Diagnosis and Treatment of Dyslipidemia

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Introduction

Disorders of lipoprotein metabolism, in conjunction with the prevalence of high-fat diets, obesity, and physical inactivit epidemic of atherosclerotic disease in the United States and other developed countries. The interaction of common ge disorders of lipoproteins with these adverse environmental factors leads to the premature development of atheroscler mortality from coronary artery disease (CAD), particularly in persons younger than 60 years, has been declining since atherosclerotic cardiovascular disease remains the most common cause of death among both men and women.

Formerly, hyperlipidemia was defined as elevation of a lipoprotein level in the population. The recognition that a low le lipoprotein (HDL) and the presence of small, dense low-density lipoprotein (LDL) are clinically important in the pathop has led to the use of the term dyslipidemia to describe a range of disorders that include both abnormally high and low as disorders in the composition of these particles. Dyslipidemias are clinically important, principally because of their c Pancreatitis and fatty liver disease are less common but clinically significant manifestations of lipid disorders.

Lipoprotein Physiology

Lipoprotein Composition and Metabolism

Lipoproteins are spherical macromolecular complexes of lipid and protein [*see Figure 1*]. Clinically important lipids in t (both unesterified and esterified) and triglyceride (molecules consisting of three fatty acids attached to a glycerol back three primary functions: it plays a role in the structure of cell membranes, in the synthesis of steroid hormones, and in The major functions of triglyceride are energy storage (in fat) and energy use (by muscle). Because fat cannot readily cholesterol and triglyceride are made miscible by incorporation into lipoproteins (e.g., very low density lipoprotein [VLI Apolipoproteins are the protein component of lipoproteins; they aid in the lipid transport and delivery process in three structural elements, as ligands for receptors, and as regulatory cofactors [*see Table 1*].
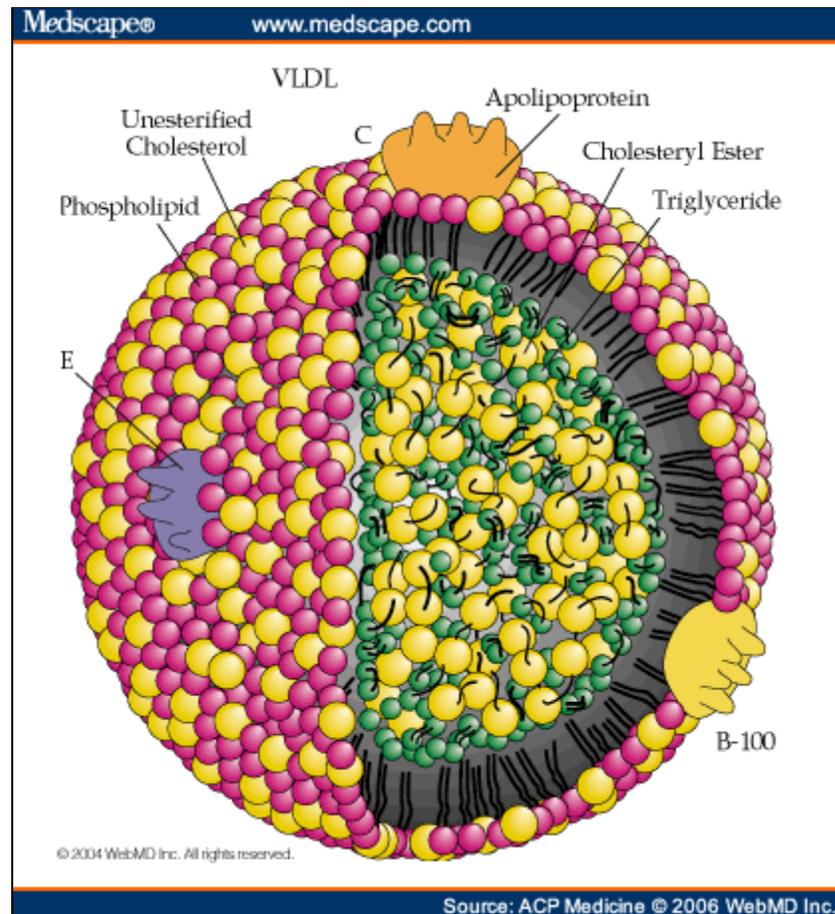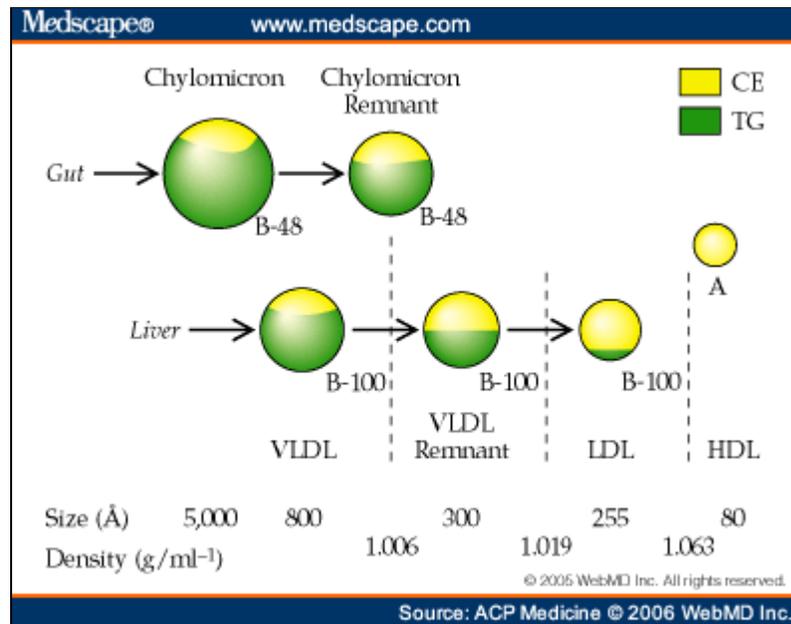
Figure 1.

Lipoproteins transport water-insoluble triglyceride and cholesterol through the bloodstream. All apo B-containir
structure similar to that shown for very low density lipoproteins (VLDL). The core is composed of triglyceride ar
whereas the monolayer surface is composed of phospholipid, unesterified cholesterol, and protein in the form (
VLDL contains apolipoproteins B-100, C-I, C-II, and E. Low-density lipoprotein (LDL), which transports most of
found in blood, contains primarily apo B-100.

Lipoprotein Structure and Classification

A mature lipoprotein particle is a sphere consisting of a central core of lipids (triglyceride and cholesteryl ester) surrou
surface of phospholipid, unesterified cholesterol, and apolipoproteins [*see Figure 1*]. Operationally, the lipoproteins ca
of their size and buoyancy characteristics [*see Figure 2*].

Figure 2.

Size and buoyancy characteristics of lipoproteins. Chylomicrons, which are composed largely of triglyceride, a[re]
most buoyant of the lipoproteins. High-density lipoprotein (HDL) particles are substantially smaller and denser
mostly of cholesteryl ester. (CE-cholesteryl ester; TG-triglyceride)

Chylomicron. Chylomicrons are the largest of the lipoprotein particles. The major structural protein is apolipoprotein
(~80%) of the lipid core consists of triglyceride. Synthesized and secreted from the intestine, chylomicrons transport e[ssential fatty]
acids, and fat-soluble vitamins absorbed from digested food [*see* Exogenous Pathway, *below*].

VLDL. This triglyceride-rich particle (~80% of the lipid core consists of triglyceride) is synthesized in the liver, delivers
and is the precursor for intermediate-density lipoproteins (IDLs) and LDL. The major structural protein of this lipoprote[in is apo B-100 see]
Endogenous Pathway, *below*].

IDL. The remnant of VLDL is of IDL density. It is formed after triglyceride in VLDL is hydrolyzed by lipoprotein lipase. [This particle is 50%]
triglyceride and 50% cholesteryl ester. Approximately half of the body's IDL particles are cleared from the plasma into [the liver; the rest are]
further processed to form LDL [*see* Endogenous Pathway, *below*]. In clinical practice, assessment of LDL levels inclu[des]
cholesterol in both IDL and LDL fractions.

LDL. This lipoprotein results from the hepatic processing of VLDL remnants. The core is rich in cholesteryl ester and a[ccounts for most of the]
cholesterol circulating in the blood. LDL plays a major role in the development of atherosclerosis [*see* LDL Catabolism[, below].

HDL. HDL forms from the unesterified cholesterol and phospholipid removed from peripheral tissues and the surface
[*see* Function and Regulation of HDL, *below*]. The major structural protein is apo A-I; the core is predominantly choles[teryl ester. HDL assists in]
the return of lipoprotein and tissue cholesterol to the liver for excretion in the process referred to as reverse cholester[ol transport. One of HDL's]
functions is to shuttle apo E and apo C-II to and from chylomicrons and VLDL.

Lipoprotein Assembly and Catabolism

Exogenous Pathway

After a meal, intestinal cells absorb fatty acids and cholesterol, esterify them into triglyceride and cholesteryl ester, an[d incorporate them into the]
core of chylomicrons.[1] Triglyceride greatly predominates over cholesterol ester in the chylomicron core. The chylomi[cron passes into the]
plasma, where apo C-II on the chylomicron surface activates endothelial-bound lipoprotein lipase (LPL). LPL in turn h[ydrolyzes]

core triglyceride and releases free fatty acids, which are taken up by adipose tissue for storage and by muscle for ene
chylomicron decreases in size, and some surface components are transferred to HDL; the remaining particle is the ch
This chylomicron remnant next acquires apo E from HDL and is subsequently taken up by the liver after binding to sit
then degraded, thereby delivering dietary cholesterol to the liver.

Endogenous Pathway

The liver secretes triglyceride-rich VLDL into plasma, where they too acquire apo C-II from HDL. As with chylomicrons
on the capillary endothelium, and the core triglyceride is hydrolyzed to provide fatty acids to adipose and muscle tissu
catabolized VLDL remnants (IDL density) are taken up by hepatic receptors that bind to apo E for degradation; the oth
particles, depleted of triglyceride relative to cholesteryl ester—are converted by the liver to cholesteryl ester-rich LDL.
apo E becomes detached, leaving only one apolipoprotein, apo B-100. Each particle in this cascade from VLDL to LD
apo B-100.

In the metabolism of both chylomicrons and VLDL, apo C-II permits the hydrolysis of triglyceride by lipoprotein lipase,
uptake of remnants. A major difference in the metabolism of these particles is that chylomicrons contain a truncated f
48), whereas VLDL contains the complete form (i.e., apo B-100). Another difference is that chylomicron remnants are
absorbed by the liver, whereas many of the VLDL remnants are most likely processed in the hepatic sinusoids to bec

Regulation of Lipoprotein Metabolism

There are four major clinically significant physiologic steps in the lipoprotein cascade from VLDL to LDL—namely, VL
LPL, remnant catabolism, and LDL catabolism [*see Figure 3*].[1,2] Defects at any step in the cascade can lead to hype
can be genetic or acquired (i.e., secondary to disease or the effects of drugs) or the result of an interaction of genetic
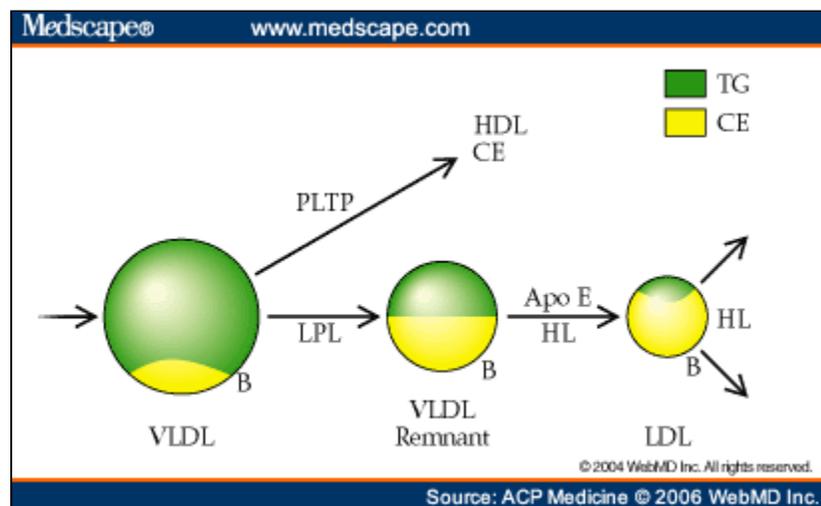
Figure 3.

