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Chapter 15: Lipids and Lipoproteins

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Lipid Chemistry

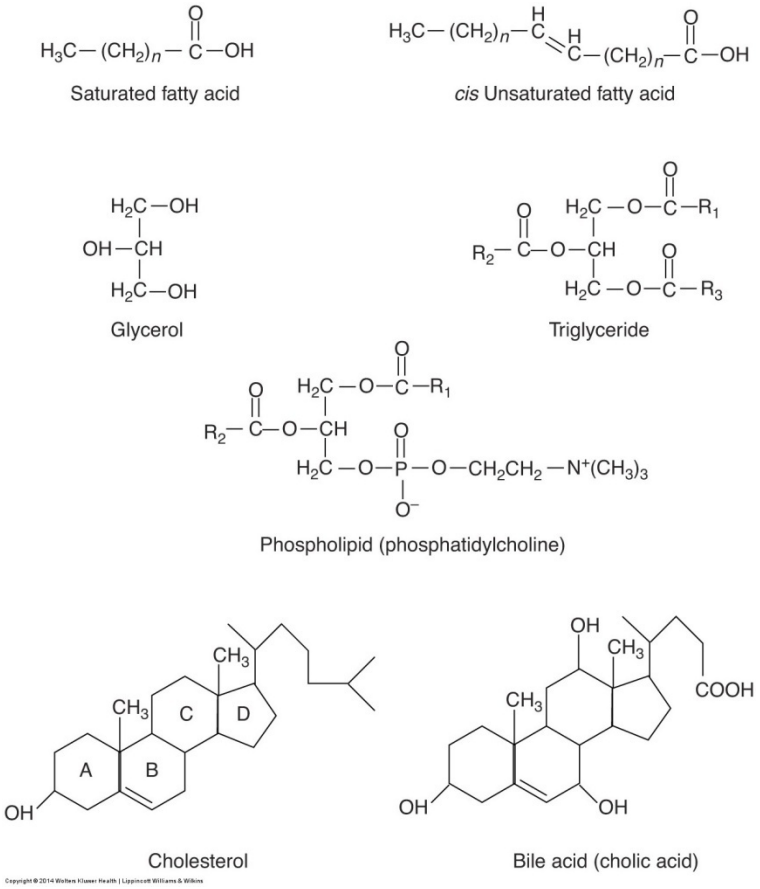
- Roles of Lipids (Fats)
  - Rich source of energy & efficient way for body to store calories
  - Integral part of cell membranes and structure
- Fatty Acids
  - Linear chains of carbon-hydrogen bonds terminating in carboxyl group
- Triglycerides
  - 3 fatty acid molecules attached to 1 molecule of glycerol by ester bonds

Lipid Chemistry (cont'd)

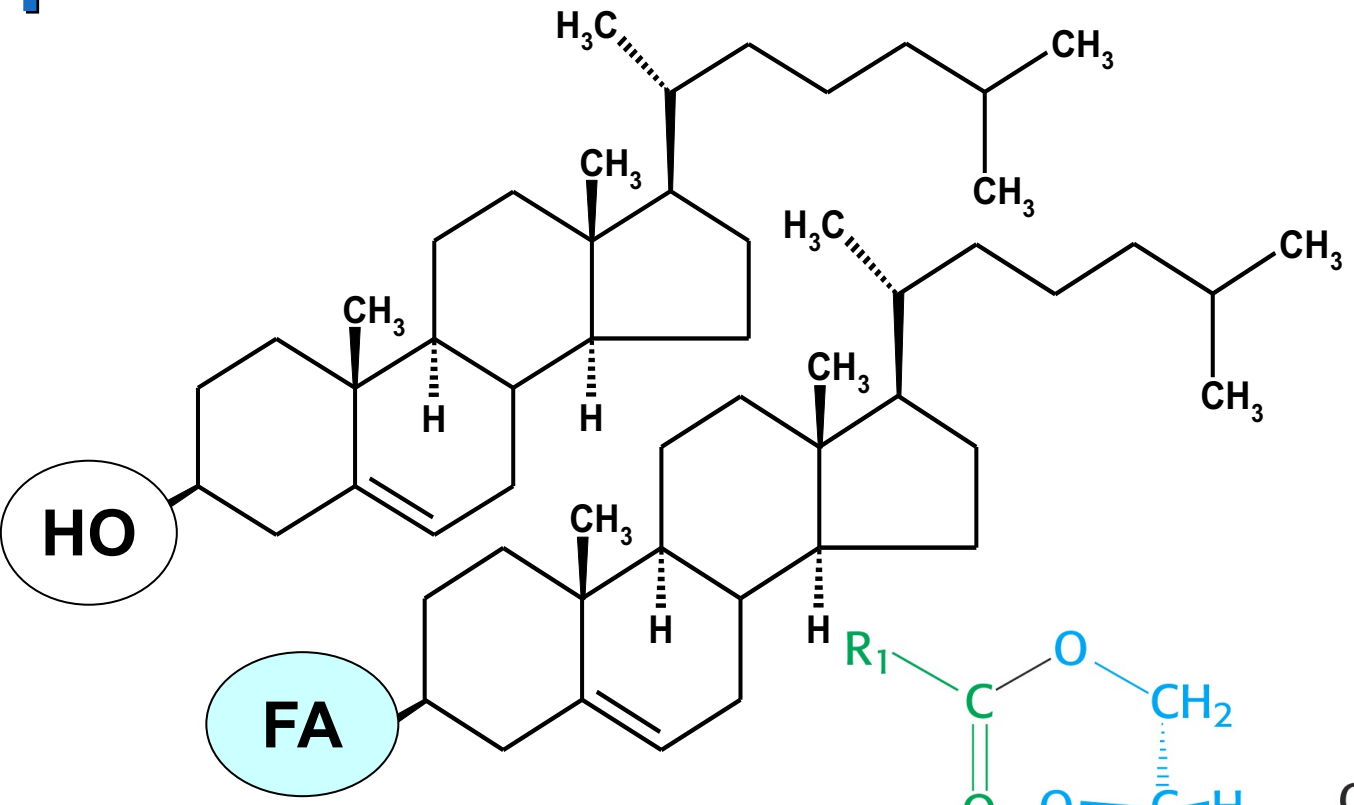
- Phospholipids
  - Similar to triglycerides, except with only 2 esterified fatty acids
  - Third position on glycerol backbone contains phospholipid head group.
  - Types of head groups: choline, inositol, serine, ethanolamine, all of which are hydrophilic in nature
- Cholesterol
  - An unsaturated steroid alcohol containing 4 rings & single side chain tail
  - Synthesized almost exclusively by animals; not readily catabolized by most cells, not a source of fuel

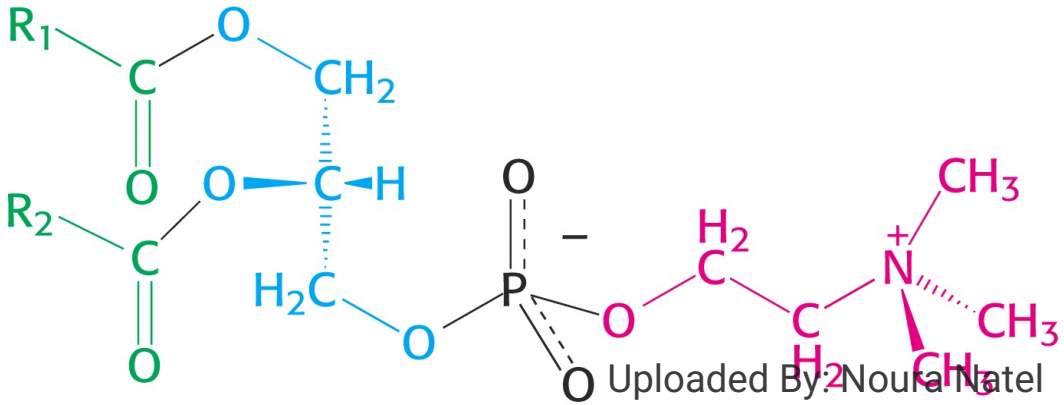
Lipid Chemistry (cont'd)

- Chemical structures of lipids



Mark the hydrophobic and hydrophilic parts on these molecules





Lipoproteins

- Liporproteins are the body's "petroleum industry"> like oil tankers

- **Chylomicrons**: ferry their cargo dietary TG, throughout the circulatory system and finally docking at the liver
  - Largest & least dense; diameters as large as 1,200 nm
  - Produced by intestine; deliver dietary lipids to hepatic & peripheral cells

Lipoproteins

- **VLDLs**: like tanker trucks
  - Produced by liver; major carriers of endogenous triglycerides
  - Redistribute dietary & hepatic synthesized TG to peripheral cells for energy needs or storage as fat
- **LDLs**: rich in cholesterol, like nearly empty tankers that just delivered TG to peripheral cells and liver after their main cargo TG have been off-loaded
- **HDLs**: clean up crew, gathering up excess cholesterol for transport back to liver

General Lipoprotein Structure

- Lipoproteins are spherical in shape, 10-1200 nm
- Composed of lipids & apolipoproteins; deliver fuel to peripheral cells
- Size correlated with lipid contents
- Core of TG and CE
- Surface of phospholipids and some cholesterol
- Apolipoproteins (regulators of LP metabolism)

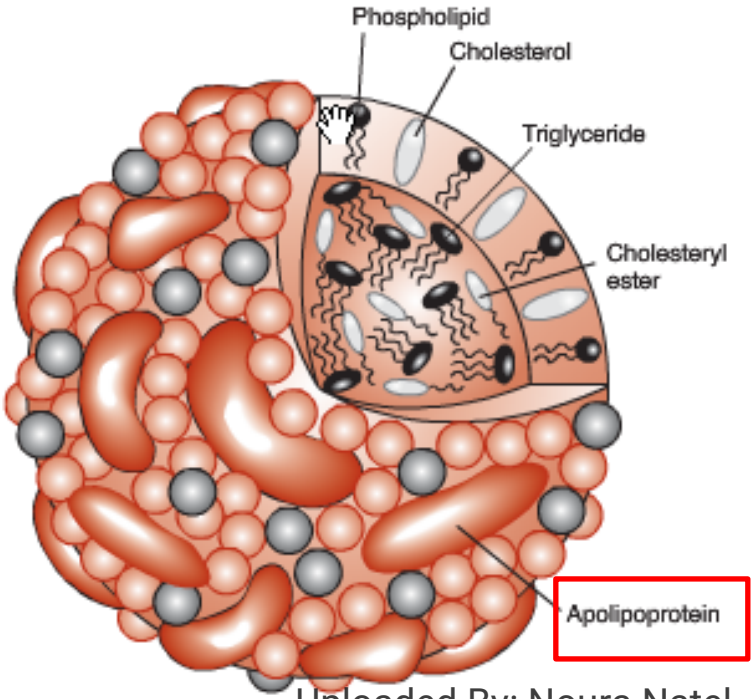


FIGURE 15-2 Model of lipoprotein structure.

