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Chapter 17

Whole-body Lipid Metabolism

This chapter quizzes the student on the flow and storage of lipids (primarily cholesterol and triglyceride) throughout the body.

QUESTIONS

Select the single best answer.

1 You have a patient whose blood work indicates high total cholesterol and elevated liver enzymes. You place him on cholestyramine to lower his cholesterol. Cholestyramine acts to lower cholesterol by inhibiting which of the following enzymes/pathways?
(A) HMG-CoA reductase
(B) Hepatic cholesterol synthesis
(C) Release of bile salts from the gall bladder
(D) Enterohepatic circulation reabsorption of bile salts
(E) The production of chylomicrons

2 You have placed a patient on Pravachol pravastatin to reduce her cholesterol. This class of drugs is effective due to a direct inhibition of which of the following?
(A) Medium chain acyl-CoA dehydrogenase (MCAD)
(B) HMG-CoA synthase
(C) HMG-CoA reductase
(D) Carnitine acyltransferase 1 (CAT-1)
(E) Citrate lyase

3 A knockout mouse was created in which the ability to create conjugated bile salts was greatly impaired. The net result of this mutation in a mouse fed a normal diet is which of the following?
(A) Steatorrhea
(B) Elevated levels of chylomicrons
(C) Deficiency of B vitamins
(D) Reduced pH in the intestinal lumen
(E) Reduced secretion of pancreatic zymogens

4 A patient has enlarged orange tonsils, hepatosplenomegaly, loss of sensation in hands and feet, and clouding of the corneas. His HDL levels are 18 mg/dL. The molecular defect in this patient is present in which of the following proteins?
(A) HMG-CoA reductase
(B) AMP-activated protein kinase
(C) Lecithin cholesterol acyltransferase
(D) ABC1
(E) Cholesterol ester transfer protein

5 Current American Heart Association Guidelines indicate that an adult male should have HDL levels equal to or greater than 40 mg/dL. A necessary enzyme contributing to HDL's protective effect is which of the following?
(A) CETP
(B) LCAT
(C) ACAT
(D) AMP-activated protein kinase
(E) Protein kinase A

6 Many clinical labs report lipid values using a calculated value for LDL. This calculation estimates the cholesterol content in which of the following particles under fasting conditions?
(A) HDL
(B) LDL
(C) IDL
(D) VLDL
(E) Chylomicron

7 Statins are ineffective in lowering cholesterol levels in individuals with homozygous familial hypercholesterolemia due to which of the following?
(A) HMG-CoA reductase is resistant to statins
(B) Statins cannot enter the liver cells
(C) LDL receptors are nonfunctional
(D) Reverse cholesterol transport is inoperative in these patients
(E) LCAT is resistant to statin action

8 You see a patient who has steatorrhea, with very low levels of chylomicrons and VLDL in the circulation. Circulating triglyceride levels are extremely low. Examination

of intestinal epithelial cells shows lipid-laden cells. A possible enzymatic defect leading to these findings is which of the following?
(A) LPL
(B) Apolipoprotein CII
(C) MTTP
(D) LCAT
(E) CETP

9 A type 1 diabetic who has neglected to take his insulin for a few days displays both hyperglycemia and hypertriglyceridemia. The hypertriglyceridemia is due, in part, to which of the following?
(A) Reduced synthesis of VLDL
(B) Reduced production of apolipoprotein CII
(C) Increased fatty acid oxidation
(D) Reduced secretion of LPL
(E) Increased synthesis of B100

10 A 12-year-old female presented with severe abdominal pain and was found to have a markedly elevated plasma triglyceride concentration (750 mg/dL). A lipoprotein analysis revealed elevated levels of chylomicrons and VLDL and reduced levels of HDL. Which protein might be defective in this patient?
(A) Apo B100
(B) Apo B48
(C) Apo CII
(D) Pancreatic lipase
(E) LCAT

11 A 43-year-old woman presents with steatorrhea. Fecal analysis reveals the presence of elevated triglycerides, phospholipids, and cholesterol esters. Levels of carbohydrate and protein were normal. Physical exam is unremarkable. A possible defect in the release of which of the following would lead to these results?
(A) Cholecystokinin
(B) Insulin
(C) Glucagon
(D) Secretin
(E) Cortisol

12 A 46-year-old man has been progressively having trouble breathing while walking. Walking from his car to his office has become difficult, and he has to stop to rest along the way. He visits his physician, who orders an angiogram, which shows blockage of major arteries leading to the heart. An initiating factor for the development of the blockage is which of the following?
(A) LDL
(B) Oxidized LDL
(C) Triglycerides
(D) HDL
(E) Oxidized HDL

13 Your 27-year-old male patient, with a BMI of 34, has a total cholesterol of 450 mg/dL and triglycerides of 610 mg/dL. He exhibits planar xanthomas and has already had one angioplasty last year. This patient may be exhibiting a rare autosomal recessive disorder which generates a mutation in which of the following proteins?
(A) LPL
(B) Apolipoprotein CII
(C) Apolipoprotein E
(D) Apolipoprotein B100
(E) Apolipoprotein B48