The apolipoprotein B-100 (apo B-100) cascade. VLDL is secreted from the liver with one apo B on the surface
cholesteryl ester in the core. Core triglyceride is hydrolyzed by lipoprotein lipase and becomes a remnant lipop
recognized by the liver-in part, by apo E. The remnant lipoprotein is further processed to form LDL, which has
core and an intact apo B on its surface. The LDL particle can be removed by peripheral or hepatic LDL recepto
is hydrolyzed, the unesterified cholesterol and phospholipid are transferred to HDL by phospholipid transfer pro
cholesteryl ester of HDL. (CE-cholesteryl ester; HL- hepatic lipase; LPL-lipoprotein lipase; PLTP-phospholipid
triglyceride)

Lipoprotein Assembly

Apo B-100 is synthesized constitutively in the endoplasmic reticulum of the hepatocyte, and much of it is degraded in

Triglyceride is added to the surviving apo B that will be secreted as VLDL. It is transported to the Golgi complex, whe lipid, forming the nascent VLDL particle. This particle is secreted into plasma, where it acquires apolipoproteins (e.g., HDL.[1]

Abnormalities in VLDL secretion can occur in two genetic forms of hyperlipidemia: familial hypertriglyceridemia (FHTG hyperlipidemia (FCHL). FHTG is characterized by the overproduction of triglyceride contained within a normal numbe results in each particle's having an excessive amount of triglyceride. In FCHL, an excessive amount of apo B-100 is s particles; these particles tend to be smaller than normal.[3]

The metabolic syndrome, which is a common condition in the general population, is a component of most cases of FC the residual dyslipidemia seen in patients with type 2 diabetes mellitus who have been treated with insulin or insulin s molecular basis of the hepatic triglyceride or apo B oversecretion in these disorders is unknown.

A deficiency in lipoproteins containing apo B is referred to as hypobetalipoproteinemia; an absence of apo B is termed Abetalipoproteinemia may occur because of a defect involving both apo B genes that prevents the production of apo individuals who are homozygous for mutations in the microsomal triglyceride transport protein, which is critical for apc endoplasmic reticulum. Homozygous hypobetalipoproteinemia and abetalipoproteinemia lead to deficiencies in fat-so of these conditions results in a shortage of apo B-containing lipoproteins, which are needed to transport fat-soluble vi Hypobetalipoproteinemia, which is characterized by apo B levels of 50% normal, can be caused by a defect in a singl

Lipoprotein(a). Lipoprotein(a) [Lp(a)] is a specific class of lipoprotein particles that are synthesized in the liver and th similar to that of LDL. Lp(a) differs from LDL by the presence of apolipoprotein(a) [apo(a)], a protein whose structure i plasminogen.[5] The apo(a) protein is bound by a disulfide linkage to apo B-100 to form Lp(a). High levels of Lp(a) are atherogenic.[5] Levels of Lp(a) in plasma are almost completely determined by genetic variation in the *Lp(a)* gene.
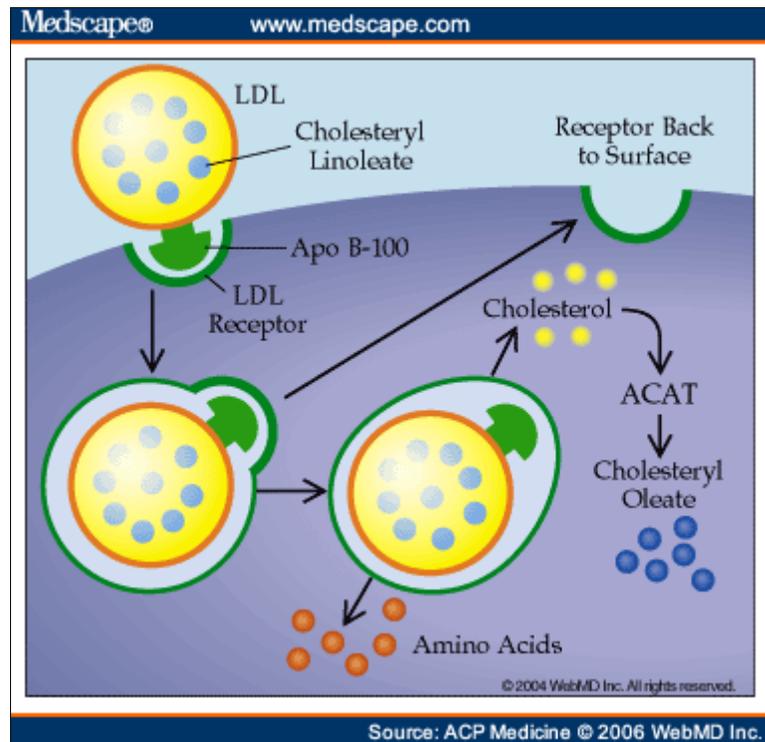
Lipoprotein Catabolism

Lipoprotein Lipase-mediated Triglyceride Removal. LPL is synthesized in adipose tissue and muscle and then tra surface of the endothelial lining of the adjacent capillary, where it acts on triglyceride-rich lipoproteins. The fatty acids processing of triglyceride-rich particles (i.e., chylomicrons and VLDL) can be used for energy by muscle, or they can b triglyceride and stored in adipocytes for later use.[6] Apo C-II, the LPL activator, is carried on the triglyceride-rich lipop VLDL.

Genetic defects that result in impaired lipoprotein lipase synthesis or function are rare autosomal recessive causes of these mutations present in neonates or infants as severe hypertriglyceridemia. Heterozygote parents of these childre hypertriglyceridemia. Acquired defects of LPL, such as untreated diabetes or uremia, are more common causes of hy acquired defect of LPL is associated with a disorder characterized by excessive input of VLDL, marked hypertriglyceri coexistence of two or more disorders that independently increase the level of triglycerides in plasma (e.g., FHTG or F untreated diabetes) can lead to marked hypertriglyceridemia.[6]

Remnant Catabolism. Both chylomicron and VLDL remnants acquire apo E from HDL before they can bind to hepati and degradation or further processing to LDL. Three alleles of the *APOE* gene (i.e., *APOE*E2, APOE*E3*, and *APOE* combinations. The *APOE*E4* allele product has the greatest affinity for hepatic receptors, followed by the *APOE*E3* a allele product has markedly reduced receptor affinity.

Individuals who are homozygous for the *APOE*E2* allele (E2/E2) have marked impairment of hepatic remnant lipopro the accumulation of these remnants in the plasma and in very low levels or the absence of LDL. Interestingly, individu have either normal or low cholesterol levels because of the paucity of LDL particles characteristic of this disorder.[7] If, is homozygous for the *APOE*E2* allele (E2/E2) has a defect—either inherited or acquired—that causes excessive inp accumulation of VLDL remnants and hyperlip idemia occur. This results in remnant removal disease. Because chylom contain roughly equal amounts of triglyceride and cholesterol, the hyperlipidemia of remnant removal disease is chara hypercholesterolemia and hypertriglyceridemia.[7]

LDL Catabolism. The final step at which a defect in lipoprotein metabolism can occur is in LDL catabolism. Apo B-10 binds to its receptor on the cell surface; LDL is then absorbed into the cell, where it is catabolized [*see Figure 4*]. Afte lipids, unesterified cholesterol is used by cells for synthesis of membranes, bile acids, and steroid hormones and for v that prevent overaccumulation of cholesterol within the cell. The vast majority of LDL particles in plasma are taken up LDL receptor.

Figure 4.

LDL is absorbed by cells through the LDL receptor. This receptor recognizes apo B-100, the apolipoprotein on
Once internalized, the lipoprotein is catabolized, releasing cholesterol and amino acids. The free cholesterol is
cholesteryl oleate by the enzyme acyl-coenzyme A: cholesterol acyltransferase (ACAT). The LDL receptor is re
cell surface.

Mutations of the LDL receptor (as found in familial hypercholesterolemia [FH]) or, less commonly, mutations in the ap
in familial defective apo B-100) lead to an impairment in the interaction of LDL with its receptor; this can result in eleva
also can be influenced by dietary factors. For example, dietary cholesterol delivered to the liver by chylomicron remna
LDL receptors, leading to impaired LDL removal from plasma. Dietary saturated fats also may reduce LDL receptor ac
LDL production. Hypothyroidism can also be associated with defective LDL receptor-mediated cholesterol removal.[8]

Function and Regulation of HDL

The major HDL apolipoproteins are apo A-I and apo A-II, which are formed in the liver and small intestine.[9] Apo A-I is
in a disklike structure called nascent HDL. Most of the apolipoproteins and phospholipid destined to become nascent
the surface of chylomicrons and VLDL. After LPL hydrolyzes triglyceride in chylomicrons and VLDL, the core lipid con
particles becomes smaller, and redundancies of unesterified cholesterol and phospholipid occur in the surface layer.
components are transferred to HDL by phospholipid transfer protein. Nascent HDL particles also pick up excess unes
phospholipid from peripheral tissues via the transporter ABCA1. This HDL cholesterol then undergoes esterification b
lecithin-cholesterol acyltransferase (LCAT). LCAT is activated by apo A-I on the HDL surface to esterify free cholester
causing it to move into the core. In this process, the particle becomes the larger, more buoyant HDL_3 particle and prog
HDL_2 particle.[9,10]. At some point, apo A-II may be added to the HDL_2 particle, which then is directed to deliver choles
cholesteryl ester transfer protein (CETP). Hepatic lipase activity on the liver surface hydrolyzes the phospholipid and t
particle, promoting the decrease in size and density to HDL_3 and then to even smaller HDL particles.[10] Recycling of s
the process to repeat itself [*see Figure 5*].
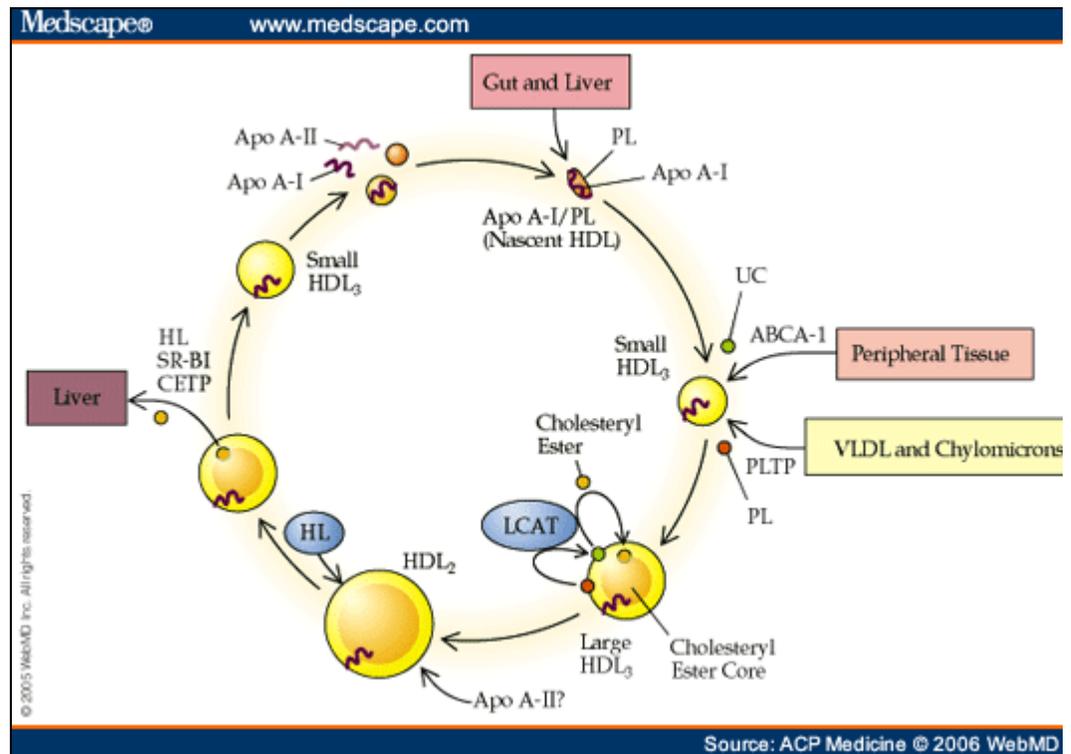
Figure 5.

