لجان الدفعات

PATHOPHYSIOLOGY

MORPHINE ACADEMY

welcome back ☆

Hyperlipidemia

أشياء معم تطلع فيها من الشابتر ؟

1- تشوفم lipoproteins و Apolipoproteins اللي عليهم

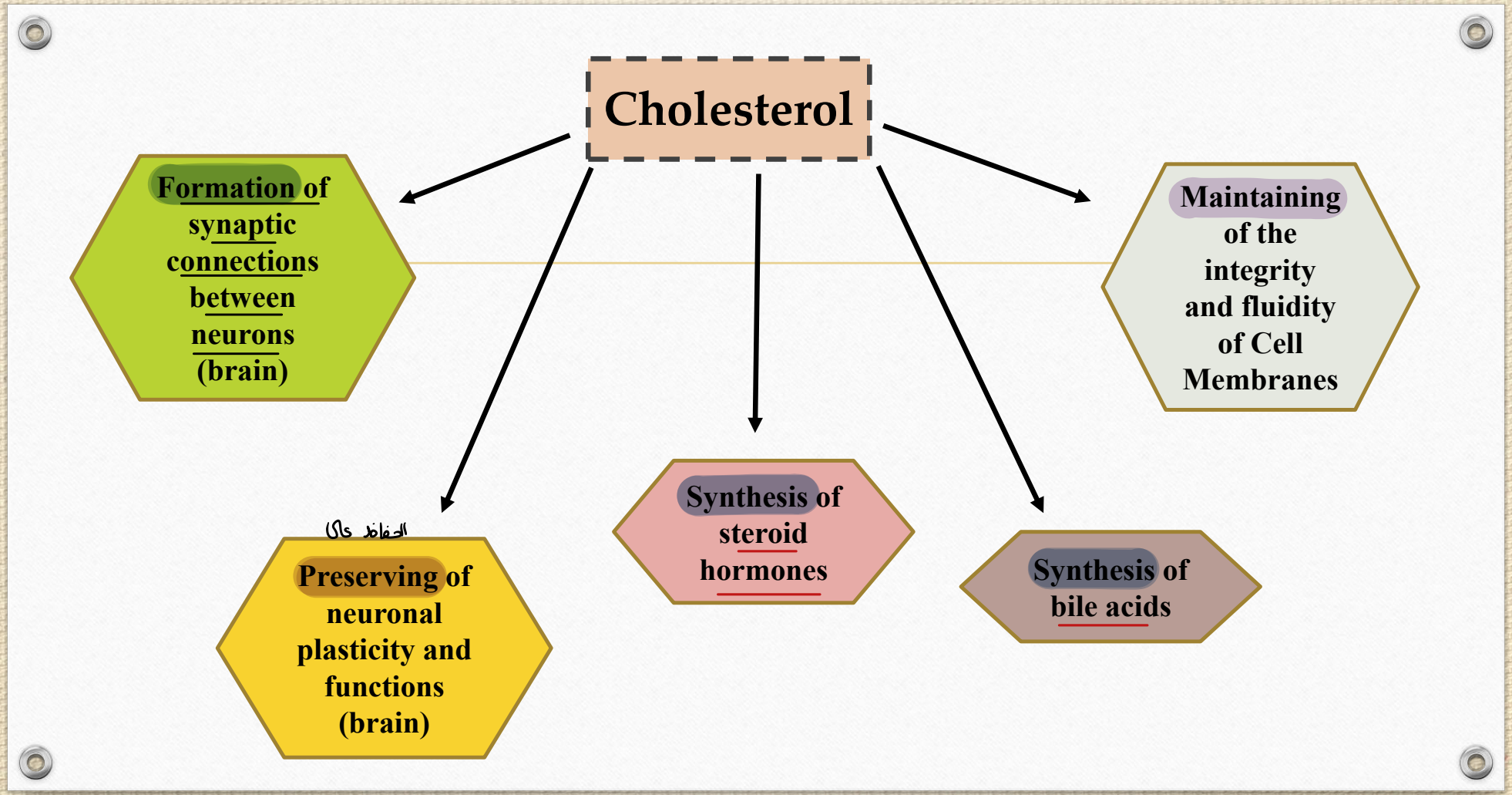
2- ميت يزيد the risk of atherosclerosis

3- أي type ما يعمل xathomas + كل type تشو الـ xathomas تكتة

Introduction

- **Cholesterol is essential** for ① cell membrane formation & ② hormone synthesis.

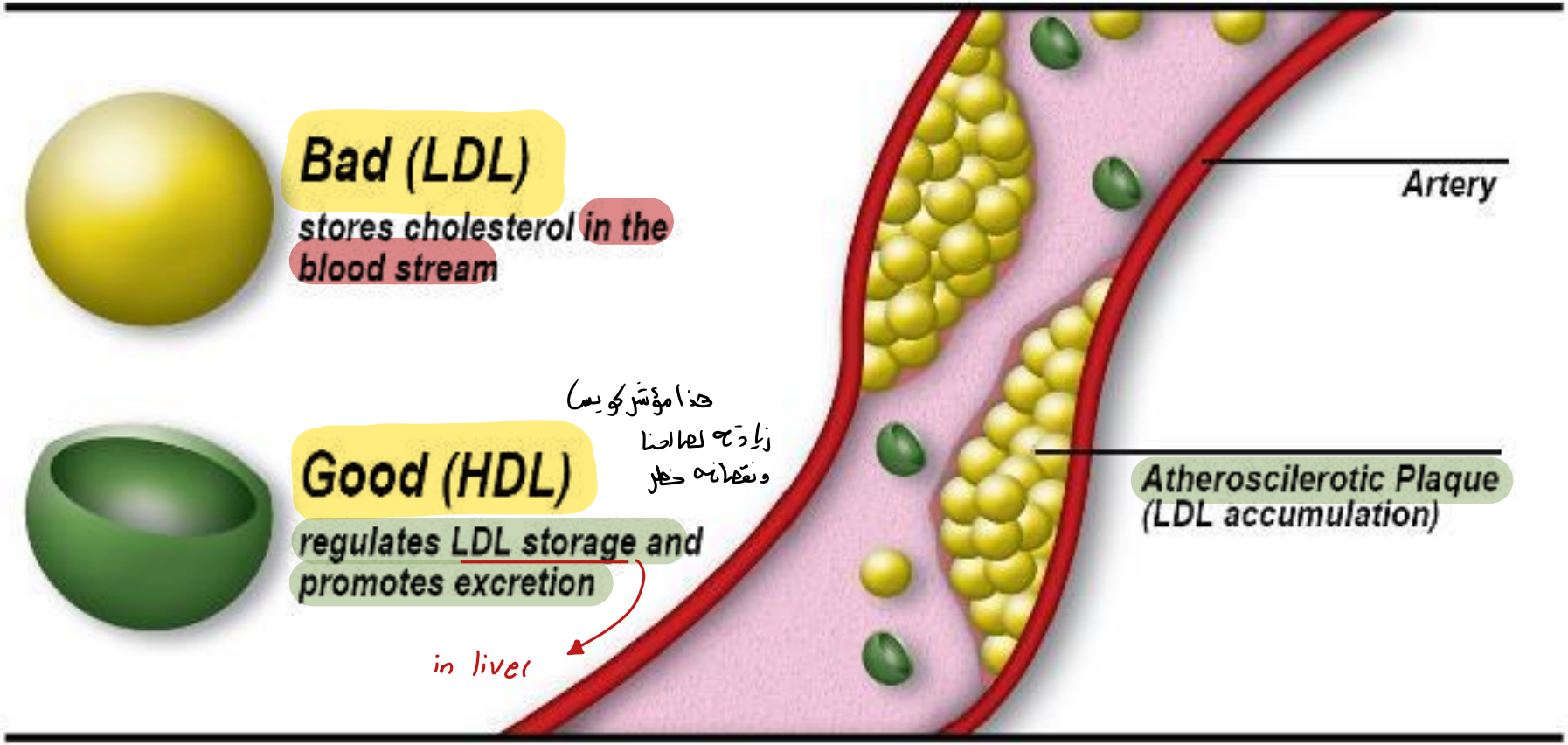
- **Lipids are not present in free form in plasma**; circulate as lipoproteins (complexes of lipids and proteins), they are transported in blood using lipoproteins.


Cholesterol
Formation of synaptic connections between neurons (brain)
Maintaining of the integrity and fluidity of Cell Membranes
Preserving of neuronal plasticity and functions (brain)
Synthesis of steroid hormones
Synthesis of bile acids

