Hyperlipidemia

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 350)

Definition

- Hyperlipidemia is characterized by elevated levels of lipids (cholesterol, triglycerides, lipoproteins) in the blood.
- Lipoproteins
  - Complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides, and fat-soluble vitamins
  - Divided into 5 major classes, based on their relative densities
    - Chylomicrons
    - Very low-density lipoproteins (VLDL)
    - Intermediate-density lipoproteins (IDL)
    - Low-density lipoproteins (LDL)
    - High-density lipoproteins (HDL)
- Apolipoproteins
  - Required for assembly and structure of lipoproteins
  - Activate enzymes important in lipoprotein metabolism and mediate binding of lipoproteins to cell-surface receptors
  - Major apolipoproteins include apoA, apoB, apoC, and apoE.
- Lipid disorders
  - Group of disorders characterized by an excess of cholesterol, triglycerides, and/or lipoproteins present in the blood
  - Disorders may be primary (genetic) or secondary (due to medical diseases, diet, or drugs).
  - Primary disorders include isolated hypercholesterolemia and isolated hypertriglyceridemia.
  - Isolated hypercholesterolemia
    - Familial hypercholesterolemia (FH)
    - Familial defective apoB-100
    - Polygenic hypercholesterolemia
  - Isolated hypertriglyceridemia
    - Familial hypertriglyceridemia (FHTG)
    - Lipoprotein lipase (LPL) deficiency
    - Familial apoC-II deficiency
  - Hypercholesterolemia and hypertriglyceridemia
    - Familial combined hyperlipidemia (FCHL)
    - Familial dysbetalipoproteinemia (FDBL)
- Lipid-lowering therapy
  - Significantly reduces the development of atherosclerotic cardiovascular disease
  - LDL cholesterol (LDL-C) is the primary target of therapy.
  - The National Cholesterol Education Program (NCEP) provides guidelines for risk assessment and treatment.

- Adult Treatment Panel III (ATP-III) recommendations were last published in 2001.
- Some recommendations were updated in an interim report in July 2004.

Epidemiology

- Prevalence
  - Approximately 50% of US adults have a total serum cholesterol level >5.2 mmol/L (200 mg/dL).
  - Secondary hyperlipidemia
    - ~22% of adult Americans have metabolic syndrome (increased waist circumference, elevated serum triglyceride level, low HDL cholesterol (HDL-C) level, hypertension, and hyperglycemia)
  - Primary hyperlipidemia
    - FCHL
      - The most common primary lipid disorder: ~500 per 100,000 persons
      - ~20% of patients who develop coronary heart disease (CHD) before age 60 years have FCHL.
    - FH: 400 per 100,000 persons
    - FHTG: ~200 per 100,000 persons
    - Familial defective apoB-100: ~100 per 100,000 persons in Western populations
    - FDBL ~10 per 100,000 persons
    - LPL deficiency: 1 per 100,000 persons
    - Familial hepatic lipase deficiency, apoC-II deficiency, autosomal recessive hypercholesterolemia, Tangier disease, lecithin–cholesterol acyltransferase (LCAT) deficiency, and sitosterolemia: <0.1 per 100,000 persons
- Age
  - General
    - More common in men than women before age 50 years
    - More common in women than men after age 50 years
  - FCHL can manifest in childhood but may not be fully expressed until adulthood.
  - Most patients with biallelic FH mutations present in childhood.
- Distribution
  - Worldwide
  - Autosomal recessive hypercholesterolemia is a rare disorder, except in Sardinia.
  - FH has a higher incidence in certain groups, such as Afrikaners, Christian Lebanese, and French Canadians, due to a founder effect.
  - Homozygous deficiency of cholesteryl ester transfer protein occurs predominantly in Japan.

Mechanism

Primary hyperlipidemia

- Identification and characterization of genes responsible for the genetic hyperlipidemias have provided important molecular insight into the critical roles of apolipoproteins, enzymes, and receptors in lipid metabolism.

Disorders of apoB-containing lipoprotein metabolism (known etiology)

- Single-gene defects result in accumulation of specific classes of lipoprotein particles.
- Mutations in genes encoding key proteins in the metabolism and clearance of apoB-containing lipoproteins cause hyperlipoproteinemias, classified as 1 of the following types.
    - Type I (chylomicronemia)
    - Type II (elevations in LDL level)
    - Type III (elevations in IDL level)
- LPL and apoC-II deficiency (familial chylomicronemia syndrome; type I hyperlipoproteinemia)
    - Rare autosomal recessive disorder
    - Caused by numerous different mutations in *LPL* and *APOC2* genes.
    - Genetic deficiency of LPL or apoC-II results in impaired lipolysis and profound elevations in plasma chylomicrons.
    - Triglyceride-rich chylomicrons persist for days rather than being removed from the circulation after meals.
- Familial hepatic lipase deficiency
    - Rare autosomal recessive disorder
    - Caused by inactivating mutations in the *LIPC* gene
    - Results in elevation of VLDL remnants, elevated plasma cholesterol and triglyceride levels (mixed hyperlipidemia) due to accumulation of lipoprotein remnants
- FDBL (type III hyperlipoproteinemia or familial broad β disease)
    - Autosomal recessive or dominant disorder
    - Due to genetic variations in apoE that interfere with its ability to bind to lipoprotein receptors
        - Polymorphisms in the *APOE* gene result in the expression of 3 common isoforms: apoE3, apoE2, and apoE4.
        - apoE2 has a lower affinity for the LDL receptor.
        - Persons who are homozygous for the E2 allele form the most common subset of patients with FDBL.
        - Only a minority of these patients develop FDBL.
        - Additional factors precipitate the disorder (i.e., diet, obesity, coexisting diabetes).
    - Causes elevation in levels of both chylomicrons and VLDL remnants
    - Characterized by mixed hyperlipidemia due to accumulation of remnant lipoprotein particles
- FH
    - Autosomal codominant disorder
    - Caused by >750 mutations in the LDL receptor gene (*LDLR*)
    - A gene dosage effect occurs, such that persons with 2 mutated *LDLR* alleles are more severely affected than individuals with 1 mutated allele.
    - Results in markedly elevated LDL levels due to delayed catabolism of LDL and its precursors
- Familial defective apoB-100
    - Autosomal dominant disorder
    - Caused by missense mutations in the gene encoding in apoB-100 (predominantly R3500Q; additional rare mutations have also been reported)
    - Mutations result in reduced affinity of LDL for the LDL receptor, and therefore, reduced clearance of LDL.

