تفريغ فارما ١

اسم الموضوع: ***Dyslipidemia***

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Soul Academy

لجان الدُّفعات

DYSLIPIDEMIA

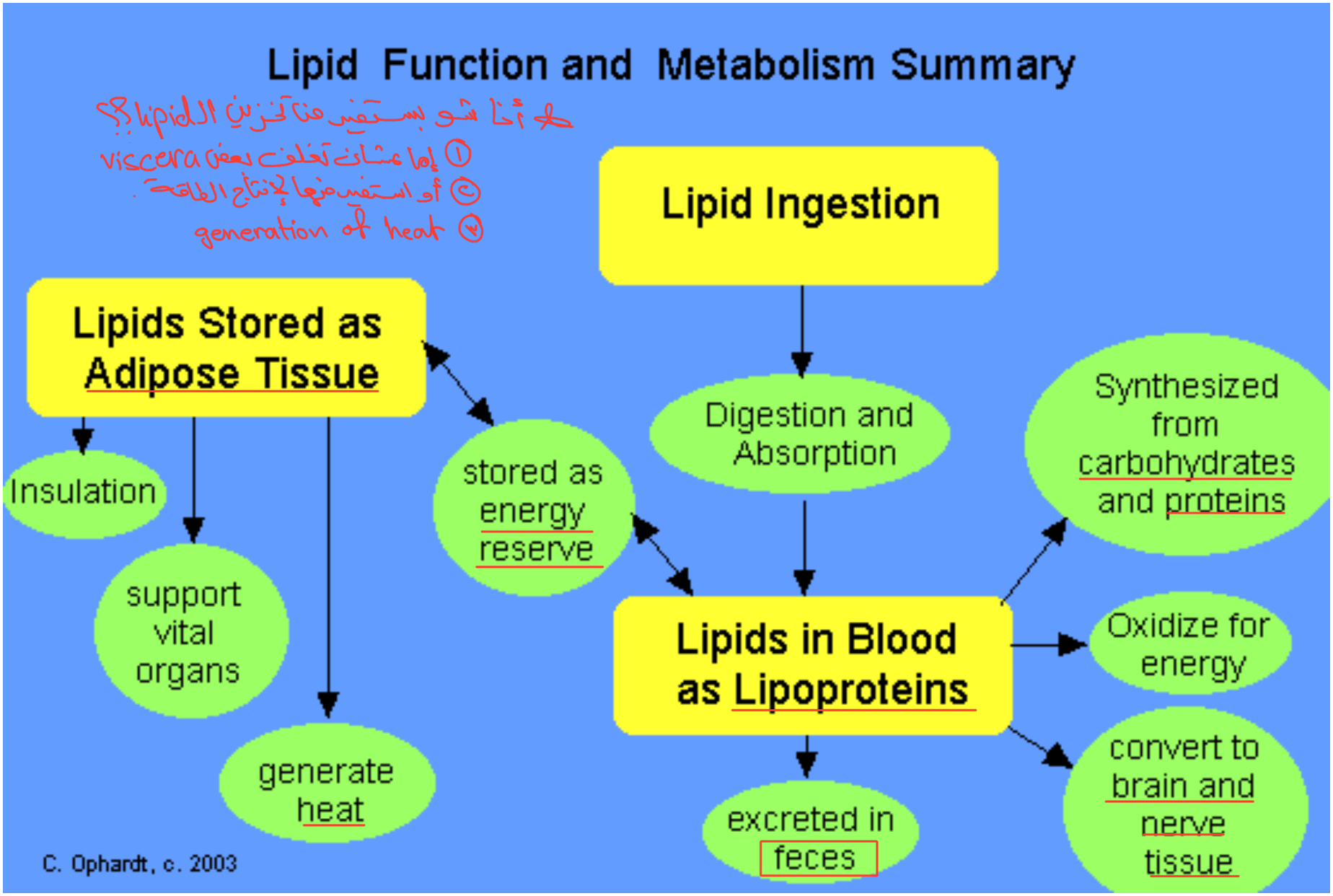
- Hyperlipidemia is a major cause of **atherosclerosis** and atherosclerosis-associated conditions.
- The incidence and absolute number of annual events will likely increase over the next decade because of