LDL : carries cholesterol from liver to tissues

HDL : carries cholesterol from tissues back to liver

Bad vs. Good Cholesterol



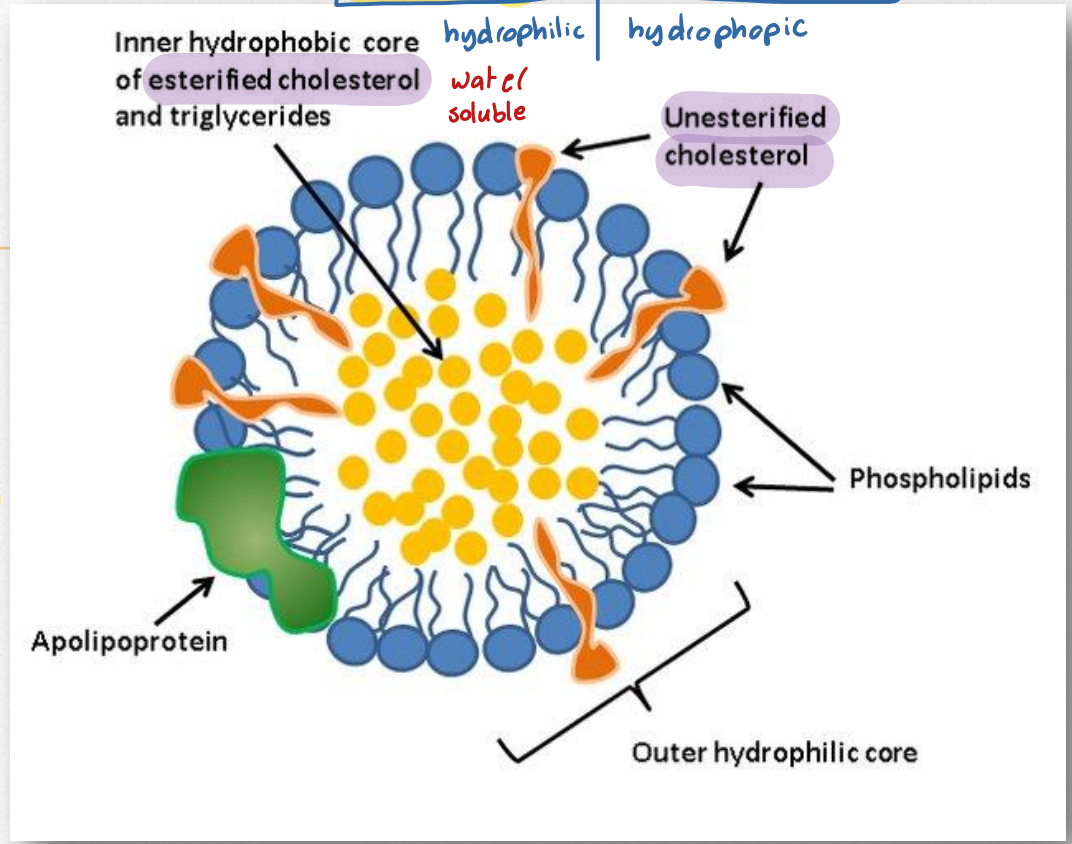
surface
- free cholesterol
- phospholipids
- Apolipoproteins

core
- tryglyceride
- cholesterol ester

- **Lipoproteins:** spherical macromolecular complexes with **SURFACES** that consist largely of "phospholipid, free cholesterol, and apolipoprotein" and **CORES** composed mostly of "triglyceride and cholesterol ester".

1

- **Function:** To keep the **lipid-soluble** for *transporting* them between organs and also 2 provide an efficient mechanism for *delivering* their lipid contents to the tissues.



https://www.researchgate.net/publication/282356824_Mast_Cells_and_HDL__Studies_on_Cholesterol_Efflux_and_Reverse_Cholesterol_Transport/figures?lo=1

Question 17 / 40

Lipoprotein surface consists of phospholipids, cholesterol ester, and apolipoprotein.

1. True
2. False

1. The ***main*** function of lipoproteins is to:
   A) Transport lipids in the blood
   B) Convert cholesterol into bile acids
   C) Break down triglycerides in adipose tissue
   D) Inhibit cholesterol synthesis

Hyperlipidemia

- **Hyperlipidemia is defined** as an elevation in total cholesterol, LDL, triglycerides, or low HDL concentration OR some combination of these abnormalities.

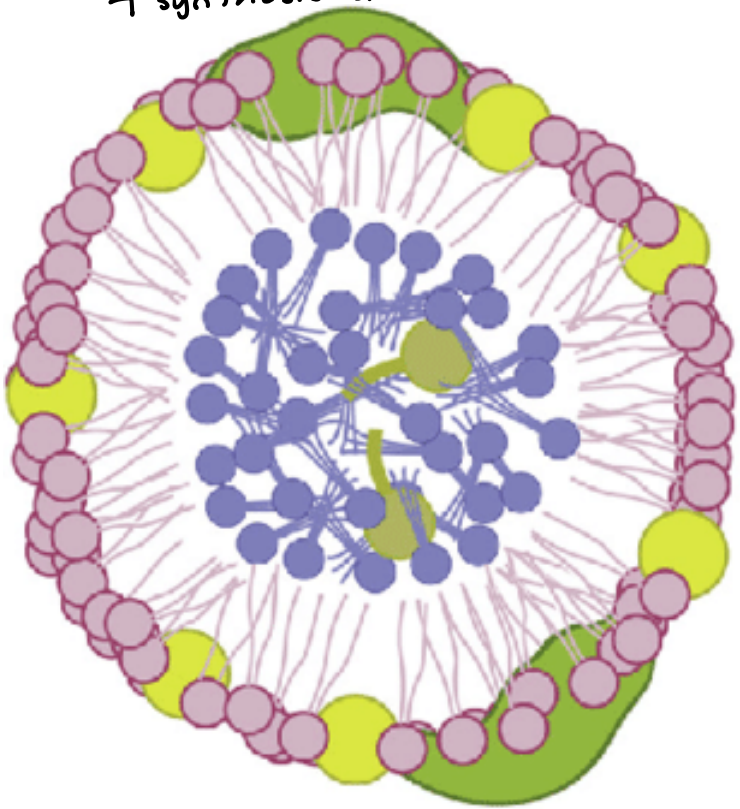
LDL ↑

cholesterol ↑

tryglycerides ↑

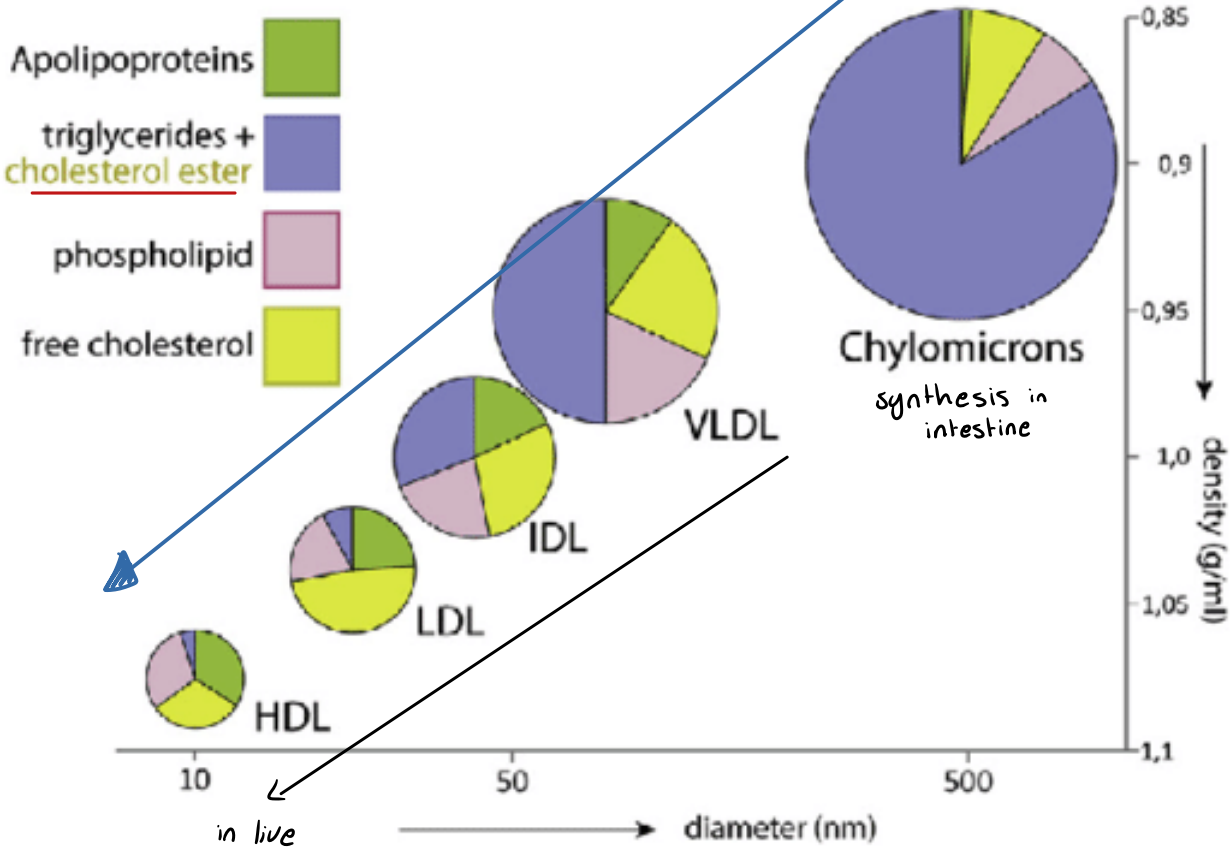
HDL ↓

5 lipoproteins
1 synthesised in intestine (chylomicron)
4 synthesised in liver



liver synthesis cholesterol

density increase
downward
size decrease



Food ← stomech ← intestine ← chylomicrons تصنع ليتفاعم ← to blood

In capillaries the enzyme capillary lipase (LPL) is secreted by vascular endothelium

contain cholesterol + tryglycerides

↳ يكسر tryglycerides to fatty acids

Adipose tissue — stored

skeletal mucles — ATp production

Tryglyceride ↓ but still higher than cholesterol

why? لأنه exogenous cholesterol

chylomicrons remnants بعدين أخذ cholesterol + إضافة tryglycerides to LIVER

زيادة

Liver من cholesterol + chylomicron remanints ينقل الأشياء إلى كانت مع VLDL lipoproteins تصنع