- Autosomal recessive hypercholesterolemia
  - Caused by mutations in the gene encoding a protein (*ARH*) involved in LDL receptor–mediated endocytosis in the liver
  - Results in elevated LDL levels
- Wolman disease
  - Rare autosomal recessive disorder
  - Caused by deletions, insertions, or nonsense mutations in the *LAL* gene, leading to very low or absent activity of lysosomal acid lipase
  - Cholesterol ester storage disease is a less severe disorder caused by missense mutations in the *LAL* gene, associated with low but detectable acid lipase activity.
  - Both result in mixed hyperlipidemia, due to elevations in levels of plasma LDL and VLDL.
- Sitosterolemia
  - Rare autosomal recessive disorder
  - Caused by mutations in 1 of 2 members of the adenosine triphosphate–binding cassette transporter family (*ABCG5* and *ABCG8* genes)
    - Transporters normally form a functional complex to limit intestinal absorption and promote biliary excretion of plant- and animal-derived neutral sterols.
    - Mutations lead to increased intestinal absorption and reduced biliary excretion of plant sterols.
  - Results in elevated LDL cholesterol level

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.
  - Multiple genetic and nongenetic factors contribute to the hyperlipidemia.
- FHTG
  - Also referred to as *type IV hyperlipoproteinemia*
  - Autosomal dominant disorder of unknown molecular cause
  - Characterized by an elevated plasma triglyceride level accompanied by more modest elevations in cholesterol levels
  - VLDL is the major class of lipoprotein that is elevated in this disorder.
- FCHL
  - Autosomal dominant disorder of unknown molecular etiology
  - Results in moderate elevation of plasma triglyceride and cholesterol levels and reduced plasma HDL-C level
- Polygenic hypercholesterolemia
  - Characterized by hypercholesterolemia with a normal plasma triglyceride level in the absence of secondary causes 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 cholesterol levels.
  - Genetic forms of hypoalphalipoproteinemia (low HDL-C level) are not always associated with accelerated atherosclerosis.
  - Risk associated with low plasma levels of HDL-C depends on underlying mechanism.
- 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.

    - Plasma and tissue levels of free cholesterol are increased, resulting in development of corneal opacities and planar xanthomas.
    - Missense mutations in the apoA-I gene have been identified in selected patients with low plasma HDL cholesterol levels but are very rare causes of low HDL-C levels in the general population.
        - These patients have no clinical sequelae other than corneal opacities.
- Tangier disease
    - Autosomal codominant disorder
    - Caused by mutations in the gene encoding ABCA1, a cellular transporter that facilitates efflux of unesterified cholesterol and phospholipids from cells to apoA-I
        - ABCA1 has a critical role in the generation and stabilization of the mature HDL particle.
        - Loss of ABCA1 function leads to rapid HDL clearance.
    - Results in low plasma HDL-C level
- Classic LCAT deficiency (complete deficiency) and fish-eye disease (partial deficiency)
    - LCAT deficiency is caused by mutations in the gene encoding lecithin: cholesterol acyltransferase.
        - LCAT mediates the esterification of cholesterol, so 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 apoA-I.
    - Results in low plasma levels of HDL-C and apoA-I

Disorders of HDL metabolism (unknown etiology)

- The gene defect in some patients with a very high or very low plasma HDL-C level is not known.
- Familial hypoalphalipoproteinemia ("isolated low HDL level")
    - Autosomal dominant disorder
    - Caused by a disorder of HDL metabolism, the molecular basis of which is unknown
    - Appears to be associated with accelerated catabolism of HDL and its apolipoproteins

Secondary hyperlipidemia

- Significant changes in plasma levels of lipoproteins are seen in several common diseases.
- Alcohol consumption
    - Regular alcohol consumption has a variable effect on plasma lipid levels.
    - Most common effect is to increase triglyceride levels.
    - Alcohol stimulates hepatic secretion of VLDL, possibly by inhibiting the hepatic oxidation of free fatty acids.
    - Promotes hepatic triglyceride synthesis and VLDL secretion
- Type 2 diabetes mellitus
    - Dyslipidemia is common even if diabetes is well controlled.
    - High levels of insulin and insulin resistance associated with type 2 diabetes have multiple effects on fat metabolism.
        - Decrease in LPL activity, resulting in reduced catabolism of chylomicrons and VLDL
        - Increase in the release of free fatty acid from the adipose tissue
        - Increase in fatty acid synthesis in the liver
        - Increase in hepatic VLDL production

- Obesity
  - Increased VLDL (and sometimes LDL) production secondary to:
    - Increased adipocyte mass, decreased insulin sensitivity, and high dietary intake of simple carbohydrates
- Hypothyroidism
  - Associated with elevated LDL levels, due primarily to a reduction in hepatic LDL receptor function and delayed clearance of LDL
- Nephrotic syndrome
  - Causes a combination of increased hepatic production and decreased clearance of VLDL, with increased LDL production
- Cholestasis
  - Cholesterol is normally excreted into bile, either directly or after conversion to bile acids.
  - Cholestasis blocks this critical excretory pathway and leads to cholesterol accumulation in the circulation.
- Glycogen storage disease (e.g., von Gierke's disease)
  - Inability to mobilize hepatic glucose during fasting results in hypoinsulinemia and increased release of free fatty acids from adipose tissue.
  - Hepatic fatty acid synthesis is also increased, resulting in fat accumulation in the liver and increased VLDL secretion.
- Certain drugs have a significant effect on metabolism and can result in alterations in the lipoprotein profile.
  - Estrogens, β-adrenergic blockers, furosemide, glucocorticoids, retinoic acids, protease inhibitors, thiazides, tegretol

Symptoms & Signs

General

- Primary hyperlipidemias may present with such systemic manifestations such as xanthomas and such complications as pancreatitis.
- Secondary hyperlipidemias are typically asymptomatic.
- All hyperlipidemias can manifest with signs and symptoms of atherosclerosis and CAD.