The circular pathway of HDL formation and degradation.[11] HDL begins as an apo A-1 phospholipid complex. cholesterol and phospholipid are added to the nascent HDL via adenosine triphosphate-binding cassette trans phospholipid transfer protein to begin the formation of the smaller HDL3 particle. LCAT transfers a fatty acid fr unesterified cholesterol to cholesteryl ester, which moves to the HDL core. In this process, the HDL particle be more buoyant HDL_3 particle and progresses to the even larger HDL_2 particle. Cholesteryl ester transfer protein transfer of cholesteryl ester from HDL2 to the liver and various lipoproteins; with this loss of cholesteryl ester, t shrinks in size. Hepatic lipase hydrolyzes the phospholipid and triglyceride in the HDL_2 particle, promoting the density to HDL_3 and then to even smaller HDL particles, including apo A-1. Recycling of some of the apo A-I c repeat itself. The role of apo A-II in this process in humans is not clear. (ABCA1-ATP-binding cassette transpo cholesteryl ester transfer protein; LCAT-lecithin-cholesterol acyltransferase; LPL-lipoprotein lipase; PL-phosph phospholipid transfer protein; SR-BI-scavenger receptor BI; UC-unesterified cholesterol)

Abnormally high or low levels of HDL cholesterol may be caused, rarely, by genetic defects. Elevations in the HDL ch from genetic hyperalphalipoproteinemia or CETP deficiency. Markedly reduced HDL cholesterol levels may be cause mutation; homozygosity for mutations in *ABCA1*,[11] leading to Tangier disease; or homozygosity for mutations in the LCAT deficiency and fish-eye disease. Factors associated with an increase in HDL levels include female sex, aerobic high-fat diets, and certain drugs (e.g., alcohol, estrogens, fibrates, and nicotinic acid) [*see Table 2*]. Factors associate levels include male sex, central obesity, cigarette smoking, low-fat diets, hypertriglyceridemia, uremia, being heterozy and certain drugs (e.g., androgens, progestins, and some antihypertensive agents) [*see Table 2*]. Low HDL particle n associated with increased triglyceride levels, as seen in the metabolic syndrome.

Function of Hepatic Lipase

Hepatic lipase is synthesized in the hepatocyte, binds to endothelial surfaces in the liver sinusoids, and acts on lipopr rich VLDL particles exchange triglyceride for the cholesteryl ester in LDL and HDL, hepatic lipase can hydrolyze the p in LDL and HDL [*see Figure 6*]. This process leads to the formation of small, dense LDL and converts HDL_2 to HDL_3. by the presence of excessive levels of triglyceride-rich VLDL in the presence of normal hepatic lipase activity or by in hepatic lipase. Factors such as male sex and the accumulation of intra-abdominal fat predispose to increased hepatic

associated with an increase in small, dense LDL levels and a decrease in HDL$_2$ levels. Increased hepatic lipase activi
the dyslipidemia of the metabolic syndrome.[10,12] Hepatic lipase also may facilitate hepatic recognition and uptake of
remnant lipoproteins.
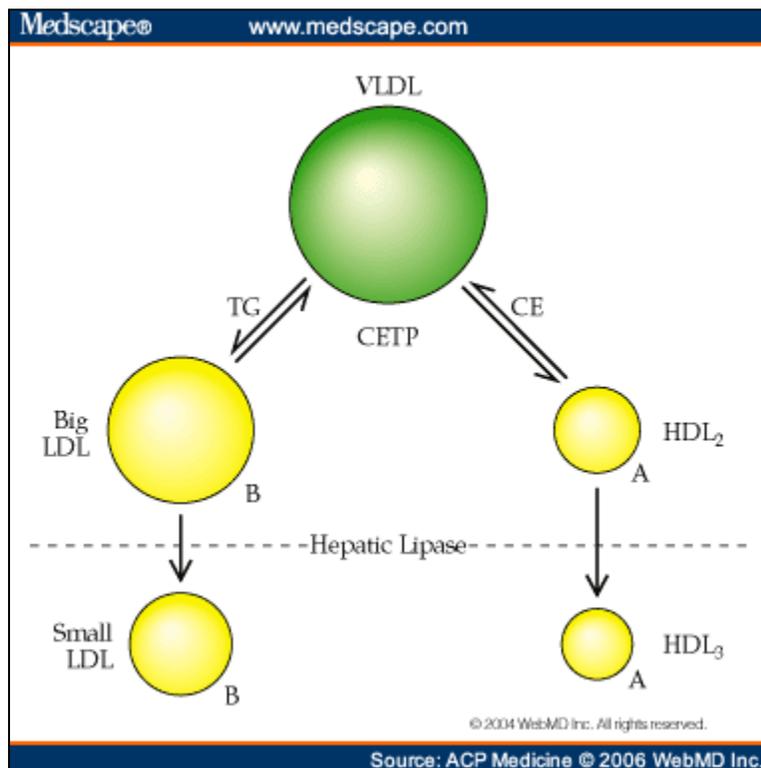
Figure 6.

Dyslipidemia in the metabolic syndrome. Triglyceride-rich VLDL exchanges triglyceride for the cholesteryl este
particles. This change in lipoprotein composition is initiated by cholesteryl ester transfer protein. Hepatic lipase
triglyceride and phospholipid in large LDL and HDL particles, decreasing the size of each particle. (CE-choleste
triglyceride; CETP-cholesterol ester transfer protein)

Clinical Manifestations of Dyslipidemia

The main clinical consequences of hyperlipidemia are premature atherosclerosis; pancreatitis, which is usually associ
chylomicronemia syndrome; and nonalcoholic fatty liver disease. Atherosclerosis is most clearly associated with eleva
cholesterol and reduced levels of HDL cholesterol. In both pancreatitis and fatty liver disease, the underlying lipid diso

Dyslipidemia in Atherosclerosis

There is consensus that elevated plasma LDL levels and reduced HDL levels are associated with an increased risk of
hypertriglyceridemia as a cardiovascular risk factor is more complex. Hypertriglyceridemia may be a marker for other
(e.g., increased levels of small, dense LDL particles; low levels of HDL; or remnant accumulation) that are part of the
associated with FCHL, type 2 diabetes mellitus, and the metabolic syndrome. In these settings, hypertriglyceridemia i
premature cardiovascular risk. However, other forms of hypertriglyceridemia may not be associated with premature ca
Familial Hypertriglyceridemia, *below*]. The precise mechanisms whereby increased levels of LDL result in increased a
unclear. Very high levels of large, buoyant LDL particles, such as occur in FH and familial defective apo B-100, as we
moderate numbers of small, dense LDL particles, are associated with an increased risk of cardiovascular disease. Ac
suggests that LDL needs to be modified before it becomes atherogenic.[13] Oxidation of LDL may increase its atherog
many biologic properties that may cause it to become atherogenic. The atherogenicity of small, dense LDL particles n
LDL to enter the arterial intima, where it is retained by matrix molecules and undergoes oxidation more readily than la

particles. The antiatherogenic properties of HDL are probably related to its role in reverse cholesterol transport, and H
inflammatory and antioxidant effects.

Dyslipidemia in the Chylomicronemia Syndrome

Pancreatitis is associated with chylomicronemia, usually with elevated levels of VLDL. The mechanism by which chylo
pancreatitis is unclear. Pancreatitis is believed to be caused by the release of free fatty acids and lysolecithin from ch
binding capacity in the capillaries of the pancreas by pancreatic lipase.

The chylomicronemia syndrome occasionally occurs when LPL is defective as a result of genetic variation in the enzy
Much more commonly, chylomicronemia is caused by the coexistence of a genetic form of hypertriglyceridemia comb
disorder of plasma triglyceride metabolism, the most common being untreated diabetes. Other conditions may be imp
and nephrotic syndrome), as may the use of drugs that raise triglyceride levels.

The chylomicronemia syndrome is associated with abdominal pain, eruptive xanthomas, and transient memory loss. E
most frequently on the buttocks and the extensor surfaces of the upper limb. A reversible loss of memory, particularly
peripheral neuropathy, which sometimes mimics the carpal tunnel syndrome, also may occur. The retinal vessels occ
lipemia retinalis. If the chylomicronemia syndrome is not corrected, it may lead to acute pancreatitis. Acute pancreatiti
recurrent until low triglyceride levels are maintained. The risk of pancreatitis caused by severe hypertriglyceridemia m
triglyceride levels over 2,000 mg/dl.

Dyslipidemia in Nonalcoholic Fatty Liver Disease

Fatty liver disease seems to occur in both genetic and acquired hypertriglyceridemia. It usually is caused by the synth
in amounts that are excessive relative to the amount of apo B that is synthesized; this leads to accumulation of triglyc
the hepatic secretion of VLDL triglyceride. Fatty liver disease also may occur in heterozygous familial hypobetalipopro
decreased synthesis of hepatic apo B associated with this disorder. Alcoholic fatty liver disease also occurs with incre
synthesis in the face of impaired apo B synthesis.[14] Fatty liver disease has been associated with the metabolic syndr
central obesity, insulin resistance, and hypertriglyceridemia.

Any severe form of hypertriglyceridemia with defective VLDL catabolism also can be associated with fatty liver and he
familial LPL deficiency—a form of hypertriglyceridemia caused entirely by an extrahepatic defect in triglyceride hydrol
associated with fatty liver disease; in this setting, fatty liver disease regresses rapidly with restriction of dietary fat. In s
disease progresses to steatohepatitis that is associated with fibrosis and necrosis; the reasons for such a progression
second insult is needed for these patients to develop nonalcoholic steatohepatitis and then progress to cirrhosis.

Approach to the Patient with Abnormal Lipid Levels

Patients With Isolated Elevation of LDL Cholesterol Levels

A patient's cholesterol level is said to be "above desirable" in an individual with low atherosclerotic risk if the LDL chol
mg/dl. High LDL levels are those above 190 mg/dl. The patient's triglyceride level is by definition normal,[15] and the H
variable but is often normal. The lipid disorders in these patients are usually discovered through routine cholesterol sc
observers question the cost-effectiveness of screening men and women older than 20 years, the high prevalence of e
the United States warrants population screening, as recommended by the National Cholesterol Education Program (N

Severely elevated cholesterol levels are an indication of FH. The ability to diagnose FH is valuable because affected i
therapy from a relatively young age [see Familial Hypercholesterolemia, below].

