohol consumption is type IV (increased VLDL), but persons with an underlying primary lipid disorder may develop severe hypertriglyceridemia (type V) if they drink alcohol. Regular alcohol use is also associated with a mild to moderate increase in plasma levels of HDL-C.

**Estrogen**

Estrogen administration is associated with increased VLDL and HDL synthesis resulting in elevated plasma triglycerides and HDL-C. This lipoprotein pattern is distinctive since the levels of plasma triglyceride and HDL-C are typically inversely related. Estrogen treatment may convert a person with type IV to type V hyperlipidemia. Plasma triglyceride levels should be monitored when birth control pills or estrogen replacement therapy is initiated. Use of low-dose estrogen preparations or the estrogen patch can minimize the effect of exogenous estrogen on lipids.

**Glycogen Storage Diseases**

Other rarer causes of secondary hyperlipidemias include glycogen storage diseases such as von Gierke’s disease, which is caused by mutations in glucose-6-phosphatase. The inability to mobilize hepatic glucose during fasting results in hypoinsulinemia and increased release of free fatty acids from adipose tissue. Hepatic fatty acids synthesis is also increased, resulting in fat accumulation in the liver and increased VLDL secretion. The hyperlipidemia associated with this disease can be very severe but responds well to treatment of the underlying disorder.

**Cushing Syndrome**

Glucocorticoid excess is associated with increased VLDL synthesis and hypertriglyceridemia. Patients with Cushing syndrome can also have mild elevations in plasma LDL-C.

**Drugs**

Many drugs have a significant impact on lipid metabolism and can result in significant alterations in the lipoprotein profile (Table 18–5).

**SCREENING**

Guidelines for the screening and management of lipid disorders have been provided by an expert Adult Treatment Panel (ATP) convened by the National Cholesterol
Education Program (NCEP) of the National Heart Lung and Blood Institute. The NCEP ATPIII guidelines published in 2001 recommend that all adults over age 20 have plasma levels of cholesterol, triglyceride, LDL-C, and HDL-C measured after a 12-h overnight fast. In most clinical laboratories, the total cholesterol and triglycerides in the plasma are measured enzymatically and then the cholesterol in the supernatant is measured after precipitation of apoB-containing lipoproteins to determine the HDL-C. The LDL-C is estimated using the following equation:

$$\text{LDL-C} = \frac{\text{total cholesterol}}{1.005} - \frac{(\text{triglycerides}/5) - \text{HDL-C}}{1.002}$$

The VLDL-C is estimated by dividing the plasma triglyceride by 5, reflecting the ratio of cholesterol to triglyceride in VLDL particles. This formula is reasonably accurate if test results are obtained on fasting plasma and if the triglyceride level is less than 4.0 mmol/L (350 mg/dL). The accurate determination of LDL-C levels in patients with triglyceride levels greater than this requires application of ultracentrifugation techniques (beta quantification), although direct assays for LDL-C are also available in some laboratories.

**Nonpharmacologic Treatment**

**DIET**

Dietary modification is an important component in the management of hyperlipidemia. In the hypercholesterolemic patient, dietary saturated fat and cholesterol should be restricted. For patients who are hypertriglyceridemic, the intake of simple sugars should also be curtailed. For severe hypertriglyceridemia (>11.3 mmol/L (>1000 mg/dL)), restriction of total fat intake is critical. The most widely used diet to lower the LDL-C level is the “Step 1 diet” developed by the American Heart Association. Most patients have a relatively modest (<10%) decrease in plasma levels of LDL-C on a step I diet in the absence of any associated weight loss. Almost all persons experience a decrease in plasma HDL-C levels with a reduction in the amount of total and saturated fat in their diet.

**FOODS AND ADDITIVES**

Certain foods and dietary additives are associated with modest reductions in plasma cholesterol levels. Plant stanol and sterol esters are available in a variety of foods such as spreads, salad dressings, and snack bars. They interfere with cholesterol absorption and reduce plasma LDL-C levels by 10 to 15% when taken three times per day. The addition to the diet of psyllium, soy protein, or Chinese red yeast rice (which contains lovastatin) can have modest cholesterol-lowering effects. Other herbal approaches such as guggulipid require further study to assess their effectiveness.