Apolipoproteins

- Located on surface of lipoprotein particles
- Functions
  - Maintain structural integrity of lipoproteins
  - Ligands for interaction with LP receptors that determine disposition of individual particles
  - Activators & inhibitors of various enzymes involved in LP and plasma lipid metabolism
- Amphipathic helix on the surface
  - hydrophobic part binds to lipids, hydrophilic residues facing the aqueous surface

The 4 classes of lipoproteins

(all contain characteristic amounts of TG, Cholesterol, cholesteryl esters, phospholipids and apolipoproteins)

Increasing density ↓

Class	Average Diameter (nm)	Source, function	Major apolipoproteins
CM	500	Intestine. transport of dietary TAG	A, B48, C(I,II,III), E
VLDL	43	Liver. Transport of endogenously synthesized TAG	B100, C(I,II,III), E
LDL	22	Delivers cholesterol to peripheral tissues	B100
HDL	8	Liver. Removes used cholesterol from tissues and takes it to liver.	A, C(I,II,III), D, E

TABLE 15-1 CHARACTERISTICS OF THE MAJOR HUMAN LIPOPROTEINS

CHARACTERISTICS	CHYLOS	VLDL	LDL	HDL
Density (g/mL)	<0.93	0.93–1.006	1.019–1.063	1.063–1.21
Molecular weight (kD)	$(0.4–30) \times 10^9$	$(10–80) \times 10^6$	2.75×10^6	$(1.75–3.6) \times 10^5$
Diameter (nm)	80–1,200	30–80	18–30	5–12
Total lipid (% by weight)	98	89–96	77	50
Triglycerides (% by weight)	84	44–60	11	3
Total cholesterol (% by weight)	7	16–22	62	19

CHYLOS, chylomicrons; VLDL, very low density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

TABLE 15-2 CHARACTERISTICS OF THE MAJOR HUMAN APOLIPOPROTEINS

APOLIPOPROTEIN	MOLECULAR WEIGHT (kD)	PLASMA CONCENTRATION (mg/dL)	MAJOR LIPOPROTEIN LOCATION	FUNCTION
Apo A-I	28,000	100–200	HDL	Structural, LCAT activator, ABCA1 lipid acceptor
Apo A-II	17,400	20–50	HDL	Structural
Apo A-IV	44,000	10–20	Chylos, VLDL, HDL	Structural
Apo B-100	5.4×10^5	70–125	LDL, VLDL	Structural, LDL receptor ligand
Apo B-48	2.6×10^5	<5	Chylos	Structural, remnant receptor ligand
Apo C-I	6,630	5–8	Chylos, VLDL,HDL	Structural
Apo C-II	8,900	3–7	Chylos, VLDL, HDL	Structural, LPL cofactor
Apo C-III	9,400	10–12	Chylos, VLDL, HDL	Structural, LPL inhibitor
Apo E	34,400	3–15	VLDL, HDL	Structural, LDL receptor ligand
Apo(a)	$(3–7) \times 10^5$	<30	Lp(a)	Structural, plasminogen inhibitor

HDL, high-density lipoprotein; Chylos, chylomicrons; LCAT, lecithin:cholesterol acyltransferase; VLDL, very low density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase.

Type	Association	Function
B48	Chylomicron	Carry cholesterol esters Lacks LDL receptor binding domain
B100	VLDL, IDL, LDL	Binds LDL receptor
C-II	Chylo, VLDL, IDL, HDL	Activates Lipoprotein lipase (LPL)
C-III	Chylo, VLDL, IDL, HDL	Inhibits LPL
E	Chylo, remnant, VLDL, IDL HDL	Binds LDL-receptor related protein (LRP)
A-1	HDL	LCAT activator (lecithin:cholesterol acyltransferase)

Chylomicrons

- Chylos contain apo B-48
- Largest and least dense of lipoprotein particles
- Diameter up to 1200 nm
- *Primary function of Chylos: delivery of dietary lipids to hepatic & peripheral cells*
- Can scatter light, and accounts for the turbidity or milky appearance of postprandial plasma
- Chylos are so light, readily float to the top of plasma when stored for hours at 4°C
- Produced by intestine & packaged with absorbed lipids & apolipoproteins
- In circulation, TG & cholesteryl esters in chylos are rapidly hydrolyzed by lipases, & converted to chylos remnant particles, recognized by liver

Very low density lipoproteins (VLDL)

- Produced primarily by liver
- Contain apo B-100 (main lipoprotein), apo E and apo Cs
- Rich in TG
- Major carriers of endogenous TG from liver to peripheral tissues for energy & storage
- Light & contribute to turbidity observed in fasting hyperlipidemic plasma, but do not form a creamy top layer
- Excess dietary intake of carbohydrate, saturated fatty acids, and trans fatty acids enhances the hepatic synthesis of triglycerides, which in turn increases VLDL production

Intermediate density lipoproteins (IDL)

- Also called VLDL remnants
- Normally exist transiently during conversion of VLDL to LDL
  - Not typically present in normal plasma
  - Efficient conversion of VLDL to IDL → do not accumulate in the plasma after an overnight fast
- TG & cholesterol content is intermediate between those of VLDL and LDL
- Type III hyperlipoproteinemia (TIIIHL), a rare inborn error of metabolism, shows elevated levels of IDLs in plasma. Due to abnormal form of apo E that delays clearance of IDL> risk of peripheral vascular disease & coronary artery disease

Low density lipoproteins (LDL)

- Primarily contain apo B-100 & is more cholesterol rich than other apo B-containing lipoproteins
- Form as a consequence of lipoplysis of VLDL
- Because of their small size, they infiltrate into extracellular space of vessel wall & are taken up macrophages > transform into foam cells > fatty streaks, early precursor of atherosclerosis
- Can be separated into 8 subclasses
  - Smaller LDLs are denser and contain more TG than CE. More atherogenic

Lipoprotein (a)

- Lp(a) particles are LDL-like particles
- Contain apo (a) linked to apo B-100 by a disulfide bond
- Heterogeneous in size and density (contain differing number of repeating peptide sequences, called kringles, in the apo (a) portion of the molecule)
- Larger than LDL and has a higher lipid content and a slightly lower density
- Elevated levels of Lp(a) increases risk of premature CHD and stroke.
- Measuring Lp(a) is useful in patients with a strong family history of CHD, particularly in absence of other known risk factors
- ***Question:*** *What is a possible mechanism for the induction of clots by Lp(a) through its kringles domain?*

High density lipoproteins (HDL)

- Smallest and most dense lipoprotein particle
- Synthesized by liver and intestine
- Exists as disk shaped (more active in extracting lipids) or spherical (core is filled with lipids)
  - Reverse cholesterol transport
  - Antiatherogenic
- It is highly heterogeneous and has 13-14 different subfractions
  - Two major types of spherical HDL
    - HDL_2 (1.063 to 1.125 g/mL) larger in size, less dense, and richer in lipid and may be more efficient in the delivery of lipids to the liver
    - HDL_3 (1.125 to 1.21 g/mL)

Lipoprotein X

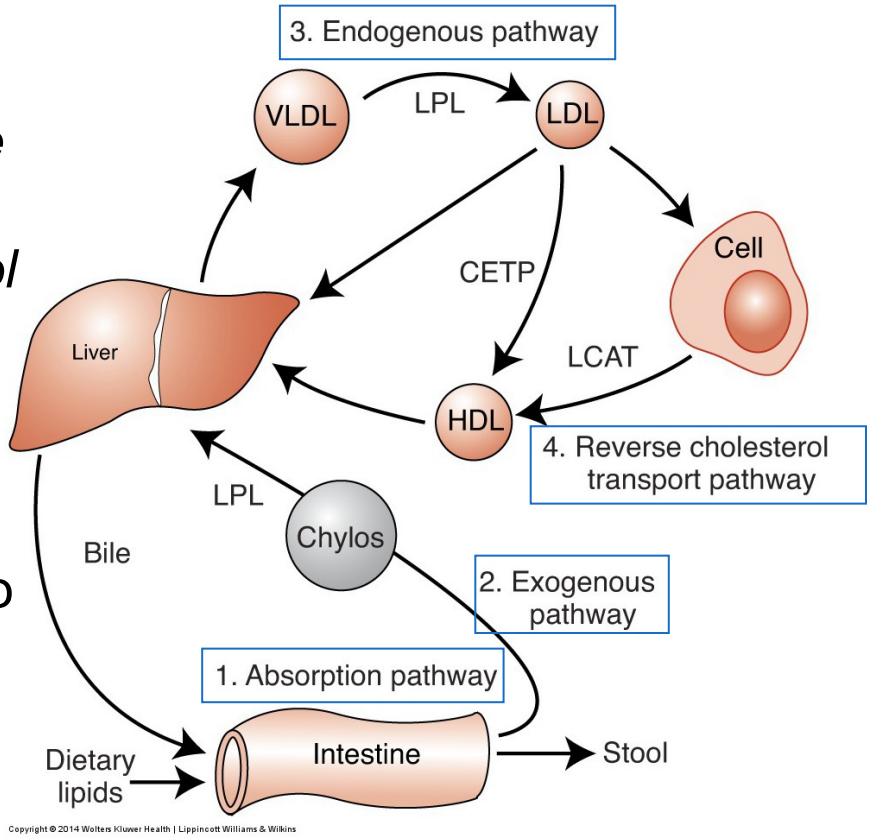
- Abnormal lipoprotein that exists in patients with biliary cirrhosis or cholestasis and in particular mutations in LCAT, the enzyme that esterifies cholesterol
- Different from other lipoproteins in the endogenous pathway due to the lack of apo B-100.
- Contains phospholipids and non-esterified cholesterol (~90% by weight) and albumin and apo C (<10% by weight)
- Mainly removed by the reticuloendothelial system of the liver and the spleen.
- Lipoprotein X is typically included in the LDL-C value as calculated by the **Friedewald equation**:
  - **LDL = TotalChol - (Triglyceride / 5) – HDL (all in mg/dL)**

Lipoprotein Physiology and Metabolism

- Four Major Pathways Involved in Lipoprotein Metabolism

Net result of these 1-3 pathways is the transport of dietary lipid and cholesterol to peripheral cells

When peripheral cells in the vessel wall accumulate too much cholesterol, this can lead to **atherosclerosis**



The Reverse cholesterol transport which is mediated via HDL, where excess cholesterol in peripheral cells is transported back to liver, where it is excreted into the bile as free cholesterol and converted to bile acids

- Peripheral cells are prone to accumulating cholesterol because:
  - They also synthesize their own cholesterol
  - Unlike liver, they do not have enzymatic pathways to catabolize it
  - Cholesterol is relatively water insoluble and cannot readily diffuse away from its site of deposition or synthesis

- There are several genetic defects in the genes that encode for proteins in the forward and reverse cholesterol transport pathways
- Most individuals with CAD, do not have a clear, single, genetic defect but instead have multiple genetic variations or gene polymorphisms that most likely interact with various lifestyle habits such as exercise, diet, and smoking, leading to a predisposition for disease