LPL and apoC-II deficiency

- Usually presents in childhood, with recurrent episodes of severe abdominal pain caused by acute pancreatitis
- Eruptive xanthomas
  - Small yellowish-white papules
  - Often in clusters on the back, buttocks, and extensor surfaces of the arms and legs
  - Typically painless; may become pruritic as they regress
- Hepatosplenomegaly
- Recurrent pancreatitis
- Lipemia retinalis
- Premature atherosclerotic cardiovascular disease (ASCVD) has not been consistently demonstrated to be a feature of these syndromes.

Familial hepatic lipase deficiency

- Premature atherosclerosis

FDBL

- Patients usually present in adulthood with xanthomas and premature CAD and peripheral vascular disease.
    - Seldom presents in women before menopause
- 2 distinctive types of xanthomas are seen.
    - Palmar xanthoma (xanthomata striata palmaris)
        - Orange-yellow discolorations of the creases in the palms
    - Tuberoeruptive xanthomas
        - Begin as clusters of small papules on elbows, knees, or buttocks
        - Can grow to the size of small grapes
- Coronary heart disease (CHD)
- Peripheral vascular disease

FH

- Homozygous
    - Most patients present in childhood with cutaneous xanthomas on hands, wrists, elbows, knees, heels, or buttocks.
    - Corneal arcus is usually present.
    - Some patients have xanthelasmas (yellow, lipid-rich plaques present on the eyelids).
    - Atherosclerosis
        - CAD manifests in childhood or adolescence.
        - Often develops first in the aortic root
        - Can cause aortic valvular or supravalvular stenosis
        - Typically extends into the coronary ostia
    - Children with homozygous FH develop symptomatic vascular disease before puberty, when symptoms are atypical, and sudden death is common.
- Heterozygous
    - The age of onset of ASCVD is highly variable.
        - Possible from birth, although the disease is often not detected until adulthood
    - Tendon xanthomas
        - Involve the dorsum of the hands, elbows, knees, and especially the Achilles tendons
        - Present in ~75%
    - Premature development of symptomatic coronary atherosclerotic disease
    - Corneal arcus is common.

Familial defective apoB-100

- Tendon xanthomas
- Increased incidence of premature ASCVD
- Clinically resembles heterozygous FH

Autosomal recessive hypercholesterolemia

- Tendon xanthomas
- Premature coronary artery disease
- Clinically resembles homozygous FH

Wolman disease

- Presents within the first weeks of life
- Hepatosplenomegaly
- Steatorrhea
- Adrenal calcification
- Failure to thrive

Cholesteryl ester storage disease

- In childhood
  - Hepatomegaly
  - Mixed hyperlipidemia
    - Due to elevations in levels of plasma LDL and VLDL
- Adults
  - Hepatic fibrosis
  - Portal hypertension or premature atherosclerosis

Sitosterolemia

- Cutaneous and tendon xanthomas
- Premature atherosclerosis
- Episodes of hemolysis, presumably secondary to the incorporation of plant sterols into the erythrocyte membrane, are a distinctive clinical feature of this disease.

FHTG

- No specific clinical features suggest this diagnosis.
  - No xanthomas
  - No pancreatitis

FCHL

- Can manifest in childhood, but is often not fully expressed until adulthood
- Features of the metabolic syndrome (visceral obesity, glucose intolerance, insulin resistance, hypertension, and hyperuricemia) are often present.
- Patients do not develop xanthomas.

Polygenic hypercholesterolemia

- 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 familial defective apoB-100.

apoA-I deficiency

- Complete deficiencies of apoA-I
  - Clinically apparent coronary atherosclerosis typically appears between the fourth and seventh decades.
  - Corneal opacities
  - Planar xanthomas

- Missense mutations of apoA-I
  - Corneal opacities are present, but no other clinical sequelae.
  - No increase in the risk of premature CAD
  - A few specific mutations in apoA-I cause systemic amyloidosis.

Tangier disease

- Premature atherosclerotic disease
- Cholesterol accumulation in the reticuloendothelial system, resulting in:
  - Hepatosplenomegaly
  - Pathognomonic enlarged, grayish-yellow or orange tonsils
- May be accompanied by intermittent peripheral neuropathy (mononeuritis multiplex) or a sphingomyelia-like neurologic disorder

LCAT deficiency

- Progressive corneal opacification due to deposition of free cholesterol in the lens
- Variable hypertriglyceridemia
- In partial LCAT deficiency, there are no other known clinical sequelae.
- In complete LCAT deficiency
  - Hemolytic anemia
  - Progressive renal insufficiency

Differential Diagnosis

Distinguishing among disorders of lipid metabolism

- Patients with familial defective apoB-100 cannot be clinically distinguished from patients with heterozygous FH.
  - Patients with familial defective apoB-100 tend to have lower plasma LDL cholesterol levels than FH heterozygotes.
  - The apoB-100 gene mutation can be detected directly.
  - Genetic diagnosis is not encouraged because the recommended management of familial defective apoB-100 and heterozygous FH is identical.
- Autosomal recessive hypercholesterolemia clinically resembles homozygous FH.
  - The degree of hypercholesterolemia tends to be intermediate between levels seen in FH homozygotes and FH heterozygotes.
  - Skin biopsy and measurement of LDL receptor activity can differentiate these 2 conditions.
    - Autosomal recessive hypercholesterolemia: LDL receptor function in cultured fibroblasts is normal or only modestly reduced, whereas LDL receptor function in lymphocytes and the liver is negligible.
    - FH: LDL receptor activity in culture skin fibroblasts is reduced.
- FHTG
  - FDBL and familial combined hyperlipidemia FCHL should be ruled out, as these 2 conditions are associated with a significantly increased risk of ASCVD.
  - Plasma apoB levels and the ratio of plasma cholesterol to triglyceride tend to be lower in FHTG than in FDBL or FCHL.
- FCHL
  - FDBL should be considered and ruled out by beta quantification in suspected patients who have a mixed hyperlipidemia.

    - FCHL-affected family members typically have 1 of 3 possible phenotypes.
        - Elevated plasma LDL-C level
        - Elevated plasma triglyceride and VLDL-C levels
        - Elevated plasma LDL-C and VLDL-C levels
- FH
    - Clinical diagnosis is usually not problematic, but it is critical to exclude hypothyroidism, nephrotic syndrome, and obstructive liver disease before initiating therapy.