✓ Epidemic of obesity

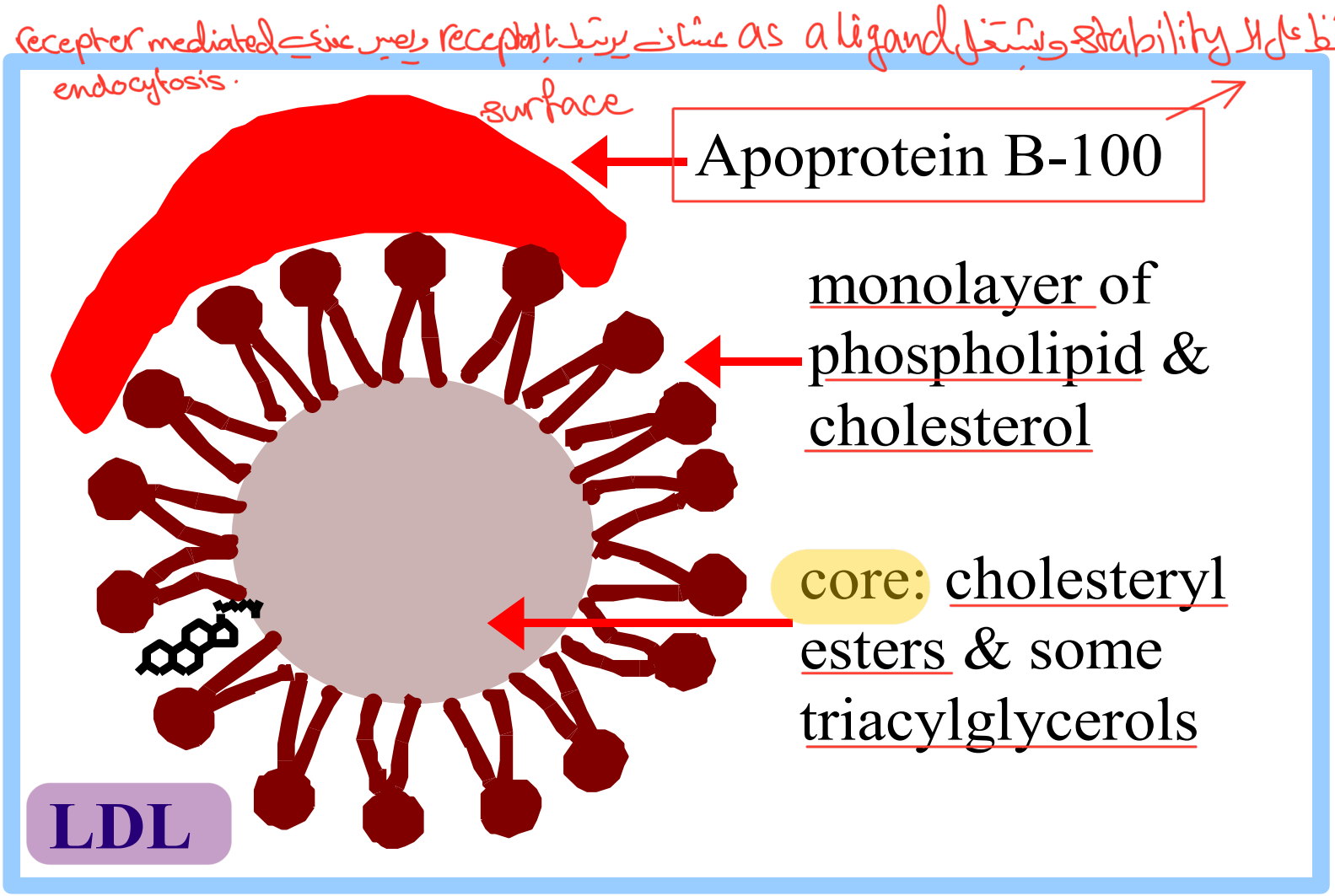
✓ Aging

✓ Genetic disorders

✓ Lifestyle (sedentary behavior and diets high in calories, saturated fat, and cholesterol) contribute to the dyslipidemias seen in developed countries.


Lipid Function and Metabolism Summary
Lipid Ingestion
Lipids Stored as Adipose Tissue
Digestion and Absorption
Insulation
support vital organs
generate heat
stored as energy reserve
Synthesized from carbohydrates and proteins
Lipids in Blood as Lipoproteins
Oxidize for energy
convert to brain and nerve tissue
excreted in feces
C. Ophardt, c. 2003

Representative Scheme



PLASMA LIPOPROTEIN METABOLISM

- Lipoproteins are **macromolecular assemblies** that contain **lipids** and **proteins**
- The lipid constituents include free and esterified cholesterol, triglycerides, and phospholipids
- The protein components, known as apolipoproteins or **apoproteins**, provide structural stability to the lipoproteins, and also may function as ligands in lipoprotein-receptor interactions

- In all spherical lipoproteins:

1. The most **water-insoluble** lipids (cholesteryl esters and triglycerides) are **core** components,
2. The **more polar**, water-soluble components (apoproteins, phospholipids, and unesterified cholesterol) are located on the **surface**

Table 35-1. Characteristics of Plasma Lipoproteins

LIPOPROTEIN CLASS	DENSITY OF FLOTATION, g/ml	MAJOR LIPID CONSTITUENT	TG:CHOL RATIO	SIGNIFICANT APOPROTEINS	SITE OF SYNTHESIS	MECHANISM(S) OF CATABOLISM
Chylomicrons and remnants	<<1.006	Dietary triglycerides and cholesterol	10:1	B-48, E, A-I, A-IV, C-I, C-II, C-III	Intestine	Triglyceride hydrolysis by LPL ApoE-mediated remnant uptake by liver
VLDL	<1.006	"Endogenous" or hepatic triglycerides	5:1	B-100, E, C-I, C-II, C-III	Liver	Triglyceride hydrolysis by LPL
IDL	1.006-1.019	Cholesteryl esters and "endogenous" triglycerides	1:1	B-100, E, C-II, C-III	Product of VLDL catabolism	50% converted to LDL mediated by HL, 50% apoE-mediated uptake by liver 50% apoE-mediated uptake by liver
LDL	1.019-1.063	Cholesteryl esters	NS	B-100	Product of VLDL catabolism	ApoB-100-mediated uptake by LDL receptor (~75% in liver)

water insoluble

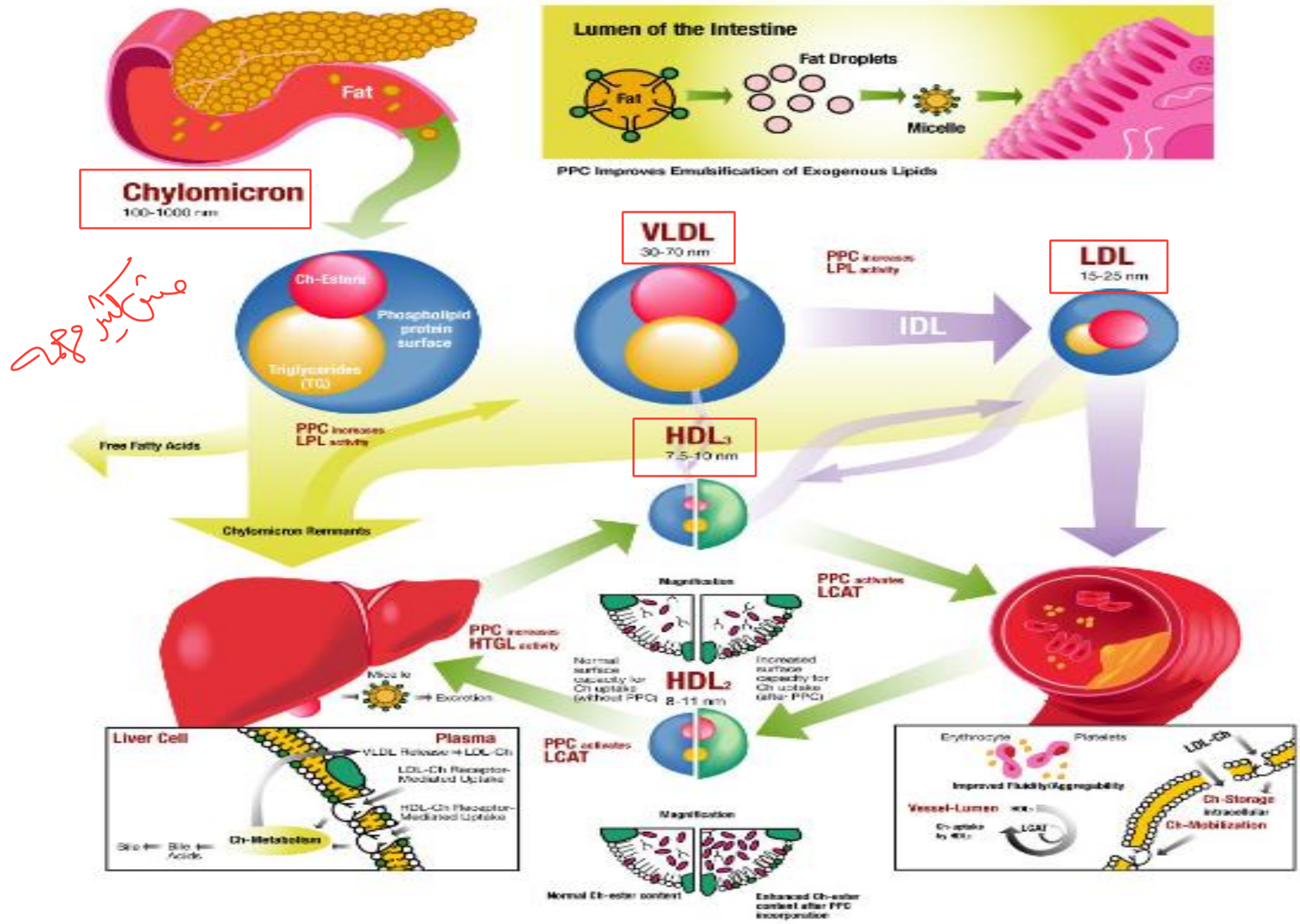
HDL	1.063-1.21	Phospholipids, NS cholesteryl esters	A-I, A-II, E, C-I, C-II, C-III	Intestine, liver, plasma