but still Tryglycerides > cholesterol

↳ to blood Again capillary lipase (LPL) is secreted

↳ يكسر tryglycerides to fatty acids

Adipose tissue — stored

skeletal mucles — ATp production

cholesterol = Tryglycerides صار

IDL تسمى VLDL remnants

Liver

secrete LDL + cholesterol

cholesterol > tryglycerides

IDL + endgenous cholesterol

LDL bad cholesterol

=> to blood stream

HDL يجي

Apo A I activate LCAT

Free cholesterol ياخذ من liver

enzyme LCAT convert

Free cholesterol -> ester cholesterol

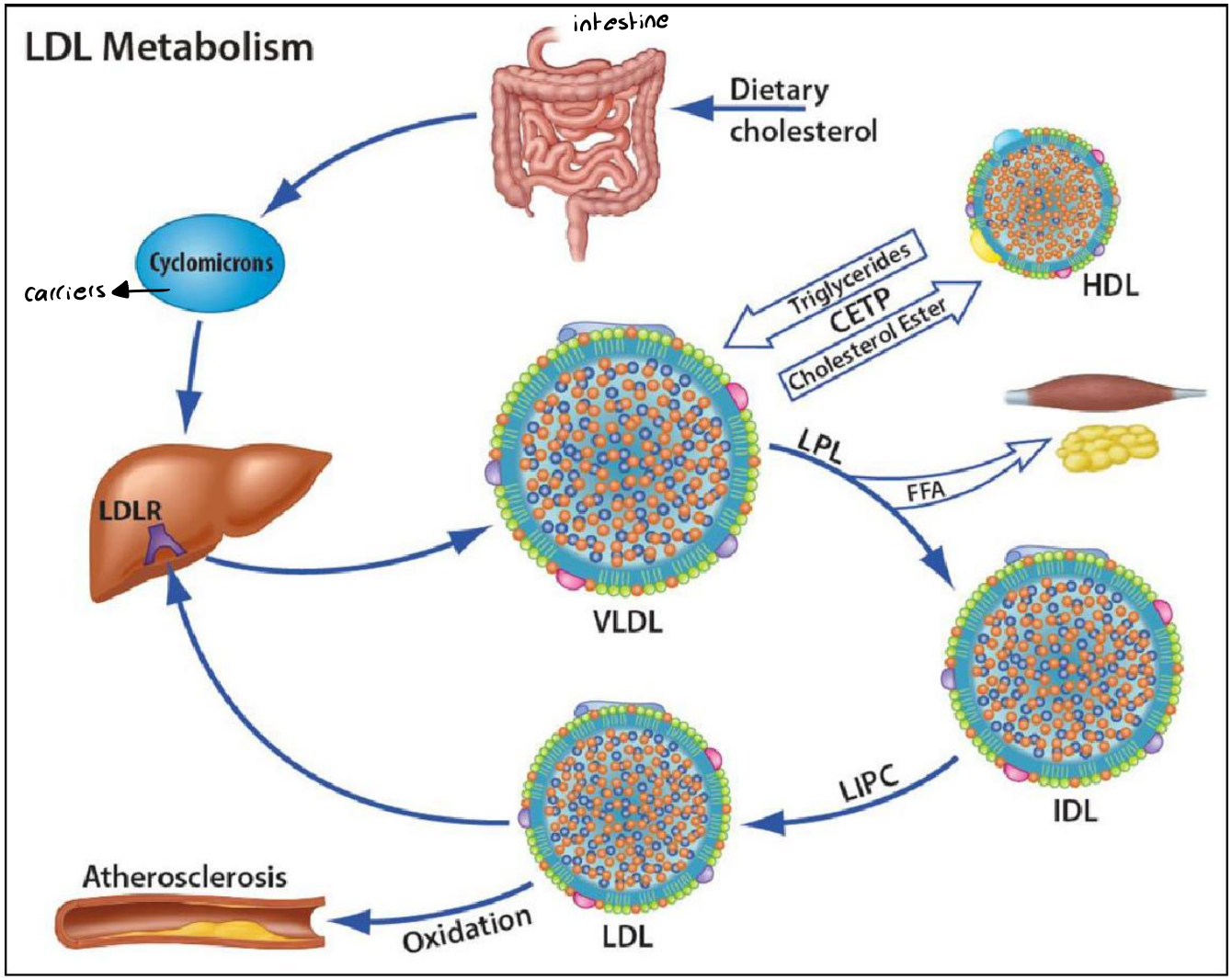
حالات ما تقدر lipoprotein lipase تحطيم tryglycerides -> Fatty acids

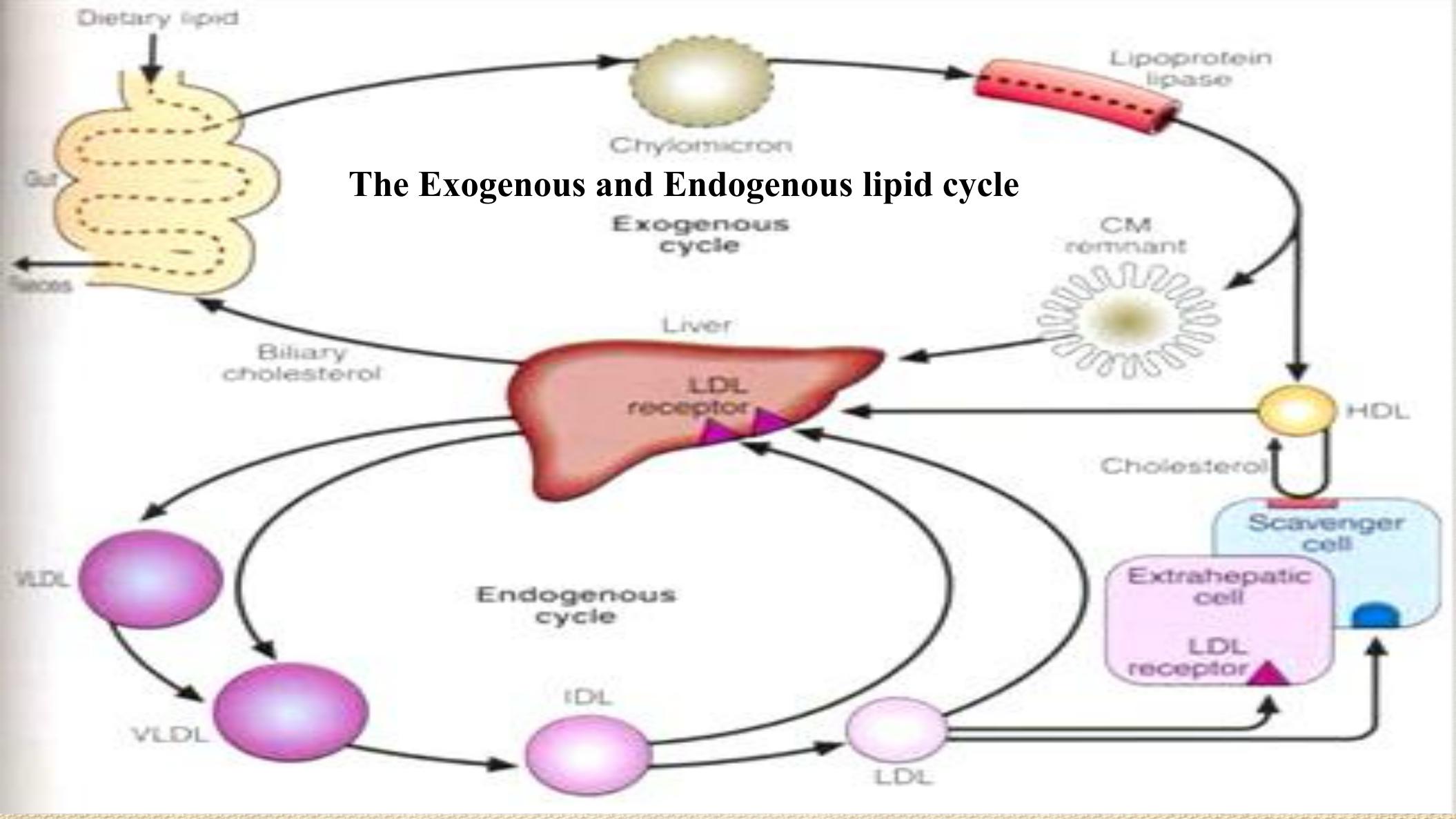
LPL

1. deficiency in apo C II
2. exeptional amount of Apo C III منافس ما لازم يكون موجود
3. deficiency in lipoprotein lipase

VLDL + IDL + LDL ↑

atherosclerosis زيادتهم تزيد خطر الإصابة بـ


LDL Metabolism
intestine
Dietary cholesterol
Cyclomicrons
carriers
HDL
Triglycerides
CETP
Cholesterol Ester
LDLR
LPL
FFA
VLDL
IDL
LIPC
LDL
Atherosclerosis
Oxidation



The Exogenous and Endogenous lipid cycle

1. Chylomicrons: Apo C II Apolipoprotein

- Lowest density.
- Synthesized in the gut wall. intestine
- Mainly transport dietary triglycerides from the small intestine into the blood.

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2. VLDL (very low-density lipoproteins): tryglycerides > cholesterol Apo C II lipoprotein

- Synthesized in the liver.
- Contains approximately 50% triglycerides with the remainder; roughly equal amounts of phospholipids and cholesterol.
- May be converted to IDLs in the blood.

3. IDL (intermediate-density lipoproteins):

- Composed of approximately equal amounts of triglycerides, phospholipids, and cholesterol.
- Precursor for LDLs

تمهيد

Question 20 / 40

VLDL is considered as precursor for:

1. ○ Chylomicron
2. ○ HDL
3. ✓ IDL
4. ○ LDL
5. ○ None of the above

4. LDL (low-density lipoprotein):

cholesterol > tryglycerides

- Composed of approximately 50% cholesterol.
- Main carrier of cholesterol from the liver to tissues.
- Internalized into cells bound to a specific cell-surface LDL receptor.
- "Bad cholesterol" due to its role in atherosclerosis.

LDL oxidation causes ↗

5. HDL (high-density lipoprotein):

- ✓ Synthesized in the liver.
- ✓ Carries cholesterol from the tissues and plasma back to the liver.
- "Good cholesterol" because it removes cholesterol from the circulation; high circulating HDL levels associated with a reduced potential for atherosclerosis.

