cholesterol, resulting in the formation of foam cells and atheromatous plaques.

The anti-atherogenic effect of HDL is attributed to the removal of excess cholesterol from tissue sites and other lipoproteins. HDL is synthesized in the liver and intestine (see Fig. 69-1). Excess phospholipids, cholesterol, and apolipoproteins on remnant chylomicrons, VLDL, IDL, and LDL, are transferred to HDL particles and thus increase HDL mass. Apo A-I, a surface lipoprotein on HDL particles, mobilizes cholesterol from intracellular pools and accepts cholesterol released during lipolysis of triglyceride-rich lipoproteins. It also activates lecithin-cholesterol acyltransferase (LCAT), an enzyme that esterifies cholesterol. These cholesterol esters move the hydrophilic HDL surface to the hydrophobic HDL core. Cholesterol ester transfer protein (CETP) transfers core HDL cholesterol esters to other lipoproteins such as VLDL. These lipoproteins deliver cholesterol to peripheral sites for hormone and cell membrane synthesis.

Defects in the production or removal of lipoproteins results in dyslipidemia. Both genetic and acquired conditions have been implicated in the pathogenesis of lipid disorders (Tables 69-2 and 61-3). These are discussed later in the chapter.

CLINICAL PRESENTATION

Dyslipidemia plays a significant role in the development of atherosclerosis. Increased incidence of CHD with high LDL- and low HDL-cholesterol is well documented. Excess LDL results in the formation of cholesterol plaques that deposit in arteries (atheroma), skin and tendon (xanthomas), eyelids (xanthelasma), and iris (corneal arcus). The impact of triglycerides on vascular disease is less clear. Metabolic disorders such as diabetes and obesity are often associated with vascular disease and hypertriglyceridemia, and the atherogenic impact of other elements in these disorders is difficult to separate from the effect of hypertriglyceridemia. However, in several population-based studies, abnormal triglyceride levels correlated with increased risk for CHD. Marked hypertriglyceridemia (>1000 mg/dL) is associated with the chylomicronemia syndrome, characterized by pancreatitis and xanthomas.

DIAGNOSIS

Dyslipidemia is defined by a total cholesterol, triglyceride, or LDL level greater than the 90th percentile or an HDL level lower than the 10th percentile for the general population. Because chylomicrons are present in plasma for up to 10 hours after a meal, fasting total cholesterol, triglyceride, and lipoprotein assessments are required for diagnosis. It is advisable to confirm dyslipidemia with two separate determinations.

Total cholesterol, triglyceride, and HDL levels can be measured directly; VLDL and LDL levels usually are calculated. If the triglyceride concentration is lower than 400 mg/dL, then VLDL is calculated by dividing the triglyceride level by 5. LDL-cholesterol is estimated by subtracting VLDL and HDL from the total cholesterol. VLDL and LDL cannot be determined if triglyceride levels are greater than 400 mg/dL. In that case, the lipoprotein abnormality can be identified by inspecting the serum. When the triglyceride level exceeds 350 mg/dL, the

TABLE 69-2 GENETIC DISORDERS OF LIPID METABOLISM

DISORDER	GENETIC DEFECT	DYSLIPIDEMIA
Familial hypercholesterolemia	Mutation in the gene that encodes LDL receptor	Elevated TC and LDL
Familial defective apolipoprotein B100	Impaired binding of LDL to LDL receptor due to a defect in apo B100 protein	Elevated TC and LDL
Elevated plasma Lp(a)	Increased binding of LDL to apolipoprotein(a)	Elevated Lp(a)
Polygenic hypercholesterolemia	Increased binding of apo E4–containing lipoprotein to LDL receptor resulting in downregulation of the LDL receptor	Elevated TC and LDL
Familial combined hyperlipoproteinemia	Polygenic disorder associated with increased hepatic VLDL production, resulting in increased LDL and decreased HDL production; some individuals have a mutation in the LPL gene that affects expression and function of LPL	Elevated TC, LDL, and TG Low HDL
Familial dysbetalipoproteinemia	Lower affinity of apo E2 for LDL receptor	Elevated TG, TC, and LDL
Lipoprotein lipase deficiency	Mutation in the *LPL* gene	Elevated TG
Apolipoprotein C-II deficiency	Decrease in activation of LPL due to a deficiency of apo CII	Elevated TG
Familial hypertriglyceridemia	Overproduction of hepatic VLDL and increased catabolism of HDL	Elevated TG Low HDL

HDL, High-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein.

TABLE 69-3 MECHANISMS OF SECONDARY HYPERLIPIDEMIA

CLINICAL	ELEVATED LIPOPROTEIN	MECHANISM
Diabetes	Chylomicron, VLDL, LDL	Increase in VLDL production and decrease in VLDL/LDL clearance
Obesity	Chylomicron, VLDL, LDL	Increase in VLDL production and decrease in VLDL/LDL clearance
Lipodystrophy	VLDL	Increase in VLDL production
Hypothyroidism	LDL, VLDL	Decrease in LDL/LDL clearance
Estrogen	VLDL	Increase in VLDL production
Glucocorticoids	VLDL, LDL	Increase in VLDL production and conversion to LDL
Alcohol	VLDL	Increase in VLDL production
Nephrotic syndrome	VLDL, LDL	Increase in VLDL production and conversion to LDL

LDL, Low-density lipoprotein; VLDL, very-low-density lipoprotein.