14 A 44-year-old man displayed elevated cholesterol levels and was prescribed a statin to reduce such levels. Statin treatment has the potential to interfere with the synthesis of which of the following?
(A) Heme
(B) Coenzyme Q
(C) Ketone bodies
(D) Glycogen
(E) Dihydrobiopterin

15 A 57-year-old man has been taking low-dose aspirin to reduce his risk of heart disease. He adds phytosterols to his daily regime for which of the following?
(A) To reduce circulating triglyceride levels
(B) To reduce circulating cholesterol levels
(C) To reduce endogenous cholesterol synthesis
(D) To decrease insulin secretion
(E) To reduce fatty acid biosynthesis

16 Concerning the patient in the previous question, phytosterols have the same general mechanism of action as which of the following drugs?
(A) Atorvastatin
(B) Ezetimibe
(C) Pravastatin
(D) Simvastatin
(E) Metformin

17 Macrophages found in arterial fatty streaks are often lipid filled and become foam cells. Such large amounts of cholesterol uptake into these cells is possible due to which of the following?

(A) Increased activity of ACAT within the foam cell
(B) Increased activity of LCAT within the foam cell
(C) Constant SR-A1 expression on the cell surface
(D) Upregulation of HMG-CoA reductase
(E) Increased activity of the LDL receptor

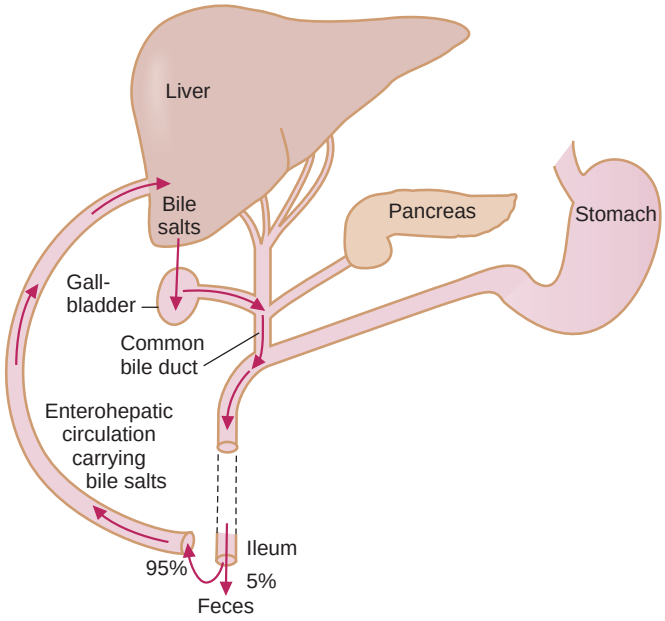
18 A patient, 45-year-old male, BMI of 25, has had a history of elevated cholesterol (~300 mg/dL), with normal triglyceride levels (~125 mg/dL), and HDL levels (48 mg/dL). Treatment with statins has reduced his serum cholesterol to 180 mg/dL. The patient's father had a similar history and died of a heart attack at age 48. A potential mutation in this patient would be in which of the following proteins?
(A) LCAT
(B) CETP
(C) ABC1
(D) Apo B100
(E) LDL receptor

19 A patient sees his or her physician for continuing treatment of hypercholesterolemia. Recent blood work has indicated a substantial increase in the level of lipoprotein (a). Such a result would suggest which of the following?
(A) Substantially reduced risk for cardiovascular complications
(B) No change in risk for cardiovascular complications
(C) Increased risk for cardiovascular complications
(D) Increased platelet count
(E) Decreased platelet count

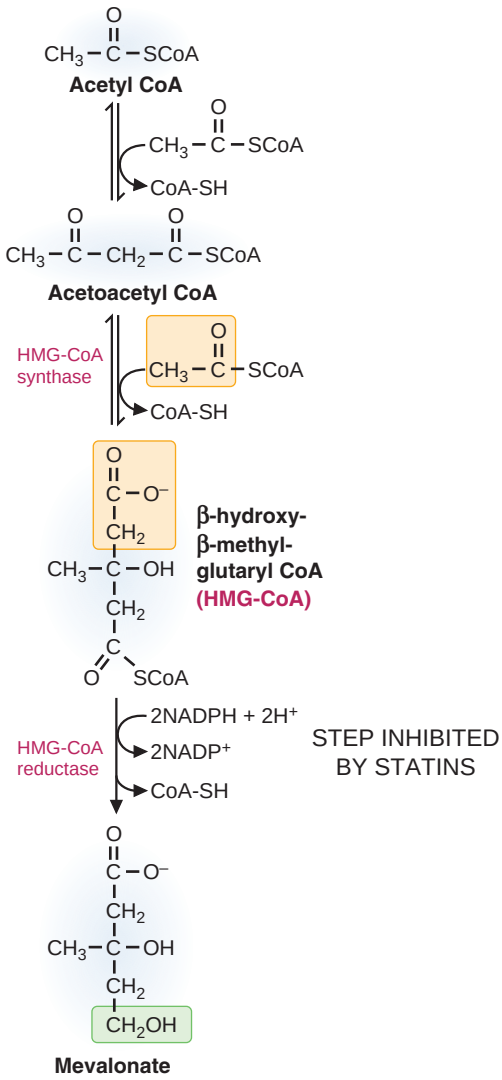
20 A 16-year-old male presents to you with xanthomas on the extensor tendons of the hand and Achilles tendon and arthritis of the knees. He has had one previous heart attack, despite normal cholesterol levels. Further analysis of his serum showed greatly elevated levels of plant sterols. The molecular defect in this patient is most likely in which of the following proteins?
(A) Apo B100
(B) Apo B48
(C) ABC1
(D) ABCG5
(E) MTTP