**WEIGHT LOSS AND EXERCISE**

The treatment of obesity, if present, can have a favorable impact on plasma lipid levels and should be actively encouraged. Plasma triglyceride and LDL-C levels tend to fall and HDL-C levels tend to increase in obese persons who lose weight. Aerobic exercise has a very modest elevating effect on plasma levels of HDL-C in most individuals but has cardiovascular benefits that extend beyond the effects on plasma lipid levels.
LDL-C to PIII guidelines call for drug therapy to reduce "CHD risk equivalents." Current NCEP ATP-III guidelines call for drug therapy to reduce LDL-C to <2.6 mmol/L (<100 mg/dL) in patients with established CHD, other ASCVD (aortic aneurysm, peripheral vascular disease, or cerebrovascular disease), diabetes mellitus, or CHD risk equivalents. Based on these guidelines, most CHD and CHD risk-equivalent patients require cholesterol-lowering drug therapy. Moderate risk patients with two or more risk factors and a 10-year absolute risk of 10 to 20% should be treated to a goal LDL-C of <3.4 mmol/L (<130 mg/dL). All other individuals have a goal of LDL-C <4.1 mmol/L (<160 mg/dL), but not all persons are candidates for drug therapy to achieve this goal.

Persons with markedly elevated plasma LDL-C levels (>4.9 mmol/L (>190 mg/dL)] should be considered for drug therapy even if their 10-year absolute CHD risk is not particularly elevated. The decision to initiate drug treatment in individuals with plasma LDL-C levels between 3.4 and 4.9 mmol/L (130 and 190 mg/dL) can be difficult. Although it is desirable to avoid drug treatment in patients who are unlikely to develop CHD, a very high proportion of patients who eventually develop CHD have plasma LDL-C levels that are in this range. Other clinical information can assist in the decision-making process. For example, a low plasma HDL-C (<1.0 mmol/L (<40 mg/dL]) supports a decision in favor of more aggressive therapy. The diagnosis of the metabolic syndrome also identifies a higher risk individual who should be targeted for therapeutic life-style changes and might be a candidate for more aggressive drug therapy. Other laboratory tests, such as an elevated plasma Lp(a) or high-sensitivity C-reactive protein, may help to identify additional high-risk individuals. In persons at low risk, the emphasis should primarily be on dietary and life-style modification.

Drug treatment is also indicated in patients with triglycerides >11.3 mmol/L (>1000 mg/dL) who have been screened and treated for secondary causes of chylomicronemia. The goal is to reduce plasma triglycerides to <4.5 mmol/L (400 mg/dL) to prevent the risk of acute pancreatitis. Most major clinical endpoint trials with statins have excluded persons with triglyceride levels >3.9 to 5.1 mmol/L (>350 to 450 mg/dL), and therefore there are few data regarding the effectiveness of statins in reducing cardiovascular risk in persons with triglycerides higher than this threshold. Combination therapy is often required for optimal control of mixed dyslipidemia.

**HMG-CoA REDUCTASE INHIBITORS**

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase) is the rate-limiting step in cholesterol biosynthesis, and inhibition of this enzyme decreases cholesterol synthesis. By inhibiting cholesterol biosynthesis, HMG-CoA reductase inhibitors (statins) lead to increased hepatic LDL receptor activity and accelerated clearance of circulating LDL, resulting in a dose-dependent reduction in plasma LDL-C. There is wide interindividual variation in the initial response to a statin, but once a patient is on the medication, the doubling of the dose produces a 6% further reduction of plasma LDL-C. The HMG-CoA reductase inhibitors currently available differ in their LDL-C reducing effects (Table 18-6). HMG-CoA reductase inhibitors also reduce plasma triglycerides in a dose-dependent fashion, which is proportional to their LDL-C lowering effects [if the triglycerides are <3.9 mmol/L (<350 mg/dL)]. HMG-CoA reductase inhibitors have a modest HDL-raising effect (5 to 10%), and this effect is not dose-dependent.