Secondary forms of hyperlipidemia

Elevated LDL level

- Hypothyroidism
- Nephrotic syndrome
- Cholestasis
- Acute intermittent porphyria
- Anorexia nervosa
- Hepatoma
- Drugs: thiazides, cyclosporine, tegretol

Decreased LDL level

- Severe liver disease
- Malabsorption
- Malnutrition
- Gaucher disease
- Chronic infectious disease
- Hyperthyroidism
- Drugs: niacin toxicity

Elevated HDL level

- Alcohol consumption on a regular basis has a variable effect on plasma lipid levels.
    - Most common effect is increased plasma triglyceride levels.
    - The usual lipoprotein pattern seen with alcohol consumption is type IV (increased VLDL).
    - Persons with an underlying primary lipid disorder may develop severe hypertriglyceridemia (type V).
    - Regular alcohol use is also associated with a mild to moderate increase in plasma levels of HDL-C.
- Exercise
- Exposure to chlorinated hydrocarbons
- Drugs: estrogen

Decreased HDL level

- Smoking
- Type 2 diabetes mellitus
- Obesity
- Malnutrition

- Gaucher disease
- Drugs: anabolic steroids, beta blockers

Elevated VLDL level

- Obesity
- Type 2 diabetes mellitus
- Glycogen storage disease
- Hepatitis due to infection, drugs, or alcohol
- Alcohol
- Renal failure
- Sepsis
- Stress
- Cushing syndrome
- Glucocorticoid excess
- Pregnancy
- Acromegaly
- Lipodystrophy
- Drugs: estrogen, beta blockers, furosemide, glucocorticoids, bile acid–binding resins, retinoic acid, HIV protease inhibitor

Elevated IDL level

- Multiple myeloma
- Monoclonal gammopathy
- Autoimmune disease
- Hypothyroidism

Elevated chylomicron level

- Autoimmune disease
- Drugs: isotretinoin

Elevated lipoprotein(a) level

- Renal insufficiency
- Inflammation
- Menopause
- Orchidectomy
- Hypothyroidism
- Acromegaly
- Nephrosis
- Growth hormone therapy

Diagnostic Approach

- History should inquire about personal and family history of hyperlipidemia and/or ASCVD.
    - In primary hyperlipidemia, family history is frequently positive for premature ASCVD on 1 side of the family, particularly among male relatives.

    - Family studies are useful to differentiate polygenic hypercholesterolemia from single-gene disorders.
        - Half of the first-degree relatives of patients with FH and familial defective apoB-100 are hypercholesterolemic.
        - <10% of first-degree relatives of patients with polygenic hypercholesterolemia are hypercholesterolemic.
    - Secondary causes of hyperlipidemias should be sought.
- Physical examination should focus on evidence of peripheral arterial disease, xanthomas, xanthelasmas, and features of the metabolic syndrome.
- Laboratory tests
    - Fasting plasma lipoprotein profile should be measured after a 12-hour overnight fast.
        - Screening should commence in all adults at age 20 years (2001 NCEP ATP-III guidelines).
        - Screening should be repeated every 5 years.
    - Specialized laboratory tests identify patients with many of the inherited disorders of lipid metabolism.

Laboratory Tests

Screening tests

- Total cholesterol and plasma triglycerides
    - Measured enzymatically
- HDL-C
    - Level in the supernatant is measured after precipitation of apoB-containing lipoproteins.
- LDL-C
    - Can be estimated by using the Friedewald equation
        - LDL-C = total cholesterol – (triglycerides/5) – HDL-C
        - Estimation is reasonably accurate if test results are obtained on fasting plasma and if the triglyceride level is < ~4.0 µmol/L (350 mg/dL).
    - If triglyceride level is > ~4.0 µmol/L (350 mg/dL), determine LDL-C by ultracentrifugation (beta quantification).
- VLDL cholesterol
    - Estimated by dividing the plasma triglyceride by 5, reflecting the ratio of cholesterol to triglyceride in VLDL particles

Tests/lipid patterns for specific genetic disorders

- LPL and apoC-II deficiency
    - Diagnoses are established enzymatically by assaying triglyceride lipolytic activity in post-heparin plasma.
    - Blood is sampled after intravenous heparin injection to release endothelial-bound lipases.
    - LPL activity is profoundly reduced in both LPL and apoC-II deficiency.
        - In patients with apoC-II deficiency, 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.
    - 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.
    - Fasting triglyceride levels are almost invariably >11.3 µmol/L (1,000 mg/dL).
    - Fasting cholesterol levels usually elevated, but to a much less severe degree.

- FDBL (type III hyperlipoproteinemia)
  - The traditional approach to diagnosis is lipoprotein electrophoresis; in FDBL, the remnant lipoproteins accumulate in a broad β band.
  - The preferred method to confirm 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 FDBL.
  - Protein methods (apoE phenotyping) or DNA-based methods (apoE genotyping) can confirm homozygosity for apoE2.
  - Absence of the apoE2/2 genotype does not rule out diagnosis of the FDBL; other mutations in apoE can cause this condition.
- FH
  - Plasma lipids should be measured in the parents and other first-degree relatives of patients with homozygous FH.
  - Elevated plasma LDL-C level (usually 5.17–10.34 μmol/L [200–400 mg/dL])
  - Diagnosis can be confirmed by skin biopsy, if necessary (see Diagnostic Procedures).
- Familial defective apoB-100
  - Elevated plasma LDL-C level with normal triglyceride level
  - Clinically indistinguishable from FH (LDL-C levels are slightly lower)
  - The apoB-100 gene mutation can be detected, but genetic diagnosis is not encouraged.
- LCAT deficiency
  - Diagnosis can be confirmed by assaying LCAT activity in the plasma.
  - Very low plasma HDL-C level (usually <0.26 mmol/L [<10 mg/dL])
- Sitosterolemia
  - Diagnosis is confirmed by demonstrating an elevated plasma sitosterol level.
- FHTG
  - Suggested by the triad of:
    - Elevated plasma triglyceride level (2.8–11.3 mmol/L [250–1,000 mg/dL])
    - Normal or only mildly increased cholesterol levels (< 6.5 mmol/L [< 250 mg/dL])
    - Reduced plasma HDL-C level
    - The plasma LDL-C level is generally not increased.
      - Often reduced due to defective metabolism of the triglyceride-rich particles
- FCHL
  - A mixed hyperlipidemia and family history suggest the diagnosis.
    - Plasma triglyceride level 2.3–9.0 mmol/L (200–800 mg/dL)
    - Cholesterol level 5.2–10.3 mmol/L (200–400 mg/dL)
    - HDL-C level <10.3 mmol/L (<40 mg/dL)
  - An elevated plasma apoB level or an increased number of small dense LDL particles in the plasma supports the diagnosis.
- Tangier disease
  - Plasma HDL-C level <0.13 mmol/L (<5 mg/dL) and very low circulating level of apoA-I