2. Which lipoprotein is primarily responsible for carrying cholesterol from the liver to peripheral tissues?
   A) HDL
   B) LDL
   C) Chylomicrons
   D) VLDL

سؤال كل العوامل التالية تزيد خطر atherosclerosis

جاي 100٪

HDL percentage increased, the risk of atherosclerosis increase:

False

LDL receptor ↑ the risk of atherosclerosis increase :

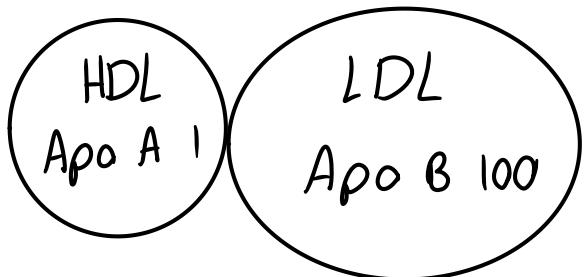
the expression for LDL receptor ↑ :

False

Deficiency in LDL receptor? risk increase ↑

VLDL ↑ risk ↑

Apolipoprotein A I expression ↑ risk decrease ↓



3. A high level of which lipoprotein is associated with a decreased risk of atherosclerosis?

A) LDL

B) HDL

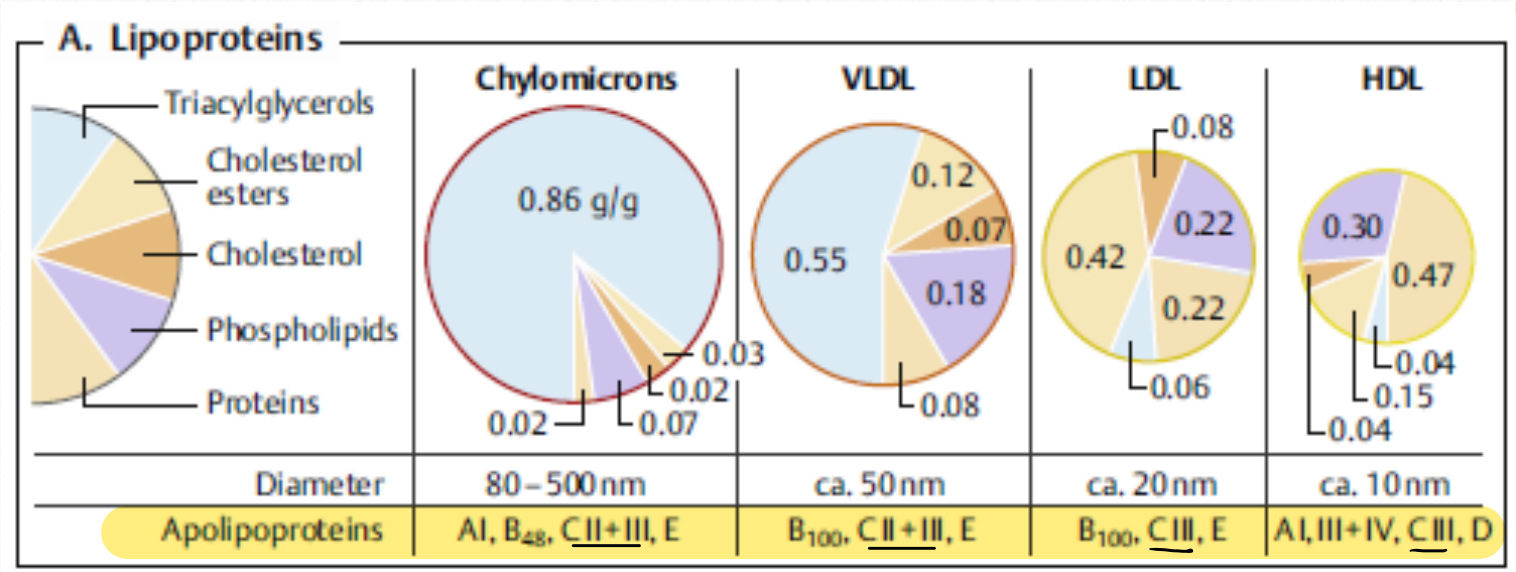
C) VLDL

D) Chylomicrons

TABLE 23-1 Composition of Lipoprotein Isolated from Normal Subjects

Lipoprotein Class	Density Range (g/mL)	Diameter (nm)	Composition (Weight %) Cholesterol				
			Protein	*Triglyceride*	*Free*	*Ester*	*Phospholipid*
Chylomicrons	<0.94	75–1200	1–2	80–95	1–3	2–4	3–9
VLDL	0.94–1.006	30–80	6–10	55–80	4–8	16–22	10–20
LDL	1.006–1.063	18–25	18–22	5–15	6–8	45–50	18–24
HDL	1.063–1.21	5–12	45–55	5–10	3–5	15–20	20–30

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



Apolipoproteins

- **These proteins have three functions:**
  - Provide structure to the lipoprotein, activate enzyme systems, bind with cell receptors.
- **The five most clinically relevant apolipoproteins are A-I, A-II, B-100, C, and E:**
  - **Apo B and E** proteins are ligands for LDL receptors:
    - **The blood concentration of apolipoprotein B 100 is an indication of the total number of VLDL and LDL particles in the circulation. An increased number of lipoprotein particles (i.e., an increased apolipoprotein B-100 concentration) is a strong predictor of CHD risk.**

Apo B 100 ↑ → CHD ↑
lipoproteins particles ↑

coronary healt disease

مهم جدًا

وجوده يسمح تكسير tryglycerides → fatty acids

in chylomicron / VLDL

يحفز triglyceride → fatty acids

- **Apo C II** is a cofactor for lipoprotein lipase, which releases fatty acids and glycerol from chylomicrons, VLDL and IDL.

وجوده منافس يعطل العمل

- **Apo C III** downregulates lipoprotein lipase activity and interferes with the hepatic uptake of VLDL remnant particles (may emerge as an important marker of atherosclerosis and provide a way for clinicians to identify patients requiring aggressive treatment).

يتطلب

main protein in HDL

- **Apo A I** protein activates LCAT (lecithin-cholesterol acyltransferase), which catalyzes the esterification of free cholesterol in HDL particles.

يحفز

convert free cholesterol ester cholesterol

  - Levels of apolipoprotein A-I have a stronger *inverse* correlation with CHD risk. HDL particles that contain only A-I apolipoproteins (LpA-I) are associated with a lower CHD risk than are HDL particles.

Apo A I ↑ CHD ↓

Question 38 / 40

The incidence of coronary heart disease is reduced with:

1. ○ High levels of Apo B-100
2. ○ High levels of Apo C-III
3. ○ Low levels of Apo B-100
4. ○ High levels of Apo A-I
5. ✓ C&D

Question 9 / 40 LPL

Lipoprotein lipase activity is increased in the presence of:

1. ○ Apo C-I
2. ● Apo C-II (its cofactor)
3. ○ Apo C-III
4. ○ Apo A-I
5. ○ Apo A-II

	Chylomicron	VLDL	LDL	HDL
Density (g/mL)	<0.94	0.94–1.006	1.006–1.063	1.063–1.210
Composition (%)				
Protein	1–2	6–10	18–22	45–55
Triglyceride	85–95	50–65	4–8	2–7
Cholesterol	3–7	20–30	51–58	18–25
Phospholipid	3–6	15–20	18–24	26–32
Physiologic origin	Intestine	Intestine and liver	Product of VLDL catabolism	Liver and intestine
Physiologic function	Transport dietary CH and TG to liver	Transport endogenous TG and CH	Transport endogenous CH to cells	Transport CH from cells to liver
Plasma appearance	Cream layer	Turbid **"Lipemia"**	Clear	Clear
Electrophoretic mobility	Origin	Pre-beta	Beta	Alpha
Apolipoproteins	A-IV, B-48, C-I, C-II, C-III	B-100, C-I, C-II, C-III, E	B-100,	A-I, A-II, A-IV

Background & Pathophysiology

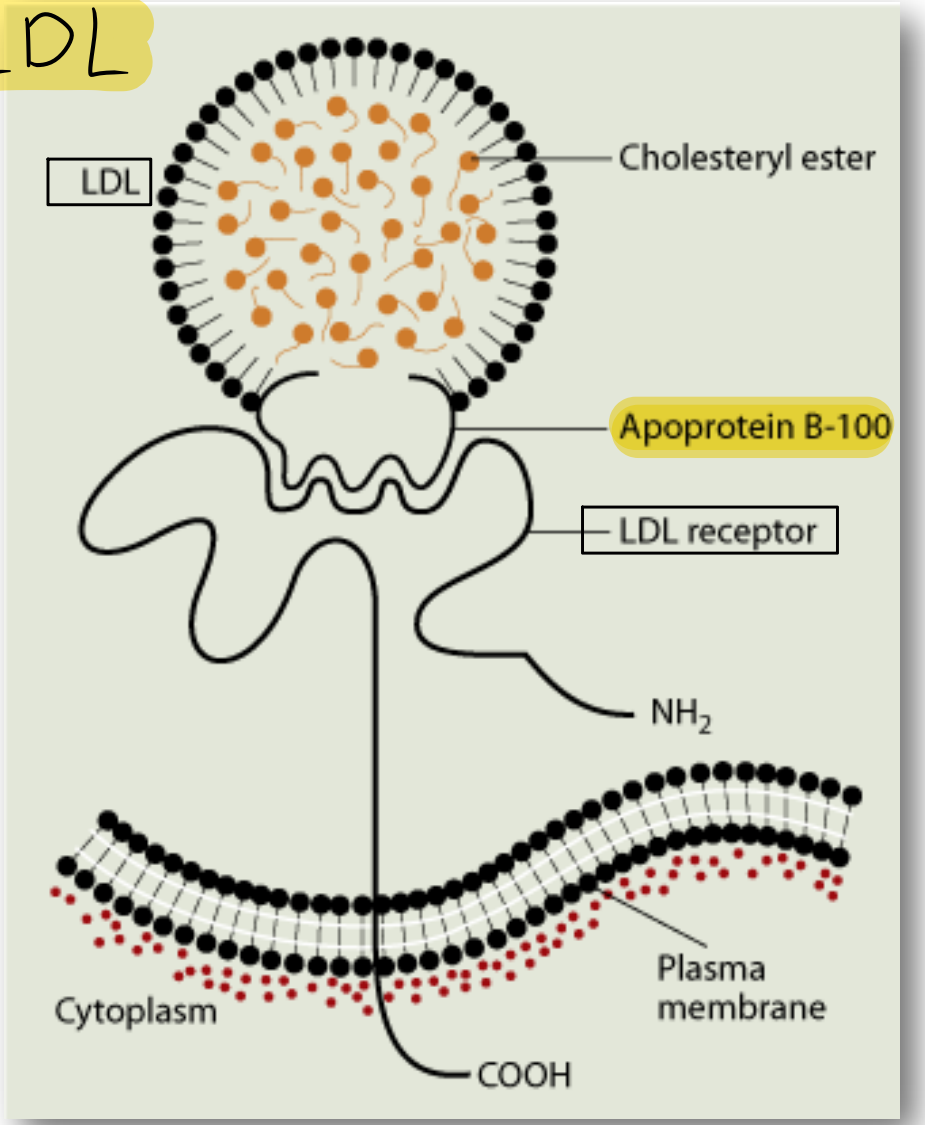
- **VLDL** secreted from the liver: converted to IDL then LDL