ANSWERS

1 **The answer is D: Enterohepatic circulation reabsorption of bile salts.** Because of the elevated liver enzymes (suggestive of liver damage), a statin would be relatively contraindicated in this patient, as a potential side effect of statins is liver damage. Cholestyramine would be a reasonable alternative to statins. Cholestyramine is one of the "bile acid binders" and prevents the reabsorption of bile salts. Since cholesterol is the precursor of bile salts, and 95% of bile salts are usually reabsorbed back into the enterohepatic circulation, losing bile salts in the feces would require increased synthesis of bile salts, thereby reducing the levels of free cholesterol in the body. Statins work by inhibiting HMG-CoA reductase. Cholestyramine does not reduce hepatic cholesterol synthesis, inhibit the release of bile salts, or interfere with the production of chylomicrons. Its sole action is in the lumen of the intestine, where it binds the bile salts so that they cannot be resorbed and sent back to the liver. The enterohepatic circulation is diagrammed below.

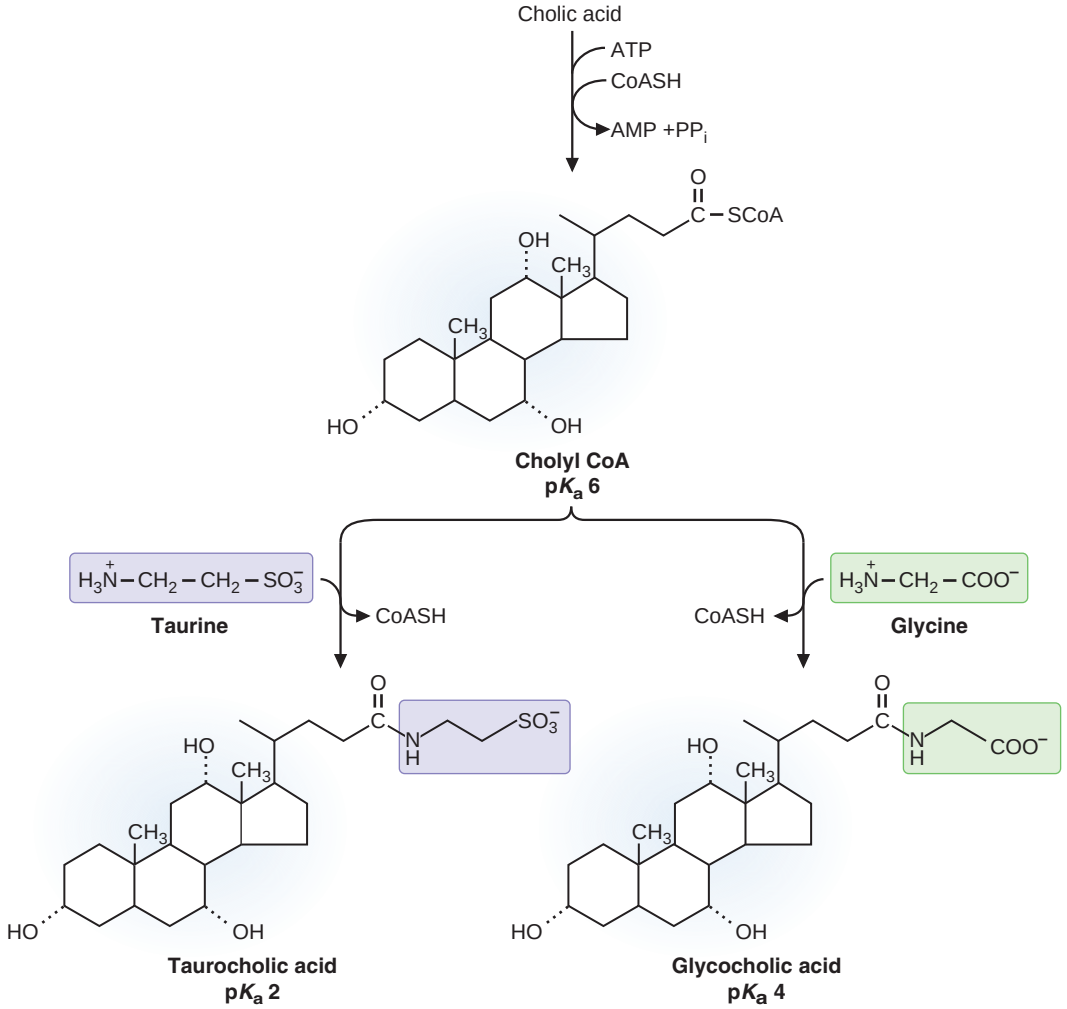


2 **The answer is C: HMG-CoA reductase.** The first stage of cholesterol synthesis leads to the production of the intermediate mevalonate. Two molecules of acetyl-CoA condense to form acetoacetyl-CoA which condenses with another acetyl-CoA to form β-hydroxymethylglutaryl-CoA (HMG-CoA). HMG-CoA synthase catalyses this step. Next, HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate. Statins (the class of drugs to which pravastatin belongs) directly inhibit HMG-CoA reductase, so mevalonate cannot be formed and cholesterol synthesis cannot continue. Statins do not inhibit the enzymes MCAD (required for fatty acid oxidation), CAT-1 (required for acyl-CoA transport into the mitochondria), or citrate lyase (needed to provide acetyl-CoA in the cytoplasm). The reactions required to produce HMG-CoA are shown below.