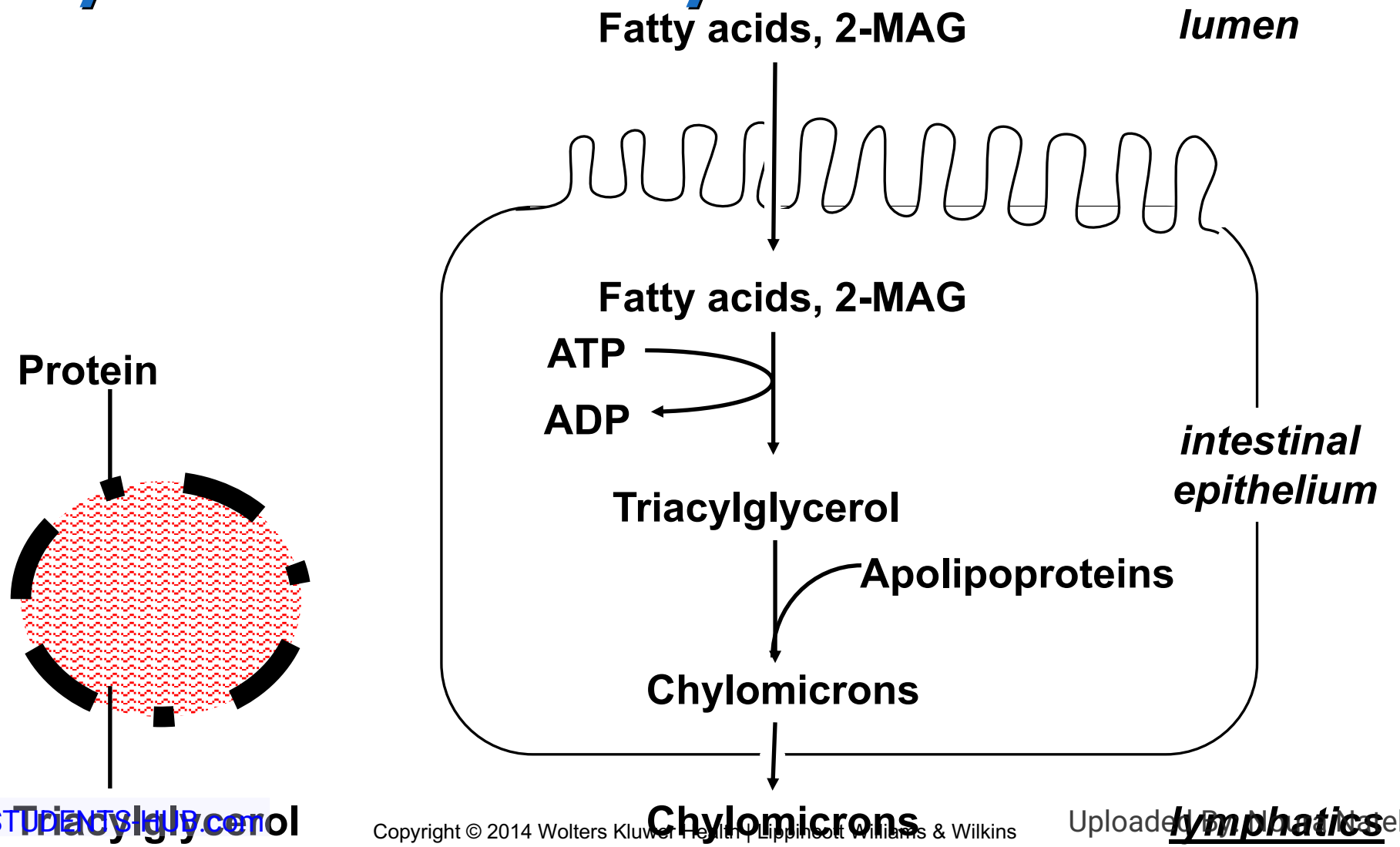
(1) Lipid absorption

- Pancreatic lipase cleaves off fatty acids → converting dietary lipids into more polar compounds with amphipathic properties
- Amphipathic lipids form micelles in intestinal lumen
  - TG → monoglycerides and diglycerides; cholesteryl esters → free cholesterol; and phospholipids → lysophospholipids
  - Absorption of some of these lipids may occur via a passive transfer process or facilitated by specific transporters (NPC1L-1 transporter for cholesterol)
  - Short-chain free fatty acids (<10 C), can readily pass directly into the portal circulation and are carried by albumin to the liver
- The absorbed long-chain fatty acids, monoglycerides, and diglycerides are esterified in intestinal cells to form triglycerides and cholesteryl esters, & packaged into CMs, along with apo B-48
  - Triglyceride absorption is efficient; greater than 90% of dietary triglycerides are taken up by the intestine.
  - In contrast, only about half of the 500 mg of cholesterol in the typical diet is absorbed each day

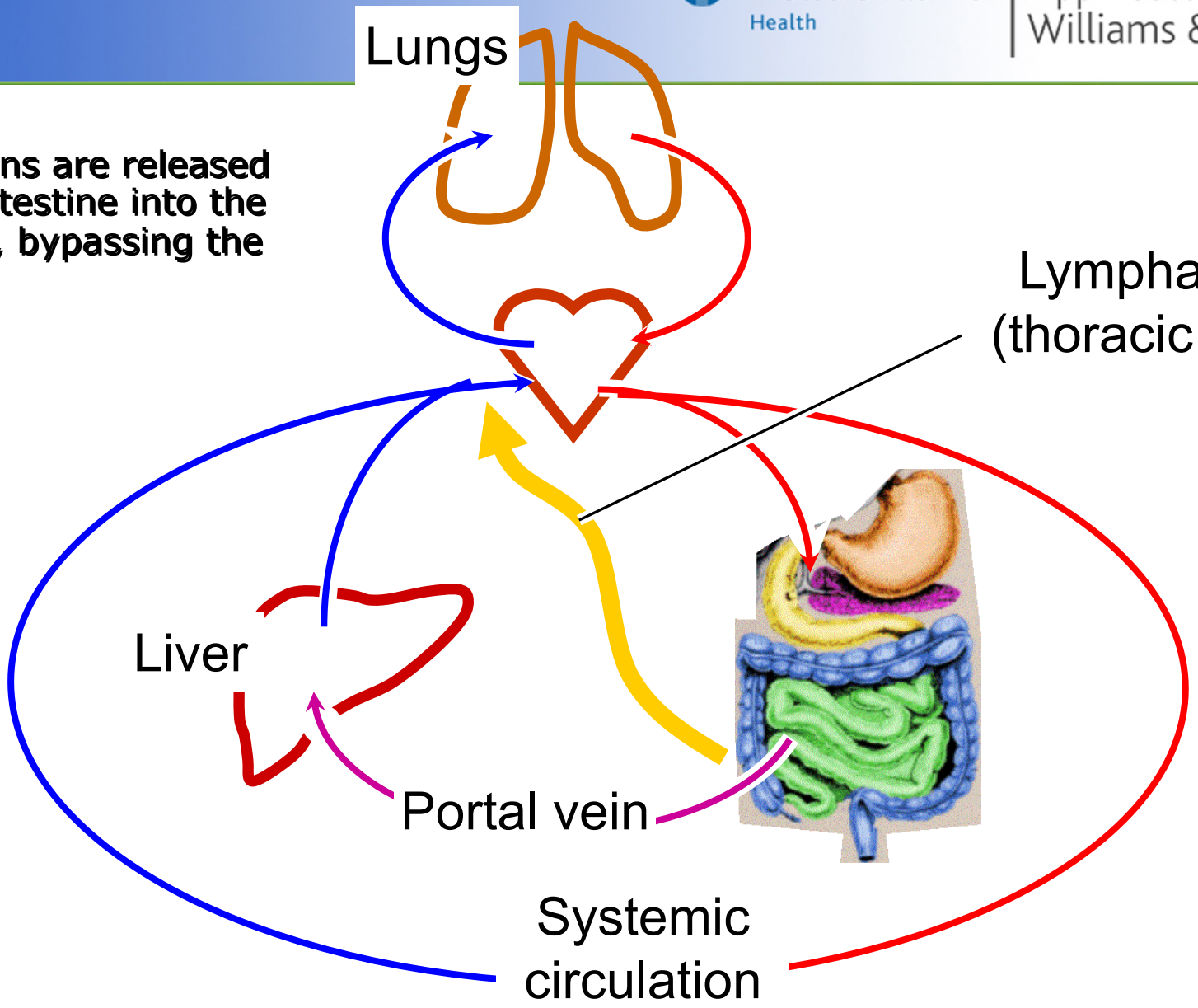
(2) Exogenous pathway

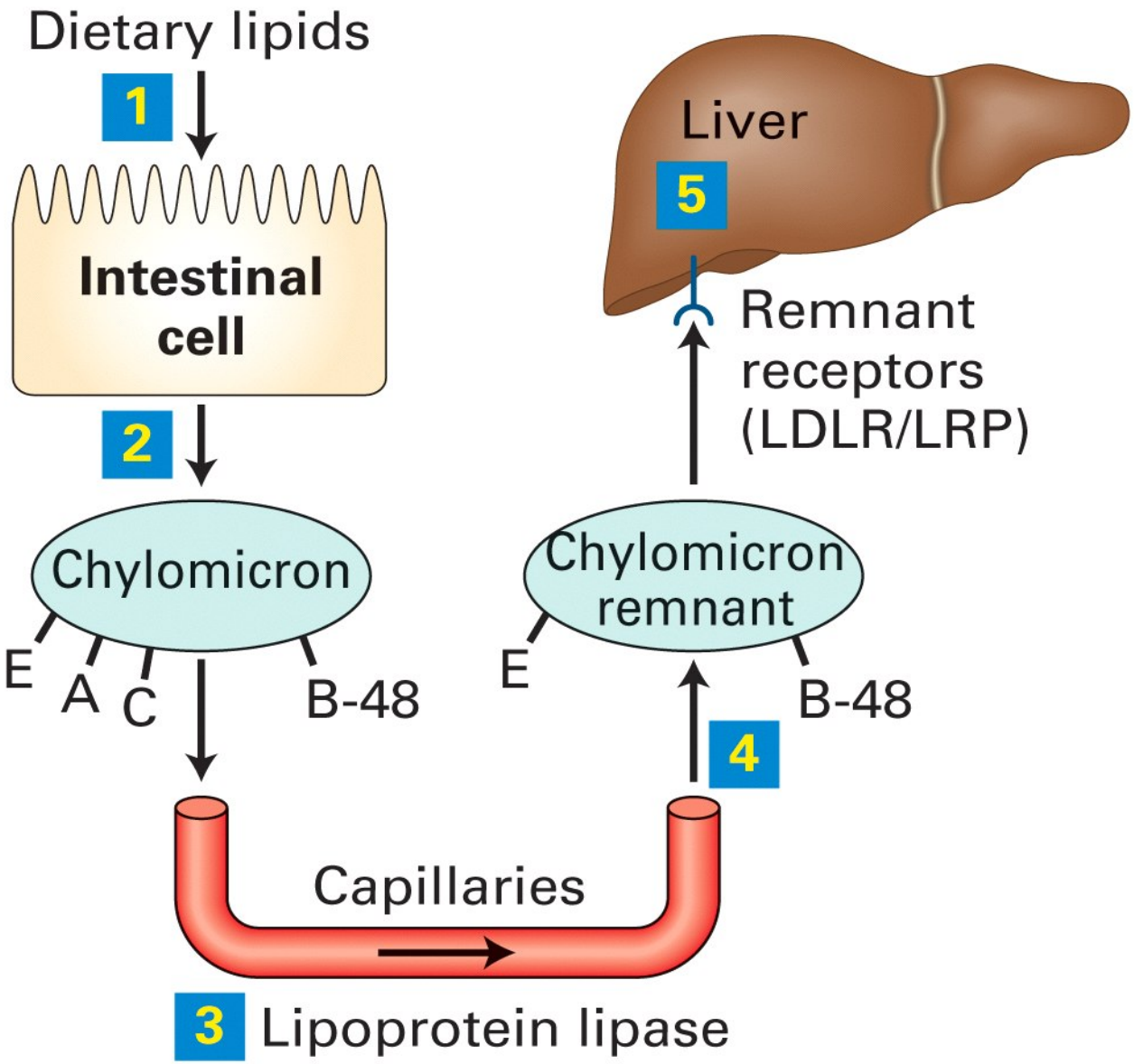
- Newly synthesized CMs in the intestine are initially secreted into lacteals and enter the circulation
- CMs interact with proteoglycans on capillaries that promote LPL (lipoprotein lipase) which hydrolyzes TG on CMs → Free fatty acids and glycerol are taken up by cells
- A key protein in TG metabolism is the Apo C-II (in VLDL) & activates LPL
- Hormone-sensitive Lipase in adipose cells releases free fatty acids from TG in case of energy needs
- Epinephrine, glucagon & cortisol play a key role in lipolysis and TG mobilization
- Insulin prevents lipolysis
- Chylomicron remnants are rapidly taken up by the liver through interaction of apo E with the LDL receptor and LDL-receptor related protein (LRP)
- Remnants are broken down in the lysosome to release free fatty acids, free cholesterol, and amino acids.
- Some cholesterol is converted to bile acids (both excreted into bile0
- Not all of the excreted cholesterol and bile salt exit the body (reabsorbed in the intestine).

