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Disorders of Lipid Metabolism

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DEFINITION AND EPIDEMIOLOGY

Lipids such as free fatty acids (FFA), cholesterol, and triglycerides are hydrophobic molecules that bind proteins for transport. Nonesterified FFA travel as anions complexed to albumin. Esterified complex lipids are transported in lipoprotein particles. Lipoproteins have a hydrophobic core (cholesteryl esters and triglycerides) and an amphiphilic surface monolayer (phospholipids, unesterified cholesterol, and apolipoproteins). Ultracentrifugation separates lipoproteins into five classes based on their density (Table 69-1).

Proteins on the surface of lipoproteins (i.e., apolipoproteins) activate enzymes and receptors that guide lipid metabolism. Defects in the synthesis and catabolism of lipoproteins result in dyslipidemia. Prevalence of dyslipidemia in the United States is approximately 20% and varies with the population studied. An estimated 70% of individuals with premature coronary heart disease (CHD) have dyslipidemia. In clinical trials, treatment of dyslipidemia improved both CHD and all-cause mortality rates. Two classes of lipids, triglyceride and cholesterol, play a significant, yet modifiable, role in the pathogenesis of atherosclerosis and therefore are the focus of this chapter.

PATHOLOGY

In the intestinal lumen, dietary triglycerides and cholesterol esters are hydrolyzed by pancreatic lipase to produce glycerol, FFA, and free cholesterol. Formation of micelles enables the absorption of glycerol and FFA into the intestinal cell. The transport of free cholesterol is mediated by a cholesterol gradient that exists between the lumen and the intestinal cell. Within the cell, glycerol combines with three fatty acid chains to form triglycerides, and cholesterol is esterified to form cholesterol esters. Chylomicrons are formed from triglycerides (85% of chylomicron mass) and cholesterol esters assembled with surface lipoproteins. Chylomicrons enter into the circulation and acquire more surface apolipoproteins such as apo C-II and apo E from high-density lipoprotein (HDL) particles (Fig. 69-1). Apo C-II activates lipoprotein lipase (LPL), which is located on the capillary endothelium. LPL hydrolyzes the core chylomicron triglycerides to release FFA, which function as an energy source. Excess fatty acids are stored in adipose tissue or utilized in hepatic lipoprotein synthesis. The triglyceride-poor chylomicron remnant is then cleared from the circulation by hepatic LDL receptors. These receptors are activated by apo E, which is located on the surface of chylomicrons.

Very-low-density lipoproteins (VLDL) are synthesized by the liver (see Fig. 69-1). FFA and cholesterol obtained from the circulation or synthesized by the liver are incorporated into VLDL particles. Any condition that increases the flux of FFA to the liver, such as poorly controlled diabetes, will increase VLDL production. The liver assembles triglycerides (55% of VLDL mass), cholesterol (20%), and surface apolipoproteins to form VLDL particles. Apo C-II, the cofactor for LPL, hydrolyzes the triglyceride core of VLDL particles to generate VLDL remnant or intermediate-density lipoprotein (IDL). The IDL, depleted of triglycerides (25%), can be cleared from the circulation by apo E–mediated LDL receptors, or it can be hydrolyzed further to form low-density lipoproteins (LDL). LDL particles are triglyceride poor (5% of LDL mass) and consist mostly of cholesterol esters (60%) and apolipoproteins. Apo B100 on the surface of LDL binds LDL receptors and facilitates LDL clearance from the circulation. Internalized LDL-cholesterol is used to synthesize hormones, produce cell membranes, and store energy.

In the liver, LDL-cholesterol is used to synthesize bile acids (see Fig. 69-1), which are secreted into the intestinal lumen along with free cholesterol. Bile acids help transport fat. Approximately 50% of the cholesterol and 97% of the bile acid entering the lumen is reabsorbed back into the circulation. The reabsorbed cholesterol regulates cholesterol and LDL receptor synthesis.

Many cells in the body, including liver parenchymal cells, synthesize cholesterol (Fig. 69-2). Acetate is converted to 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA). HMG-CoA reductase converts HMG-CoA to mevalonic acid, which is then

TABLE 69-1 PROPERTIES OF LIPOPROTEINS

LIPOPROTEIN CLASS	DENSITY (g/mL)	ORIGIN	APOLIPOPROTEINS	LIPID
Chylomicrons	<0.95	Intestine	C-II, E	TG (85%), cholesterol (10%)
VLDL	<1.006	Liver	B100, C-II, E	TG (55%), cholesterol (20%)
IDL	1.006-1.019	VLDL catabolism	B100, E	TG (25%), cholesterol (35%)
LDL	1.019-1.063	IDL catabolism	B100	TG (5%), cholesterol (60%)
HDL	1.063-1.25	Liver, intestine	A-I, E	TG (5%), cholesterol (20%)

HDL, High-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.