LDL receptors ↓ LDL from blood to liver

- Plasma **LDL** has taken up by receptors on the liver, adrenal, & peripheral cells:
  - recognize LDL apolipoprotein B-100.
  - LDL internalized & degraded by these cells.
  - Increased intracellular (→ extracellular) cholesterol levels inhibits HMG-CoA reductase & decreases LDL receptor synthesis.

inhibition

cholesterol ↑ (extracellular) HMG-CoA reductase ↓ LDL receptors ↓



The figure shows a diagrammatic representation of the structure of low-density lipoprotein (LDL), the LDL receptor, and the binding of LDL to the receptor via apolipoprotein B-100.

Background & Pathophysiology

- LDL also excreted in bile:
  - joins the enterohepatic pool.
  - eliminated in stool.
- LDL can be oxidized in subendothelial space of arteries:
  - *Oxidized* LDL in artery walls provokes *inflammatory* response.
  - Monocytes recruited & transformed into *macrophages*.
    - results in *cholesterol laden foam cell accumulation*
  - Foam cells: beginning of arterial fatty streak.
  - If processes continue angina, stroke, MI, peripheral artery disease, arrhythmias, death.

white blood cells

تستخدم

محمد

myocardial infarction

Etiology

imbalance of lipids in blood

- There are two major ways in which dyslipidemia are classified:
  - primary
    - 1- phenotype
    - 2- Genetic
  - secondary

إلى بركز عليه

1. **Primary:** when the disorder is not due to an identifiable underlying disease.
   a) **Phenotype** (Fredrickson-Levy-Lees), or the presentation in the body (including the specific type of lipid that is increased).
   b) **Genetic,** this classification can be problematic, because there are over 500 different mutations of the apolipoprotein gene. However, there are a few well-defined genetic conditions that are usually easy to identify.
2. **Secondary:** should be initially managed by correcting underlying abnormality when possible.
   - Current laboratory values can not define underlying abnormality.

20

معلم جدًا

اربط
Chylomicron = tryglyceride
VLDL = tryglyceride
LDL = cholesterol

- **Primary lipoprotein disorders: 6 Phenotype categories:**

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIb	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

no atherosclerosis risk

يزيدوا risk

combined - equal -

the risk of atherosclerosis يزيد مين المعلم +

الأسماء مش اهم اشي
الأهم تعرف مين زاد
cholesterol
triglyceride

- **Primary lipoprotein disorders: 6 Phenotype categories:**

Type I	Hyperchylomicronemia
Type IIa	Elevated LDL (familial hypercholesterolemia)
Type IIb	Elevated LDL and VLDL (familial combined hypercholesterolemia)
Type III	Broad β-VLDL (Familial dysbetalipoproteinemia)
Type IV	Elevated VLDL (Familial hypertriglyceridemia)
Type V	Elevated chylomicrons and VLDL (mixed hyperlipidemia)

Apo E
IDL

WHO: World Health Organization, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

Question 16 / 40

In phenotype III hyperlipidaemia, the lipid profile is presented as:

1. ○ Increase Cholesterol alone
2. ○ Increase Triglyceride alone
3. ○ Normal or slight increase in cholesterol with significant increase in Triglyceride
4. ○ Normal or slight increase in Triglyceride with significant increase in cholesterol
5. ✔ Significant increase in cholesterol associated with high significance increase in Triglyceride.

- **Primary lipoprotein disorders: 6 Phenotype categories:**

Frederickson Type	Classification	Lipid Profile
I	Familial lipoprotein lipase deficiency (hyperchylomicronemia, hypertriglyceridemia)	TG++, C normal, CM++, HDL–/normal
IIa	Familial hypercholesterolemia	TG normal, C+, LDL+
IIb	Familial combined hyperlipidemia	TG+, C+, LDL+, VLDL+
III	Familial dysbetalipidemia (remnant particle disease)	TG+, C+, IDL+, CM remnants+
IV	Familial hypertriglyceridemia	TG+, C normal/+, LDL++, VLDL++
V	Familial combined hypertriglyceridemia	TG+, C+, VLDL++, CM++

TG, triglycerides; C, cholesterol; CM, chylomicrons; HDL, high-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins; IDL, intermediate-density lipoproteins; +, raised; –, lowered.

https://doctorlib.info/medical/fitzpatrick-atlas-dermatology/18.html

Disorders of lipid metabolism

- Prolonged hyperlipidemia results in the accumulation of lipid in tissues and causes cell damage.

- **Lipids may accumulate in:**

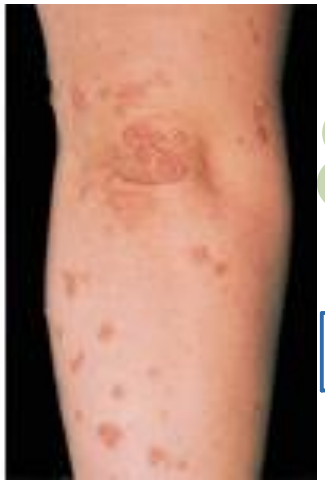
a. **Xanthomatosis**: subcutaneous tissue (**tuberoeruptive xanthomata** (over knees and elbows- **type III hyperlipidemia**)-triglyceride), tendons (**tendon xanthomas**-familial hypercholesterolemia- **type II hyperlipidemia**), palm (**palmar xanthomata-type III hyperlipidemia**), the cornea (**corneal arcus**, xanthomas, **type II hyperlipidemia**).

b. **Atherosclerosis**: Arterial wall (Cholesterol).

(اسمعهم) type مهم نعرف مكانها واي
عليهم سؤال

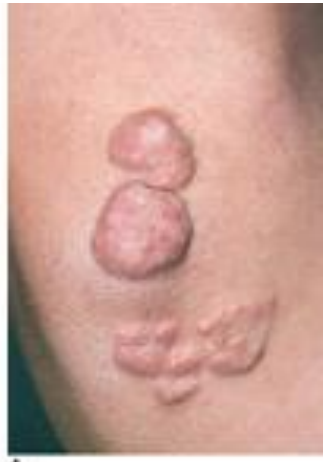
Xanthomas

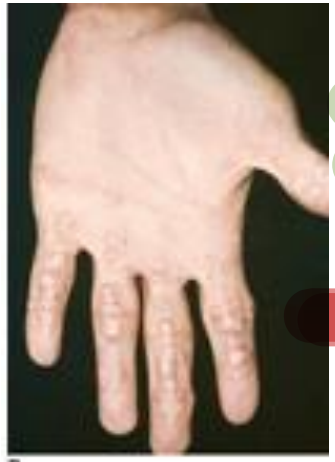
- Xanthomas are plaques or nodules consisting of abnormal lipid deposition and foam cells. They do not represent a disease but rather are symptoms of different lipoprotein disorders or arise without an underlying metabolic effect.
- Clinically, xanthomas can be classified as:
  - Eruptive, tuberoeruptive or tuberous,
  - Tendinous or planar xanthoma.
- Planar xanthomas include:
  - Xanthelasma palpebrarum/xanthelasma, (جفن)
  - Xanthoma striatum palmare,
- There are characteristic clinical phenotypes associated with specific metabolic defects.



Type I

Eruptive skin xanthomata characteristic of severe chylomicronemia.

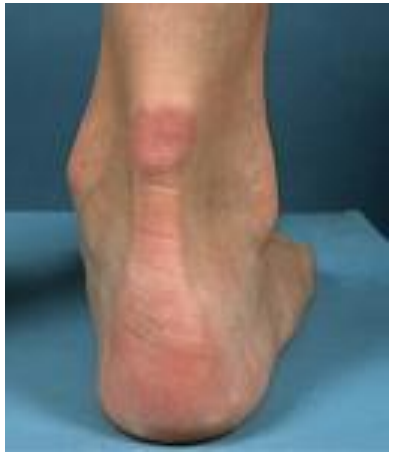




Type III

Tuberoeruptive and tuberous xanthomata typical of familial dysbetalipoproteinemia.