Isolated hypercholesterolemia may be present intermittently in patients with FCHL. A family history that is strongly po
cardiovascular disease, or the presence of any of the other criteria for FCHL, should provide clues to the diagnosis of
Combined Hyperlipidemia, below]. Not all cases of mild isolated hypercholesterolemia are indicative of FH or FCHL; s
interactions of acquired and environmental factors, particularly dietary factors, with unknown genetic factors that conf
hypercholesterolemia.

Most current treatment guidelines are based primarily on LDL cholesterol levels, because reduction of LDL has been
cardiovascular disease by as much as 50%.[16] Reduction in the consumption of dietary saturated fat and cholesterol
reduction in LDL cholesterol levels; such a reduction depends in part on the baseline diet [see CE:IV Diet and Exercis

including diet and weight loss, will suffice in some individuals for reducing LDL cholesterol levels to an acceptable ran is unlikely to suffice in patients with familial forms of dyslipidemia, such as FH or FCHL.

In patients with familial forms of the disease or in patients for whom lifestyle measures alone fail to bring LDL choleste goals, cholesterol-lowering drugs should be added to the treatment regimen [see Drug Therapy in Dyslipidemia, below LDL cholesterol levels an additional 5% to 15% beyond reductions achieved with drugs.[17] Diet therapy can therefore dosages of required drugs and should be used in combination with drug therapy. The major class of drugs used to re statins. However, bile acid–binding resins and drugs that block cholesterol absorption are of value in patients who do statins alone, and they can be used in combination with statins and other drugs.

Patients With Isolated Elevation of Triglyceride Levels

An isolated elevation in triglyceride levels may be caused by a primary disorder of lipid metabolism (e.g., FHTG or FC to the use of therapeutic drugs; or it may be a component of the metabolic syndrome or type 2 diabetes mellitus. Unli has been difficult to determine the level of triglyceride at which the risk of CAD increases or decreases. It is valuable t hypertriglyceridemia, because the therapeutic approaches may differ.

For example, it is important to distinguish FHTG, which confers no risk of premature CAD, from FCHL, which is assoc of premature atherosclerosis.[17] However, it can be difficult to distinguish these disorders when FCHL is associated w positive personal or family history of premature atherosclerosis suggests FCHL. In addition, patients with FCHL freque cardiovascular risk factors (i.e., central obesity, hypertension, insulin re sistance, impaired glucose tolerance, increase activator inhibitor-1, (PAI-1) and increased levels of circulating inflammatory markers). Hypertriglyceridemia present in presence of increased numbers of small, dense LDL particles and confers an increased risk of premature cardiovascu hypertriglyceridemia associated with type 2 diabetes mellitus and the metabolic syndrome is an important cardiovascu cardiovascular risk factors are usually present in patients with type 2 diabetes mellitus, the metabolic syndrome, or FC therapeutic strategy must consider factors beyond the lipid disorder.

Patients with FHTG do not appear to be at significantly increased risk for developing premature CAD. However, they developing the chylomicronemia syndrome when secondary forms of hypertriglyceridemia are present, such as the hy by the use of triglyceride-raising drugs. The chylomicronemia syndrome occurs in FCHL in combination with other ca as well. In patients with pancreatitis caused by hypertriglyceridemia, triglyceride levels are above 2,000 mg/dl and can recommended that plasma triglyceride levels be maintained below 2,000 mg/dl to prevent recurrent acute pancreatitis level of less than 1,000 mg/dl.

Patients With Elevations in Cholesterol and Triglyceride Levels

Patients with elevations in the levels of both total plasma cholesterol and triglyceride fall into three categories. In the f elevation in VLDL and in LDL, as seen in FCHL. In the second category, there is an elevation in VLDL remnants and remnant removal disease. The third category consists of patients with very high triglyceride levels in whom the increa result of the cholesterol in VLDL and chylomicrons.

In patients with FCHL, an increase in triglycerides and in LDL cholesterol is often seen. These patients have elevated dense LDL particles. Therapy for these individuals often requires several drugs, one aimed at lowering the triglyceride reducing the amount of small, dense LDL particles [see Drug Therapy in Dyslipidemia, below].

In patients with remnant removal disease, the levels of plasma cholesterol and triglyceride are often equal. It is import removal disease in these circumstances. Therapy in this case is related to decreasing hepatic lipoprotein secretion wi

In patients with severe hypertriglyceridemia, the increase in total plasma cholesterol is a result of the cholesterol in VL Fibrates are often the drug of choice. However, it is very important to determine the etiology of the severe hypertriglyc offending drug [see Table 2] or treat any secondary cause for the hypertriglyceridemia.

Patients With Low HDL Cholesterol Levels

Many if not most patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels. Therefore HDL cholesterol levels should be considered in the context of the management of the underlying disorder (e.g., FCHL [see Patients with Isolated Elevation of Triglyceride Levels, above]. Isolated low HDL cholesterol levels of 20 to 30 m hypertriglyceridemia or other changes in lipid and lipoprotein levels are rare, but such low levels are a risk factor for c

the past, these reductions in HDL levels were often not identified; the screening strategies that were employed were b
total cholesterol levels, and total cholesterol levels often are not elevated in patients with isolated reductions in HDL. S
HDL cholesterol is required to identify these patients. The treatment of the rare patients with isolated low levels of HD
somewhat controversial. There are no currently available drugs that effectively increase HDL cholesterol levels only.[1
decreases VLDL triglyceride levels, also raises HDL cholesterol levels. Many studies of fibrate therapy for atheroscler
inconclusive. However, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonst
cardiovascular events.[19] Nicotinic acid, which acts at many metabolic sites, also raises HDL cholesterol. It decreased
Coronary Drug Project of the 1970s.[20] Few other studies have evaluated the effect of niacin on atherosclerotic event

Patients With Atherosclerosis and Normal Lipid Levels

On rare occasions, a middle-aged patient with established atherosclerosis is seen to have no detectable lipid or lipopr
addition to the standard lipid profile, measurement of apo B and Lp(a) will often reveal subtle lipoprotein abnormalities
numbers of small, dense LDL particles in these patients. Assessment of nonlipoprotein risk factors (e.g., homocystein
such as C-reactive protein [CRP]) also may be of value in assessing cardiovascular risk factors. Although the levels o
can be reduced by various strategies (e.g., homocysteine by folate therapy), the use of statins in all categories of high
those who have established vascular disease, has been shown to be of benefit, even if lipid levels are apparently nor

Genetic Disorders of Lipoprotein Metabolism

Primary disorders of lipoprotein metabolism are those that arise from genetic defects in the metabolic pathways of lipo
disorders caused by increased hepatic secretion of lipoproteins or by catabolic defects). The disorders that cause incr
are the metabolic syndrome, familial combined hyperlipidemia, type 2 diabetes mellitus, and FHTG; elevations of Lp(a
lipoprotein secretion. Disorders of LDL catabolism are FH and familial defective apo B-100. Remnant removal disease
catabolism.

Metabolic Syndrome

The metabolic syndrome consists of a central distribution of adiposity or visceral obesity; insulin resistance; elevations
levels; impaired glucose tolerance; hypertension; dyslipidemia; and an abnormal procoagulant state. Many features o
to predispose men and women to premature CAD.[12]

Etiology and Risk Factors

An accumulation of visceral rather than subcutaneous fat has been observed in individuals with the central body fat di
the metabolic syndrome. Men have more visceral fat than premenopausal women, even when matched for body mass
suggested that these differences in visceral fat and the associated changes in lipoproteins and blood pressure could a
difference in risk of premature CAD between men and premenopausal women.[21,22] Increased visceral fat is associate
hyperinsulinemia, low plasma adiponectin, and elevations in plasma free fatty acid levels.[23] It has been suggested th
visceral fat precedes and causes insulin resistance and the resultant hyperinsulinemia, because insulin sensitivity incr
levels fall when visceral fat is decreased after caloric restriction.[24]

The levels of insulin, glucose, triglyceride, HDL cholesterol, blood pressure, PAI-1, and other inflammatory markers ar
mean normal in patients with the metabolic syndrome. Although these variables are usually shifted to high levels, som
the high-normal range in some affected individuals. HDL levels tend to be lower than mean normal. Genetic and envir
affect the distribution of these variables in both normal persons and those with the metabolic syndrome. Because the
associated with multiple cardiovascular risk factors, individuals with the metabolic syndrome are at increased risk for (
who meet the NCEP guidelines for the metabolic syndrome[25] [*see* Diagnosis, *below*] are at increased risk for premat
However, type 2 diabetes mellitus and FCHL are specific disorders of which the metabolic syndrome is a component.
account for at least 40% to 50% of premature CAD and need to be considered in the context of the metabolic syndror

The risk of abdominal fat patterning, dyslipidemia, impaired glucose metabolism, and hypertension—the sentinel sym
syndrome—increases with age.[26] Central obesity associated with the metabolic syndrome may be evident in young a
adolescent growth; however, it is more typical for central obesity and insulin resistance to manifest in midlife. Wherea
cholesterol levels may not predict the onset of atherosclerosis in the elderly, central obesity, hypertension, and insulin
for atherosclerosis, and their prevalence increases with age,[26–30] possibly because of the metabolic syndrome.

Pathophysiology

Although the association of central obesity and insulin resistance with dyslipidemia is well established, the underlying
One mechanism that would explain the association of central obesity and insulin resistance with dyslip idemia is an in
chain free fatty acids. Such an increase would inhibit hepatic apo B from undergoing degradation in the endoplasmic r
increase the likelihood of apo B undergoing hepatic secretion as triglyceride-containing lipoproteins. This would accou
of triglyceride and the increased number of VLDL and LDL particles seen in patients in insulin-resistant states.[31] Ano
fatty acids is to increase hepatic lipase on the surface of hepatic cells. Hepatic lipase hydrolyzes triglyceride and phos
decreasing the size of each particle [*see Figure 6*].[12] However, CETP also contributes to this lipoprotein remodeling
lipase or CETP has the predominant effect on the size and density of LDL and HDL particles depends on the triglycer
secretion rate of VLDL. The differences in LDL particle size and HDL_2 levels between men and premenopausal wome
for by differences in visceral fat in men and women.

Diagnosis

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) has suggested five clinical vari
for the metabolic syndrome: (1) increased waist circumference, (2) increased triglyceride level, (3) decreased HDL ch
blood pressure, and (5) elevated level of fasting plasma glucose [*see Table 3*].[15] A diagnosis of the metabolic syndr
more of these clinical variables are present. When these five variables were assessed in a survey of 8,814 adult men
24% of those surveyed met the diagnostic criteria for diagnosis of the metabolic syndrome.[32,33] The World Health Or
criteria for the metabolic syndrome. An attempt to harmonize the two sets of criteria is in progress.

Visceral obesity and insulin resistance are major contributors to the dyslipidemia associated with the metabolic syndr
abnormalities are associated with the metabolic syndrome: increased levels of triglyceride; increased numbers of sma
increased apo B levels; and decreased levels of HDL cholesterol. However, in normal, randomly selected populations
and insulin resistance were associated with only a slight increase in triglyceride levels and only a slight decrease in H
contrast, visceral obesity and insulin resistance can contribute to a more severe dyslipidemia, such as that associated
mellitus and FCHL.[12]

The dyslipidemia of the metabolic syndrome can be diagnosed by demonstrating mild to moderate increases in plasm
levels, decreased levels of HDL cholesterol, and normal levels of LDL. Although the LDL level is normal in patients wi
of LDL particles is generally increased; the predominant form is small, dense LDL particles, which are cholesterol poo
LDL particles. The presence of small, dense LDL particles can be determined by direct measurement of LDL size or c
measurement of plasma apo B levels in clinical practice is not necessary for the diagnosis of this disorder; however, r
B levels can indicate the presence of increased numbers of small, dense LDL particles. Similarly, total HDL levels refl
levels, indicating that HDL subfractions do not need to be measured.[34]

Treatment

Aerobic exercise and a diet low in saturated fat are indicated as therapy for most people with the metabolic syndrome
is severe or FCHL or type 2 diabetes mellitus is present, more aggressive therapy is indicated [*see CE:IV Diet and Ex
Therapy in Dyslipidemia, below*].