HDL → remove cholesterol from tissue and transport to liver for excretion.

chylomicron ← low density , يعني حجمه كبير كبير لأنه يحتوي على كثير lipid وشوي protein (mainly triglycerides)
← العلاقة بحجم البروتين مقارنة بال lipid.
← يصنع في entestinal epithelia.

VLDL ← نفس ال chylomicron في كثير lipid وشوي protein وال core تبعه triglycerides يعني ال density يعتبر ترتيبه 2 .
← يصنع في liver. الـ VLDL لما يصير ال lypolysis رح تخف نسبة triglycerid اللي فيه وبالتالي رح تزيد فيه نسبة ال cholesterol وتحول لـ اشي اسمه IDL صار ا intermediate لأنه نسبه lipid قلت .
ومع الوقت رح يزيد ال lypolysis وبالتالي كل ما اعلتنا الـ triglycerid تنقل وتزيد نسبة ال cholesterol ester وتتحول عنا اشي جديد اللي LDL.

HDL ← في نسبة كبيرة من ال protein بالمقابل نسبة قليلة من ال lipid عشان هيك اسمه الدهن الجيد .


Fat
Chylomicron
100-1000 nm
Lumen of the Intestine
Fat Droplets
Fat
Micelle
PPC Improves Emulsification of Exogenous Lipids
VLDL
30-70 nm
Ch-Esters
Phospholipid protein surface
Triglycerides (TG)
PPC increases LPL activity
IDL
LDL
15-25 nm
Free Fatty Acids
PPC increases LPL activity
HDL3
7.5-10 nm
Chylomicron Remnants
Magnification
PPC activates LCAT
PPC increases HTGL activity
Normal surface capacity for Ch uptake (without PPC)
Increased surface capacity for Ch uptake (after PPC)
HDL2
8-11 nm
Excretion
Liver Cell
Plasma
VLDL Release → LDL-Ch
LDL-Ch Receptor-Mediated Uptake
HDL-Ch Receptor-Mediated Uptake
Ch-Metabolism
Bile Acids
PPC activates LCAT
Magnification
Normal Ch-ester content
Enhanced Ch-ester content after PPC incorporation
Erythrocyte
Platelets
Improved Fluidity/Aggregability
Vessel-Lumen
LCAT
LDL-Ch
Ch-Storage intracellular
Ch-Mobilization

Lipoproteins differ in the ratio of protein to lipids, & in the particular apoproteins & lipids that they contain.

They are classified based on their density:

- **Chylomicron** (largest; lowest in density due to high lipid/protein ratio; highest % weight triacylglycerols)
- **VLDL** (very low density lipoprotein; 2nd highest in triacylglycerols as % of weight)
- **IDL** (intermediate density lipoprotein)
- **LDL** (low density lipoprotein, highest in cholesteryl esters as % of weight)
- **HDL** (high density lipoprotein; highest in density due to high protein/lipid ratio)

Formation of lipoproteins:

Intestinal epithelial cells synthesize triacylglycerols, cholesteryl esters, phospholipids, free cholesterol, and apoproteins, and package them into **chylomicrons**.

Chylomicrons are **secreted** by intestinal epithelial cells, and transported via the lymphatic system to the blood.

Apoprotein CII on the chylomicron surface activates **Lipoprotein Lipase**, an enzyme attached to the lumenal surface of small blood vessels.

Lipoprotein Lipase catalyzes hydrolytic cleavage of fatty acids from triacylglycerols of chylomicrons.

Released fatty acids & monoacylglycerols are picked up by body cells for use as energy sources.

As triacylglycerols are removed by hydrolysis, chylomicrons shrink in size, becoming **chylomicron remnants** with lipid cores having a relatively high concentration of cholesteryl esters.

Chylomicron remnants are taken up by liver cells, via receptor-mediated endocytosis.

Liver cells produce, and secrete into the blood, very low density lipoprotein (**VLDL**).

- The VLDL **core** has a relatively high **triacylglycerol** content.
- VLDL has several **apoproteins**, including **apoB-100**.

As VLDL particles are transported in the bloodstream, **Lipoprotein Lipase** catalyzes **triacylglycerol removal** by hydrolysis.

With removal of triacylglycerols and some proteins, the % weight that is cholesteryl esters increases.