Chylomicron assembly



Chylomicrons are released from the intestine into the lymphatics, bypassing the liver



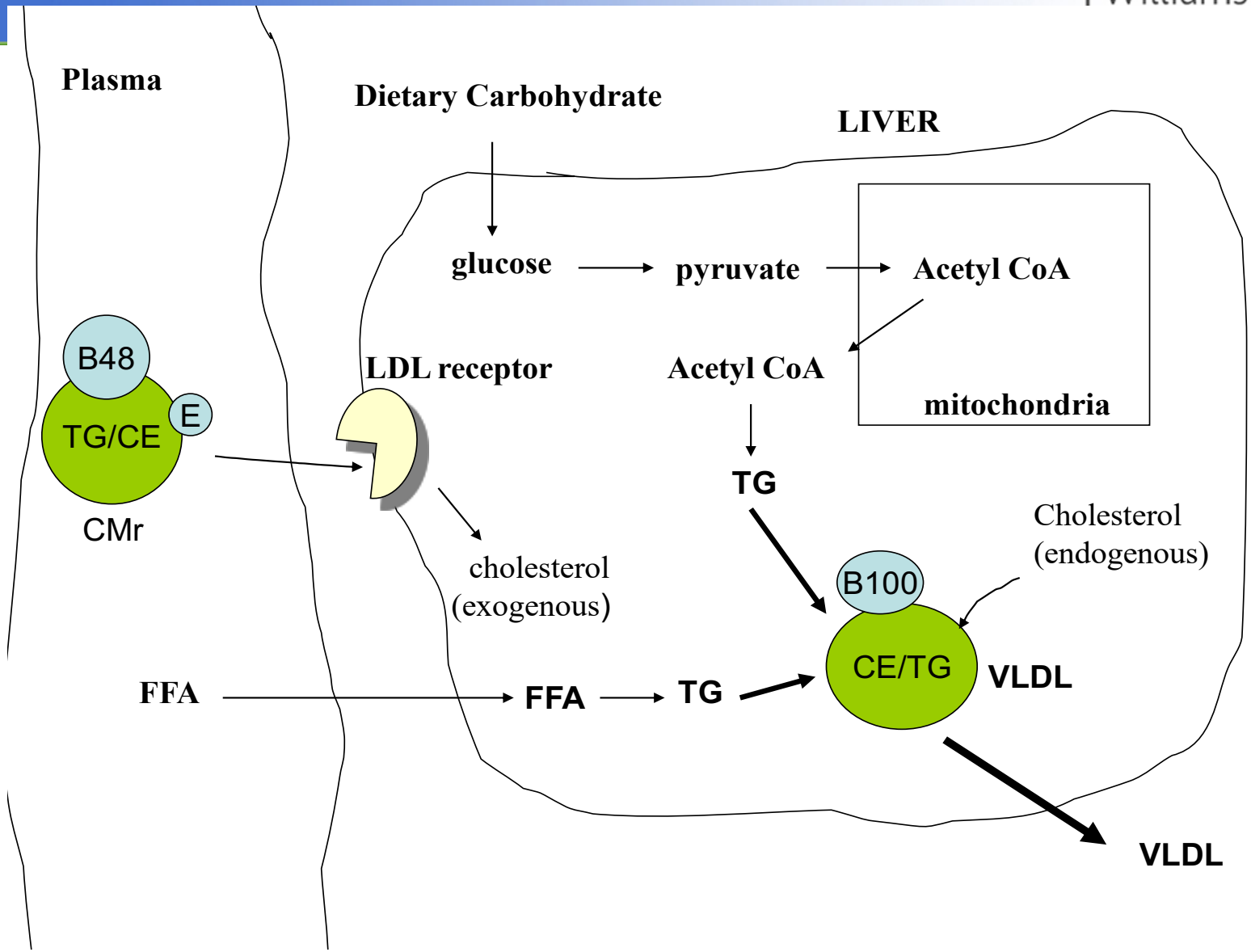


(3) Endogenous pathway

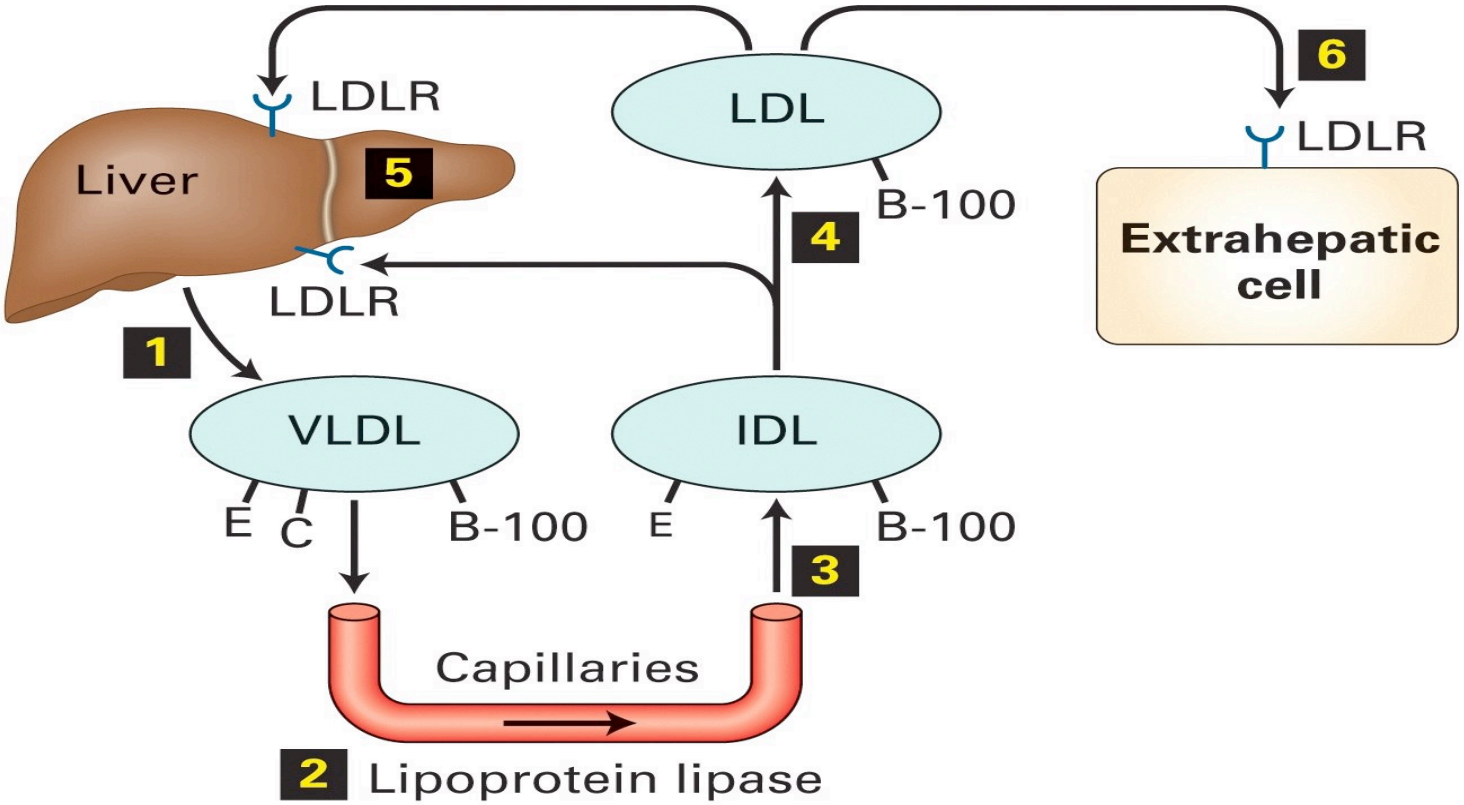
- Most TG in liver and packaged into VLDL are derived from diet
- Normally, small fractions of TG are synthesized from dietary carbohydrates
- VLDL once secreted into circulation undergo a lipolytic process similar to that of CMs
  - VLDL loses core lipids, causing dissociation & transfer of apolipoproteins & phospholipids to other lipoprotein particles.
  - During this, VLDL is converted to VLDL remnants (IDL), which can be further transformed by lipolysis into LDL.
- Half of VLDL is converted to LDL; remainder is taken up as VLDL remnants by liver remnant receptors.

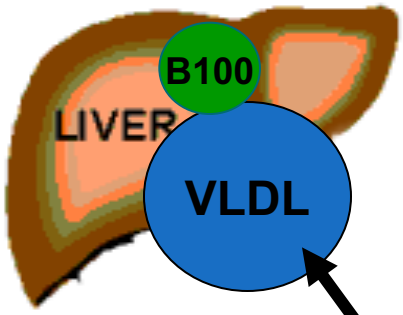
- Free cholesterol derived from LDL is used for membrane biosynthesis and excess fraction is converted by acyl-CoA:cholesterol acyltransferase (ACAT) into cholesteryl esters and stored in intracellular lipid droplets
- Cellular cholesterol biosynthesis is controlled by a complex mechanism involving availability of cholesterol delivered by LDL receptor
  - LDLR, and many cholesterol biosynthetic enzymes (e.g. HMG-CoA reductase) are downregulated by increased cellular cholesterol levels

VLDL Assembly

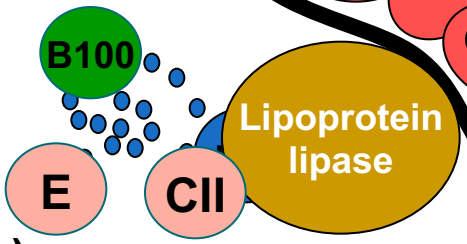


Endogenous Lipid Transport





Some LDL taken up by liver (LDL receptors)



Having lost TAG to tissues LDL contains a large proportion of cholesterol/cholesteryl esters

Capillary wall (endothelial surface)

Some LDL taken up by other tissues (LDL receptors).

LDL delivers cholesterol and TAG to the extra hepatic tissues.