3 **The answer is A: Steatorrhea.** The primary reason for synthesizing conjugated bile acids is to lower the pK_a of the acid, so that a higher percentage of the acid will be ionized in the intestine. The greater a bile acid is ionized, the more efficient the emulsification is for the digestion of the triglyceride. Without conjugation with glycine or taurine, the pK_a of the bile salts is about 6.0; at a pH of 6.0, only 50% of the bile salts will be ionized in the intestinal lumen, which would produce inefficient triglyceride digestion, and the triglyceride content of the stool would increase. By reducing the pK_a to 4.0 (conjugated with glycine) or 2.0 (conjugated with taurine), greater than 99% of the bile acids will be ionized, and triglyceride digestion will be maximal. If an inability to conjugate the bile acids leads to inefficient triglyceride digestion, then intestinal chylomicron formation will be reduced, not

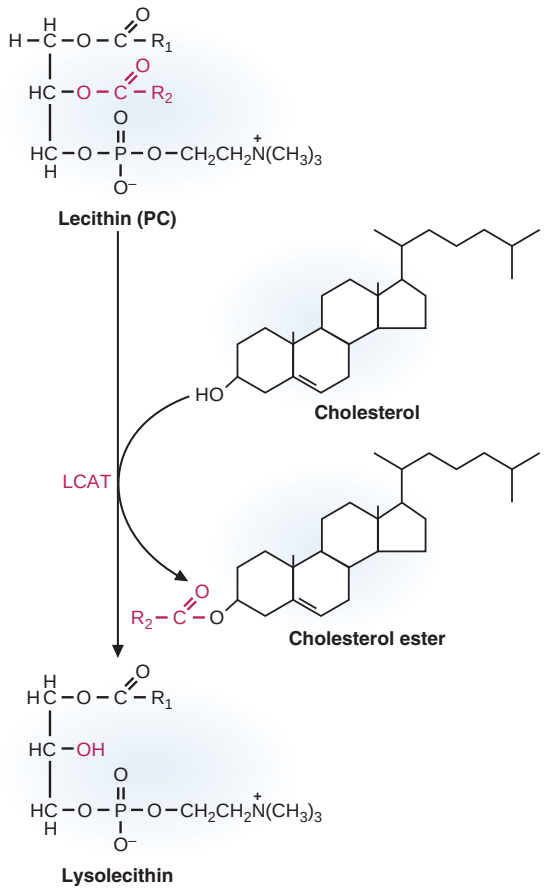
elevated (due to reduction of lipid uptake into the enterocyte). Transport of the water soluble B vitamins into the intestinal cells is not dependent on lipid digestion, as is fat-soluble vitamin absorption. The conjugation of bile acids will not affect the pH of the intestinal lumen, nor will it affect the secretion of zymogens from the pancreas to the intestine. The reactions involved in the conjugation of the bile acids are shown below.



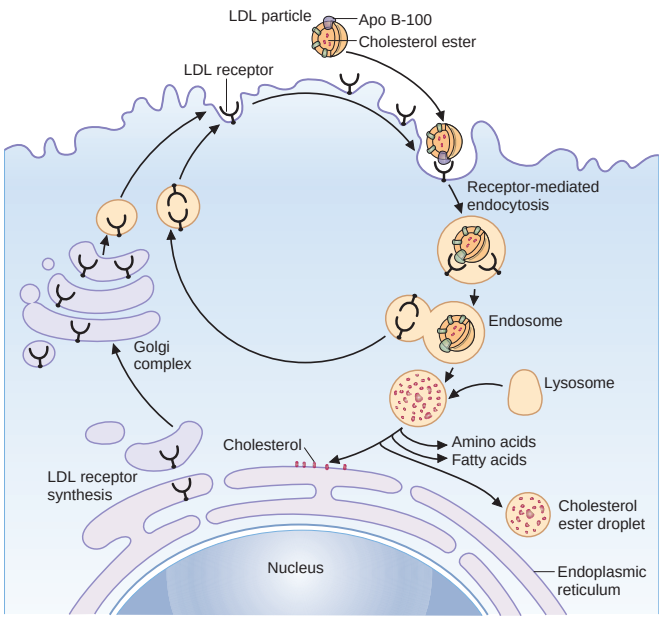
4 **The answer is D: ABC1.** The patient has Tangier disease, which is a defect in the ATP-binding cassette protein 1 (ABC1), a transporter in cell membranes which allows cholesterol efflux from the membrane into the HDL particle. Once inside the HDL particle, the cholesterol is trapped through esterification into a cholesterol ester. The HDL particle can then return the cholesterol to the liver for further recycling. The defect in the patient is not in HMG-CoA reductase (required for the biosynthesis of cholesterol), the AMP-activated kinase (a regulator of HMG-CoA reductase), LCAT (lecithin-cholesterol acyltransferase, the enzyme which esterifies cholesterol in the HDL particle), or CETP (cholesterol ester transfer protein, a protein which exchanges HDL cholesterol esters for VLDL triglyceride).