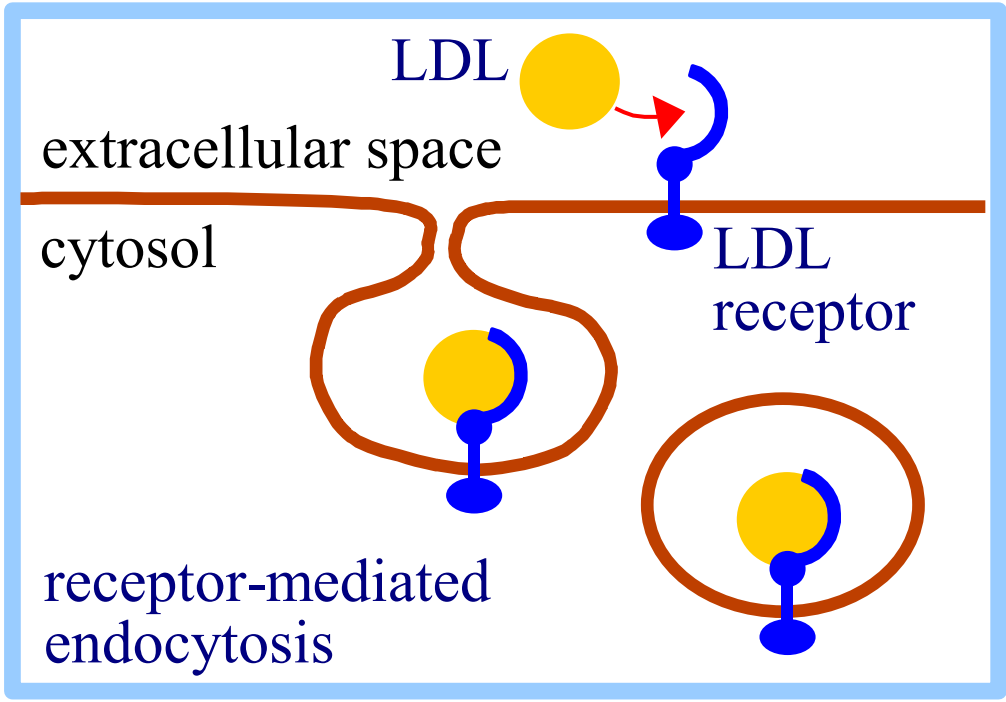
VLDL are converted to IDL, and eventually to LDL.

VLDL → IDL → LDL

The lipid core of **LDL** is predominantly **cholesteryl esters**.

Whereas VLDL contains 5 apoprotein types (B-100, C-I, C-II, C-III, & E), only one protein, **apoprotein B-100**, is associated with the surface monolayer of **LDL**.

Cells take up LDL by **receptor-mediated endocytosis**.



After the **clathrin coat disassembles**, the vesicle fuses with an **endosome**.

LDL is **released** from the receptor within the **acidic** environment of the endosome, and the **receptor** is returned to the plasma membrane.

After LDL is transferred to a **lysosome**, **cholesterol** is released & may be used, e.g., for membranes synthesis.

HYPERLIPIDEMIA AND ATHEROSCLEROSIS

Coronary Heart Disease

- Two-thirds of atherosclerosis deaths were due to CHD. About 85% of CHD deaths occurred in individuals over 65 years of age.
- The major conventional risk factors are:

✓ Elevated LDL-C

✓ Reduced HDL-C

✓ Cigarette smoking

✓ Hypertension, type 2 diabetes mellitus, advancing age, and a family history of premature (men <55 years; women <65 years) CHD events in a first-degree relative

- Reducing the consumption of dietary saturated fat and cholesterol is the cornerstone of population-based approaches to the management of hypercholesterolemia. In addition, it is clearly established that the higher the cholesterol level, the higher the CHD risk

Managing Patients with Dyslipidemia

- **National Cholesterol Education Program (NCEP) Guidelines grouped patients into two Groups**

هاد الـ group mainly راح يكون عندهم أمراض زي HTN أو HF أو diabetes
ويكفي الارتام عندهم متن كتير عالية.

I. **Group 1**: Decrease risk factors as primary goal of therapy (food, lifestyle, exercise)

II. **Group 2**: lowering LDL-C levels as the primary goal of therapy (Pharmacotherapeutics)

كل ما كثرت الـ diseases عند الشخص
فالمفروض أكون very specific بالدواء يعني
مثلاً شخص عنده LDL لازم يكون أقل من 100
ولكن إذا كان diabetic لازم يكون أقل من 70.