Imaging

- Not indicated

Diagnostic Procedures

- Funduscopy
  - Lipoprotein lipase and apoC-II deficiency: Retinal blood vessels are opalescent (lipemia retinalis).
- Liver biopsy
  - Wolman disease can be diagnosed by measuring acid lipase activity in fibroblasts or liver tissue biopsy specimens.
- Skin biopsy
  - FH
    - Diagnosis is confirmed by skin biopsy and measurement of LDL receptor activity in cultured skin fibroblasts.
    - Diagnosis is also confirmed by quantification of the number of LDL receptors on the surfaces of lymphocytes by using cell-sorting technology.
    - No definitive diagnostic test for heterozygous FH is available.
      - FH heterozygotes tend to have reduced levels of LDL receptor function in skin fibroblasts.
      - Significant overlap with levels in normal fibroblasts

Treatment Approach

General comments

- Data indicate that decreasing the plasma cholesterol level reduces the risk of clinical events due to atherosclerosis.
  - The absolute risk reduction depends on the baseline LDL-C level, the presence of established CHD, and other cardiovascular risk factors (see Atherosclerosis, Therapy and Prevention for details).
  - LDL-C is the primary target of therapy.
- Elevated plasma triglyceride levels are also associated with increased risk of CHD.
  - This relationship weakens considerably when statistical corrections are made for the plasma levels of LDL-C and HDL-C.
- Plasma levels of HDL-C are strongly and consistently inversely related to the prevalence and incidence of CHD.
- No pharmacologic agents are available that exclusively decrease plasma triglyceride levels or increase plasma HDL-C levels.
  - Since both hypertriglyceridemia and low plasma levels of HDL-C confer higher ASCVD risk, the NCEP ATP-III recommends more aggressive therapy to decrease the plasma LDL-C level in patients with dyslipidemias.

General approach

- Calculate the global risk of CAD to determine an overall strategy for cholesterol management.
  - Identify the presence of CAD or risk equivalents.
  - Determine the presence of major risk factors (other than elevated LDL-C level).
  - Assess 10-year risk.
- Determine the risk category to establish the LDL-C goal of therapy.
  - Determine the need for therapeutic lifestyle changes.
  - Determine the LDL-C level for drug consideration.
- Initiate therapeutic lifestyle changes if the LDL-C level is above the goal level.
- Consider adding drug therapy if LDL-C exceeds recommended levels.

- Identify the metabolic syndrome and treat if present after 3 months of therapeutic lifestyle changes.
- Treat elevated plasma triglyceride levels (>1.7 mmol/L or 150 mg/dL).
    - Intensify weight management.
    - Increase physical activity.
    - Primary aim should be to reach the goal LDL-C level.
        - If triglyceride levels remain >2.3 mmol/L (>200 mg/dL) after the goal LDL-C level is reached, set a secondary goal of a non–HDL-C level 0.78 mmol/L (30 mg/dL) higher than the goal LDL-C level.
        - If triglyceride levels remain 2.3–5.6 mmol/L (200–499 mg/dL) after the goal LDL-C level is reached, consider additional drug therapy to achieve the goal non–HDL-C level.
        - If triglyceride levels remain >5.6 mmol/L (500 mg/dL), first decrease triglyceride levels with a very-low-fat diet to prevent pancreatitis.
- Consider treatment of low HDL-C level.
    - First reach LDL-C goal, then:
        - Intensify weight management and increase physical activity.
        - If triglyceride levels remain 2.3–5.6 mmol/L (200–499 mg/dL), achieve the non–HDL-C goal.
        - If triglyceride levels remain >5.6 mmol/L (500 mg/dL) in patients with CHD or CHD equivalents, consider nicotinic acid or fibrate therapy.

Pharmacologic treatment

General

- The decision to use drug therapy depends on the cardiovascular risk.
- Absolute risk of a cardiovascular event over 10 years can be estimated by using a scoring system based on the Framingham Heart Study database.
    - Can be calculated online
    - Patients with a 10-year absolute CHD risk >20% are considered CHD risk equivalents.

Current NCEP ATP-III guidelines

- Very high-risk patients
    - Established CHD and 1 of the following:
        - Diabetes
        - Metabolic syndrome
        - Persistent risk factors (such as cigarette smoking)
        - Acute coronary syndrome
    - Goal: LDL-C level < 2.6 mmol/L (<100 mg/dL)
    - Optional goal: LDL-C level <1.8 mmol/L (<70 mg/dL)
    - Also: If the triglyceride level is > 2.26 mmol/L (200 mg/dL) despite an LDL-C level <2.6 mmol/L, the non–HDL-C goal is <2.6 mmol/L (100 mg/dL).
- High-risk patients
    - Established CHD or CHD risk equivalents (> 20% risk)
    - Goal: LDL-C level <2.6 mmol/L (<100 mg/dL)
- Moderate-risk patients
    - ≥2 CHD risk factors and a 10-year absolute risk of 10–20%
    - Goal: LDL-C level <3.4 mmol/L (<130 mg/dL)

    - Consider treatment options in patients with an LDL-C level of 2.6–3.4 mmol/L (100–129 mg/dL) if other factors that favor the use of drug therapy are present.
        - Advancing age
        - Continued cigarette smoking
        - Strong positive family history of premature ASCVD
        - High triglyceride level plus elevated non–HDL-C level (>4.1 mmol/L [160 mg/dL])
        - Low HDL-C level (<1.04 mmol/L [40 mg/dL])
        - Presence of the metabolic syndrome
- Low-risk patients
    - Goal: LDL-C level <4.1 mmol/L (<160 mg/dL)
    - Not all persons are candidates for drug therapy achieve this goal.
    - Persons with markedly elevated plasma LDL-C levels (>4.9 mmol/L [>190 mg/dL]) should be considered for drug therapy.
- Isolated hypertriglyceridemia
    - Drug treatment is indicated in patients with triglyceride levels >11.3 mmol/L (>1,000 mg/dL) who have been screened and treated for secondary causes of chylomicronemia.
    - Goal: Reduce plasma triglyceride level to <4.5 mmol/L (400 mg/dL).