5 **The answer is B: LCAT.** HDL is protective, in part, due to its ability to remove excess cholesterol from cell membranes and return it to the liver. In order to accomplish this, the cholesterol, after transport to the HDL particle via the participation of ABC1, needs to be trapped within the core of the HDL particle, and this is accomplished by esterification and converting the cholesterol to a cholesterol ester. LCAT (lecithin cholesterol acyl transferase) is the enzyme that creates a cholesterol ester. The reaction, on page 153, is the transfer of a fatty acid from phosphatidyl choline (lecithin) to cholesterol, creating the cholesterol ester and lysophosphatidyl choline. ACAT (acyl-CoA cholesterol acyl transferase) creates cholesterol esters in cells, but not in the HDL particles. CETP exchanges HDL cholesterol esters for VLDL triglyceride.

Protein kinase A is not involved in cholesterol transfer throughout the body. The AMP-activated protein kinase is not utilized in HDL action. The LCAT reaction is shown below.



olemia (FH) is a mutation in the LDL receptor, making the receptor unable to bind LDL. In homozygous familial hypercholesterolemia, both LDL receptor genes are mutated, and the LDL receptors are nonfunctional. Upregulating nonfunctional LDL receptors will not lead to a reduction of LDL in the circulation, so such individuals are resistant to statin action. FH is not due to a resistant HMG-CoA reductase, nor an inability of statins to reach their target. FH is not related to reverse cholesterol transport, nor to LCAT. A diagram of receptor-mediated endocytosis, indicating the role of the receptor, is shown below.

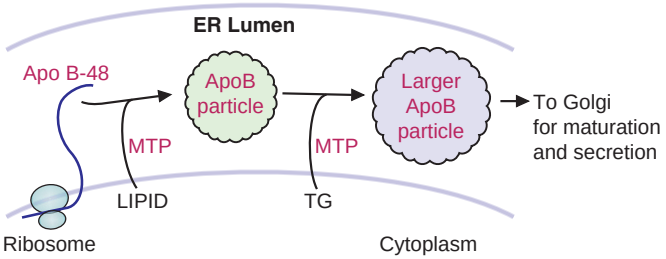


6 **The answer is D: VLDL.** Under fasting conditions, the total cholesterol measured will be the sum of the cholesterol in the HDL particles, the LDL particles, and VLDL. Chylomicrons should be nil under fasting conditions. The total cholesterol is measured, as are HDL and triglycerides. Since the VLDL is the primary triglyceride carrier under these conditions, the cholesterol content of the VLDL is estimated to be 20% that of the triglyceride content. Thus, the formula for calculating LDL values is LDL = total cholesterol – HDL – [(TG)/5].

7 **The answer is C: LDL receptors are nonfunctional.** Statins are effective in lowering circulating cholesterol levels due to a series of events. First, the statins inhibit HMG-CoA reductase, reducing intracellular synthesis of cholesterol. The reduced cholesterol levels in the cell then upregulate the synthesis of LDL receptors, which remove LDL from circulation, thereby reducing circulating cholesterol levels. Familial hypercholester-

8 **The answer is C: MTTP.** The patient has abetalipoproteinemia, an absence of apo B-containing proteins in the circulation. This leads to low chylomicron and VLDL levels. The problem is the synthesis of the chylomicrons and VLDL, both of which require the activity of the microsomal triglyceride transfer protein (MTTP). In the absence of MTTP activity, triglycerides cannot be transferred to the core particle as it is being synthesized, leading to little, if any, synthesis of these particles. The intestinal cells become laden with lipids obtained from the diet and those which cannot be exported due to the inability to produce chylomicrons. Mutations in LPL or apolipoprotein CII will not interfere with chylomicron or VLDL synthesis; mutations in those proteins would lead to an inability to remove triglyceride from those circulating particles. Deficiencies in LCAT or ABC1, which are related to HDL metabolism, would not affect the synthesis of

chylomicrons or VLDL. A schematic of MTTP action is shown below.



A model of microsomal triglyceride transfer protein (MTTP) action. MTTP is required to transfer lipid to apo B48 as it is synthesized, and to transfer lipid from the cytoplasm to the lumen of the endoplasmic reticulum as the particle (chylomicrons in the intestine, and VLDL in the liver) is being synthesized.

9 **The answer is D: Reduced secretion of LPL.** Insulin release stimulates the secretion of lipoprotein lipase (LPL) from fat and muscle cells such that the capillaries infiltrating these tissues have the lipase bound to extracellular matrix material. Then, as the triglyceride-rich particles move through the tissues, they bind to LPL via apolipoprotein CII, and the triglyceride is digested and the fatty acids used by the tissues. In the absence of insulin, LPL levels are low, and the particles have a longer half-life in circulation due to the reduced rate of digestion, which contributes to hypertriglyceridemia. If there were reduced synthesis of VLDL, triglycerides in the circulation would be reduced, not increased. Insulin does not alter the rate of apolipoprotein CII production. The release of insulin decreases fatty acid oxidation (promoting fatty acid synthesis), but if increased fatty acid oxidation did occur, then triglycerides would not accumulate in the circulation. Insulin also does not alter the synthesis of apolipoprotein B100 in the liver, which is required for VLDL synthesis.