Table 35-5. Classification of Plasma Lipid Levels*

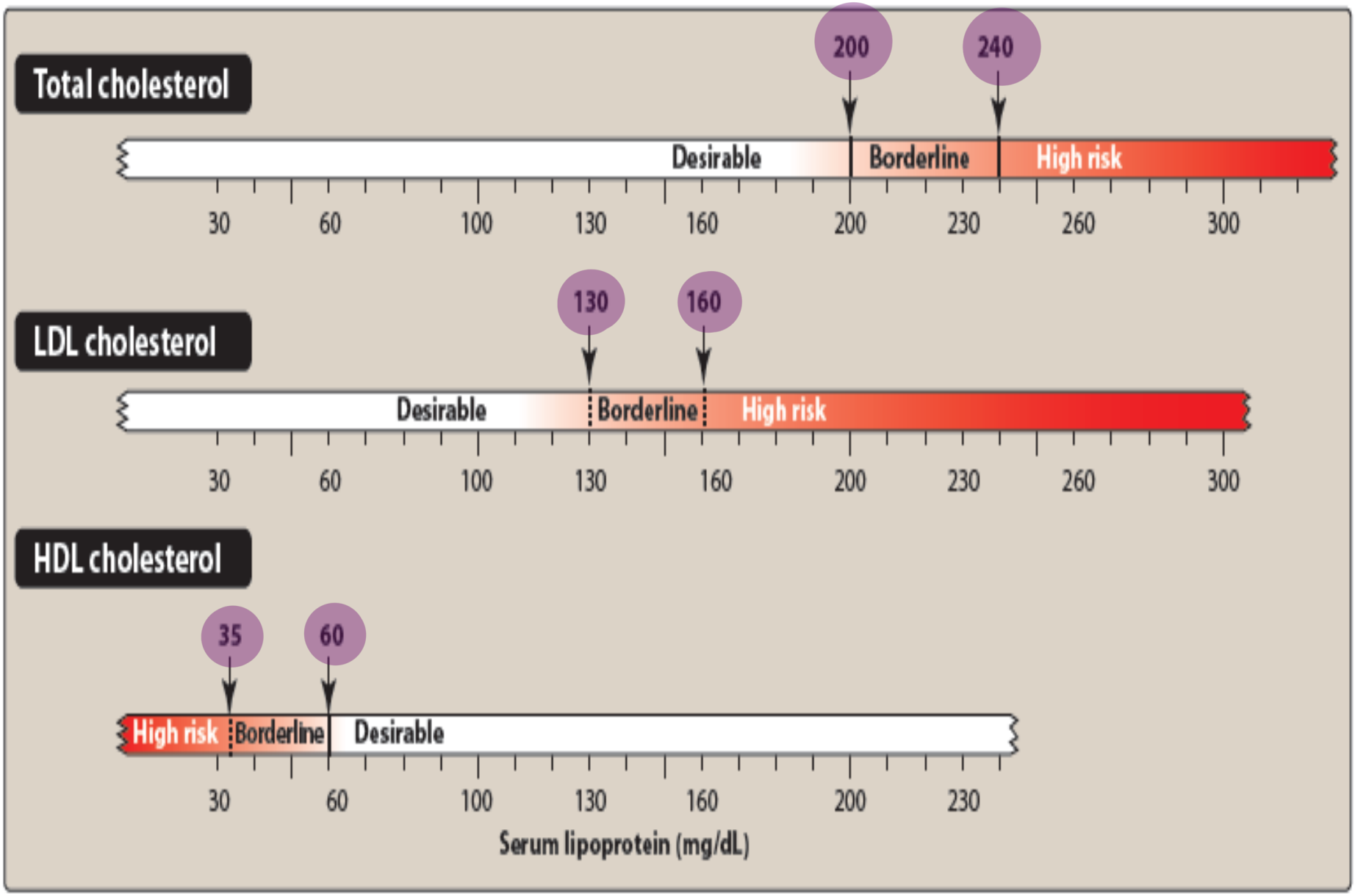
Total cholesterol	
<200 mg/dl	Desirable
200-239 mg/dl	Borderline high
≥240 mg/dl	High
HDL-C	
<40 mg/dl	Low (consider <50 mg/dl as low for women)
>60 mg/dl	High
LDL-C	
<70 mg/dl	Optimal for very high risk (minimal goal for CHD equivalent patients)
<100 mg/dl	Optimal
100-129 mg/dl	Near optimal
130-159 mg/dl	Borderline high
160-189 mg/dl	High
≥190 mg/dl	Very high

* عشان الفحص بكون بوحدة ال m mol/L
HDL ، LDL ، cholesterol ع أضرب 38.5
أما ال Triglesrid بنضرب ب 88.5 .

هيعني الشخص اللي بكون عنده مشاكل
بال heart أو diabetes ال goal تبعي
بطل يكون أقل 100 لازم يصير أقل
من 70 يعني مثلا 90 عند شخص
ما عنده مشاكل يعتبر طبيعي ولكن 90 عند شخص
هو مريض HTN أو عنده سكري يعتبر high .

Triglycerides

<150 mg/dl	Normal
150-199 mg/dl	Borderline high
200-499 mg/dl	High
≥500 mg/dl	Very high


Total cholesterol
200
240
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
LDL cholesterol
130
160
Desirable
Borderline
High risk
30
60
100
130
160
200
230
260
300
HDL cholesterol
35
60
High risk
Borderline
Desirable
30
60
100
130
160
200
230
Serum lipoprotein (mg/dL)