Specific Treatments

Nonpharmacologic treatment approach (therapeutic lifestyle changes)

- Dietary modification is an important component in the management of hyperlipidemia.
    - Dietary saturated fat and cholesterol should be restricted.
        - Saturated fat should be <7% of calories.
        - Cholesterol should be <200 mg/d.
    - For patients with hypertriglyceridemia, the intake of simple sugars should also be curtailed.
        - For severe hypertriglyceridemia (>11.3 mmol/L [>1,000 mg/dL]), restriction of total fat intake is critical.
    - The most widely used diet to decrease 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 1 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 ~10–15% when taken 3 times daily.
        - The addition to the diet of psyllium, soy protein, or Chinese red yeast rice (which contains lovastatin) can have modest cholesterol-lowering effects.
- Weight loss and exercise
    - Treatment of obesity can have a favorable effect on plasma lipid levels and should be actively encouraged.

  - Plasma triglyceride and LDL-C levels tend to decrease 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 persons but has cardiovascular benefits that extend beyond the effects on plasma lipid levels.

Pharmacologic treatment approach

- Pharmacologic treatment can be designed around major indications.
  - Isolated elevated LDL level
  - Elevated LDL, low HDL, elevated triglyceride levels
  - Elevated triglyceride, elevated remnant levels
  - Isolated low HDL level
- Combination therapy may be required for mixed hyperlipidemias.

Elevated LDL level

3-hydroxy-3-methylglutamyl coenzyme A (HMG-CoA) reductase inhibitors (statins)

- Mechanism: inhibits rate-limiting step in cholesterol biosynthesis, leading to an increase in hepatic LDL receptor activity and accelerated clearance of LDL
- Well tolerated and can be taken in tablet form once daily
- Different statins differ with respect to their potency (LDL-C reducing effects).
- In general, a doubling of the dose produces a 6% further reduction of plasma LDL-C level.
- Reduce the plasma triglyceride level in a dose-dependent fashion
- Have a modest HDL-increasing effect (5–10%), which is not dose dependent
- Common side effects
  - Myalgias, arthralgias, elevated aminotransferase levels, dyspepsia, headaches, fatigue, and muscle or joint pains
- Severe myopathy and even rhabdomyolysis occur rarely.
  - The risk 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 fibric acid derivatives.
  - Can usually be avoided by careful patient selection, avoidance of interacting drugs, and instructing the patient to contact the physician immediately in the event of unexplained muscle pain.
- Hepatitis is a potential side effect.
  - Liver alanine aminotransferase and aspartate aminotransferase should be checked before starting therapy, at 8 weeks, and then every 6 months.
  - Substantial (>3 times the upper limit of normal) elevation in aminotransferase levels is relatively rare, and mild to moderate (1–3 times normal values) elevation in the absence of symptoms does not mandate discontinuation.
  - Severe clinical hepatitis associated with HMG-CoA reductase inhibitors is exceedingly rare, and the trend is toward less frequent monitoring of aminotransferases in patients taking HMG-CoA reductase inhibitors.
  - HMG-CoA reductase inhibitor–associated transaminitis resolves after discontinuation of the medication.
- Dose
  - Lovastatin: 20 mg qd initially; can be titrated to 80 mg/d
  - Pravastatin: 40 mg at bedtime initially; can be titrated to 80 mg at bedtime
  - Simvastatin: 20 mg at bedtime initially; can be titrated to 80 mg at bedtime

    - Fluvastatin: 20 mg at bedtime initially; can be titrated to 80 mg at bedtime
    - Atorvastatin: 10 mg at bedtime initially; can be titrated to 80 mg at bedtime
    - Rosuvastatin: 10 mg at bedtime initially; can be titrated to 40 mg at bedtime
- Cytochrome p450 interactions may occur with lovastatin, simvistatin, fluvastatin, and atorvastatin.

Bile acid sequestrants

- Mechanism: promotes bile acid excretion, upregulates LDL receptors, and enhances LDL clearance
- Primarily reduce plasma LDL-C levels but can increase plasma triglyceride levels
    - Patients with hypertriglyceridemia should not be treated with bile acid–binding resins.
- Common side effects: bloating, constipation
    - May bind other drugs (e.g., digoxin, warfarin) and interfere with their absorption
    - All other medications should be taken either 1 hour before or 4 hours after the bile acid sequestrant.
    - May increase the triglyceride level
- Dose
    - Cholestyramine: 4 g qd initially; can be titrated to 32 g qd
    - Colestipol (tablet): 5 g qd initially; can be titrated to 40 g qd
    - Colesevelam: 3,750 mg qd initially; can be titrated to 4,375 qd
        - Has greater bile acid–binding capacity than traditional resins
        - Tablets are smaller, and fewer tablets per day are required.

Cholesterol absorption inhibitor

- Mechanism: decreases intestinal cholesterol absorption
- Reduces LDL-C cholesterol levels by ~18% as monotherapy or in combination with a statin
    - Useful in combination with a statin in patients unable to reach LDL-C goal on a statin
- Common side effects: elevated aminotransferase levels
- Dose
    - Ezetimibe: 10 mg qd

Elevated LDL, low HDL, elevated triglyceride levels

Nicotinic acid (niacin)

- Mechanism: decreases VLDL hepatic synthesis
- Common side effects: cutaneous flushing, GI upset, increased fasting glucose level, hepatitis, precipitation of gout, exacerbation of esophageal reflux
- Flushing can be alleviated by the following measures.
    - Continued administration
    - Aspirin given 30 minutes before drug administration
    - Use of sustained- or extended-release formulations
- Dose
    - Immediate-release crystalline niacin
        - Least expensive form of niacin
        - Should be started at a low dose and taken with meals to delay absorption
        - The dose of niacin should be increased every 4–7 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 aminotransferases) should be measured.
        - The dose can be further increased as needed up to a total dose of 6 g/d.
    - Immediate release: 100 mg tid initially; can be titrated up to 2 g tid
    - Sustained release: 250 mg bid initially; can be titrated up to 1.5 g bid
    - Extended release: 500 mg at bedtime initially; can be titrated up to 2 g at bedtime