Regulation of Lipoprotein Lipase

Fed state

↑ LPL synthesis and activity (adipocytes)

↓ LPL synthesis and activity (skeletal and heart muscle)

Fasted/ exercise state

↓ LPL synthesis and activity (adipocytes)

↑ LPL synthesis and activity (muscle)

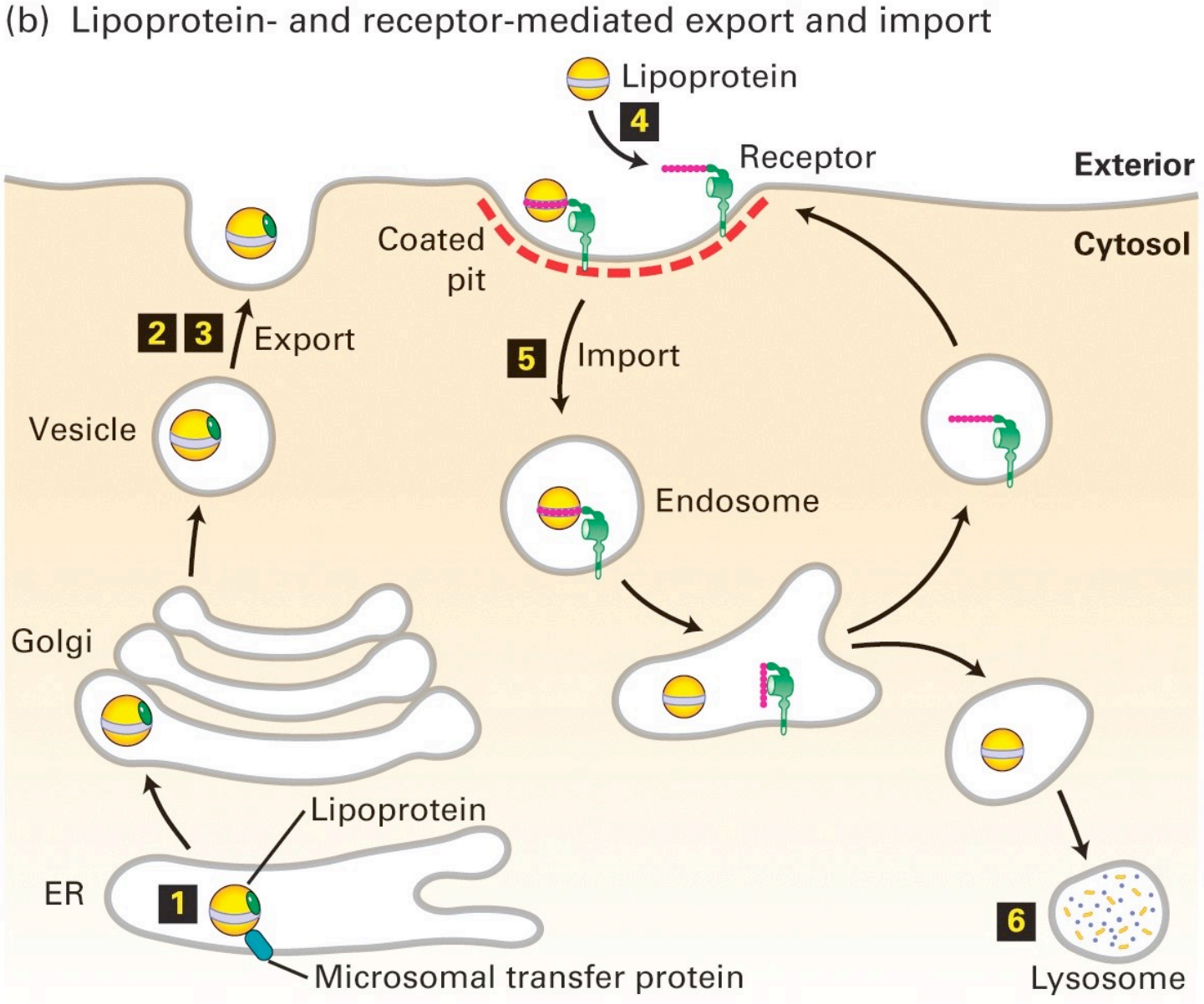
Lactating - Mammary gland

↑↑ LPL activity

The K_m for muscle LPL is lower than that of LPL in adipose

Function of LDL receptor

- Endocytosis of LDL and other LP
- Release free cholesterol into liver
  1. Incorporate into plasma membrane
  2. Inhibit formation of new LDL receptors
  3. Inhibit cholesterol synthesis
  4. Promote ACAT activity (FC → CE)
- Regulated by SREBP
- Monitors free cholesterol



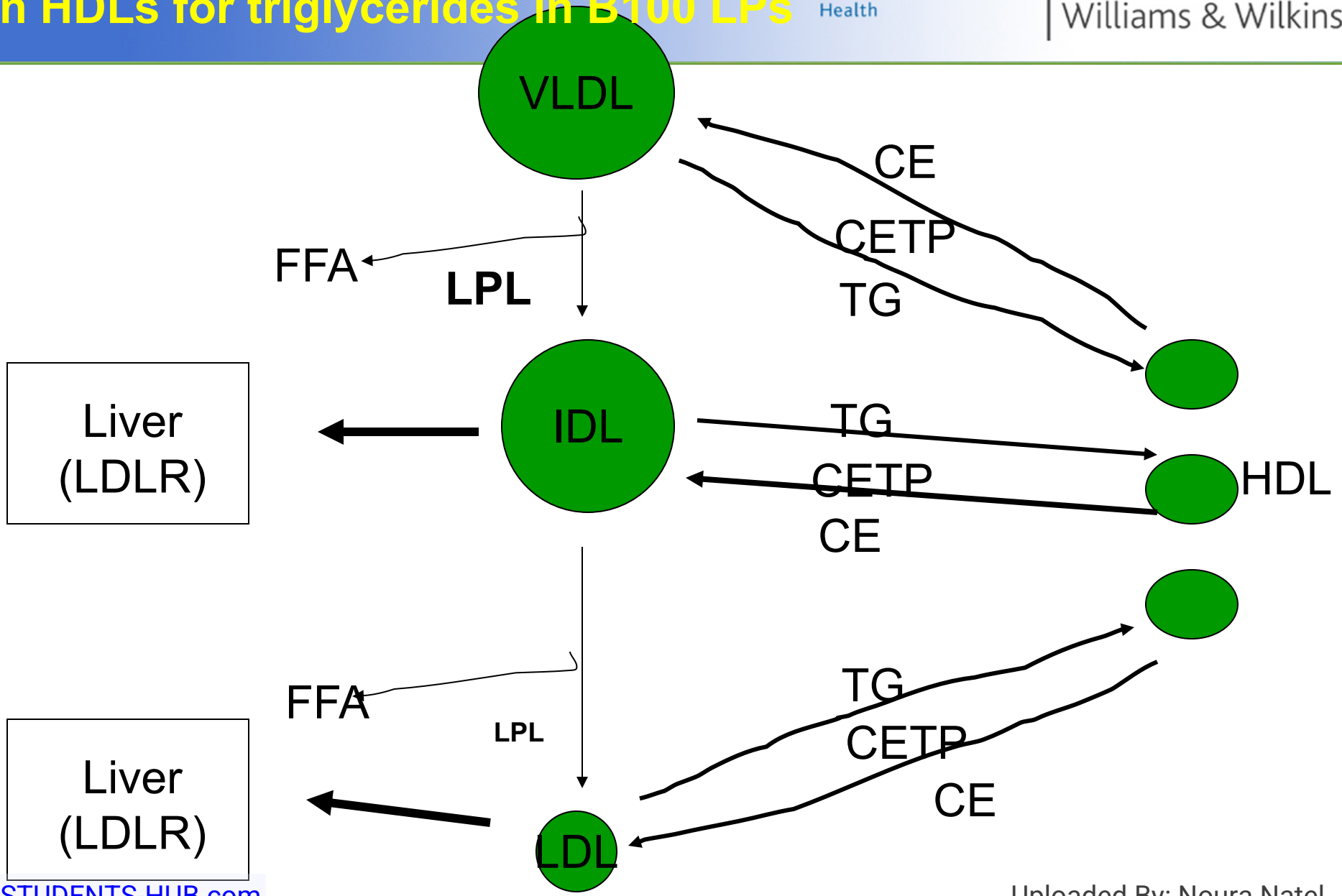
Familial Hypercholesterolemia

- Incidence of FH is 1:500
- Patients heterozygotes for FH, have half the normal number of LDL receptors
- FH lowers the hepatic uptake of LDL and increases hepatic cholesterol synthesis
- LDL accumulates in plasma and often leads to CHD by mid-adulthood in heterozygotes and even earlier for homozygotes

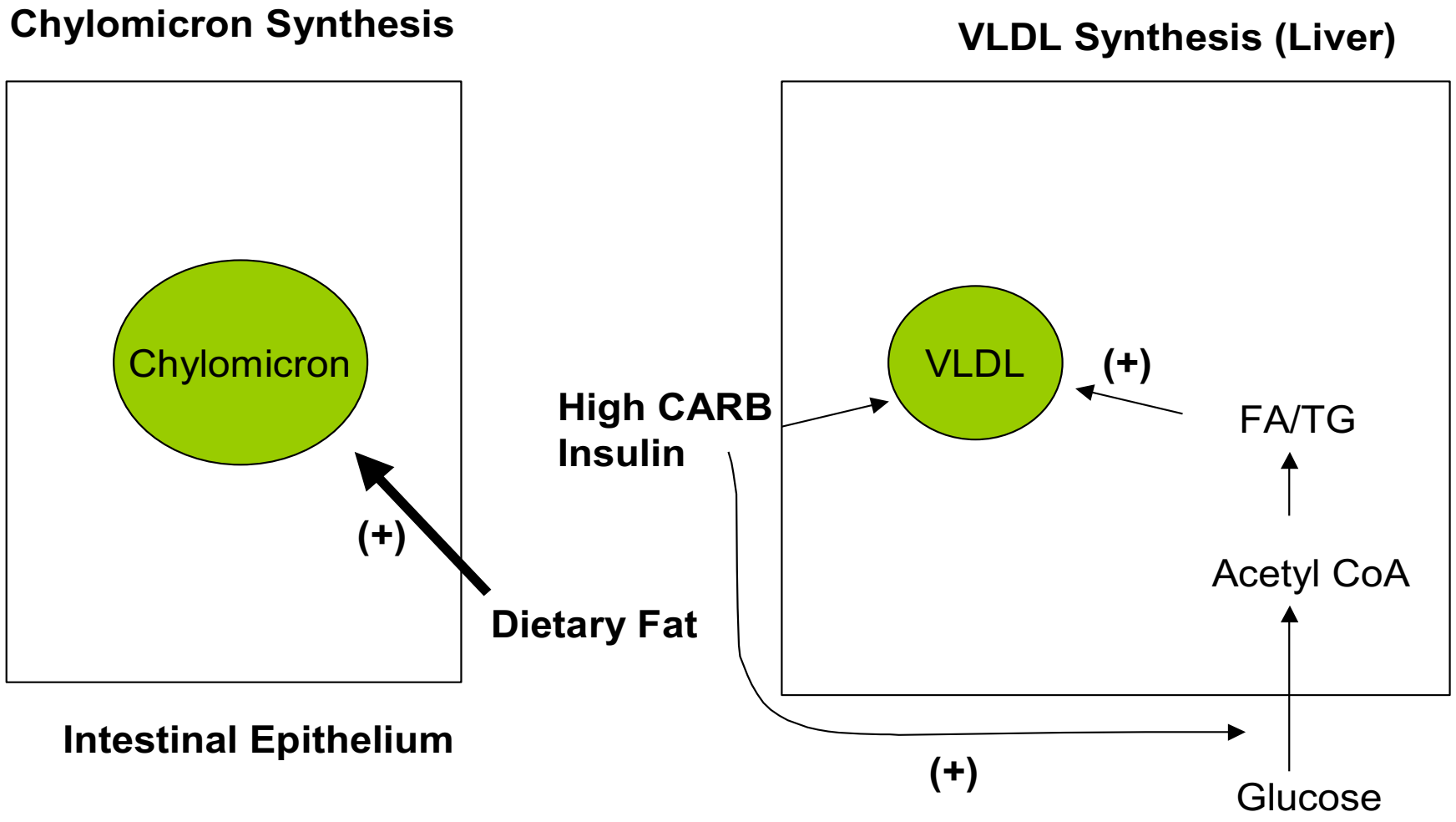
(4) Reverse cholesterol transport pathway

- HDL maintains equilibrium of cholesterol in peripheral cells by reverse transport to liver
- HDL acts like a sink for the small amount of cholesterol that can diffuse away from cells
  - Once chol is bound to HDL it is trapped by converting it via LCAT to chol ester producing HDL_3
  - Chol esters increase the capacity of the surface of HDL_3 to absorb more chol along with apo C-I, C-II, C-III and E and phospholipids from CMs and VLDL & is converted to HDL_2
- HDL_2 delivers chol to liver via scavenger receptor type BI (SR-BI)
- Approx. half of chol on HDL is returned to liver via LDL receptor after being transferred from HDL to LDL via the Chol ester transfer protein (CETP)
- Another pathway that mediates transfer of Chol from cells via HDL involves the ABCA1 transporter
  - ABCA1 mutation → Tangier disease, a disorder associated with low HDL and a predisposition to premature CHD