Familial Combined Hyperlipidemia

FCHL is an autosomal dominant disorder that accounts for up to half of the familial causes of CAD[35]; it was first desc
of myocardial infarction.[36–38] FCHL is characterized by elevations in triglyceride or cholesterol levels, or both, in affe
increases in triglyceride and cholesterol levels, patients with FCHL characteristically have elevations in apo B levels a
small, dense LDL particles.[39]

Genetic linkage analysis suggests that the inheritance of the lipid phenotype in FCHL involves separate gene effects[4
levels[41] and the increased numbers of small, dense LDL particles that are present in FCHL families. Further evidenc
comes from studies that found that in one third of individuals with FCHL, the activity level of LPL in postheparin plasm
Visceral obesity and insulin resistance contribute to the dyslipidemia seen in FCHL but cannot account for the elevatic

In the Familial Atherosclerosis Treatment Study (FATS), intensive lipid-lowering therapy with nicotinic acid or lovastat
colestipol led to decreased hepatic lipase activity; decreased numbers of small, dense LDL particles; and elevated lev
with subsequent regression of CAD, as evidenced by angiography.[44] Intensive lipid lowering resulted in subsequent r
atherosclerosis, particularly in individuals with small, dense LDL particles who had FCHL or who had elevated Lp(a) le

An aggressive approach to modify reversible cardiovascular risk factors should be undertaken in individuals affected [
and therapeutic lifestyle modification that includes physical activity should be undertaken [*see CE:IV Diet and Exercis*
lowering drug therapy [*see* Drug Therapy in Dyslipidemia, *below*][18] and management of other cardiovascular risk fac
drug to use depends to some extent on whether the primary lipid manifestation is hypercholesterolemia, hypertriglyce
elevations of cholesterol and triglyceride. If hypercholesterolemia is the primary manifestation, the approach should be
hypercholesterolemic patient [*see* Patients with Isolated Elevation of LDL Cholesterol Levels, *above*]. If hypertriglycer
abnormality, the initial approach might be that used for patients with isolated hypertriglyceridemia. However, most pat
both triglyceride and LDL levels and will require combination therapy; regimens may combine a statin and niacin, fibra
Therapy in Dyslipidemia, *below*].

Type 2 Diabetes Mellitus

Patients undergoing treatment of type 2 diabetes mellitus characteristically have visceral obesity and insulin resistanc
secretion is present in insulin-resistant individuals who develop hyperglycemia. First-degree relatives of individuals wi
may be centrally obese and insulin resistant or may experience decreased insulin secretion in response to glucose; fir
both centrally obese and who have a defect in insulin secretion invariably develop type 2 diabetes mellitus. Although t
central obesity, insulin resistance, and defective insulin secretion are mostly unknown, type 2 diabetes mellitus is a cl
oligogenic disorder. Determining all of the genes involved will require careful phenotypic characterization of subsets o
diabetes mellitus.

The dyslipidemia of untreated diabetes mellitus and hypergly cemia is discussed later in this chapter under acquired c
Disorders That Cause Dyslipidemia, *below*]. The dyslipidemia of treated type 2 diabetes mellitus is similar to that of th
FCHL; it is characterized by a mild increase in triglyceride levels, decreased HDL_2 cholesterol levels, and increased n
particles. Treatment entails diet therapy, increased physical activity, and lipid-lowering drug therapy [*see* Drug Therap

Familial Hypertriglyceridemia

FHTG is a common inherited disorder, thought to be autosomal dominant, that affects about 1% of the population. FH
increase in triglyceride synthesis resulting in VLDL particles enriched with triglyceride secreted in normal numbers. Af
VLDL levels but low levels of LDL and HDL and are generally asymptomatic unless severe hypertriglyceridemia (i.e.,
develops. FHTG does not appear to be associated with an increase in the risk of premature CAD.[17]

A diagnosis is made by family history and examination of fasting lipoprotein profiles of the patient and relatives. The tr
250 to 1,000 mg/dl in approximately one half of first-degree relatives; a strong family history of premature CAD usuall
LDL levels should not be present.

Patients with FHTG should lose weight if necessary, exercise regularly, and reduce their intake of saturated fatty acid
exogenous estrogens, and other drugs that increase VLDL levels might need to be restricted. Diabetes, if present, sh
Hypertriglyceridemia in patients with FHTG often responds to these measures. If triglyceride levels exceed 500 mg/dl
nonpharmacologic therapy, drug therapy with a fibrate should be considered[19]; at levels above 1,000 mg/dl, drug the

Fibrates are the drugs of choice to reduce elevated triglyceride levels in patients with familial hypertriglyceridemia [*se*
Dyslipidemia, *below*]. In familial combined hyperlip idemia, niacin can be very useful. Niacin has several additional be
lipids—it increases HDL cholesterol levels; it reduces levels of small, dense LDL particles; and it may reduce Lp(a) lev
dramatic effect on triglycerides than fibrates, statins have been shown to be of value in high-risk patients with modera
increased levels of small, dense LDL particles, such as occur in patients with type 2 diabetes mellitus and FCHL.

Familial Hypercholesterolemia

FH is an autosomal dominant disorder caused by a mutation in the gene encoding the LDL receptor protein. The extre
FH has two mutant alleles at the LDL receptor locus, leaving the person with an absolute or nearly absolute inability to
circulation by the LDL receptor.[8] Heterozygotes with FH possess one normal allele, giving them approximately one h
activity. Because the LDL receptor contributes to VLDL remnant clearance from the plasma, a deficiency of LDL rece
accumulation of remnant lipoproteins. High concentrations of LDL result in nonreceptor-mediated uptake of LDL by th
including that of the arterial wall, which leads to the formation of xanthomas and atherosclerosis. The heterozygous fc
prevalence of about one in 500 people, making it one of the more common genetic diseases.[8]

Diagnosis

Hypercholesterolemia can be detected at birth in umbilical cord blood. If FH is not detected at birth, various associate the diagnosis later in life. Tendon xanthomas are a highly specific sign of FH; typically, they begin to appear by 20 yea present in up to 70% of older patients. Occasionally, xanthomas are seen on the patellar tendon. Because xanthomas examination of the dorsal hand tendons and Achilles tendon is required for their detection. Xanthelasma (cutaneous x and corneal arcus are common in patients with FH after 30 years of age; however, they also occur in normocholester corneal arcus is seen superiorly and inferiorly in the eyes and later becomes totally circumferential.

CAD develops early, with symptoms often manifesting in men in the fourth or fifth decade. Approximately 5% of all ca in patients with heterozygous FH.[8] Before the development of statin therapy, at least 50% of men with heterozygous years of age; in women, symptoms tend to develop about 10 years later. The total cholesterol level in heterozygous p from 350 to 550 mg/dl. The triglyceride level may be mildly elevated, and the HDL cholesterol level is reduced in abou LDL receptor function can be measured only in special laboratories.

Heterozygous FH should be suspected when severe hypercholesterolemia from elevated LDL is detected. If tendon x diagnosis is virtually certain. If tendon xanthomas are absent, secondary causes of hypercholestero lemia (e.g., hypot sought, but the diagnosis of familial hypercholesterolemia is not excluded. A comprehensive family history should rev premature CAD and hypercholesterolemia without hy pertriglyceridemia; the disorder affects approximately one half o presence of hypercholesterolemia and tendon xanthomas in a parent or sibling is virtually diagnostic, as is hyperchole family. Careful screening of family members is mandatory, because 50% of first-degree relatives will be affected and lowering therapy.[18,46]

Treatment

Management of FH requires both dietary intervention and drug therapy. The goal of therapy is to lower the LDL chole mg/dl, or even lower if the patient exhibits CAD. In patients with heterozygous FH, effective treatment is possible with intestinally active drugs, and nicotinic acid. Because LDL cholesterol levels tend to be very high, combination therapy required, and three drugs may be necessary [*see* Drug Therapy in Dyslipidemia, *below*]. Although diet therapy alone i with heterozygous FH, reducing saturated fatty acid and cholesterol intake will lower LDL levels and reduce the amou This is particularly important in children and adolescents before initiation of drug therapy. Tendon xanthomas have be LDL levels are maintained in a desirable range. Aggressive reduction of LDL cholesterol in men and women who have cause a regression of coronary atherosclerosis.

Familial Defective Apolipoprotein B-100

A mutation in apo B-100 that inhibits its binding to the LDL receptor is another genetic cause of elevations in the LDL disorder is unknown but is estimated to be 5% to 10% that of FH. LDL receptor structure and function are normal. A fu molecule is produced with a single amino acid substitution; this results in apo B that binds poorly to LDL receptors, le in the plasma.

Affected individuals are clinically indistinguishable from patients with heterozygous FH: they may present with severe tendon xanthomas, and premature atherosclerosis. Treatment with statins appears to lower LDL cholesterol levels in Specialized tests available only in selected research laboratories are required to distinguish affected people with defe defective LDL receptors.

Increased Levels of Lipoprotein(a)

Lp(a) is a specific class of lipoprotein particles synthesized in the liver.[5] An important component of Lp(a) is apo(a), homologous with plasminogen, a key protein in the coagulation cascade. Plasma concentrations of Lp(a) vary marke ranging from undetectable to 200 mg/dl. Lp(a) plasma concentration is strongly controlled by genetic factors.

Most epidemiologic studies suggest that Lp(a) is a risk factor for CAD and stroke. If Lp(a) is atherogenic, it may be be properties: Lp(a) has been shown to undergo endothelial uptake and oxidative modification and to promote foam cell has a high degree of homology with plasminogen, it may play a role in thrombosis by interfering with the binding of pl Elevated Lp(a) levels appear to increase the atherogenicity of other cardiovascular risk factors, with earlier onset of c

Data suggest that reducing LDL cholesterol levels in patients with high levels of Lp(a) may be an effective strategy to atherosclerosis and to prevent coronary events. The Lp(a) level itself can be reduced with high-dose niacin, estrogen, with LDL apheresis. Insufficient data exist regarding the efficacy of lowering the Lp(a) level per se to inhibit atheroscle

events.[5]

Remnant Removal Disease

Remnant removal disease, also called type III hyperlipoproteinemia, dysbetalipoproteinemia, and broad-beta disease, of VLDL particles that migrate in the beta position on electrophoresis (normal VLDL particles migrate in the pre-beta lo particles are chylomicron and VLDL remnants.