Elevated triglyceride, elevated remnant levels

Fibric acid derivatives

- Mechanism: agonist of peroxisome proliferator-activated receptor α, stimulates LPL activity, reduces apoC-III synthesis, reduces VLDL synthesis
- Drug class of choice in patients with severe hypertriglyceridemia (11.3 mmol/L [>1,000 mg/dL)
    - Reasonable consideration in patients with moderate hypertriglyceridemia (4.5–11.3 mmol/L [400–1,000 mg/dL])
- Common side effects
    - Dyspepsia, myalgia, gallstones, elevated aminotransferase levels
    - Fibrates can potentiate the effect of warfarin and certain oral hypoglycemic agents.
    - Can be associated with increases in LDL-C level
- Dose
    - Gemfibrozil: 600 mg bid
    - Fenofibrate: 160 mg qd

Fish oil supplements

- Mechanism: decrease chylomicron and VLDL production
- Can be used in combination with fibrates, niacin, or statins to treat hypertriglyceridemia
- Are well tolerated and appear to be safe
- Side effects
    - The large number of capsules required for a therapeutic effect, the associated dyspepsia, and fishy aftertaste have limited clinical use of these agents.
    - Have been associated with a prolongation in the bleeding time, but no increase in bleeding has been seen in clinical trials
- Dose
    - Omega-3 fatty acids: 3 g/d initially; titrated up to 12 g/d
    - At least 6 g/d is required for triglyceride-lowering effects, and 9–12 g/d may be required.

Low HDL level

- Severely reduced plasma HDL-C level (<0.5 mmol/L [<20 mg/dL]) accompanied by triglyceride level <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
    - An HDL-C level <0.5 mmol/L (<20 mg/dL) is usually associated with severe hypertriglyceridemia, in which case the primary focus should be on management of triglycerides.

- Moderate reductions in plasma HDL-C level (0.5–10.3 mmol/L [20–40 mg/dL])
  - Secondary causes should be considered.
    - Smoking should be discontinued.
    - Obese persons should be encouraged to lose weight.
    - Sedentary persons should be encouraged to exercise.
    - Diabetes should be optimally controlled.
    - Medications associated with reduced plasma levels of HDL-C should be discontinued.
  - Isolated low plasma HDL-C level in a patient with a borderline plasma LDL-C level
    - Should prompt consideration of LDL-lowering drug therapy in high-risk persons
    - Niacin is the most effective therapeutic agent and can increase plasma HDL-C levels by up to ~30%.
    - Statins increase plasma levels of HDL-C only modestly (~5–10%).
    - Fibrates also have a modest effect on plasma HDL-C levels (increasing levels ~5–15%), except in patients with coexisting hypertriglyceridemia, in whom they can be more effective.
  - Low HDL-C level and plasma LDL-C level at or below the goal in persons with established CHD
    - May be reasonable to initiate therapy (with a fibrate or niacin) directed specifically at reducing plasma triglyceride levels and increasing the plasma HDL-C level

Combination drug therapy

- Frequently used in the following situations:
  - Inability to reach LDL-C goal on a single drug
  - Inadequate control of combined hypertriglyceridemia and hypercholesterolemia by using a single drug
  - Elevated LDL-C and low HDL-C levels
- Inability to achieve LDL-C goal on statin monotherapy
  - Options include (if triglyceride levels are normal):
    - Addition of a bile acid sequestrant
    - Addition of a cholesterol absorption inhibitor
    - Addition of niacin 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 level <10.3 mmol/L (<40 mg/dL).
- Persistent hypertriglyceridemia in patients using statin monotherapy
  - Addition of niacin or a fibrate can reduce the plasma triglyceride level.
- Hypertriglyceridemic patients treated with a fibrate often do not reach their LDL-C goal and are therefore candidates for addition of a statin.
  - Coadministration of statins and fibrates has obvious appeal in patients with combined hyperlipidemia.
  - The long-term safety of this combination is not known.
  - Should be used cautiously in patients with underlying renal or hepatic insufficiency; in elderly, frail, and chronically ill persons and in those using 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 apheresis

- Preferred option for management of patients with refractory or drug-resistant hypercholesterolemia
- Patient's plasma is passed over a column that selectively removes LDL, and the LDL-depleted plasma is returned to the patient.
- Candidates for every-other-week LDL apheresis
    - Patients using maximally tolerated combination drug therapy who have:
        - CHD and a plasma LDL-C level >5.2 mmol/L (>200 mg/dL)
        - No CHD and a plasma LDL-C level >7.8 mmol/L (>300 mg/dL)

Partial ileal bypass

- The procedure interrupts the enterohepatic circulation of bile acids, resulting in upregulation of the hepatic LDL receptor and reduction in plasma LDL-C levels.
- Indicated for patients with severe hypercholesterolemia with normal triglyceride levels who cannot tolerate existing lipid-lowering medications and do not have access to LDL apheresis
- Common side effects
    - Diarrhea
    - Increased risk of kidney stones, gallstones, and intestinal obstruction

Secondary forms of hyperlipidemia

- Hypothyroidism
    - Thyroid replacement therapy usually ameliorates the hypercholesterolemia.
- Nephrotic syndrome
    - Effective treatment of the underlying renal disease normalizes the lipid profile, but most patients with chronic nephrotic syndrome require lipid-lowering drug therapy.
    - Because the risk of ASCVD is increased in hyperlipidemic patients with end-stage renal disease, they should be treated aggressively with lipid-lowering agents.
    - Patients with renal transplants are usually hyperlipidemic owing to the effects of immunosuppressant drugs (cyclosporine and glucocorticoids); they present a difficult management problem, as HMG-CoA reductase inhibitors must be used cautiously in these patients.
- Diabetes
    - Hypertriglyceridemia responds dramatically to administration of insulin in insulin-deficient patients with type 1 diabetes mellitus.
    - Dyslipidemia associated with type 2 diabetes mellitus should be treated with statins (except if the chylomicronemia syndrome is present).

Specific primary disorders

LPL and apoC-II deficiency

- Major therapeutic intervention 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 does not resolve the chylomicronemia, fish oils may be 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.