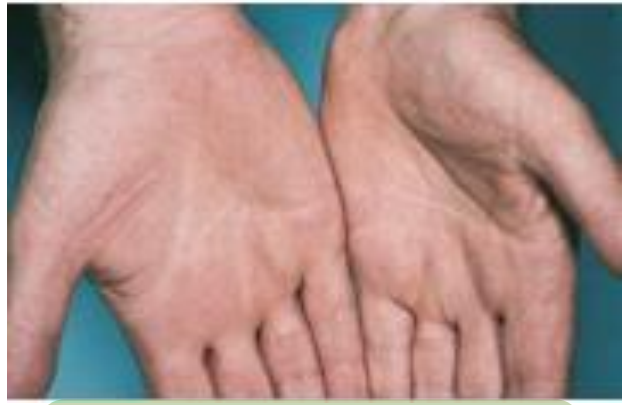
A. Knee B. Palm.



Type II

Tendon xanthomata: typical of heterozygous **familial hypercholesterolemia.** Similar xanthomata occur in patients with **familial defective apolipoprotein B-100, cerebrotendinous xanthomatosis,** and **sitosterolemia**.

LDL ↑ = Apo B 100



Xanthoma striatum palmare characteristic of familial dysbetalipoproteinemia.

Type III

eruptive skin xanthomata

- chylomicronemia

Type I

tuberoeruptive / tuberous xanthomata

- familia dysbetalipoproteinemia

IDL ↑ Type III

Knees

elbow

Tendon xanthomata

- heterozygote familial hypercholesterolemia

Type II

xanthoma striatum palmare

- familial dyslipoproteinemia IDL ↑

Type III

corneal arcus xathoma

Type II

- the cornea

سائدة متنحية صفة

Dominant trait	Recessive trait
1. The trait which appears in F1 generation are called dominant trait.	1. The trait which does not appear in F1 generation are called recessive trait.
2. It appears in more number.	2. It appears in less number.
3. Dominant trait can express itself in the presence of recessive trait.	3. Recessive trait cannot express itself in the presence of dominant trait.
4. The presence of another similar allele is not required to produce its phenotype. أليل Aa	4. The presence of another similar allele is required to produce its phenotype. aa

one is enough

27

Lipoprotein lipase

Familial LPL deficiency

- **LPL** is normally released from vascular endothelium or by heparin and hydrolyzes chylomicrons and VLDL.
- Familial LPL deficiency is rare.
- Diagnosis is based on low or absent enzyme activity with normal human plasma or apolipoprotein C-II, a cofactor of the enzyme.

Familial LPL deficiency

- **Type I lipoprotein pattern (chylomicrons):**
  - Characterized by a massive **accumulation of chylomicrons** and a corresponding increase in plasma **triglycerides.** **VLDL concentration is normal.**
  - Presenting manifestations include repeated attacks of pancreatitis and abdominal pain, eruptive cutaneous xanthomatosis, and hepatosplenomegaly beginning in childhood.
  - Symptom severity is proportional to dietary fat intake and consequently to the elevation of chylomicrons
  - ☆ **Accelerated atherosclerosis is not associated with the disease.**

Familial LPL deficiency

- **Type V (VLDL and chylomicrons):**

  - Abdominal pain, pancreatitis, eruptive xanthomas, and peripheral polyneuropathy.
  - Symptoms may occur in childhood, but usually the disorder is expressed at a later age.
  - **The risk of atherosclerosis is increased with the disorder.**
  - Patients commonly are obese, hyperuricemia, and diabetic, and alcohol intake, exogenous estrogens, and renal insufficiency tend to be **exacerbating factors**.

uric acid excess in blood

5. Which lipid disorder is ***MOST*** likely to cause acute pancreatitis?

A) Hypercholesterolemia

B) Hypertriglyceridemia

C) Low HDL

D) High LDL

Question 23 / 40

Lipoprotein lipase deficiency leads to:

1. ○ Phenotype I hyperlipidaemia
2. ○ Phenotype IIa hyperlipidaemia
3. ○ Phenotype III hyperlipidaemia
4. ○ Phenotype V hyperlipidaemia
5. ✓ A&D

LDL ↑ Familial hypercholesterolemia

homozygote
heterozygote

Type II

- **Characterized by:**
  a. Selective elevation in the plasma level of LDL.
  b. Deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (theromas). + Corenal Arcus>> Dominant (Type II)
  c. Inheritance as an autosomal dominant trait with homozygotes more severely affected than heterozygotes.

- The primary defect in familial hypercholesterolemia is the inability to bind LDL to the LDL receptor (Apo B-100) or, rarely, a defect of internalizing the LDL receptor complex into the cell after normal binding.

Familial hypercholesterolemia

- **Homozygotes** have essentially **no** functional LDL receptors.
  - This leads to lack of LDL degradation by cells and unregulated biosynthesis of cholesterol, with total cholesterol and LDL-C inversely proportional to the deficit in LDL receptors.

- **Heterozygotes** have only about **half** the normal number of LDL receptors, total cholesterol levels in the range from 300 to 600 mg/dL.

Question 8 / 40

The number of LDL receptors in patient suffering from heterozygote familial hypercholesterolemia is:

1. ○ Total loss of LDL receptors
2. ○ 20% of the normal LDL receptors
3. ◉ 50% of the normal LDL receptors
4. ○ 70% of the normal LDL receptors
5. ○ None of the above

Type III

IDL ↑

Dysbetalipoproteinemia Recessive

Apo E problem

- **Familial type III hyperlipoproteinemia** (also called, *broad-band*, or β-*VLDL*)
- **Patients develop the following clinical features after age 20 years:**
  - **Xanthoma striata palmaris** (yellow discolorations of the palmar and digital creases); تجاعيد
  - **Tuberous or tuberoeruptive xanthomas** (bulbous cutaneous xanthomas);
  - **Severe atherosclerosis** involving the coronary arteries, internal carotids, and abdominal aorta. Premature atherosclerosis

Type III IDL ↑

Type III

Dysbetalipoproteinemia

- A **defective structure of apolipoprotein E** does not allow normal hepatic surface receptor binding of remnant particles derived from chylomicrons and VLDL (known as IDL).

IDL ↑

- **Aggravating factors** such as obesity, diabetes, and pregnancy may promote overproduction of apolipoprotein B–containing lipoproteins.

IIb

LDL ↑
VLDL ↑
equal

Familial combined hyperlipidemia

- Characterized by elevations in total cholesterol and triglycerides, decreased HDL, increased apolipoprotein B, and small, dense LDL.

& LDL

- It is associated with premature CHD (coronary heart disease) and may be difficult to diagnose because lipid levels do not consistently display the same pattern.

VLDL ↑

Type IV hyperlipoproteinemia

- Two genetic patterns:
  - **Familial hypertriglyceridemia**, which does not carry a great risk for premature CVD, cardiovascular disease
  - **Familial combined hyperlipidemia**, which is associated with increased risk for cardiovascular disease.

Type IV hyperlipoproteinemia

- Type IV hyperlipoproteinemia is common and occurs in adults, primarily in patients who are obese, diabetic, and hyperuricemia and do not have xanthomas.

- It may be secondary to alcohol ingestion and can be aggravated by stress, progestins, oral contraceptives, thiazides, or β-blockers.

موانع حمل diuretics

Lipoprotein Abnormalities: 2° Causes

Type IIa

Hypercholesterolemia:

LDL ↑

- Hypothyroidism
- Obstructive liver disease
- Nephrotic syndrome
- Anorexia nervosa
- Acute intermittent porphyria

hypercholesterolemia

فقدان شهية عصبي

Medications:

اقرأهم

- Progestins
- Thiazide diuretics
- Glucocorticoids
- β-blockers
- Isotretinoin
- Protease inhibitors
- Cyclosporine
- Mirtazipine
- Sirolimus

Hypertriglyceridemia

- Obesity.
- DM. Diabetes mellitus
- Lipodystrophy. توزع الدهنيات مختلف
- Glycogen storage disease.
- Ileal bypass surgery.
- Sepsis.
- Pregnancy.
- Acute hepatitis ☆ hypertriglyceridemia
- Systemic lupus erythematous.

Medications

- Asparaginase
- Interferons
- Azole antifungals
- Mirtazipine
- Anabolic steroids
- Sirolimus
- Alcohol
- Estrogens
- Isotretinoin
- β-blockers
- Glucocorticoids
- Bile acid resins

- **Hypocholesterolemia:**
  - Malnutrition. سوء تغذية
  - Malabsorption. سوء امتصاص
  - Myeloproliferative diseases.
  - Chronic infectious diseases:
    - Acquired immune deficiency syndrome
    - Tuberculosis
  - Monoclonal gammopathy.
  - Chronic liver disease.

hypocholesterolemia

- **Low high-density lipoprotein:**
  - Malnutrition
  - Obesity
  - Medications
    - non-ISA β-blockers
    - anabolic steroids
    - isotretinoin
    - progestins

Question 18 / 40

Hypocholesterolaemia can occur secondary to:

1. ○ Nephrotic syndrome
2. ○ Acute intermittent porphyria
3. ○ Pregnancy
4. ○ Sepsis
5. ✓ Leukaemia

} hypercholesterolemia

} hypertryglycelidemia

تحفظ

Total cholesterol	
<200	Desirable
200–239	Borderline high
240	High
LDL cholesterol	
<100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
190	Very high
HDL cholesterol	
<40	Low
60 mg/dL	High
Triglycerides	
<150	Normal
150–199	Borderline high
200–499	High
500	Very high

All values unit are mg/dL

Major risk factors – exclusive of LDL-C – that modify the LDL goals

Age Men: ≥ 45 years Women: ≥ 55 years or premature menopause without estrogen replacement therapy
Family history of premature CHD (definite myocardial infarction or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative)
Cigarette smoking Within the past month
Hypertension (140/90 mm Hg or taking antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)[b]

[a] **Diabetes** regarded as coronary heart disease (CHD) risk equivalent.