10 **The answer is C: Apo CII.** A lack of apolipoprotein CII would mean that lipoprotein lipase could not be activated, and the triglyceride in both chylomicrons and VLDL would be unable to be digested. This would lead to elevated levels of these particles, and a very high serum triglyceride level. Since VLDL is not being converted to IDL or LDL cholesterol levels are not elevated. Defects in either apo B100 or apo B48 would lead to a loss of either VLDL or chylomicrons, which is not observed. A defect in pancreatic lipase would lead to steatorrhea, as the dietary triglycerides would not be able to be digested. A defect in LCAT would affect HDL metabolism, but not triglyceride metabolism. An overview of the functions of the lipoproteins is presented in Table 17-1.

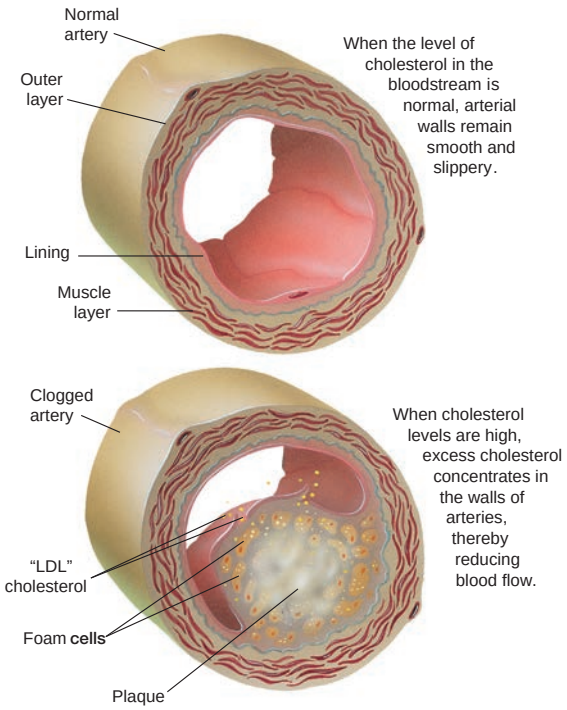
Table 17-1. Characteristics of the major apoproteins

Apoprotein	Primary Tissue Source	Molecular Mass (Daltons)	Lipoprotein Distribution	Metabolic Function
Apo A-1	Intestine, liver	28,016	HDL (chylomicrons)	Activates LCAT; structural component of HDL
Apo A-II	Liver	17,414	HDL (chylomicrons)	Unknown
Apo A-IV	Intestine	46,465	HDL (chylomicrons)	Unknown
Apo B-48	Intestine	264,000	Chylomicrons	Assembly and secretion of chylomicrons from small bowel
Apo B-100	Liver	540,000	VLDL, IDL, LDL	VLDL assembly and secretion; structural protein of VLDL, IDL, and LDL; ligand for LDL receptor
Apo C-1	Liver	6,630	Chylomicrons, VLDL, IDL, HDL	Unknown; may inhibit hepatic uptake of chylomicron and VLDL remnants
Apo C-II	Liver	8,900	Chylomicrons, VLDL, IDL, HDL	Cofactor activator of lipoprotein lipase (LPL)
Apo C-III	Liver	8,800	Chylomicrons, VLDL, IDL, HDL	Inhibitor of LPL; may inhibit hepatic uptake of chylomicrons and VLDL remnants
Apo E	Liver	34,145	Chylomicron remnants, VLDL, IDL, HDL	Ligand for binding of several lipoproteins to the LDL receptor, to the LDL receptor-related protein (LRP) and possibly to a separate apo-E receptor
Apo(a)	Liver		Lipoprotein "little" a (Lp(a))	Unknown

11 **The answer is D: Secretin.** Secretin is released from the intestine when food enters, and it signals the pancreas to release a watery mixture of bicarbonate into the intestine, in order to help neutralize the acid present from the digestion that occurred in the stomach. If the pH of the intestinal lumen is too low, the bile salts will not be ionized, and emulsification of the dietary fats will be inefficient, as will be the formation of mixed micelles to allow intestinal absorption of fat components. Digestion of carbohydrates and protein is not dependant on bile salt ionization. A loss of cholecystokinin would result in no pancreatic zymogens being secreted, and there would be no digestion of carbohydrates, proteins, or lipids within the intestine. A lack of insulin secretion, or glucagon secretion, does not affect digestion in the intestinal lumen. Cortisol secretion also does not alter intestinal digestion of nutrients.

12 **The answer is B: Oxidized LDL.** Oxidized LDL is taken up by macrophages, which eventually turn into foam cells in the development of an atherosclerotic plaque. The higher one's LDL levels are, the more likely that oxidized LDL will form, leading to plaque formation. The receptor which recognizes and takes up oxidized LDL, SR-A1, is not downregulated, so the macrophage has an unlimited capacity to take up and store the oxidized LDL. Plaque formation does not occur due to elevated levels of nonoxidized LDL, HDL of any form, or triglycerides. A cartoon depiction of a normal and an atherosclerotic artery is shown below.