CETP exchanges cholesterol esters in HDLs for triglycerides in B100 LPs



Dietary Regulation of Lipoprotein Synthesis



Postprandial Changes in Plasma Lipid Metabolism

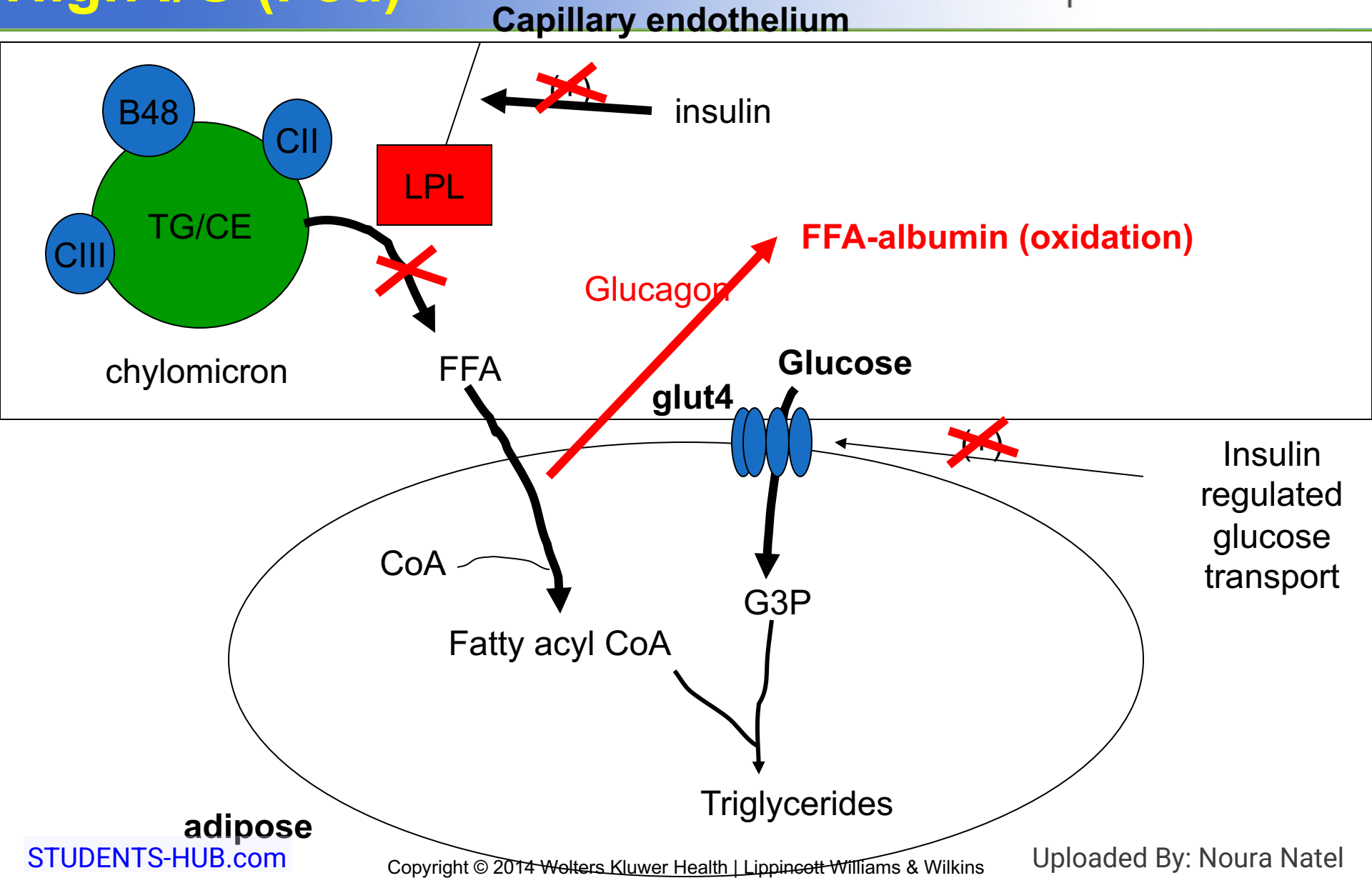
↑ Fat storage via LPL

↑ Exchange of cholesterol for VLDL TG in HDL (CETP)

↑ LCAT activity = esterification of free cholesterol (HDL)

These postprandial changes are beneficial in maintaining whole body homeostasis of glycerides and cholesterol

Fat accumulation in adipose: High I/G (Fed)



Lipid and Lipoprotein Population Distributions

- Women have, on average, higher HDL cholesterol levels but lower total cholesterol & triglyceride levels than men.
- After menopause, no difference in total cholesterol
- Total & LDL cholesterol & triglyceride levels all increase with age, in both men & women.
- Total & LDL cholesterol & triglycerides are much lower in young children than adults.
- At puberty, boys' HDL cholesterol drops 20% to adult male levels, but girls' does not change.
- Lower rates of LDL cholesterol & heart disease in Asians (food and lifestyle differences)

TABLE 15-4 CORONARY HEART DISEASE RISK FACTORS DETERMINED BY THE NCEP ADULT TREATMENT PANELS

POSITIVE RISK FACTORS
• Age: ≥ 45 y for men; ≥ 55 y or premature menopause for women
• Family history of premature CHD
• Current cigarette smoking
• Hypertension (blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication)
• LDL-C concentration ≥ 160 mg/dL (≥ 4.1 mmol/L), with ≤ 1 risk factor
• LDL-C concentration ≥ 130 mg/dL (3.4 mmol/L), with ≥ 2 risk factors
• LDL-C concentration ≥ 100 mg/dL (2.6 mmol/L), with CHD or risk equivalent
• HDL-C concentration < 40 mg/dL (< 1.0 mmol/L)
• Diabetes mellitus = CHD risk equivalent
• Metabolic syndrome (multiple metabolic risk factors)
NEGATIVE RISK FACTORS
• HDL-C concentration ≥ 60 mg/dL (≥ 1.6 mmol/L)
• LDL-C concentration < 100 mg/dL (< 2.6 mmol/L)

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

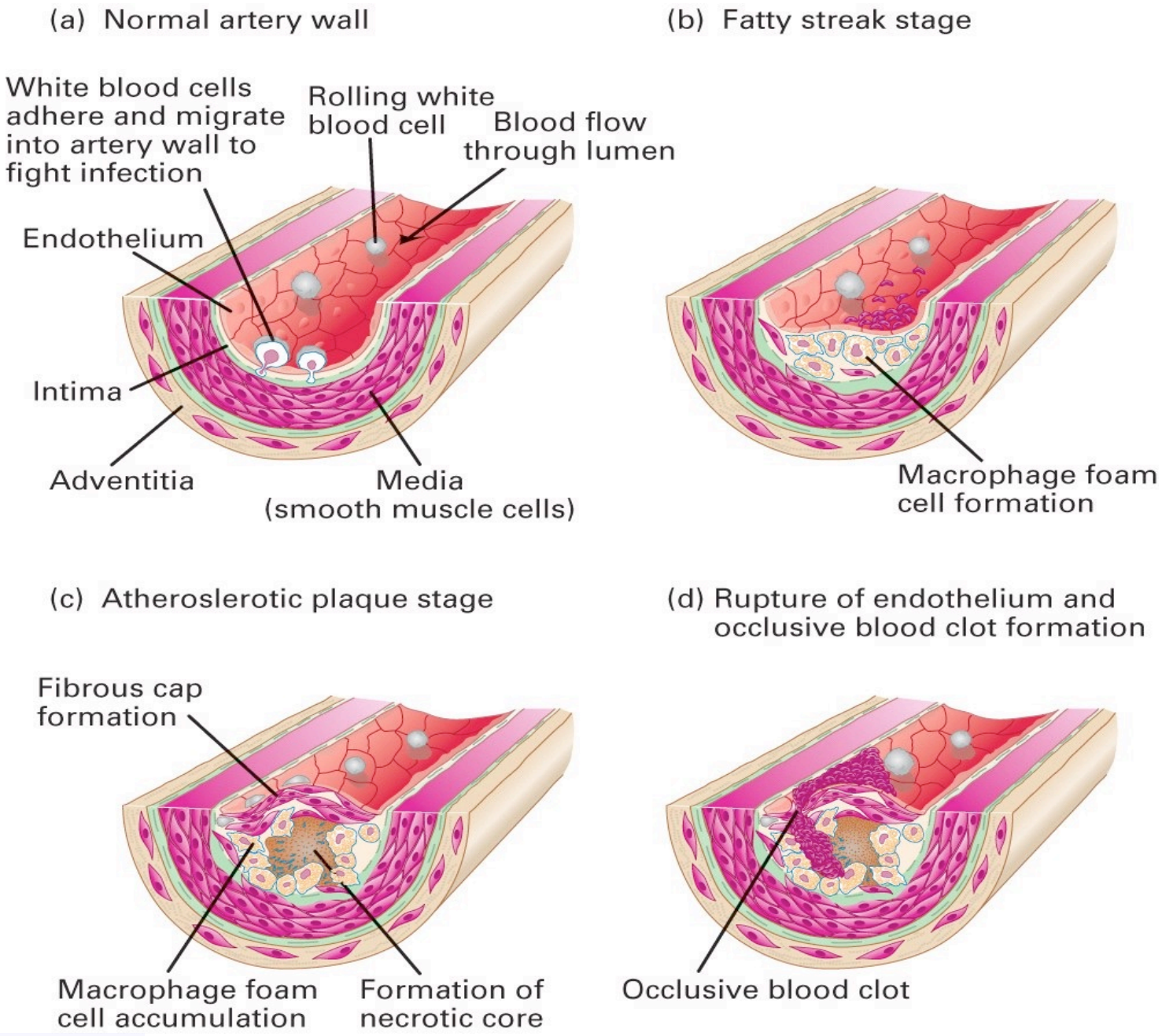
NCEP: National cholesterol education program in USA

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Dyslipidemias - diseases associated with abnormal blood lipid concentrations
- Arteriosclerosis
  - Single leading cause of death & disability in U.S.
  - Caused by lipids, in form of esterified cholesterol, being deposited in artery walls, resulting in fatty streaks
  - Fatty streaks develop into plaques that can block blood flow.
  - When plaque develops in arteries of the arms or legs → peripheral vascular disease (PVD); when it develops in the heart → coronary artery disease (CAD); when it develops in the vessels of the brain → cerebrovascular disease (CVD)
  - Plaque formation involves repeated cycles of cell injury, followed by infiltration and cell proliferation to repair the site. LDL is believed to play a central role in initiating and promoting plaque formation. It is deposited into the subendothelial space where it is taken up by various cells, including macrophages

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Arteriosclerosis drugs/therapy
  - HDL increasing drugs (fibric acid derivatives and niacin-containing compounds; Cholesteryl esters transfer proteins (CETP) inhibitors)
  - Bile acid sequestrants (cholestyramine, colesevelam, and colestipol) work by sequestering cholesterol in the gut so that it is not absorbed → enhancing conversion of cholesterol into bile acids in the liver, reduces hepatic cholesterol content. Interfere with absorption of fat-soluble nutrients
  - Ezetimibe inhibits cholesterol absorption by inhibiting the Niemann-Pick C1-Like 1 (NPC1-L1) transporter in the intestine without impacting the absorption of fat-soluble nutrients.
  - HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, etc.) block intracellular cholesterol synthesis → increasing LDLR expression → removal of LDL from circulation.
  - Fish oils (omega-3) lower TG and increase HDL



Effect of Exercise

- Increases LPL activity in muscle.
- Reduces TGL from the particle.
- Reduction in weight
- Increases HDL