FDBL

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

FH: homozygous

- Combination therapy with an HMG-CoA reductase inhibitor and a bile acid sequestrant sometimes results in modest reductions in plasma LDL-C in FH homozygotes.
    - Patients invariably require additional lipid-lowering therapy.
- Current treatment of choice is LDL apheresis.
    - Can promote regression of xanthomas
    - May slow the progression of atherosclerosis.
    - Initiation of LDL apheresis should be delayed until approximately 5 years of age, except when evidence of atherosclerotic vascular disease is present.
    - Patients with FH should be treated aggressively to decrease plasma levels of LDL-C.
- Initiation of a low-cholesterol, low-fat diet is recommended.
- Liver transplantation is effective in decreasing plasma LDL-C levels.
    - Associated with substantial risks, including the requirement for long-term immunosuppression

FH: heterozygous

- Initiation of a low-cholesterol, low-fat diet is recommended, but 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 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.

- Patients whose condition cannot be adequately controlled with combination drug therapy are candidates for LDL apheresis.

Autosomal recessive hypercholesterolemia

- 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.

Sitosterolemia

- Hypercholesterolemia in patients is unusually responsive to reductions in dietary cholesterol content.
- Does not respond to HMG-CoA reductase inhibitors
- Bile acid sequestrants and cholesterol-absorption inhibitors, such as ezetimibe, are effective in reducing plasma sterol levels in these patients.
- Sitosterolemia should be suspected when the plasma cholesterol level decreases by > 40% on a low-cholesterol diet (without associated weight loss).

FHTG

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

FCHL

- Should be treated aggressively because of the significantly increased risk of premature CHD
    - Decreased dietary intake of saturated fat and simple carbohydrates
    - Aerobic exercise
    - Weight loss
    - Patients with diabetes should be treated aggressively to maintain good glycemic control.
- Most patients require lipid-lowering drug therapy to reduce lipoprotein levels to the recommended range.
    - HMG-CoA reductase inhibitors are very effective in decreasing plasma levels of LDL-C and can also significantly reduce VLDL-C levels.
    - Nicotinic acid decreases both LDL-C and VLDL-C levels while increasing the plasma HDL-C level, and is frequently effective for this condition when used in combination with HMG-CoA reductase inhibitors.

Monitoring

- Fasting lipid panel
    - 3–6 months after initiation of therapy
    - Annual or biannual screening, depending on risk factors

- Plasma triglyceride levels
  - Should be monitored when use of birth control pills or estrogen replacement therapy is initiated
- Statins
  - Liver aminotransferases should be checked before starting therapy, at 8 weeks, and then periodically during therapy.
  - Serum creatine phosphokinase (CPK) levels do not need to be monitored on a routine basis.
    - An elevated CPK level in the absence of symptoms does not predict development of myopathy and does not necessarily suggest the need to discontinue the drug.
  - If muscle symptoms develop, the plasma CPK level should be obtained to document the myopathy.
- Fibrates
  - Patients with diabetes mellitus should have plasma glucose levels monitored closely.
  - Patients receiving anticoagulation with warfarin should have anticoagulation status monitored closely.
- Niacin
  - Liver aminotransferases, uric acid, and glucose should be monitored carefully.
  - A sudden decrease in plasma lipid levels may signify hepatitis.
- Statin–fibrate combinations
  - Patients treated with this combination must be carefully counseled regarding the potential for myopathy and should be monitored closely.

Complications

- All hyperlipidemias
  - Myocardial infarction
  - Stroke
  - Peripheral vascular disease
- Marked hypertriglyceridemia
  - Pancreatitis
- Statin–fibrate combinations
  - Associated with an increased incidence of severe myopathy (up to 2.5%) and rhabdomyolysis

Prognosis

- Prognosis is related to:
  - Presence or absence of a specific genetic disorder
  - Comorbid conditions
  - Timing of detection and treatment of hyperlipidemia
  - Compliance with therapy

Prevention

- There are no specific preventive measures for patients with genetic forms of hyperlipidemia.
- Aggressive treatment of conditions known to cause secondary hyperlipidemia may forestall development of hyperlipidemia.
- Regular exercise and a diet low in saturated fat and cholesterol may help prevent hyperlipidemia.

ICD-9-CM

- 272.4 Other and unspecified hyperlipidemia

See Also

- Approach to Stroke
- Atherosclerosis, Therapy and Prevention
- Cardiovascular Complications of Diabetes Mellitus
- Chronic Pancreatitis
- Health Care Screening and Disease Prevention
- Hypothyroidism
- Metabolic Syndrome
- Myocardial Infarction
- Nephrotic Syndrome
- Peripheral Arteriosclerosis
- Type 2 Diabetes Mellitus

Internet Sites

- Professionals
  - Hyperlipidemia
    ClinicalTrials.gov
  - Guidelines
    National Guideline Clearinghouse
- Patients
  - Hyperlipidemia
    American Heart Association
  - High blood cholesterol and triglycerides
    MedlinePlus

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PEARLS

- Frequent causes of secondary hypertriglyceridemia include diabetes mellitus, nephrotic syndrome, chronic renal failure, excessive alcohol intake, and medications.
- Benefits of lipid-lowering therapy usually require 6–24 months of therapy.
- Non–HDL-C concentrations are a secondary target for patients with hypertriglyceridemia.
    - The goal for non–HDL-C in patients with hypertriglyceridemia (>2.3 mmol/L or 200 mg/dL) is 0.78 mmol/L (30 mg/dL) higher than that for LDL-C.
- CHD equivalents include clinical CAD, symptomatic or significant carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, or multiple risk factors that confer a 10-year risk of CAD >20%.
- Best results are obtained when doses of statins achieve an LDL-C reduction of 30–40%.
- Statin doses required to attain an approximate 30–40% LDL-C reduction
    - Atorvastatin: 10 mg/d
    - Fluvastatin: 40-80 mg/d
    - Lovastatin: 40 mg/d
    - Pravastatin: 40 mg/d
    - Rosuvastatin: 5-10 mg/d
    - Simvistatin: 20-40 mg/d
- HMG-CoA reductase inhibitors are the drug class of choice for LDL-C reduction.
- Bile acid resins are the drugs of choice for children and pregnant women.
- Niacin is the most effective drug available for increasing the HDL-C level.
- Fibrates are the most effective drugs available for reducing triglyceride levels.