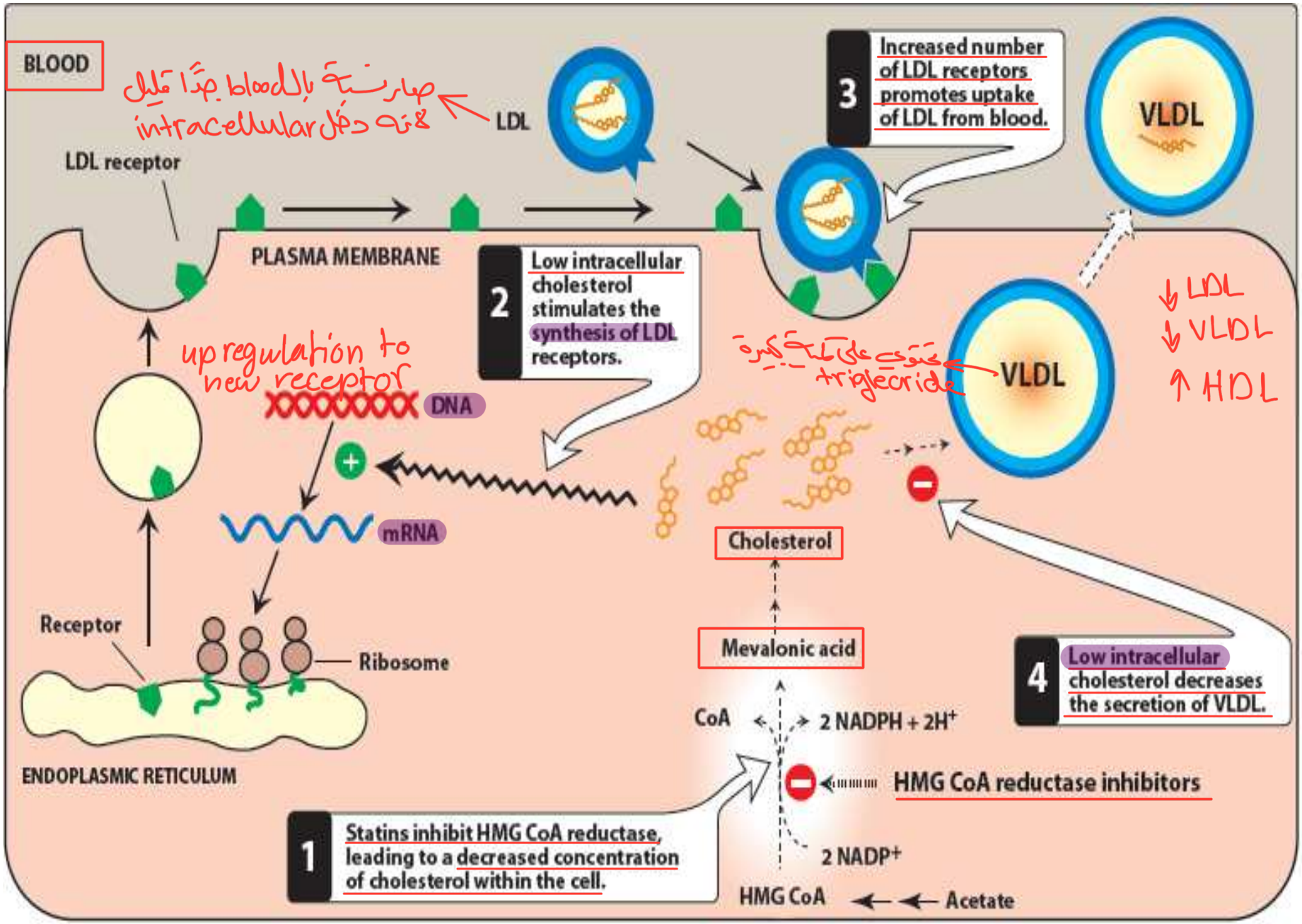
DRUG THERAPY OF DYSLIPIDEMIA

- Statins
- Bile-Acid Sequestrants
- Niacin (Nicotinic Acid) Vitamine B_3
- Ezetimibe and the Inhibition of Dietary Cholesterol Uptake
- Inhibitors of Cholesteryl Ester Transfer Protein

Statins

HMG CoA reductase inhibitors

- The statins are the most effective and best-tolerated agents for treating dyslipidemia
- These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis


BLOOD
صارت نسبة بالblood جدًا قليل
intracellular فتح دخل
LDL
LDL receptor
PLASMA MEMBRANE
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
up regulation to new receptor
DNA
تحتوي على نسبة كبيرة triglecride
VLDL
↓ LDL
↓ VLDL
↑ HDL
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

- By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis.
- Triglyceride levels >250 mg/dl are reduced substantially by statins.
- An increase in HDL-C of 5% to 10% was observed, irrespective of the dose or statin employed
- Statins lower LDL-C by 20% to 55%, depending on the dose and statin used

Table 35-11. Doses (mg) of Statins Required to Achieve Various Reductions in Low-Density-Lipoprotein Cholesterol from Baseline

	20%-25%	26%-30%	31%-35%	36%-40%	41%-50%	51%-55%
(2) Atorvastatin	—	—	10	20	40	80
(5) Fluvastatin	20	40	80			
Lovastatin	10	20	40	80		
(4) Pravastatin	10	20	40			
(1) Rosuvastatin	—	—	—	5	10	20, 40
(3) Simvastatin	—	10	20	40	80	

* هون الـ statin مختلفين بالـ potency والتي تعتمد على dose

efficacy لـ

* يعني أنا لو بدي أشغل ماشي على Atorvastatin بجرعة 80mg وكانت النتائج غير موجودة أنا بهاي الحالة بعطيه مثلاً Rosuvastatin بكون 20mg اللي هي تكافئ
• Atorva في 80mg

* هنا يعني الـ 20mg من Rosuvastatin تكافئ 80mg من الـ Atorvastatin وهم الماشين الوحيدين اللي إلهم قدرة على تنزيل الـ cholesterol من 51% – 55%

* ما بصير أبداً استبدل Rosuva 20mg بـ Atorva جرعة 20mg لأنه مش متكافئين أبداً في الـ efficacy.

Characteristic	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Serum LDL cholesterol reduction produced (%)	50	24	34	34	50	41
Serum triacylglycerol reduction produced (%)	29	10	16	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	12	8	12
Plasma half-life (hr)	14	1–2	2	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	20	10	13

Actions

- Statins show cardioprotective effects
- Correct endothelial dysfunction
- Play Anti-inflammatory role
- May help or predispose depression!!

* أدوية الدهون جميعها تعطى once daily قبل النوم ولكن يفضل أحكي للشخص متى لأنه عشان المريض ما يلتزم بموعد نوم معين وأدوية الStatin الأفضل أخذها بالليل لأنه عملية synthesis of cholesterol في تكون مابين 1am الى 2 am.

* أما بالنسبة لـ Rosuvastatin أو Atorva ال half life الهم طويل مابين 14-19 h فيمكن أخذه بأي وقت لحتى يبدأ مفعول الدواء ولكن الأفضل دائماً أدوية الدهون بشكل عام تؤخذ بالليل

Pharmacokinetics

- After oral dose, intestinal absorption of the statins varies between 30% and 85%
- Simvastatin and lovastatin are administered as prodrugs
- There is extensive first-pass hepatic uptake of all statins
- All have active metabolites except fluvastatin and pravastatin
- Atorvastatin and rosuvastatin, which have half-lives of about 20 hours.
- Hepatic cholesterol synthesis is maximal between midnight and 2:00 A.M. Thus, statins with half-lives of 4 hours or less (all but atorvastatin and rosuvastatin) should be taken in the evening

Adverse Effects and Drug Interactions

- Elevation in hepatic enzymes was reported in3% of patients
- It is therefore reasonable to measure alanine aminotransferase (ALT) at baseline and thereafter when clinically indicated.

هذا النوع اللي رح يأثروا عليه أدوية ال statins ويكن مش على كل المرضى.

Hepatic Enzymes

Alanine Aminotransferase (ALT):
Aspartate Aminotransferase (AST)
Gamma-Glutamyl Transferase (GGT)
Alkalin phosphatase (ALP)

الطبيعي (15-35) هسا إذا كان عندي الرقم 36، 37 هاد ما بعتبره ارتفاع الارتفاع هو انه يرتفع عندي two to three times يعني بدل 35 يكون 70 أو 100.

طيب هسا أنا عندك يكون عندي مشاكل ب hepatic enzymes بسبب مشاكل في الكلى أو مشاكل في البول طيب كيف بدي أعرف شو السبب الرئيسي لأنه بمرضه ممكن يكونوا عنده ارتفاع بدون سبب. فـ نا بهاي الحالة بروح بعمله فحص لوظائف الكبد وبطلب منه يرجع بعد 3 أشهر ونقارن هاي الأرقام الجديدة بـ ال baseline اللي أخذتها قبل 3 أشهر.