Effect of diet

- Vegetarian diet – Cholesterol intake less
- Reduced Carbohydrate – VLDL TG Reduced
- Reduced Fat – Reduces CM TG
- Unsaturated fats (Mono and Poly)- Reduction in Plasma cholesterol
- Fiber – decreases cholesterol absorption

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Hyperlipoproteinemia
  - Diseases associated with elevated lipoprotein levels
  - Caused by malfunctions in the synthesis, transport, or catabolism of lipoproteins.
  - Includes hypercholesterolemia, hypertriglyceridemia, & combined hyperlipidemia

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Hypercholesterolemia
  - Lipid abnormality most closely linked to heart disease
  - Familial hypercholesterolemia (FH): genetic abnormality predisposing people to elevated cholesterol levels
    - Homozygotes: rare (1:1 million); first heart attack in teens
      - Treated by LDL pheresis (similar to dialysis) blood is periodically drawn from the patient, processed to remove LDL, and returned to the patient.
    - Heterozygotes: more common (1:500)
      - Treatment with HMG-CoA reductase inhibitors

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Hypertriglyceridemia
- Elevated triglyceride: high, 200–500 mg/dL; very high, >500 mg/dL
- Due to either genetic abnormalities or hormonal abnormalities
  - Genetic abnormalities - familial hypertriglyceridemia (FTG)
  - Hormonal abnormalities (associated with the pancreas, adrenal gland, and pituitary or of diabetes mellitus or nephrosis)
- Severe hypertriglyceridemia (>500 mg/dL) is usually not associated with high risk of CHD, but it is a potentially life-threatening abnormality because it can cause acute and recurrent pancreatitis
  - Can cause eruptive xanthomas
- Severe hypertriglyceridemia is caused by a deficiency of LPL or by a deficiency in apo C-II which is a necessary cofactor for LPL activity
- Treatment of HTG consists of dietary modifications, fish oil and or TG lowering drugs (primarily Fibric acid derivatives)

Management of Hypetriglyceridemia

- *Nonpharmacotherapy*
  - Nonpharmacologic management of hypertriglyceridemia is generally the initial treatment for patients with this condition. This primarily involves lifestyle modifications such as diet, exercise, weight reduction, smoking cessation, and limiting alcohol intake.
- *Pharmacotherapy*
  - Fibric acid derivatives (eg, gemfibrozil, fenofibrate)
  - Niacin
  - Omega-3 fatty acids (eg, omega-3-acid ethyl esters)
  - HMG-CoA reductase inhibitors (eg, atorvastatin, simvastatin)

Management of Hypetriglyceridemia

- *Surgical option*
  - In general, surgical intervention is not necessary to treat hypertriglyceridemia.
- Plasmapheresis
  - It can be used in the setting of severe hypertriglyceridemia to reduce triglycerides in the acute setting.
- Ileal bypass
  - Surgery has been shown to improve all lipid parameters but should be reserved for severe hypertriglyceridemia refractory to all treatment.

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias)

- Combined Hyperlipoproteinemia (CH)
  - Elevated levels of serum total cholesterol & triglycerides
  - Increased risk for coronary heart disease (CHD)
  - Genetic forms
    - Familial CH: some in family have only elevated cholesterol, others only elevated triglycerides, others both
    - Familial dysbetalipoproteinemia: very rare
- Lp(a) Elevation
  - Increased risk of CHD & cerebrovascular disease
  - Most LDL-lowering drugs have no effect on Lp(a) concentration, even when LDL-C is significantly lowered.
  - The two drugs shown to have some effect are niacin and estrogen replacement in postmenopausal women.

Non-HDL Cholesterol

- Reflects total cholesterol minus HDL-C
  - LDL, VLDL, IDL, Lp(a)
  - Elevated non-HDL-C associated with increased risk. of CVD (even if the LDL-C levels are normal).
  - On average, non–HDL-C levels are approximately 30 mg/dL higher than LDL-C levels.

Diagnosis and Treatment of Lipid Disorders (Dyslipidemias) (cont'd)

- Hypolipoproteinemia
  - Low levels of lipoproteins
  - Two forms: hypo*alpha*lipoproteinemia (low HDL) & hypo*beta*lipoproteinemia (low LDL)
- Hypoalphalipoproteinemia
  - Isolated decrease in circulating HDL (concentration <40 mg/dL), without presence of hypertriglyceridemia
  - *Alpha* denotes region in which HDL migrates on agarose electrophoresis.
  - Associated with several defects, often genetic, most of which are linked to increased risk of premature CHD
  - Tangier disease is an extreme form of hypoalphalipoproteinemia

CASE STUDY 15-2

A 30-year-old man with chest pain was brought to the emergency department after a softball game. He was placed in the coronary care unit when his ECG showed erratic waves in the ST region. A family history revealed that his father died of a heart attack at the age of 45 years. The patient had always been athletic in high school and college, so he had not concerned himself with a routine physical. The laboratory tests listed in Case Study Table 15-2.1 were run.

Questions

1. Given the symptoms and the family history, what additional tests should be recommended?
2. If his follow-up total chol esterol remains in the same range after he is released from the hospital, and his triglycerides and HDL-C are within the normal range, what course of treatment should be recommended?

CASE STUDY TABLE 15-2.1
LABORATORY RESULTS

PATIENT ANALYTE	VALUES	RANGE
Na^+	139	135–143 mmol/L
K^+	4.1	3.0–5.0 mmol/L
Cl^-	101	98–103 mmol/L
CO_2 content	29	22–27 mmol/L
Total protein	6.9	6.5–8.0 g/dL
Albumin	3.2	3.5–5.0 g/dL
Ca^{2+}	9.3	9.0–10.5 mg/dL
Cholesterol	278	140–200 mg/dL
Uric acid	5.9	3.5–7.9 mg/dL
Creatinine	1.1	0.5–1.2 mg/dL
BUN	20	7–25 mg/dL
Glucose	97	75–105 mg/dL
Total bilirubin	0.8	0.2–1.0 mg/dL
Alkaline phosphatase	20	7–59 IU/L
Lactate dehydrogenase	175	90–190 IU/L
Aspartate transaminase	35	8–40 IU/L
Amylase	98	76–375 IU/L

1. *Cardiac enzyme CK and CK isoenzyme and LDH and LDH isoenzyme would be useful. Fasting total chol, TG, and HDL-C and LDL-C as well.*
2. *LDL-C can be calculated >190 mg/dL (Total chol = 280 mg/dL and normal TG and HDL-C), which is extremely elevated. Treatment should start with diet change before leaving the hospital. After a few weeks, if no improvement occurs, the physician should start him on medication. The patient has a family history of CHD, and, presumably, the patient has now been diagnosed with CHD. Therefore, the goal would be to reduce LDL-C values to <100 mg/dL.*

Lipid and Lipoprotein Analyses

- Lipid Measurement
  - Lipids & lipoproteins are important measures of CHD risk.
- Cholesterol Measurement
  - Hexane extraction after hydrolysis with alcoholic KOH, followed by reaction with Liebermann-Burchard color reagent (old)
  - Current reference method GC-MS
  - Coupled enzymatic reactions
- Triglyceride Measurement
  - Useful in detecting metabolic disorders & CVD risk
  - Reference method GC-MS

Cholesterol measurement

- Specimen: serum or plasma
- Fasting: at least 12 hrs, preferred for chol & required for TG
- Method: enzymatic methods

1. Cholesteryl ester + H_2O $\xrightarrow{\text{Cholesteryl esterase}}$ Cholesterol + Fatty acid

2. Cholesterol + O_2 $\xrightarrow{\text{Cholesterol oxidase}}$ Cholestenone + H_2O_2

3. H_2O_2 + Dye $\xrightarrow{\text{Peroxidase}}$ Color

FIGURE 15-4 Enzymatic assay sequence—cholesterol.

Triglyceride measurement

- Used in estimation of LDL-C
- Current methods will measure also endogenous serum glycerol (10 to 20 mg/dL overestimation of triglycerides)

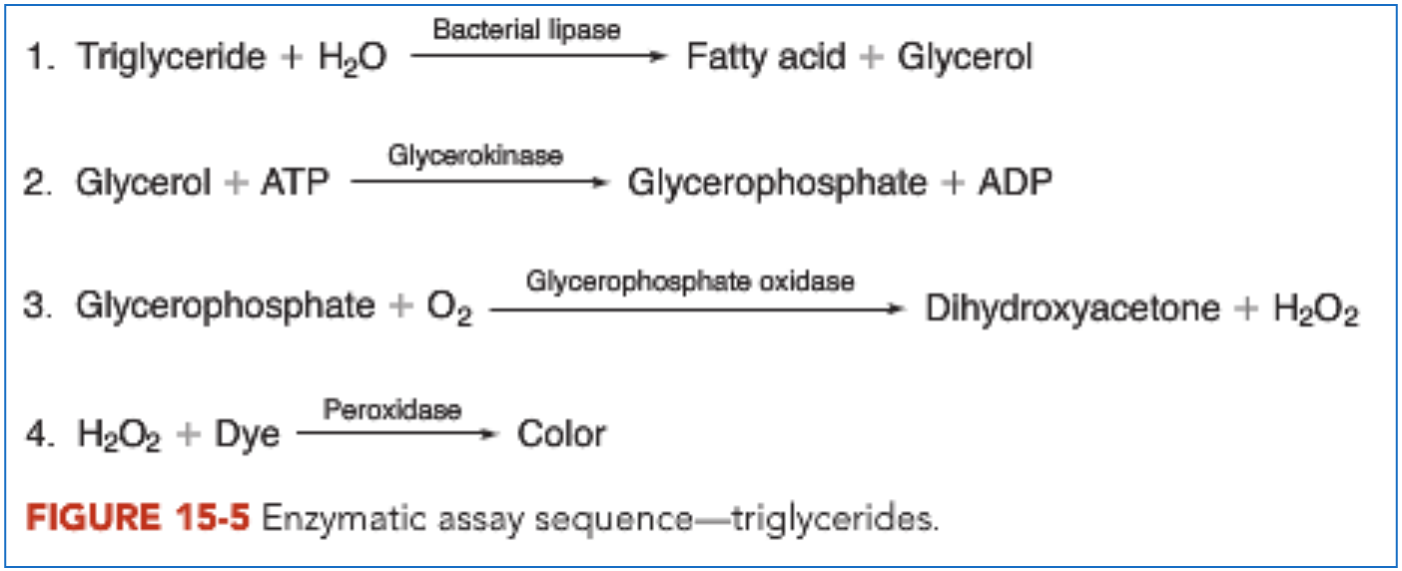


FIGURE 15-5 Enzymatic assay sequence—triglycerides.