Remnant removal disease is caused in part by a mutation in the *APOE* gene[7] [*see* Regulation of Lipoprotein Catabol leads to an impairment in the hepatic uptake of apo E-containing lipoproteins and stops the conversion of VLDL and I presence of additional genetic, hormonal, or environmental factors, remnants do not accumulate to a degree sufficien because they are cleared by hepatic receptors that also bind, with less avidity, to apo B-48 and apo B-100. Remnant when an apo E defect (almost always the E2/E2 genotype) occurs in conjunction with a second genetic or acquired de overproduction of VLDL (such as occurs with FCHL) or a reduction in LDL receptor activity (such as occurs in heteroz hypothyroidism). The E2/E2 genotype is found in 1% of the white population and in virtually all persons with remnant i

Diagnosis

Persons with remnant removal disease have elevations in both cholesterol and triglyceride levels and are likely to dev reasons that are not understood, these patients are at particularly increased risk for peripheral vascular disease. Hype develop before adulthood. Palmar xanthomas (xanthoma striata palmaris)—orange-yellow discolorations of the palma pathognomonic for genetic remnant removal disease, but they are not always present. Palmar xanthomas may be diff carefully sought using good lighting. Tuboeruptive xanthomas are occasionally found at pressure sites, particularly the knees.

The diagnosis of remnant removal disease should be suspected in a person with elevated total cholesterol and triglyc and IDL cholesterol levels, and reduced LDL and HDL cholesterol levels. Cholesterol and triglyceride levels range fro are roughly equal, except during an acute exacerbation, at which time hypertriglyceridemia tends to predominate. Bet on electrophoresis, although this test is seldom used today. Ultracentrifugation demonstrates that the ratio of VLDL ch triglyceride is greater than 0.3. Definitive diagnosis is made by detecting the E2/E2 phenotype by isoelectric focusing genotype by gene analysis.

Treatment

Generally, therapy for remnant removal disease is the same as that for other forms of hypertriglyceridemia. A low-fat d exercise can have a major effect on lipid levels. Fibrates, statins, and nicotinic acid have been used successfully in th that increase triglyceride levels, such as bile acid–binding resins, must be avoided.

Rare Disorders

Severe hypertriglyceridemia can present in childhood as a result of LPL deficiency or, extremely rarely, as apo C-II de at risk for acute pancreatitis with severe hypertriglyceridemia and must be treated with moderate to severe dietary-fat triglyceride levels are below 1,000 to 2,000 mg/dl.

Homozygous FH is extremely rare and leads to severe hypercholesterolemia, atherosclerosis, and death, often in the Patients with homozygous FH may benefit from LDL apheresis. At the other extreme, the absence of apo B-containing from defects in the synthesis of apo B (e.g., homozygous hypobetalipoproteinemia) or from defects in the transport of endoplasmic reticulum. Individuals with very low apo B levels are not at risk for atherosclerosis.

The absence of HDL can occur in persons with homozygosity for defects in the cholesterol and phospholipid transpor heterozygous state is an uncommon cause of isolated low-HDL cholesterolemia11 (i.e., hypoalphalipoproteinemia).

Miscellaneous Common Dyslipidemias

Polygenic hypercholesterolemia was once thought to be common. Polygenic hypercholesterolemia is a term used to r mild elevations in LDL cholesterol in the apparent absence of a familial form of dyslipidemia or of dyslip idemia of sec of dyslipidemia continues to shrink as LDL variants such as Lp(a) and small, dense LDL particles are discovered.

Mild to moderate hypertriglyceridemia may occur in the presence of modest defects in LPL. Typically, it presents as a
conjunction with a decrease in HDL cholesterol levels. It is seen in the obligate heterozygote parents of children with l
may predispose to premature CAD.

Secondary Disorders of Lipoprotein Metabolism

Secondary dyslipoproteinemias are caused by acquired defects in lipoprotein metabolism that result in hypercholester
hypertriglyceridemia, or combined hyperlipidemia; the HDL level may or may not be low. Secondary hypertriglycerider
common genetic form of hypertriglyceridemia may be severe enough to cause chylomicronemia with pancreatitits. Dy
be caused by selected medications.

Endocrine Disorders That Cause Dyslipidemia

Untreated Hyperglycemia

Untreated hyperglycemia in patients with diabetes mellitus causes an increase in VLDL synthesis, a reduction in VLD
accompanying reduction in LPL activity, or both. These abnormalities result in hypertriglyceridemia and a reduction in
level usually is normal. Fasting chylomicronemia occurs when there is a coexisting primary form of hypertriglyceridem
compete to interact with LPL, and both lipoproteins may accumulate. A low HDL level results from impaired lipolysis o
lipoproteins, which supply lipid components for HDL development. These defects occur in both untreated type 1 and u
mellitus. Lipid levels should approach normal with comprehensive treatment of diabetes; if they fail to do so, additiona
[*see* Genetic Disorders of Lipoprotein Metabolism, *above*]. In diabetic patients with persistent moderate to severe hyp
acid is suitable because it reduces the secretion of VLDL and enhances the activity of LPL. Nicotinic acid may be use
in patients with type 2 diabetes mellitus, because it may exacerbate hyperglycemia.[47] Statins are effective in reducin
diabetic patients.[45]

Hypothyroidism

Hypothyroidism may cause a severe elevation of LDL levels because of reduced LDL receptor activity; in addition, it fr
hypertriglyceridemia and an associated reduction in the HDL level as a result of reduced LPL activity. Remnants of ch
also accumulate and unmask remnant removal disease. The dyslipoproteinemia that occurs with hypothyroidism is co
replacement.

Dyslipidemia Secondary to Estrogen and Progestin Therapy

Oral contraceptives that contain a combination of estrogen and progestin can have variable effects on lipoproteins, de
combination used. Estrogen tends to raise VLDL and HDL levels and lower LDL levels. Progestins tend to lower VLDl
LDL levels, but the effect varies considerably. Postmenopausal estrogen replacement therapy lowers LDL levels and
addition of progesterone to protect the uterus lessens these effects but does not eliminate them.[48] Estrogen may incr
levels in women who have an underlying primary triglyceride disorder, leading to pancreatitis; therefore, triglyceride le
monitored in these patients.[6] Oral combination therapy with estrogen and progesterone was associated with a mild in
Women's Health Initiative Study. In this randomized study of 16,608 women, use of oral hormone replacement therap
an excess rate of breast cancer. In women who have undergone hysterectomies, estrogen therapy has been shown to
[*see* Managing Dysplipidemia in Women, *below*].[49] These studies have led to a decrease in the use of postmenopau
therapy.

Renal Disorders That Cause Dyslipidemia

Nephrotic Syndrome

The nephrotic syndrome causes enhanced hepatic secretion of apo B-100-containing lipoproteins (i.e., VLDL) in resp
and other proteins in the urine. Hepatic synthesis of cholesterol is also increased. The LDL level is typically elevated,
elevated. The VLDL level elevation may be associated with a reduction in the HDL level as lipolysis becomes impaire
nephrotic syndrome are at increased risk for CAD, and the lipid disorder should be treated aggressively. Dietary chan
exercise may improve lipoprotein levels, but pharmacologic therapy is necessary to achieve desirable lipoprotein leve
effective in the treatment of this disorder because it inhibits hepatic secretion of apo B-100-containing lipoproteins; ho
studied extensively for this use. The statins are useful in lowering LDL cholesterol levels in patients with the nephrotic
drug therapy with statins, nicotinic acid, fibrates, or ezetimibe may be necessary for the reduction of LDL cholesterol a

Drug Therapy in Dyslipidemia, *below*]. Studies are needed to evaluate the effects of various drug combinations on ca

Chronic Renal Failure

Chronic renal failure produces hypertriglyceridemia as a result of a decrease in LPL and hepatic triglyceride lipase.[50] range from 150 to 750 mg/dl, and the HDL level is usually low; the risk of CAD is increased. Dietary measures should treatment is being considered. Gemfibrozil, a drug that enhances LPL activity, has been shown to be effective in lowe patients with renal insufficiency.[51] Gemfibrozil is preferred over other fibrates (e.g., fenofibrate and clofibrate) in this is partly cleared by the liver; as such, it carries a lower risk of drug-induced myopathy than do fibrates that are cleared Nonetheless, because gemfibrozil is partially excreted renally, the drug should be administered in the lowest effective statins have been less well studied in this condition. Combination therapy with nicotinic acid, statins, or gemfibrozil ma therapeutic goal.

Gastrointestinal Disorders That Cause Dyslipidemia

Primary biliary cirrhosis is the most significant gastrointestinal cause of dyslipidemia. In the early stages of primary bil hepatocellular function remains, mild elevations of VLDL and LDL levels occur because of elevations in the levels of r HDL. Terminal liver disease with cirrhosis results in severe elevation in cholesterol levels because of increased produ abnormal lipoprotein particle containing albumin and other plasma components that is rich in free cholesterol and pho terminal disorder requires liver transplantation.

Other Causes of Secondary Dyslipidemia

Many commonly used drugs have adverse effects on lipoproteins [*see Table 2*]. Discontinuance of the drug often will increase in VLDL, LDL, and HDL cholesterol levels can result from the use of drugs for the prevention of rejection afte Pravastatin is the drug of choice for lowering LDL levels because of its unique catabolic pathways. Immunosuppressiv cyclosporine compete with atorvastatin and simvastatin for the cytochrome P-450 3A4 system. The use of antifungal a with the metabolism of these statins. The predominant dyslipidemia that is seen in patients with AIDS is similar to the patients with the metabolic syndrome; mild hypertriglyceridemia is common, and low HDL cholesterol is seen in some extreme hypertriglyceridemia can result from the use of HIV drugs, and the resultant hypertriglyceridemia may be ass The etiology of dyslipidemia in AIDS is complex: excessive free fatty acid mobilization is seen, along with the develop insulin resistance. In addition, AIDS patients typically use dyslipidemia-causing drugs. The specific therapy in each pa individualized.

Prevention and Treatment of Coronary Artery Disease

Primary Prevention

The treatment of lipid disorders in individuals who do not have clinical evidence of CAD is considered primary prevent based on the assumption that modification of lipid risk factors will alter the natural history of the untreated condition—hypothesis. An association between cholesterol and CAD has been known since the early 1950s; however, it was not Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in 1984 that there were data to support the lipi

The LRC-CPPT enrolled almost 4,000 men with moderate hypercholesterolemia; patients were followed for 7 years. T prescribed cholestyramine, which resulted in LDL cholesterol levels being 12.6% lower than those of the control subje placebo. The cholestyramine group had a 19% reduction in CAD deaths and nonfatal myocardial infarcts (*P* < 0.05), a mortality was observed.[53] Further analysis demonstrated that the extent of benefit depended upon the achieved redu (reflecting drug compliance). Use of a proportional hazards model indicated that a 25% decrease in total cholesterol c cholesterol would be expected to decrease the risk of a CAD event by 50%.[54]

The Helsinki Heart Study used the fibrate gemfibrozil to treat dyslipidemic men without CAD. After 6 years of follow-up events was seen in the treatment group, compared with the group receiving placebo.[55] Again, no decrease in CAD m

In both the Helsinki Heart Study and the LRC-CPPT, the sample size was calculated on the power to detect CAD eve alone. As such, the lack of an effect on mortality was not surprising, but an increase (not statistically significant) in nor treatment groups of both these studies was troublesome[53–55] and confounded the recommendations for primary prev hypercholesterolemic patients. These concerns were not completely addressed until 1995, when results of the West c Prevention Study (WOSCOPS) were published.[56]

The WOSCOPS trial evaluated the effect of 5 years of treatment with pravastatin on the incidence of nonfatal myocar
deaths in 6,595 men. The men were middle-aged (45 to 64 years of age) and moderately hypercholesterolemic (LDL
mg/dl). The treatment group manifested a 20% reduction in total cholesterol, a 26% reduction in LDL cholesterol, a 12
and a 5% increase in HDL cholesterol, as compared with the control group. On the basis of intention-to-treat principle
associated with a 31% risk reduction in nonfatal MI or CAD deaths ($P < 0.001$), a 32% risk reduction in all cardiovascu
a 22% risk reduction in total mortality ($P = 0.051$). In addition, coronary interventions (i.e., angiography, angioplasty, a
surgery) were reduced 31% to 37% ($P < 0.01$).