HMG-CoA reductase inhibitors are well tolerated and can be taken in tablet form once a day. Potential side effects include dyspepsia, headaches, fatigue, and muscle or joint pains. Severe myopathy and even rhabdomyolysis occurs rarely. The risk of myopathy is increased by the presence of renal insufficiency and by coadministration of drugs that interfere with the metabolism of HMG-CoA reductase inhibitors, such as erythromycin and related antibiotics, antifungal agents, immunosuppressive drugs, and fibrin acid derivatives. Severe myopathy can usually be avoided by careful patient selection, avoidance of interacting drugs, and by instructing the patient to contact the physician immediately in the event of unexplained muscle pain. In the event of muscle symptoms, the plasma creatine phosphokinase (CPK) level should be obtained to document the myopathy, but serum CPK levels do not need to
TABLE 18-6
SUMMARY OF THE MAJOR DRUGS USED FOR THE TREATMENT OF HYPERLIPIDEMIA

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MAJOR INDICATIONS</th>
<th>STARTING DOSE</th>
<th>MAXIMAL DOSE</th>
<th>MECHANISM</th>
<th>COMMON SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Elevated LDL</td>
<td>20 mg daily</td>
<td>80 mg daily</td>
<td>Cholesterol synthesis, hepatic LDL receptors</td>
<td>Myalgias, arthralgias, elevated transaminases, dyspepsia</td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
<td>40 mg qhs</td>
<td>80 mg qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td>20 mg qhs</td>
<td>80 mg qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td>20 mg qhs</td>
<td>80 mg qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
<td>10 mg qhs</td>
<td>80 mg qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td>10 mg qhs</td>
<td>40 mg qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Elevated LDL</td>
<td>20 mg daily</td>
<td>80 mg daily</td>
<td>VLDL production</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td></td>
<td>4 g daily</td>
<td>32 g daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colestipol</td>
<td></td>
<td>5 g daily</td>
<td>40 g daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td></td>
<td>3750 mg daily</td>
<td>4375 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Elevated LDL, low HDL, elevated TG</td>
<td>100 mg tid</td>
<td>2 g tid</td>
<td>Bile acid excretion</td>
<td>Bloating, constipation, elevated triglycerides</td>
</tr>
<tr>
<td>Immediate-release</td>
<td></td>
<td>250 mg bid</td>
<td>1.5 g bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained-release</td>
<td></td>
<td>500 mg qhs</td>
<td>2 g qhs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Elevated TG, elevated remnants</td>
<td>600 mg bid</td>
<td>600 mg bid</td>
<td>VLDL hepatic synthesis</td>
<td>Cutaneous flushing; GI upset; elevated glucose, uric acid, and liver function tests</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td></td>
<td>160 mg qd</td>
<td>160 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish oils</td>
<td>Severely elevated TG</td>
<td>3 g daily</td>
<td>12 g daily</td>
<td>LPL, VLDL synthesis</td>
<td>Dyspepsia, myalgia, gallstones, elevated transaminases</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>Elevated LDL</td>
<td>10 mg daily</td>
<td>10 mg daily</td>
<td>Chylomicron and VLDL production</td>
<td>Dyspepsia, diarrhea, fishy odor to breath</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: LDL, low-density lipoprotein; VLDL, very low density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; LPL, lipoprotein lipase.

be monitored on a routine basis as an elevated CPK in the absence of symptoms does not predict the development of myopathy and does not necessarily suggest the need for discontinuing the drug.

Another side effect of HMG-CoA reductase inhibitor therapy is hepatitis. Liver transaminases (ALT and AST) should be checked before starting therapy, at 8 weeks, and then every 6 months. Substantial (>3 × upper limit of normal) elevation in transaminases is relatively rare, and mild to moderate (1 to 3 × normal) elevation in transaminases in the absence of symptoms need not mandate discontinuing the medication. Severe clinical hepatitis associated with HMG-CoA reductase inhibitors is exceedingly rare, and the trend is toward less frequent monitoring of transaminases in patients taking HMG-CoA reductase inhibitors. The HMG-CoA reductase inhibitor–associated elevation in liver enzymes resolves after discontinuation of the medication.

Overall, HMG-CoA reductase inhibitors appear to be remarkably safe. Over 50,000 patients have been treated with HMG-CoA reductase inhibitors for over 5 to 6 years as a part of large randomized controlled clinical trials and no increase in any major noncardiac diseases have been seen in these individuals. HMG-CoA reductase inhibitors are the drug class of choice for LDL-C reduction and are by far the most widely used class of lipid-lowering drugs.

BILE ACID SEQUESTRANTS (RESINS)

Bile acid sequestrants bind bile acids in the intestine and promote their excretion in the stool. In order to maintain an adequate bile acid pool, the liver diverts cholesterol to bile acid synthesis. The decreased hepatic intracellular cholesterol content upregulates the LDL receptor and enhances LDL clearance from the plasma. Bile acid sequestrants, including cholestyramine, colestipol, and colesevelam (Table 18-6), primarily reduce plasma LDL-C levels but can increase plasma triglycerides. Therefore, patients with hypertriglyceridemia should not be treated with bile acid–binding resins.