Lipid and Lipoprotein Analyses (cont'd)

- Lipoprotein Methods
  - Measure physical properties: density, size, charge, apolipoprotein
  - Methods: ultracentrifugation, electrophoretic separation, chemical precipitation, chromatographic, immunochemical
- HDL Methods
  - In past, 2-step separation by chemical precipitation was used.
  - Now, 3-step process: ultracentrifugation to remove VLDL, heparin manganese precipitation to remove LDL, & analysis of supernatant cholesterol by Abell-Kendall assay

Lipid and Lipoprotein Analyses (cont'd)

- LDL Methods
  - **Beta-quantification:** most common; combines ultracentrifugation & chemical precipitation
  - **Friedwald calculation:** bypasses centrifugation; commonly used in routine & sometimes research labs
- Compact Analyzers
  - Mobile point-of-care testing systems
  - Can measure cholesterol, triglycerides, HDL cholesterol, & glucose from a finger stick sample

Lipid and Lipoprotein Analyses (cont'd)

- Apolipoprotein Methods
  - Apo B is measured directly in serum by immunoassay.
  - Apo A-I is measured by separation & analysis of HDL cholesterol.
  - Lp(a) is commonly measured by various immunoassays.
- Phospholipid Measurement
  - Can be measured by an enzymatic reaction sequence
- Fatty Acid Measurement
  - Commonly analyzed by gas-liquid chromatography

TABLE 15-3 ADULT REFERENCE RANGES FOR LIPIDS

ANALYTE	REFERENCE RANGE
Total cholesterol	140–200 mg/dL (3.6–5.2 mmol/L)
HDL-C	40–75 mg/dL (1.0–2.0 mmol/L)
LDL-C	50–130 mg/dL (1.3–3.4 mmol/L)
Triglycerides	60–150 mg/dL (0.7–1.7 mmol/L)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Calculations

- Total chol (chol) = VLDL-C + LDL-C + HDL-C
- Friedewald Equation:
- LDL-C (mg/dL)= [Total chol] – [HDL-C] – [TG]/5
- LDL-C (mmol/L) = [Total chol] – [HDL-C] – [TG]/2.2
- Other formulas uses a factor of 0.16*[TG] as an approx of VLDL

CASE STUDY 15-1

A 52-year-old man went to his physician for a physical examination. The patient had been a district manager for an automobile insurance company for the past 10 years and was 24 pounds overweight. He had missed his last two appointments with the physician because of business. The urinalysis dipstick finding was not remarkable. His blood pressure was elevated. The blood chemistry results are listed in Case Study Table 15-1.1.

Questions

1. Given the abnormal tests, what additional information would you like to have?
2. If this patient had triglycerides of 100 mg/dL (1.1 mmol/L) and an HDL-C of 23 mg/dL (0.6 mmol/L), what would be his calculated LDL-C value?
3. If, however, his triglycerides were 476 mg/dL (5.4 mmol/L), with an HDL-C of 23 mg/dL (0.6 mmol/L), what would be his calculated LDL-C value?

CASE STUDY TABLE 15-1.1
LABORATORY RESULTS

ANALYTE	PATIENT VALUE	REFERENCE RANGE
Na^+	151	135–143 mmol/L
K^+	4.5	3.0–5.0 mmol/L
Cl^-	106	98–103 mmol/L
CO_2 content	13	22–27 mmol/L
Total protein	5.7	6.5–8.0 g/dL
Albumin	1.6	3.5–5.0 g/dL
Ca^{2+}	7.9	9.0–10.5 mg/dL
Cholesterol	210	140–200 mg/dL
Uric acid	6.2	3.5–7.9 mg/dL
Creatinine	2.5	0.5–1.2 mg/dL
BUN	95	7–25 mg/dL
Glucose	88	75–105 mg/dL
Total bilirubin	1.2	0.2–1.0 mg/dL
Alkaline phosphatase	27	7–59 IU/L
Lactate dehydrogenase	202	90–190 IU/L
Aspartate transaminase	39	8–40 IU/L
Amylase	152	76–375 IU/L

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1. *Triglyceride and HDL cholesterol values*
2. *The estimated LDL cholesterol, 167 mg/dL (4.3 mmol/L), is considered high.*
3. *The LDL cholesterol concentration could not be estimated because the triglycerides were >400 mg/dL (4.5 mmol/L). Lipoproteins would need to be measured in a specialty laboratory following ultracentrifugation.*

CASE STUDY 15-3

A 43-year-old white man was diagnosed with hyperlipidemia at age 13 years, when his father died of a myocardial infarction at age 34 years. The man's grandfather had died at age 43 years, also of a myocardial infarction. Currently, the man is active and asymptomatic with regard to CHD. He is taking 40 mg of lovastatin (Mevacor), 2 times/d (maximum dose). He had previously taken niacin but could not tolerate it because of flushing and gastrointestinal distress, nor could he tolerate cholestyramine resin (Questran). His physical examination is remarkable for bilateral Achilles tendon thickening/xanthomas and a right carotid bruit (Case Study Table 15-3.1).

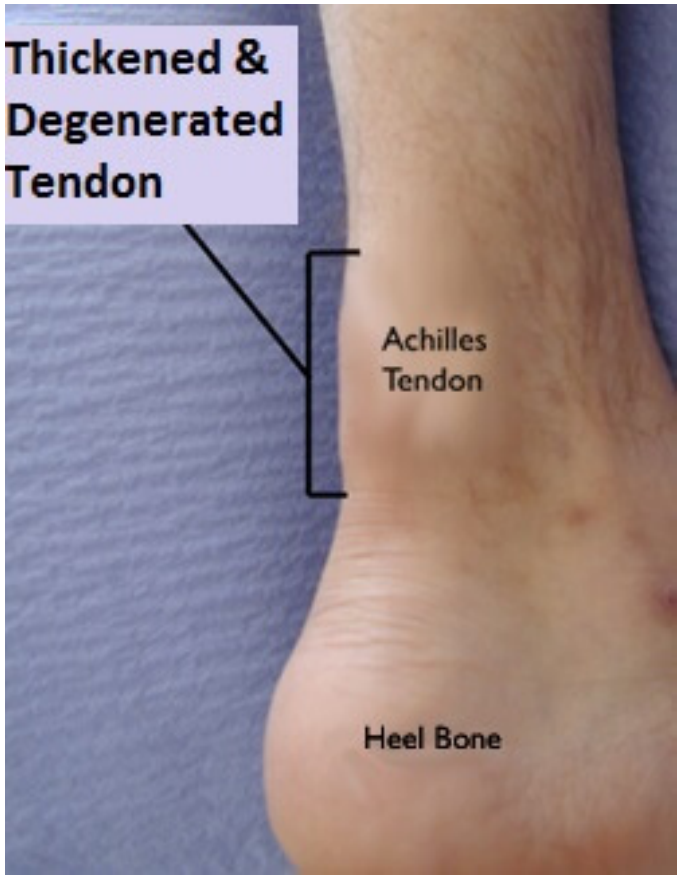
CASE STUDY TABLE 15-3.1
LABORATORY RESULTS

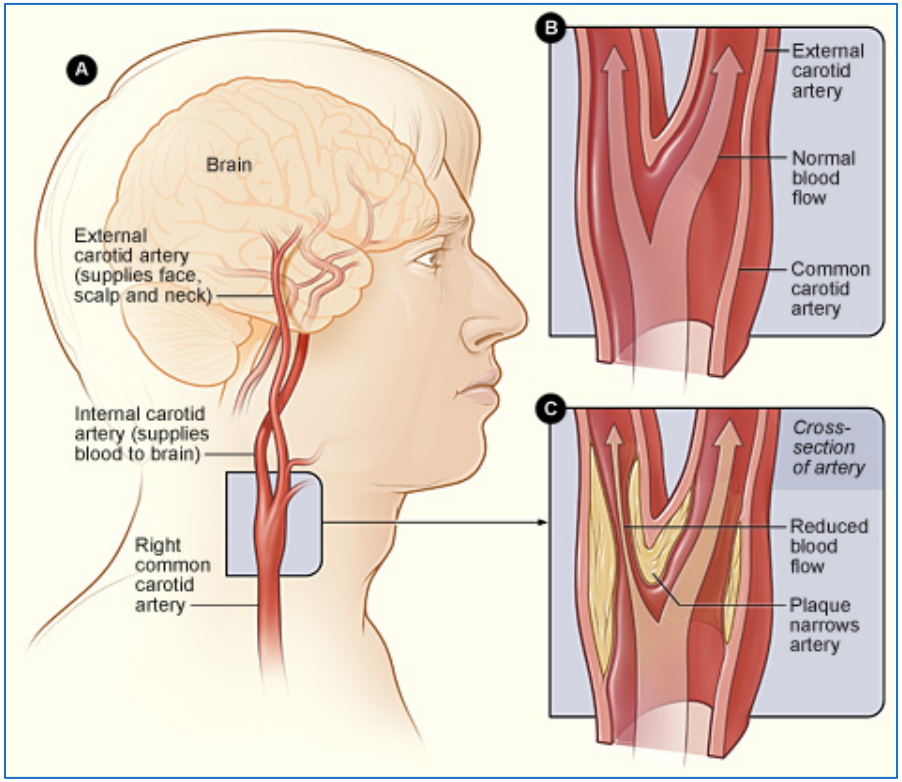
Triglycerides	91 mg/dL
Total cholesterol	269 mg/dL
HDL-C	47 mg/dL
LDL-C	204 mg/dL
Aspartate aminotransferase	34 U/L
Alanine aminotransferase	36 U/L
Alkaline phosphatase	53 U/L
Electrolytes and fasting glucose	Normal

Questions

1. What is his diagnosis?
2. Does he need further workup?
3. What other laboratory tests should be done?
4. Does he need further drug treatment? If so, what?

1. *FH heterozygote*
2. *Yes, the patient needs an exercise stress test and carotid ultrasound to evaluate his current risk.*
3. *Lp(a), homocysteine*
4. *Yes, further therapy could include a more potent statin or combination drug therapy or a retrial of niacin to further lower his LDL cholesterol; however, his liver function tests would need careful monitoring. Other options are low-dose aspirin and vitamin E.*





CASE STUDY 15-5

A 49-year-old woman was referred for a lipid evaluation by her dermatologist after she developed a papular rash over her trunk and arms. The rash consisted of multiple, red, raised lesions with yellow centers. She had no previous history of such a rash and no family history of lipid disorders or CHD. She is postmenopausal, on standard estrogen replacement therapy, and otherwise healthy (Case Study Table 15-5.1).

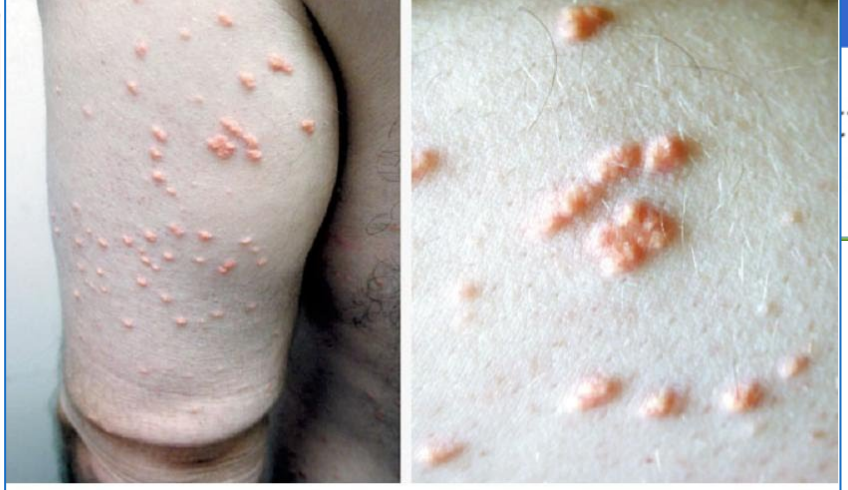


Figure 4. Images in Clinical Medicine. Eruptive xanthomas associated with hypertriglyceridemia and new-onset hypertriglyceridemia.

CASE STUDY TABLE 15-5.1
LABORATORY RESULTS

SERUM	GROSSLY LIPEMIC
Triglycerides	6,200 mg/dL
Total cholesterol	458 mg/dL
Fasting glucose	160 mg/dL
Liver function tests and electrolytes	Normal

Questions

1. What is the rash? What is the cause of her rash?
2. Is her oral estrogen contributing?
3. Is her glucose contributing?
4. What treatments are warranted, and what is her most acute risk?

1. *Eruptive xanthomas; triglycerides*
2. *Yes*
3. *Yes, she has diabetes mellitus.*
4. *Cessation of estrogen replacement therapy, with consideration of transdermal estrogen therapy, triglyceride-lowering diet and medication, hypoglycemic medication. Most acute risk is pancreatitis.*