Atherosclerosis: The consequence of high cholesterol



13 **The answer is C: Apolipoprotein E.** The patient has dysbetalipoproteinemia, a mutation in apolipoprotein E, such that the patient exhibits the rare E2 form instead of the normal E3 form. Apolipoprotein E has affinity for the LDL receptor and the LDL receptor-related protein and, as such, is important for chylomicron remnant and IDL uptake from the circulation by the liver. With the homozygous E2 form, binding of the particles to their receptors is weak, and the particles circulate longer than normal, contributing to the high cholesterol and triglyceride levels seen in the circulation. Only about 10% of the individuals who are homozygous for E2 will develop this condition, and in those, obesity (BMI of 34) is a key factor which links the condition to the mutation. This disorder is not a problem with lipoprotein lipase (LPL) digesting triglycerides from particles, so neither LPL nor apo CII is defective. As both chylomicrons and VLDL are produced, it is not a defect in either apo B48 or B100 production or function.

14 **The answer is B: Coenzyme Q.** Coenzyme Q is derived from isoprene units, which are produced in the pathway of cholesterol biosynthesis, after the HMG-CoA reductase step. If HMG-CoA reductase is inhibited (as it is by statins), then the production of the isoprenes is also reduced, and both Coenzyme Q and dolichol levels could become limiting. The biosynthesis of heme, ketone bodies, glycogen, or dihydrobiopterin is not dependent on isoprene units.

15 **The answer is B: To reduce circulating cholesterol levels.** Phytosterols interfere with cholesterol absorption in the intestine (through blockage of cholesterol incorporation into the mixed micelles, which are necessary for intestinal epithelial cells to absorb dietary cholesterol), thereby leading to a reduction in circulating cholesterol levels. The phytosterols do not interfere with the biosynthesis of cholesterol, nor do they alter the secretion of insulin. Phytosterols are also not capable of altering the rate of fatty acid biosynthesis, nor do they affect circulating triglyceride levels. The effect of phytosterols is specific for the inhibition of cholesterol absorption from the intestine.

16 **The answer is B: Ezetimibe.** Ezetimibe reduces circulating cholesterol levels by blocking cholesterol absorption in the intestine, which is similar to the mechanism of action of phytosterols. Atorvastatin is a statin, and its mechanism of action is inhibition of HMG-CoA reductase. Pravastatin is also a statin and works as does atorvastatin. Simvastatin is yet another statin. Metformin is a lipid- and glucose-lowering drug which works via activation of the AMP-activated protein kinase and does not alter cholesterol absorption

Table 17-2. Mechanism(s) of action and efficacy of lipid-lowering agents

Agent	Mechanism of Action	Percentage Change in Serum Lipid Level (monotherapy)			
		Total Cholesterol	LDL Cholesterol	HDL Cholesterol	Triacylglycerols
Statins	Inhibit HMG-CoA reductase activity	↓15%–60%	↓20%–60%	↑5%–15%	↓10%–40%
Bile acid resins	Increase fecal excretion of bile salts	↓15%–20%	↓10%–25%	↑3%–5%	Variable, depending on pretreatment level of triacylglycerols (may increase)
Niacin	Activates LPL; reduces hepatic production of VLDL; reduces catabolism of HDL	↓22%–25%	↓10%–25%	↑15%–35%	↓20%–50%
Fibrates	Antagonizes PPAR-α, causing an increase in LPL activity, a decrease in apoprotein C-III production, and an increase in apoprotein A-I production.	↓12%–15%	Variable, depending on pretreatment levels of other lipids	↑5%–15%	↓20%–50%
Ezetimibe	Reduces intestinal absorption of free cholesterol from the gut lumen	↓10%–15%	↓15%–20%	↑1%–3%	↓5%–8% if triacylglycerols are high pretreatment