Cholestyramine and colestipol are insoluble resins that must be mixed with liquids. Colestipol is also available in large tablets but multiple tablets must be taken to achieve significant lowering of
plasma LDL-C levels. The newest bile acid sequestrant, colesevelam, has greater bile acid-binding capacity than traditional resins. The colesevelam tablets are smaller, and fewer tablets per day are required. Most side effects of resins are limited to the gastrointestinal tract and include bloating and constipation. Bile acid sequestrants may bind other drugs (e.g., digoxin, warfarin) and interfere with their absorption. Therefore, all other medications should be taken either 1 h before or 4 h after the bile acid sequestrants.

Bile acid sequestrants are not systemically absorbed and are very safe. They are the cholesterol-lowering drug of choice in children and in women of childbearing age who are lactating, pregnant, or could become pregnant. These drugs can also be useful in young, well-motivated patients with moderate hypercholesterolemia who wish to avoid systemic drug therapy. This class of drugs is also useful in combination with HMG-CoA reductase inhibitors in patients who are unable to reach their LDL-C goal on HMG-CoA reductase inhibitor monotherapy and have relatively normal triglyceride levels.

**NICOTINIC ACID (NIACIN)**

Nicotinic acid, or niacin, is a B-complex vitamin that reduces plasma triglyceride and LDL-C levels and raises the plasma HDL-C (Table 18-6) in high doses. Niacin is the only currently available lipid-lowering drug that significantly reduces plasma levels of Lp(a). If properly prescribed and monitored, niacin is a safe and effective lipid-lowering agent.

The cheapest form of niacin is immediate-release crystalline niacin. Niacin should be started at a low dose (100 mg three times a day) and taken with meals to delay absorption. The dose of niacin should be increased every 4 to 7 days by 100 mg until a dose of 500 mg tid is obtained. After 1 month on this dose, lipids and pertinent chemistries (glucose, uric acid, liver transaminases) should be measured. The dose can be further increased as needed up to a total dose of 6 g/d. The most frequent side effect is cutaneous flushing, but this improves with continued administration. In many patients, taking an aspirin 30 min prior to the niacin prevents flushing. Over-the-counter sustained-release forms of niacin are generally administered twice a day and are associated with less flushing, but some have been associated with rare cases of severe hepatitis. A clue to the development of niacin-induced hepatitis is a sudden, precipitous drop in the plasma lipid levels. A prescription form of extended-release niacin that is administered once daily at bedtime has not been associated with severe hepatic toxicity. Mild elevations in transaminases occur in up to 15% of patients treated with any form of niacin, but these elevations rarely require discontinuation of the medication. Niacin potentiates the effect of warfarin, and these two drugs should be prescribed together with caution. Acanthosis nigricans and maculopathy are infrequent side effects of niacin. Niacin is contraindicated in patients with peptic ulcer disease and can exacerbate the symptoms of esophageal reflux. Niacin can raise plasma levels of uric acid and precipitate gouty attacks in susceptible patients.

Niacin can raise fasting plasma glucose levels, but concerns regarding the use of niacin in diabetic patients have been allayed by the results of two studies. In one study, short-acting niacin treatment of dyslipidemia was associated with only a slight increase in fasting glucose and no significant change from baseline in the HbA1c. In the other, low-dose niacin was found to reduce triglycerides effectively and raise HDL-C in diabetics without adversely impacting glycemic control.

Successful therapy with niacin requires careful education and motivation of the patient. Its advantages are its low cost and long-term safety. It is the most effective drug currently available for raising HDL-C levels. It is particularly useful in patients with combined hyperlipidemia and low plasma levels of HDL-C and is effective in combination with statins.

**FIBRIC ACID DERIVATIVES (FIBRATES)**

Fibric acid derivatives, or fibrates, are agonists of PPARα, a nuclear receptor involved in the regulation of carbohydrate and lipid metabolism. Fibrates stimulate LPL activity (enhancing triglyceride hydrolysis), reduce apoC-III synthesis (enhancing lipoprotein remnant clearance), and may reduce VLDL production. Fibrates are the most effective drugs available for reducing triglyceride levels, and they also raise HDL-C levels (Table 18-6). Fibrates have variable effects on LDL-C, and in hypertriglyceridemic patients can sometimes be associated with increases in plasma LDL-C levels.