The reduction in clinical events began within 6 months of randomization and were independent of other risk factors, su
blood pressure, family history of CAD, and the ratio of total cholesterol to HDL cholesterol.[57] Although there was no r
decrease in LDL cholesterol, a decrease in LDL cholesterol of approximately 24% was adequate to see the full benefi
treatment effect was proportionately the same regardless of baseline lipid levels and the reduction in LDL cholesterol.
alone did not account for all the benefits of treatment with pravastatin.[58] Importantly, there was no increase in nonco
reported in earlier primary preventive trials.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was the first large primary inte
effects of cholesterol lowering in individuals with average cholesterol levels.[59] That is, the mean total and LDL choles
average value for the general population (221 mg/dl and 150 mg/dl, respectively). In addition, it was the first large stu
a total of 6,605 patients). Lovastatin was the treatment agent in this randomized, placebo-controlled trial. LDL cholest
follow-up was 5 years. The total absolute benefit was 2%, meaning that 50 patients had to be treated for 5 years to pr
treatment group had a 28% reduction in cardiovascular hospitalizations, a 23% decrease in angioplasty, and a 32% re
surgery. An analysis of the cost-effectiveness of lovastatin treatment demonstrated a 27% (or $524 per patient) reduc
care costs for the lovastatin group, as compared with the group that received placebo.[60]

Persons with average cholesterol levels were also evaluated in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid
LLA).[61] Nearly 20,000 hypertensive patients were randomized to one of two antihypertensive regimens. The lipid-low
randomized 10,305 patients with total cholesterol levels of 251 mg/dl or lower to treatment with atorvastatin or placeb
early because a significant benefit was observed in the treatment group. Median follow-up was 3.3 years. The study d
statistically significant reductions in cardiovascular or all-cause mortality; however, significant reductions were seen in
cardiovascular events and procedures, and stroke.[61]

The effect of atorvastatin (10 mg/day) on primary prevention of cardiovascular disease in diabetic patients was exami
Atorvastatin Diabetes Study (CARDS).[45] CARDS randomized almost 3,000 diabetic patients with LDL levels of 160 r
levels of 600 mg/dl or lower, and at least one of the following: retinopathy, albuminuria, smoking habit, or hypertensio
years early because predetermined criteria had been met. The atorvastatin group demonstrated a 36% reduction in c
reduction in coronary revascularization procedures, a 48% decrease in stroke, and a 27% reduction in all-cause deatl
placebo group.

These studies support lipid-lowering therapy as primary prevention for patients with high LDL and average LDL values
on primary prevention in patients with other lipid abnormalities, such as isolated low HDL cholesterol levels or elevate

Secondary Prevention

Lipid-lowering therapy in patients with documented CAD is considered secondary prevention. Lipid levels have a sign
death rates in those with and without CAD; however, the impact is significantly greater in patients with established CA

Several trials have investigated the effect of aggressive lifestyle intervention in patients with CAD. The Saint Thomas
Study (STARS) randomized men with CAD and total cholesterol levels above 232 mg/dl to conventional care or a low
Despite relatively modest changes in lipid levels (the intervention group had an LDL cholesterol average of 162 mg/dl
decreased and the rate of regression increased in the intervention group. Angina symptoms also improved.[63]

The effects of a Mediterranean diet (increased α-linoleic acid) were compared with those of a prudent Western diet in
[64] All study participants had had a first MI. Those consuming the Mediterranean diet had lower rates of primary (deat
(unstable angina, stroke, heart failure) end points than those on the prudent Western diet at 27 months. This effect pe
follow-up. The group on the Mediterranean diet had a rate of combined primary and secondary end points of 2.59 eve
year, compared with 9.03 events per 100 patients per year in the group on the prudent diet.[65]

A variety of pharmacologic agents have been used alone and in combination in secondary prevention trials. Some tria

end points in assessing progression or regression of CAD, whereas others have used clinical end points. The Familia
Study (FATS) examined the effect of several lipid-reducing regimens in men with elevated apo B levels. The two most
(nicotinic acid-colestipol and lovastatin-colestipol) were equally effective; both regimens were associated with delayed
25%, respectively, versus 46% in the placebo-colestipol group) and an increased likelihood of regression of coronary
39%, respectively, versus 11% in the placebo-colestipol group). Clinical end points (death, MI, worsening angina, and
also reduced in the more aggressively treated groups (4.2% and 6.5%, respectively, versus 19% in the placebo-coles
first major study to document the regression of CAD with aggressive lipid-lowering therapy. A subsequent analysis of
the change in CAD severity with therapy-induced changes in LDL buoyancy and hepatic lipase activity.[66]

The Scandinavian Simvastatin Survival Study (4S) evaluated 4,444 patients with known CAD and moderate to severe
baseline (total cholesterol concentration ranging from 212 to 309 mg/dl).[67] Patients were randomized to a regimen of
plus placebo. At 5.4 years, there was a significant reduction in total mortality (8% on simvastatin versus 12% on place
(19% versus 28%), CAD deaths (42% reduction), and cerebrovascular events (2.7% versus 4.3%). The reduction in c
correlated with total cholesterol and LDL cholesterol levels and with changes from baseline.[68]

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial randomized approximately 9,000 men
of recent MI or unstable angina to receive either placebo or pravastatin.[69] The study was stopped prematurely at 60
significant benefit associated with pravastatin therapy. CAD death was reduced in the treatment arm of the study (6.4
total mortality (11% versus 14%), stroke (20% relative decrease), need for bypass surgery (8.9% versus 11.3%), and
The benefit was primarily related to changes in lipid levels and was seen in all predefined subgroups. The greatest re
was seen in those patients thought to be at highest risk, as assessed by concomitant risk factors.[70]

The Cholesterol and Recurrent Events (CARE) trial evaluated 4,159 patients with relatively low lipid levels. The avera
was 209 mg/dl, and the average LDL cholesterol level was 139 mg/dl. Treatment with pravastatin over 5 years resulte
coronary death or nonfatal myocardial infarction (10.2% versus 13.2% for placebo), need for revascularization (14.1%
frequency of stroke (2.6% versus 3.8%).[71] However, in contrast to the results seen with 4S and LIPID, the absolute c
LDL had little relationship to coronary events.[72] The benefits were seen only in patients with LDL levels above 125 m

The Heart Protection Study enrolled over 20,000 persons with a history of cardiovascular disease (coronary, cerebrov
vascular disease), diabetes, or treated hypertension.[73] As such, it was a mixture of primary and secondary interventi
individuals had baseline LDL cholesterol levels below 116 mg/dl, and 25% had initial LDL levels ranging from 116 to 1
randomized to receive simvastatin or placebo. After an average follow-up of 5.5 years, the lipid-lowering group showe
cardiovascular events, an 18% reduction in cardiovascular deaths, and a 13% reduction in all-cause mortality, as com
group. The percentage reductions in events were similar in all three tertiles of baseline LDL cholesterol levels and in p
levels below 100 mg/dl at baseline. These results differ from those reported in the CARE study, but they are consister
and LIPID trials. The results of the Heart Protection Study also suggest that there may not be a threshold beyond whic
therapy ceases to improve outcome, at least in patients at high risk for recurrent coronary events.

Aggressive LDL-lowering therapy appears to be more effective than standard lipid-lowering treatment. The Pravastati
and Infection Therapy (PROVE-IT) trial compared standard LDL-lowering treatment (pravastatin, 40 mg daily) with int
treatment (atorvastatin, 80 mg daily) in more than 4,000 patients recently hospitalized with an acute coronary syndrom
up was 24 months. The median LDL cholesterol level achieved with atorvastatin was 62 mg/dl, compared with 96 mg/
pravastatin. The primary composite end point was death from any cause, MI, unstable angina not requiring hospitaliza
revascularization, and stroke. The rate of reaching the primary end point was 22.4% in the atorvastatin group and 26.
The benefit of aggressive therapy with atorvastatin was apparent as early as 30 days after initiating therapy and was

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial also compared moderate LDL-low
40 mg daily) with more intensive LDL-lowering therapy (atorvastatin, 80 mg daily).[75] The study used coronary intrava
sensitive means of measuring plaque volume, as a baseline measurement and primary end point. The median percer
volume was -0.4% in the atorvastatin group, compared with +2.7% in the pravastatin group. This finding correlated wi
levels of 79 mg/dl in the atorvastatin group and 110 mg/dl in the pravastatin group. These results gave further suppor
LDL-lowering therapy is superior to standard LDL-lowering therapy.

Few studies have examined the benefit of raising HDL cholesterol levels in the secondary prevention of CAD. The VA
patients with known CAD and with LDL cholesterol levels below 140 mg/dl, HDL cholesterol levels of 40 mg/dl or abov
300 mg/dl or below.[19] The patients were randomized to receive gemfibrozil or placebo. The subsequent mean HDL c
gemfibrozil group was 6% higher than that in the placebo group, and the mean triglyceride level in the gemfibrozil gro
mean LDL cholesterol levels were 113 mg/dl in both groups. The combined primary end point of cardiac death and nc
was 17% in the gemfibrozil group and 22% in the placebo group (relative risk reduction, 22%). The beneficial effect of

apparent until 2 years after randomization.

Combination therapy using a statin to lower LDL cholesterol levels and niacin to raise HDL cholesterol levels has bee
increased cardioprotection. In one study, patients were randomized to one of four groups: simvastatin plus niacin, vita
plus antioxidants, or placebos. At entry, the HDL choleseterol level was below 35 mg/dl, and the LDL cholesterol leve
mean LDL and HDL cholesterol levels were unaltered in the antioxidant and placebo groups but were changed signifi
plus niacin groups (mean LDL cholesterol level reduced by 42% and mean HDL cholesterol level raised by 26%). At 3
clinical events in the simvastatin and niacin groups was greater than that which is usually reported in studies of statins
0.4 compared with placebo), suggesting that a benefit may be associated with the elevation of HDL cholesterol levels
no additional benefit and may even have attenuated the benefits of combination therapy.[76]

Risk Stratification

CAD risk factors seldom occur in isolation, and the risk associated with each varies widely in combination with other r
risk prompted the NCEP ATPIII to standardize guidelines for risk assessment of CAD. Over time, the guidelines were
more aggressive lipid-lowering targets as a means of reducing CAD risk. This evolution in guidelines is the result of cc
that extend our understanding of dyslipidemia, associated risk factors and their relationship to CAD, and the utility of r

The ATP guidelines focus primarily on LDL cholesterol levels as the major lipid risk factor. More recently, low HDL lev
risk assessment. In ATPIII, the metabolic syndrome was added as a risk factor in an attempt to assess risk for CAD in
who have modest elevations in triglyceride levels, low HDL cholesterol levels, and small, dense LDL particles, as well
or FCHL. In an effort to better identify those at highest risk for CAD events, the NCEP recognizes several CAD equiva
diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, and mu
a 10-year risk of CAD greater than 20%.[15] The presence of these CAD equivalents requires a level of therapeutic ag
recommended for patients with established CAD.

The American College of Physicians (ACP) has adopted a somewhat less aggressive recommendation for treatment
diabetes mellitus. The ACP reserves the use of statins for patients with type 2 diabetes and other CAD risk factors.[77]
not differentiate between the risk of CAD in patients with type 1 diabetes and that in patients with type 2 diabetes. An
the CAD risk is greater in type 2 diabetes and that treatment guidelines should differentiate between these entities.