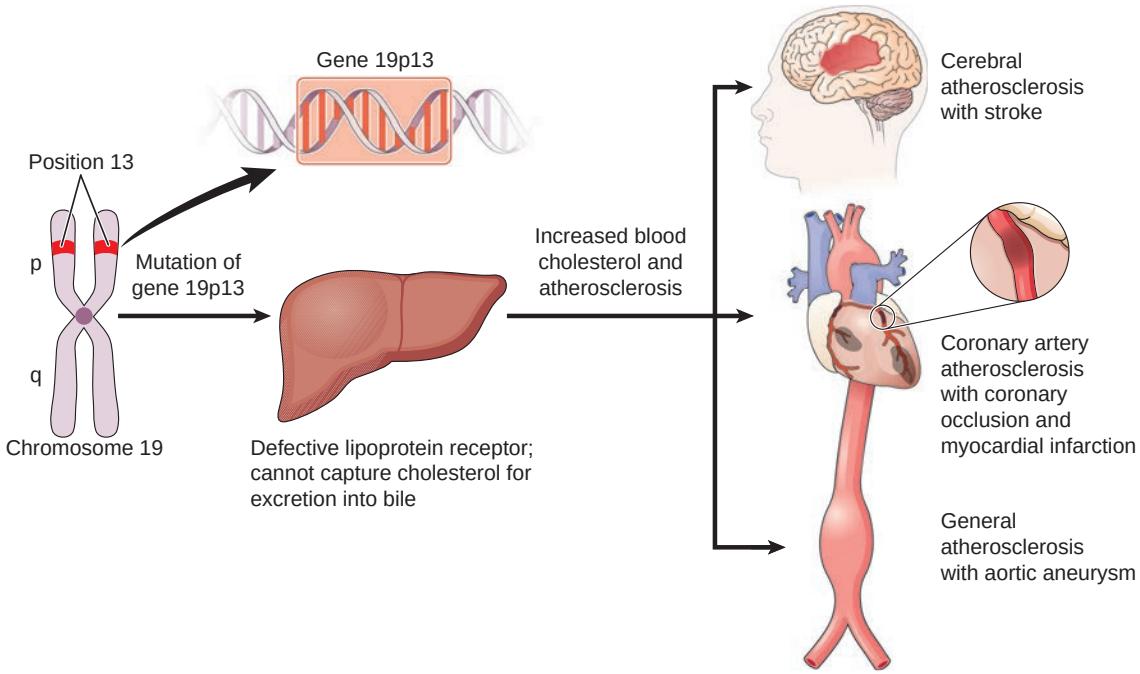
LPL, lipoprotein lipase; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; triacylglycerols, triglycerides; *PPAR*, peroxisome proliferator-activated receptor.

Adapted from Circulation. Grundy SM, Becker D, Clark LT etal. 2002;106:3145–3457.

in the intestine. Table 17-2 summarizes the action of cholesterol lowering drugs.

17 **The answer is C: Constant SR-A1 expression on the cell surface.** The macrophages take up oxidized LDL using a scavenger receptor, SR-A1, which is not down-regulated. This allows the receptor to remain on the cell surface and to constantly import oxidized LDL into the cell. The high levels of cholesterol in the foam cells is not due to a change in activity of ACAT or LCAT (which is found in HDL particles), nor is there upregulation of HMG-CoA reductase (which would produce more endogenous cholesterol, which is unlikely since the cell is filled with cholesterol and cholesterol esters). Macrophages do not use the LDL receptor for importing oxidized LDL.

18 **The answer is E: LDL receptor.** The patient is heterozygous for a mutation in the LDL receptor (familial hypercholesterolemia). This condition leads to elevated LDL levels since there are insufficient receptors available to remove LDL from the circulation. If left untreated, heart attacks are common in such patients before the age of 50. This condition is treated with statins, which reduce endogenous cholesterol synthesis, thereby leading to an upregulation of LDL receptors, which allows for normal LDL uptake from the circulation. Mutations in LCAT (familial LCAT deficiency) are rare and do not often lead to premature atherosclerotic disease (although some exceptions are noted), but do lead to kidney and corneal damage due to large amounts of unesterified cholesterol present in those tissues. HDL level in these individuals is usually less than 10 mg/dL, which is not observed in our patient. Mutations in CETP (cholesterol ester transfer protein) lead to elevations in HDL levels and would not be responsive to statin action. Mutations in ABC1 lead to Tangier disease, which would lead to a reduction in HDL levels, which is not seen in this patient. A deficiency in apo B100 would impair VLDL synthesis and would actually reduce circulating LDL levels since there is less VLDL present to be converted to LDL. The diagram on page 157 depicts potential problems which result from defects in the LDL receptor.



Answer 18: Potential results of mutations within the LDL receptor.

19 **The answer is C: Increased risk for cardiovascular complications.** Lipoprotein (a) is an LDL particle with a covalently linked apoprotein A (linked to apoprotein B100) attached to the particle. The presence of this unusual lipoprotein particle has been positively correlated with the presence of heart disease. The role of this particle is unknown, but may be related to coagulation, since apoprotein A resembles plasminogen in structure. Lp (a) levels do not regulate the levels of platelets in the circulation.

20 **The answer is D: ABCG5.** The patient has sitosterolemia, an accumulation of plant sterols (phytosterols) in cells and tissues. Under normal conditions, phytosterols can diffuse into the epithelial cells, but they are actively transported back into the intestinal lumen by an ABC-cassette (ATP-binding) containing protein, ABCG5 (the other protein responsible for phytosterol efflux is ABCG8).Those sterols which make it to the liver are exported by the same proteins in the liver to the bile duct, where they will be released along with the bile during fat digestion. In the absence of activity of either ABCG5 or ABCG8, the phytosterols are packaged into chylomicrons and are eventually delivered to the liver, where they are packaged into VLDL. While human cells cannot utilize phytosterols, their increased presence interferes with the synthesis of cholesterol and the normal cholesterol recycling within the affected patient. Patients with this disorder develop premature coronary artery disease. It has been hypothesized that the high levels of plant sterols in the circulating lipoprotein particles accelerate the deposition of these sterols in the walls of the arteries, promoting atherosclerosis. This disorder is not due to mutations in either apo B100 or apo B48, as both VLDL and chylomicrons are synthesized normally in the patient. The defect is not in ABC1, as the patient does not display the symptoms of Tangier disease. The defect is also not in MTTP, as a defect in that protein leads to abetalipoproteinemia.