[b] **HDL cholesterol ≥60 mg/dL** counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Metabolic syndrome is considered as CHD risk

Goals & Cutpoints

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (optional goal: <70)	>100	>100 (<100 mg/dL; consider drug options)[a]
Moderately high risk: 2+ risk factors (10-year risk >10%–20%)	<130 (optional goal <100)	≥130	≥130 (100–129: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor[b]	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

Risk is estimated from Framingham risk score

[a]Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by **therapeutic lifestyle changes (TLC).** Others prefer to use drugs that primarily modify triglycerides and high-density lipoprotein, e.g., nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory.

[b]Almost all people with 0–1 risk factor have a 10-year risk <10%; thus,10-year risk assessment in people with 0–1 risk factor is not necessary.

Calculation of LDL-c

- The majority of labs, including the insurance labs, do not directly measure the LDL portion of the lipid profile. On the other hand, **total cholesterol, HDL and triglycerides are directly measured** with values determined for each of these three tests. LDL is usually not measured directly due to the expense and time required to perform the analysis. Therefore, to estimate LDL, labs use the **"FRIEDEWALD FORMULA"** which is (in mg/dl):

LDL = Total Cholesterol - HDL - 1/5 Trigs, but only if the serum triglyceride is 400 or less.

↓

VLDL

$$LDL = 300 - 50 - \frac{125}{5} = 225$$

Two examples illustrate its use. Person A has directly calculated total cholesterol of 300, HDL of 50, and trigs of 125, which results in an indirectly calculated value for LDL of 225. Person B has the same total cholesterol and HDL as A, but his trigs are 250, which results in an indirectly calculated LDL of 200.

If you have any three of the four values, you can determine the fourth by use of the same formula. For example, when the total cholesterol is 220, the trigs are 150, and the LDL is 120, the HDL must be 70.

Better yet, the formula can be used when you know only two of the values, as long as you also have the HDL ratio available. For example, the cholesterol/HDL ratio is 6, the HDL is 40, and trigs are 180. You first solve for the cholesterol by multiplying 6 times 40 to obtain a total cholesterol of 240. From there, you simply use the above formula to calculate a LDL of 164.

Atherosclerosis

- Definition: literally means "hardening of the arteries"; it is a generic term reflecting arterial wall thickening and loss of elasticity.

- There are three general patterns:

1. **Arteriolosclerosis,** affects small arteries and arterioles and may cause downstream ischemic injury.

2. **Mönckeberg medial sclerosis**, is characterized by calcific deposits in muscular arteries in persons typically older than age 50.

3. **Atherosclerosis,** from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern.

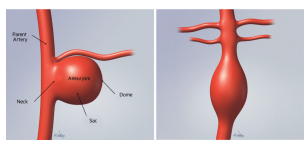
- **Atherosclerosis** is characterized by intimal lesions called *atheromas* (also called *atheromatous* or *atherosclerotic plaques*) that protrude into vessel lumens.

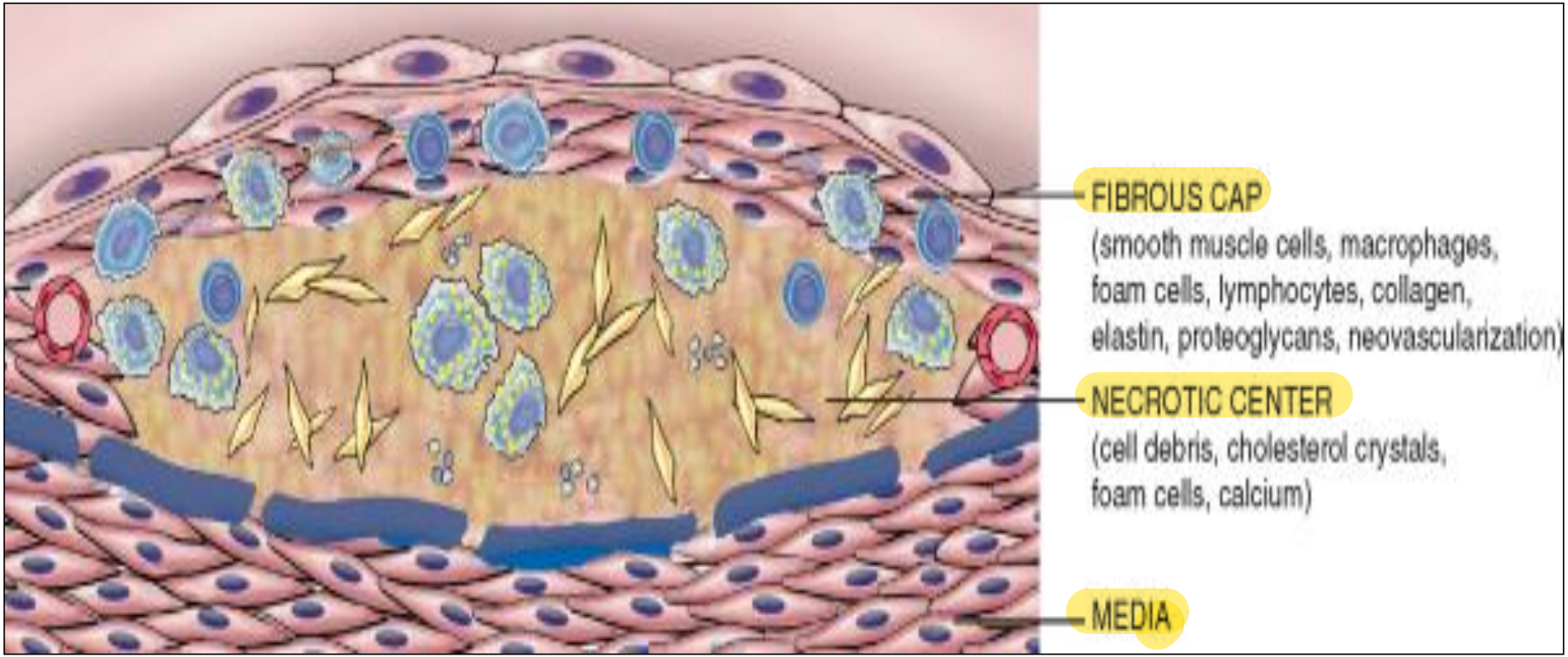
تبرز

- An atheromatous plaque consists of a raised lesion with a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a white fibrous cap.

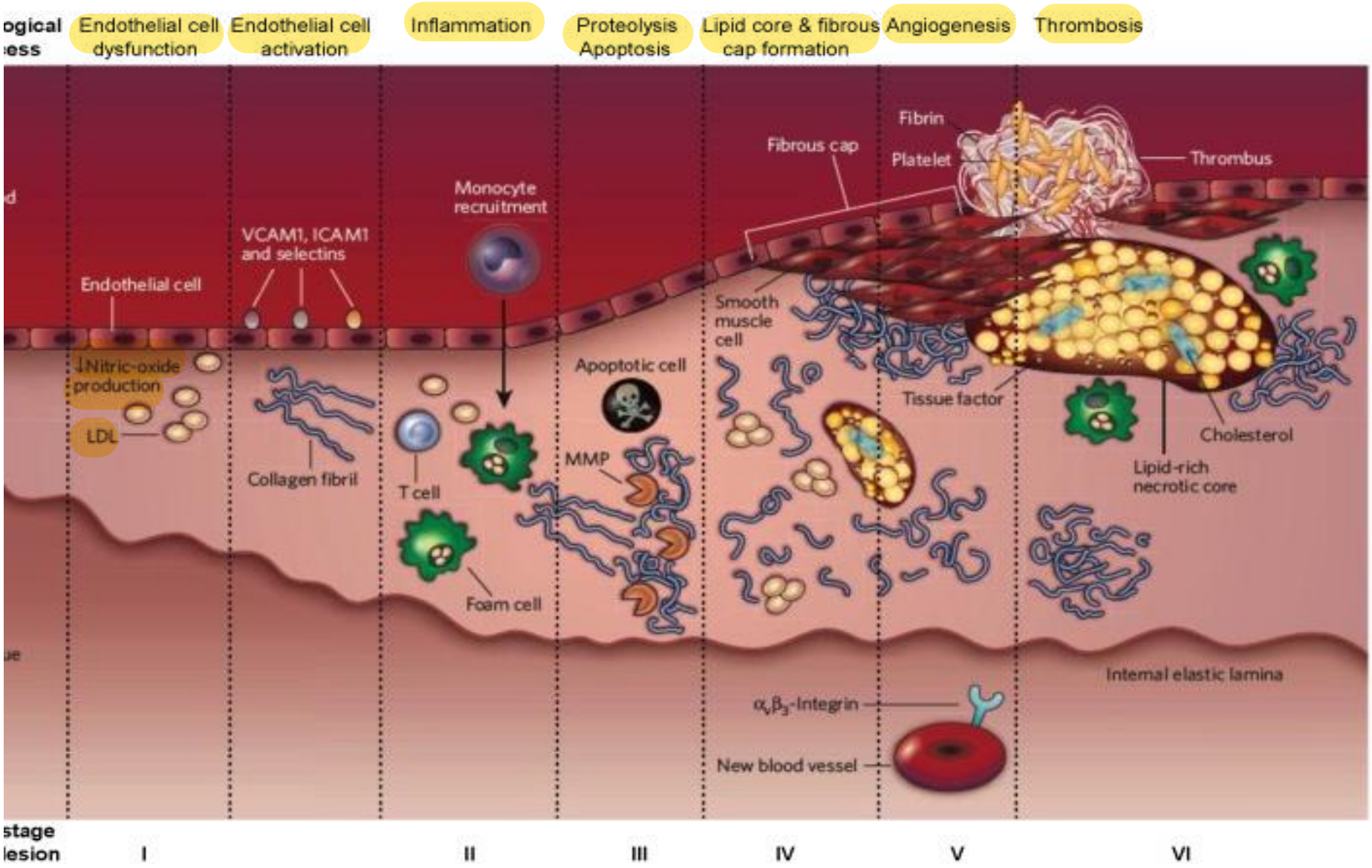
- Atherosclerotic plaques can:
  - obstruct blood flow
  - rupture leading to thrombosis
  - weaken the underlying media and thereby lead to aneurysm formation.