Fibrates are generally very well tolerated. The most common side effect is dyspepsia. Myopathy and hepatitis occur rarely in the absence of other lipid-lowering agents. Fibrates promote cholesterol
secretion into bile and are associated with an increased risk of gallstones. Importantly, fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents; the anticoagulation status and plasma glucose levels should be closely monitored in patients on these agents.

Fibrates are the drug class of choice in patients with severe hypertriglyceridemia [11.3 mmol/L (>1000 mg/dL)] and are a reasonable consideration in patients with moderate hypertriglyceridemia [4.5 to 11.3 mmol/L (400 to 1000 mg/dL)]. The Veterans Affairs High-Density Lipoprotein Intervention Trial study also suggests that they may have a role in high-risk patients with well-controlled LDL-C levels but elevated plasma triglyceride levels and low plasma levels of HDL-C. The relative indications of fibrates vs. statins and the role of combined therapy will be determined by ongoing and future trials.

OMEGA-3 FATTY ACIDS (FISH OILS)
N-3 polyunsaturated fatty acids (PUFAs) are present in high concentration in fish and in flax seeds. The most widely used n-3 PUFAs for the treatment of hyperlipidemias are the two active molecules in fish oil, eicosapentanoic acid (EPA) and docohexanoic acid (DHA). N-3 PUFAs have been concentrated into tablets and in doses of 3 to 6 g/d decrease fasting and postprandial triglycerides. At least 6 g/d is usually required for a substantial triglyceride-lowering effect, and many patients require 9 to 12 g/d. Fish oil treatment of hypertriglyceridemia can be associated with a significant increase in plasma LDL-C levels. Fish oil supplements can be used in combination with fibrates, niacin, or statins to treat hypertriglyceridemia. In general, fish oils are well tolerated and appear to be safe, at least at doses up to 3 g. The large number of capsules required for a therapeutic effect, the associated dyspepsia, and fishy aftertaste have limited the clinical use of these agents. Although fish oil administration is associated with a prolongation in the bleeding time, no increase in bleeding has been seen in clinical trials.

CHOLESTEROL ABSORPTION INHIBITORS
A new mechanism of cholesterol-lowering is the inhibition of intestinal cholesterol absorption. Ezetimibe (Table 18-6) inhibits the absorption of dietary and biliary cholesterol from the intestinal lumen. It reduces LDL-C cholesterol levels by ~18% as monotherapy or in combination with a statin. Cholesterol absorption inhibitors are particularly useful in combination with a statin in patients unable to reach their LDL-C goal on statin monotherapy.

COMBINATION DRUG THERAPY
Combination drug therapy is frequently used in the following situations: (1) patients unable to reach their LDL-C goal on a single drug, (2) patients with combined hypertriglyceridemia and hypercholesterolemia that cannot be adequately controlled with a single drug, and (3) patients with elevated LDL-C and low HDL-C levels. Inability to achieve LDL-C goal is not uncommon on statin monotherapy. If the patient has a normal plasma triglyceride level, a bile acid sequestrant can be added. A cholesterol absorption inhibitor can also be used in this setting. Combination of niacin with a statin is an attractive option for high-risk patients who do not attain their target LDL-C level on statin monotherapy and who have an HDL-C < 1.0 mmol/L (<40 mg/dL). One product currently available offers the combination of lovastatin and extended-release niacin in a single tablet.

Patients with combined hyperlipidemia frequently have persistent hypertriglyceridemia on statin monotherapy. Addition of niacin or a fibrate can reduce the plasma triglyceride level in these patients. Conversely, hypertriglyceridemic patients treated with a fibrate often fail to reach their LDL-C goal and are therefore candidates for the addition of a statin. Coadministration of statins and fibrates has obvious appeal in patients with combined hyperlipidemia, but no clinical trials have assessed the effectiveness of a statin-fibrate combination compared with either a statin or a fibrate alone in reducing cardiovascular events, and the long-term safety of this combination is not known. Statin-fibrate combinations are known to be associated with an increased incidence of severe myopathy (up to 2.5%) and rhabdomyolysis, and patients treated with these two drugs must be carefully counseled and monitored. This combination of drugs should be used cautiously in patients with underlying renal or hepatic insufficiency; in the elderly, frail, and chronically ill; and in those on multiple medications.