The ATPIII guidelines use the Framingham scoring system for estimating the 10-year risk of CAD. Some studies indic
score overestimates risk in Japanese-American and Hispanic men, Native-American women, and some European an
also has been suggested that the Framingham score weights age too heavily as a risk factor. The Pravastatin in Elde
Vascular Disease (PROSPER) study, which is the only prospective study to assess statin therapy in men and women
demonstrated that statin therapy was of no benefit in those without preexisting atherosclerosis.[81] Any age bias prese
scoring system is eliminated when the system is used to predict risk in nonelderly patients.

A multicenter, international study confirmed the validity of risk stratification. In this study of over 15,000 patients with a
over 90% of the population-attributable risk could be accounted for by nine potentially modifiable risk factors.[82] Most
by an elevated apo B to apo A1 ratio, smoking, hypertension, and diabetes. These risk factors were more important in
individuals. As such, principles of cardiovascular disease prevention are similar worldwide and have the potential to h

Drug Therapy in Dyslipidemia

Drugs Used to Lower LDL Cholesterol Levels

Several classes of drugs lead to a reduction in LDL cholesterol levels [see Table 4].[16] Before the introduction of stati
major drugs used for this purpose were the bile-acid sequestrants and niacin. The introduction of statins, with their po
cholesterol, their tolerability, and their relative lack of toxicity, provided a significant advance in the management of pa
hypercholesterolemia. The introduction of intestinally active drugs has provided additional approaches both for monot
individuals who are unable to tolerate statins—and, more particularly, for combination therapy.

Statins. Several statins are now available, and new ones continue to be introduced. To date, statins have been highly
reducing clinical events, including stroke. Although some of the benefits of statins have been attributed to the so-calle
class of drugs, the extent of reduction in LDL cholesterol levels nonetheless appears to be the major determinant of ri

Intestinally Active Compounds. Bile-acid sequestrants were among the earliest drugs to become available for the tr

hypercholesterolemia, and they were the first class of drugs to demonstrate that the reduction of LDL cholesterol was
risk of CAD; however, their use was limited by their very poor tolerability and their modest effect in reducing LDL chol
triglyceride levels tend to increase with their use in patients with high baseline plasma triglyceride levels. The introduc
acid sequestrant, colesevelam, resulted in improved compliance with this class of drugs, especially when used in com
with very high LDL cholesterol levels (e.g., for patients with FH).

Unlike bile-acid sequestrants, the intestinally active drug ezetimibe directly inhibits cholesterol absorption. Although cl
appears ezetimibe is able to reduce LDL cholesterol by approximately 20%, whether used as monotherapy or in comb
lowering agents.[83] In addition, ezetimibe does not cause an increase in plasma triglyceride levels, as occurs with bile
Ezetimibe has not yet been reported in clinical trials with cardiovascular end points.

Drugs Used Primarily to Lower Triglyceride Levels

The preferred drugs for treatment of hypertriglyceridemia are the fibrates and niacin. Niacin is the best drug currently
cholesterol levels. It also produces modest reductions in LDL and reduces apo B levels, but because it worsens insuli
patients with type 2 diabetes mellitus is limited. Fibrates are the drugs of choice for patients with marked hypertriglyce
primary goal of therapy is the prevention of pancreatitis and other features of the chylomicronemia syndrome. They al
hypertriglyceridemic states (e.g., the familial forms of hypertriglyceridemia and in some patients with diabetic dyslipide
triglyceride levels are more than mildly elevated. Fibrates also have a modestly beneficial effect on HDL cholesterol le
niacin are useful in combination therapy, primarily with statins.

Omega-3 fatty acids (e.g., those found in marine oils) have been used for the treatment of hypertriglyceridemia, espe
of therapy have failed to reduce markedly elevated levels of triglycerides.

Combination Therapy

Combinations of drugs often need to be used when both LDL cholesterol and triglyceride levels are elevated. Combin
when monotherapy, especially with statins, fails in achieving target lipid and lipoprotein levels, especially LDL choleste
combinations include statins and fibrates—although little is known of their additive benefit in reducing clinical events—
Statins and bile-acid sequestrants also are a useful combination, and the use of the new cholesterol absorption inhibit
drugs, particularly statins, is likely to be of value. In some cases, triple therapy (e.g., statins, niacin, and an intestinally

Special Issues in the Management of Dyslipidemia

Screening for Hypercholesterolemia in Children

Numerous autopsy studies demonstrate that coronary atherosclerosis begins in childhood and adolescence and that l
consistently associated with the extent of such atherosclerosis. Children in families with FH and early CAD have highe
childhood cholesterol levels are significant predictors of adult levels. However, a significant proportion of children and
mildly elevated cholesterol level will not as adults develop cholesterol levels high enough to warrant intervention; scre
cholesterol would risk labeling many young people as diseased. All children older than 2 years would benefit from a d
fat; this goal should be a part of any population strategy for controlling epidemic atherosclerosis. However, the safety
drug therapy have not been established in this age group, and treatment must be approached cautiously.

Considering these and other issues, the recommendations of the NCEP's Expert Panel on Blood Cholesterol Levels ir
seem appropriate.[84] Physicians should advise patients younger than 55 years who have a known CAD or a lipid diso
grandchildren should undergo regular cholesterol testing, and patients with a genetically well-defined lipid disorder sh
genetic counseling. Physicians who care for patients younger than 20 years who have markedly elevated LDL levels s
interventions before considering medications. If such measures are ineffective, resins should be used, and referral to
considered.

Treatment of young adults with elevated cholesterol levels is controversial. The strategy of matching the intensity of in
risk of atherosclerosis has been proposed, but for young adults, a short-term (e.g., 10-year) risk assessment may be i
the potential benefit of cholesterol lowering. It is incorrect to argue that all treatment can be safely deferred to later life
an atherosclerotic event. Population-level prevention and lifestyle interventions should still be favored for young adults
technology that better enable the identification of asymptomatic patients (of any age) who should take steps to reduce
Such advances may make it possible to reliably identify or quantify vulnerable plaques; markers of inflammation; or nc
endothelial dysfunction.

Managing Dyslipidemia in Women

Before menopause, women have a lower incidence of CAD than men of the same age. Although rare, CAD does occu women, usually in association with multiple genetic and environmental risk factors, such as in patients with familial for diabetic patients who smoke cigarettes.

After menopause, some women develop the metabolic syndrome, characterized by visceral obesity, insulin resistance dyslipidemia.[21] There is some evidence that estrogen replacement therapy can reverse these findings. However, the Study demonstrated that combined oral estrogen and progesterone did not protect women from CAD and that it in fac The estrogen-alone component of the Women's Health Initiative Study indicated that estrogen therapy carried modes CAD death); the study was halted prematurely because of increased risk of stroke.[49]

Managing Dyslipidemia in Older Patients

Age is the most significant risk factor for the development of atherosclerosis. CAD is currently a major cause of disabi populations; however, the relative risk associated with any single coronary risk factor decreases with age because of noncardiovascular mortality that affect an aging population. One implication of the complex relationships between risk conditions in the pathogenesis of coronary-related events in the elderly is represented by the multiple effects of treatm such as the decrease in LDL cholesterol levels and inflammation markers yielded by statins. A growing body of evider indicates that statin therapy is effective in the elderly; lipid-lowering therapy is probably indicated in this population in for atherosclerosis or who have preexisting atherosclerosis.[73,81] Primary intervention with drug therapy in persons no is controversial. In the PROSPER trial of persons older than 70 years, no benefit was seen with statin therapy in thos preexisting clinical atherosclerosis. Indeed, there was a suggestion of increased gastrointestinal cancer with statin the patients.[81] Attention to other concomitant diseases and the nutritional state, as well as to capabilities of the elderly, a in the management of older patients with dyslipidemia.[86]

Table 1.

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Table 1   Major Apolipoproteins and Their Functions

Apolipoprotein	Function
Apo A-I	Structural protein of HDL; activates lecithin-cholesterol acyltransferase
Apo A-II	Structural protein of HDL
Apo B-48	Structural protein of chylomicron
Apo B-100	Structural protein of VLDL, IDL, and LDL; ligand for LDL receptor
Apo C-II	Activator of LPL
Apo C-III	Potential inhibitor of apo C-II and apo E functions
Apo E	Ligand for chylomicron remnant receptor and LDL receptor
Apo(a)	Function unknown; antagonizes plasminogen

HDL—high-density lipoprotein   IDL—intermediate-density lipoprotein
LDL—low-density lipoprotein   LPL—lipoprotein lipase   VLDL—very low
density lipoprotein

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Table 2.

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Table 2   Effects of Selected Drugs on Lipoprotein Levels

Drug	VLDL	LDL	HDL
Alcohol*	+	0	+
Estrogens, estradiol*	+	−	+
Androgens, testosterone	+	+	−
Progestins	−	+	−
Glucocorticoids*	+	0	+
Cyclosporines	+	+	+
Tacrolimus	+	+	+
Thiazide diuretics*	+	+	−
Beta blockers*	+	0	−
Calcium channel blockers	0	0	0
Angiotensin-converting enzyme inhibitors	0	0	0
Sertraline*	Possible+	+	0
Protease inhibitors*	+	0	0
Valproate and related drugs	+	0	−
Isotretinoin*	+	0	−

*Can cause severe hypertriglyceridemia and chylomicronemia syndrome in patients with a familial form of hypertriglyceridemia or type 2 diabetes mellitus.

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Table 3.

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Table 3   Clinical Features of the Metabolic Syndrome[15]

The presence of three or more variables indicates a diagnosis of metabolic syndrome

Abdominal obesity: waist circumference > 35 in (women) or > 40 in (men)

Triglycerides ≥ 150 mg/dl

HDL cholesterol < 50 mg/dl (women) or < 40 mg/dl (men)

Blood pressure ≥ 130/85 mm Hg

Fasting plasma glucose ≥ 110 mg/dl

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Table 4.

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Table 4   Drug Treatment of Lipid Disorders

Drug	Dosage	Cost per Month	Comment
Bile acid–binding resins	Start with one packet (2 g for colestipol tabs) b.i.d., increase over 1–2 wk to desired dose		For elevated LDL, normal trig] drugs 1 hr before or 4 hr aft nicotinic acid, statins, or fib
Cholestyramine	Maximum 24 g/day b.i.d. or t.i.d.	$69	
Colestipol	Maximum 30 g/day b.i.d. or t.i.d.	$305	t.i.d. more effective
Colestipol tablets	Maximum 16 g/day	$267	
Colesevelam	Three 625 mg tablets b.i.d. with meals or six tablets/day with a meal; maximum seven tablets/day	$142	Better tolerated than other res
Ezetimibe	10 mg/day	$72	Can reduce LDL cholesterol by increasing plasma triglycer
Fenofibrate	200 mg/day	$73	For elevated triglycerides and
Gemfibrozil	600 mg b.i.d. before meals	$17	both LDL and triglycerides used with bile acid–binding acid; decrease dose with sev
Niacin	Start with 250 mg q.d. with meals; increase to 1.5–2.0 g/day; maximum 6 g/day	$28	For elevated LDL, triglyceride used with bile acid–binding
Statins			For elevated LDL; possibly us whom both LDL and trigly may be used with bile acid–
Atorvastatin	Start with 10 mg/day; maximum 80 mg/day	$95	
Fluvastatin	Start with 20 mg b.i.d. or at bedtime; maximum 80 mg/day	$68	
Lovastatin	Start with 20 mg b.i.d. or with dinner; maximum 80 mg/day	$126	
Pravastatin	Start with 10 mg at bedtime; maximum 40 mg/day	$120	May be used with drugs that enzymes CYP450, CYP3A4
Simvastatin	Start with 10 mg at bedtime; maximum 40 mg/day	$124	

Source: ACP Med

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