Myopathy

- The major side effect of Statins
- The incidence of myopathy is quite low (~0.01%), but the risk of myopathy and increases in proportion to plasma statin concentrations.
- In most of these cases, patients usually suffered from renal insufficiency or were taking drugs such as *cyclosporine, itraconazole, erythromycin, gemfibrozil, or niacin.*

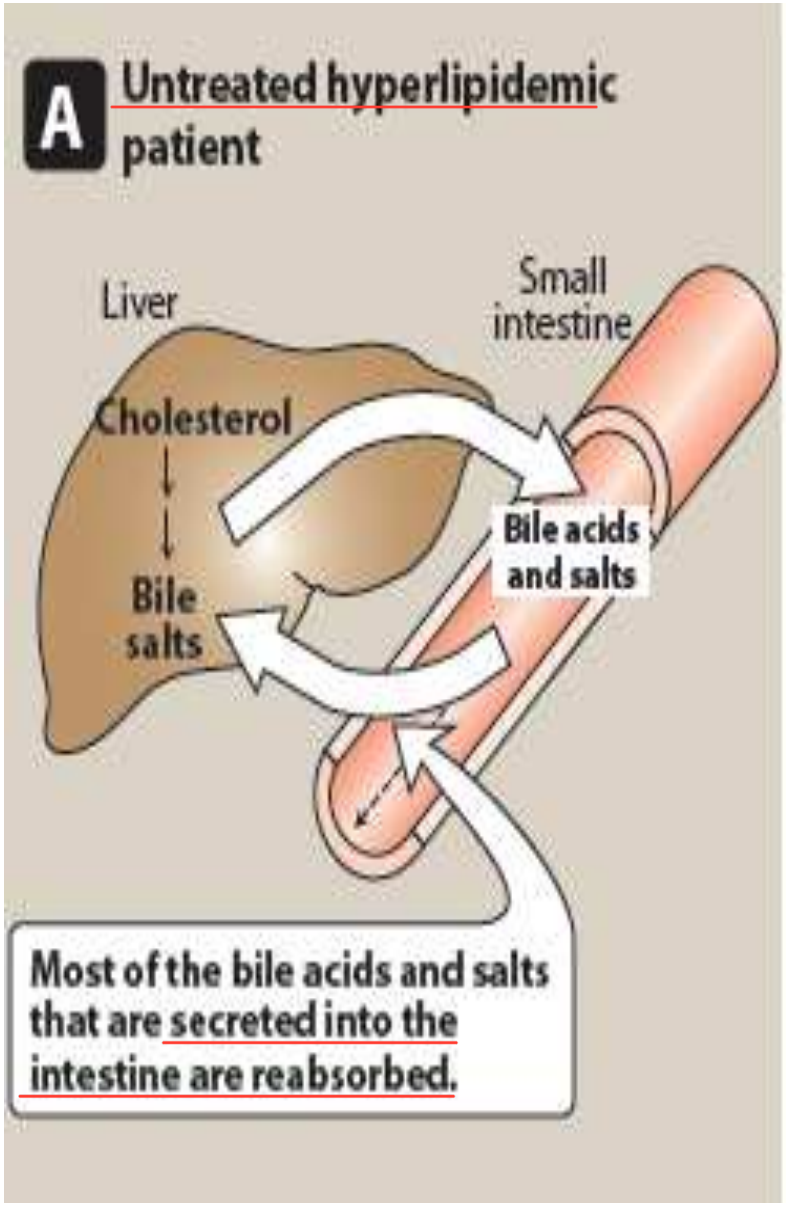
The myopathy syndrome is characterized by intense myalgia similar to flu-related myalgia, first in the arms and thighs and then in the entire body, along with weakness and fatigue