Other Approaches
Occasionally, patients cannot tolerate any of the existing lipid-lowering drugs at doses required for
adequate control of their lipid levels. Some patients, mostly those with genetic lipid disorders, remain significantly hypercholesterolemic despite combination drug therapy. These patients are at high risk for development or progression of CHD and clinical CHD events.

**LDL APERESIS**

The preferred option for management of patients with refractory or drug-resistant hypercholesterolemia is LDL apheresis. In this process, the patient's plasma is passed over a column that selectively removes the LDL, and the LDL-depleted plasma is returned to the patient. Patients on maximally tolerated combination drug therapy who have CHD and a plasma LDL-C level >5.2 mmol/L (>200 mg/dL) or no CHD and a plasma LDL-C level >7.8 mmol/L (>300 mg/dL), are candidates for every-other-week LDL apheresis.

**PARTIAL ILEAL BYPASS**

Partial ileal bypass interrupts the enterohepatic circulation of bile acids, resulting in upregulation of the hepatic LDL receptor and reduction in plasma LDL-C levels. Diarrhea is a common side effect, and the incidence of kidney stones, gallstones, and intestinal obstruction is increased after ileal bypass surgery. The clinical utility of partial ileal bypass at this time is limited to severely hypercholesterolemic patients with normal triglycerides who cannot tolerate existing lipid-lowering medications and do not have access to LDL apheresis. Partial ileal bypass has not been proven effective in patients with severe hypercholesterolemia who have not responded adequately to statins.

**Management of Low HDL-C**

Severely reduced plasma HDL-C [<0.5 mmol/L (<20 mg/dL)] accompanied by triglycerides <4.5 mmol/L (<400 mg/dL) usually indicates the presence of a genetic disorder, such as a mutation in apoA-I, LCAT deficiency, or Tangier disease. HDL-C levels <0.5 mmol/L (<20 mg/dL) are common in the setting of severe hypertriglyceridemia, in which case the primary focus should be on the management of the triglycerides. Secondary causes of more moderate reductions in plasma HDL [0.5 to 10.3 mmol/L (20 to 40 mg/dL)] should be considered (Table 18-5). Smoking should be discontinued, obese persons should be encouraged to lose weight, sedentary persons should be encouraged to exercise, and diabetes should be optimally controlled. When possible, medications associated with reduced plasma levels of HDL-C should be discontinued. The presence of an isolated low plasma HDL-C level in a patient with a borderline plasma LDL-C should prompt consideration of LDL-lowering drug therapy in high-risk individuals. Statins increase plasma levels of HDL-C only modestly (~5 to 10%). Fibrates also have a modest effect on plasma HDL-C levels (increasing levels ~5 to 15%) except in patients with coexisting hypertriglyceridemia, where they can be more effective. Niacin is the most effective therapeutic agent and can increase plasma HDL-C levels by up to ~30%.

The issue of whether pharmacologic intervention should be used to specifically raise HDL-C levels has not been adequately addressed in clinical trials. Pending these studies, it may be reasonable to initiate therapy (with a fibrate or niacin) directed specifically at reducing plasma triglyceride levels and raising the plasma HDL-C level in persons with established CHD and low HDL-C levels whose plasma LDL-C levels are at or below the goal.

**FURTHER READINGS**


  Inhibition of cholesteryl ester transfer protein (CETP) has been proposed as a strategy to raise HDL cholesterol levels. This study examined the effects of torcetrapib, a potent inhibitor of CETP, on plasma lipoprotein levels in subjects with low HDL cholesterol. Treatment with 120 mg of torcetrapib daily markedly increased HDL cholesterol levels and also decreased LDL cholesterol levels.


  This study compared standard versus intensive lipid-lowering therapy with statins in 4162 patients who had been hospitalized for an acute coronary syndrome. The intensive lipid-lowering statin regimen provided greater protection against death or major cardiovascular events, suggesting that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.
354  Section III  Diabetes Mellitus, Obesity, Lipoprotein Metabolism


**Heart Protection Study Collaborative Group:** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 360:7, 2002


**LIMA JA** et al: Statin-induced cholesterol lowering and plaque regression after 6 months of magnetic resonance imaging-monitored therapy. Circulation 110:2336, 2004


**Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486, 2001


Recent trials have demonstrated better outcomes with intensive than with moderate statin treatment. This study of patients with coronary artery disease confirmed a reduced rate of progression of atherosclerosis associated with intensive statin treatment, and documented a correlation with greater reductions in the levels of both atherogenic lipoproteins and CRP.