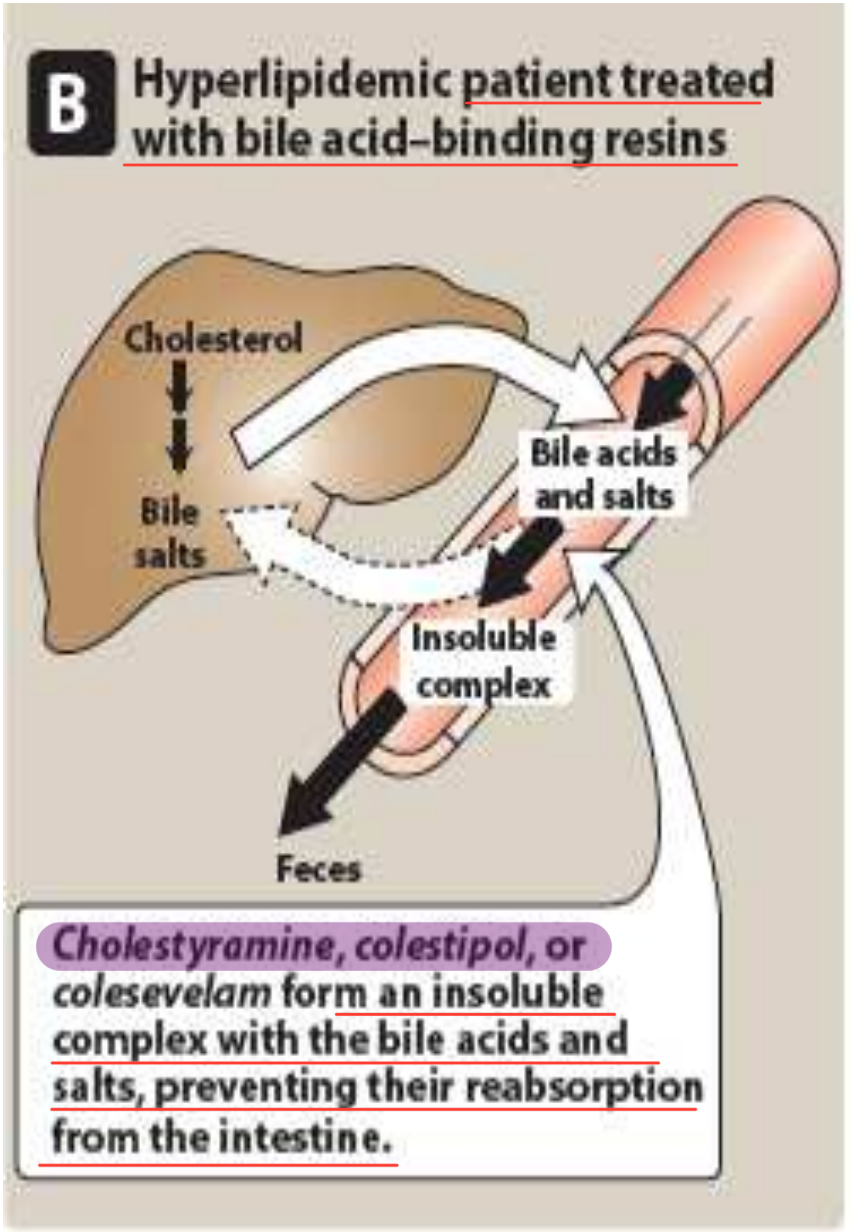
Combining Statins

- Statins, in combination with the bile acid-binding resins *cholestyramine* and *colestipol*, produce 20% to 30% greater reductions in LDL-C than can be achieved with statins alone

Bile-Acid Sequestrants

- ✓ The two established bile-acid sequestrants or resins (cholestyramine and colestipol)
- ✓ Used as 2nd choice is Statins fail to lower LDL-C
- ✓ Maximal doses can reduce LDL-C by up to 25% but are associated with unacceptable gastrointestinal side effects (bloating and constipation) that limit compliance.


A
Untreated hyperlipidemic patient
Liver
Small intestine
Cholesterol
Bile salts
Bile acids and salts
Most of the bile acids and salts that are secreted into the intestine are reabsorbed.


B
Hyperlipidemic patient treated with bile acid–binding resins
Cholesterol
Bile salts
Bile acids and salts
Insoluble complex
Feces
Cholestyramine, colestipol, or colesevelam form an insoluble complex with the bile acids and salts, preventing their reabsorption from the intestine.

- The resins are generally safe, as they are not systemically absorbed
- Cholestyramine and colestipol both are available as a powder that must be mixed with water and drunk as a slurry
- Cholestyramine and colestipol bind and interfere with the absorption of many drugs, including some thiazides, *furosemide*, *propranolol*, *l-thyroxine*, digoxin, warfarin, and some of the statins
- The powdered forms of cholestyramine (4 g per dose) and colestipol (5 g per dose)

Niacin (Nicotinic Acid)

Vitamine B_3

B-complex

Vitamin B1 (Thiamine)
Vitamin B2 (Riboflavin)
Vitamin B3 (Niacin)
Vitamin B5 (Pantothenic Acid)
Vitamin B6 (Pyridoxine)
Vitamin B7 (Biotin)
Vitamin B9 (Folate/Folic Acid)
Vitamin B12 (SinoCobalamin)

→ hyperglycemia
hyperuricemia.

- one of the oldest drugs used to treat dyslipidemia
- The hypolipidemic effects of niacin require larger doses than are required for its vitamin effects
- Niacin is the best agent available for increasing HDL-C (increments of 30% to 40%); it also lowers triglycerides by 35% to 45%

Mechanism of Action of Niacin

- In adipose tissue, niacin inhibits the lipolysis of triglycerides , which reduces transport of free fatty acids to the liver and decreases hepatic triglyceride synthesis.
- Niacin stimulates the HM74A (HM74b)-G_i-adenylyl cyclase pathway in adipocytes, inhibiting cAMP (second messenger) production and decreasing hormone-sensitive lipase activity, triglyceride lipolysis, and release of free fatty acids

- Two of niacin's side effects, flushing and dyspepsia, limit patient compliance
- twice- or thrice-daily dosing
- Hepatotoxic at high doses

Therapeutic Uses

- Niacin is indicated for hypertriglyceridemia and elevated LDL-C; it is especially useful in patients with both hypertriglyceridemia and low HDL-C levels
- Total daily dose of 2 g per day

FIBRATES

activation of LPL

- Fenofibrate, Bezafibrate, Gemfibrozil*
- Fibrates reduce triglycerides through PPARa-mediated stimulation of fatty acid oxidation.
  gene
- Fibrates usually are the drugs of choice for treating severe hypertriglyceridemia.
- All of the fibrate drugs are absorbed rapidly and efficiently (>90%) when given with a meal but less efficiently when taken on an empty stomach. The ester bond is hydrolyzed rapidly, and peak plasma concentrations are attained within 1 to 4 hours.

Adverse Effects and Drug Interactions

- Fibric acid compounds usually are well tolerated
- Gastrointestinal side effects occur in up to 5% of patients
- potentiate the action of oral anticoagulants, in part by displacing them from their binding sites on albumin
- Clofibrate use has been associated with increased risk of gallstone formation

Therapeutic Uses

- Gemfibrozil (LOPID) is usually administered as a 600-mg dose taken twice a day, 30 minutes before the morning and evening meals
- Fibrates are the drugs of choice for treating hyperlipidemic subjects with type III hyperlipoproteinemia as well as subjects with severe hypertriglyceridemia (triglycerides >1000 mg/dl)

Ezetimibe

- Ezetimibe is the first compound approved for lowering total and LDL-C levels that inhibits cholesterol absorption
- Ezetimibe inhibits a specific transport process in jejunal enterocytes, which take up cholesterol from the lumen
- The consequence of inhibiting intestinal cholesterol absorption is a reduction in the incorporation of cholesterol into chylomicrons
- Indeed, ezetimibe reduces LDL-C levels by 15% to 20%

(Ezetimibe Plus Statins).

- The actions of ezetimibe are complementary to those of statins
- Dual therapy with these two classes of drugs prevents the enhanced cholesterol synthesis induced by ezetimibe and the increase in cholesterol absorption induced by statins.

Absorption, Fate, and Excretion

Ezetimibe is highly water insoluble

After ingestion, it is glucuronidated in the intestinal epithelium, absorbed, and enters an enterohepatic recirculation

About 70% is excreted in the feces and about 10% in the urine

- Ezetimibe (ZETIA) is available as a 10-mg tablet that may be taken at any time during the day, with or without food. Ezetimibe may be taken with any medication other than bile acid sequestrants, which inhibit its absorption

يعني عالمبر آخذهم مع بعض
هعمل الدوائين