تمدد الأوعية الدموية





The major components of a well-developed intimal atheromatous plaque overlying an intact media.


ogical
ess
Endothelial cell dysfunction
Endothelial cell activation
Inflammation
Proteolysis Apoptosis
Lipid core & fibrous cap formation
Angiogenesis
Thrombosis
Fibrin
Platelet
Fibrous cap
Thrombus
Monocyte recruitment
VCAM1, ICAM1 and selectins
Endothelial cell
Smooth muscle cell
↓Nitric-oxide production
LDL
Collagen fibril
T cell
Apoptotic cell
MMP
Foam cell
Tissue factor
Cholesterol
Lipid-rich necrotic core
Internal elastic lamina
$\alpha_v\beta_3$-Integrin
New blood vessel
stage
lesion
I
II
III
IV
V
VI

permiability ↑
inflammation ↑

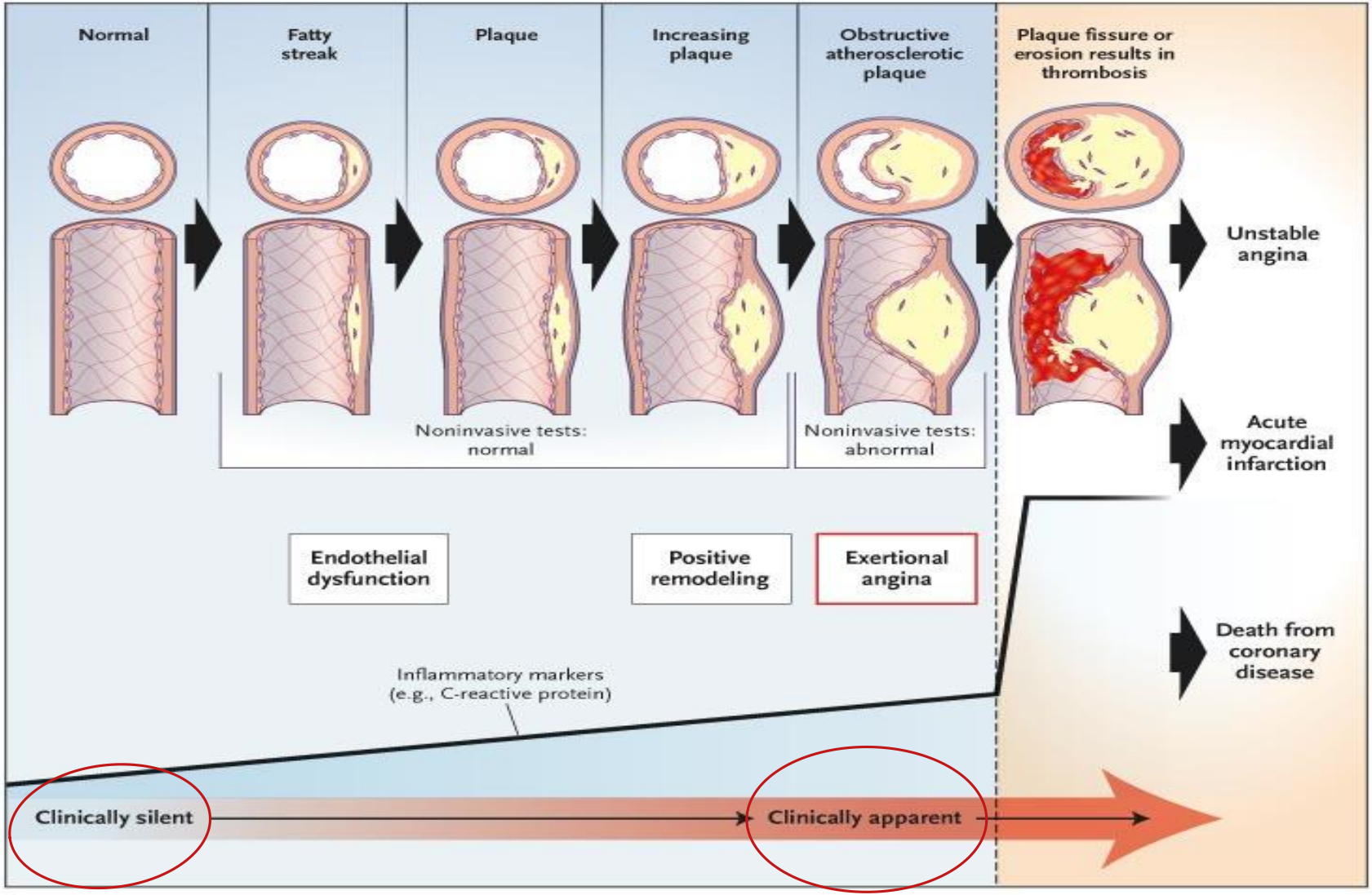
Due to endothelial dysfunction,

- **LDL particles migrate** from the blood and accumulate in the arterial intima, forming pro-inflammatory particles. inflammation ↑
- This results in the **activation of endothelial cells**, which secrete **adhesion molecules.** (ICAM-1, VCAM1)
- **Smooth muscle cells, which secrete chemokines and chemoattractants**, thereby recruiting monocytes to the arterial wall.
- Upon entry, **monocytes transform into macrophages**, which engulf the accumulated lipids to form **foam cells** which aggregate to form a lipid core.
- Plaque rupture occurs **when the fibrous cap becomes thin** and partially destroyed which leads to the **development of thrombus and ultimately coronary syndrome.**

Question 11 / 40

ICAM-1 and VCAM-1 is reduced in the presence of normal endothelial function.

1. ✓ True
2. ✗ False


Normal
Fatty streak
Plaque
Increasing plaque
Obstructive atherosclerotic plaque
Plaque fissure or erosion results in thrombosis
Unstable angina
Noninvasive tests: normal
Noninvasive tests: abnormal
Acute myocardial infarction
Endothelial dysfunction
Positive remodeling
Exertional angina
Death from coronary disease
Inflammatory markers (e.g., C-reactive protein)
Clinically silent
Clinically apparent

measure existing cases of disease and is expresse as propotion.

- **The prevalence** and severity of atherosclerosis and IHD are related to two groups of risk factors:

التشار

I. Constitutional (non-modifiable) risk factors in IHD:

- Age
- Gender
- Genetics

II. Acquired (Modifiable) risk factors in IHD:

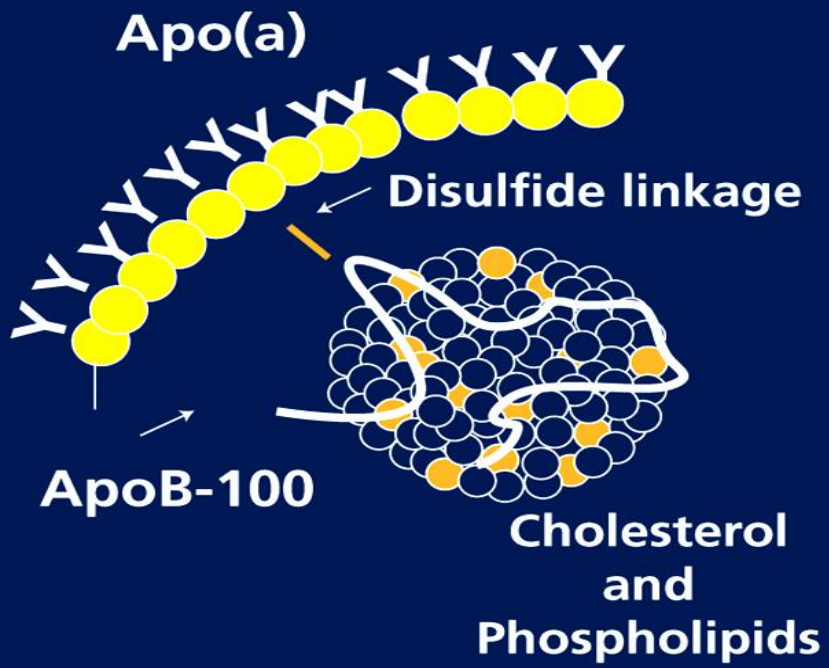
نتحكم فيهم

- Hyperlipidemia.
- Hypertension.
- Cigarette smoking.
- Diabetes Mellitus.

- **Additional risk factors:**

  - Inflammation
  - Hyperhomocystinemia
  - Metabolic syndrome
  - Lipoprotein (a) levels
  - Factors affecting homeostasis
  - Other factors

Lp(a)



- genetically determined
- marked elevation after acute ischemic coronary syndromes
- structurally homologous to plasminogen
- competes with plasminogen binding sites on endothelial cell surfaces
- oxidized Lp(a) promotes atherosclerosis same as oxidation of LDL
- stimulates PAI-1 synthesis
- risk factor for CHD events in men (Lipid Research Clinic) and women (Framingham Heart Study)

Stein JH and Rosenson RS. *Arch Intern Med* 1997;157:1170.

Pathogenesis of Atherosclerosis

- Historically, there have been two dominant hypotheses to explain the progress of the disease:

  - *one emphasizes intimal cellular proliferation.*

  - *the other focuses on the repetitive formation and organization of thrombi.*

- Recently, the *response-to-injury hypothesis* which views *atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury was adopted.*

Atherosclerosis is produced by the following pathogenic events:

- **Endothelial injury**, which causes (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis.

- **Accumulation of lipoproteins** (mainly LDL and its oxidized forms) in the vessel wall.

- **Monocyte adhesion to the endothelium**, followed by migration into the intima and transformation into macrophages and foam cells.

- **Platelet adhesion**.

Question 3 / 40

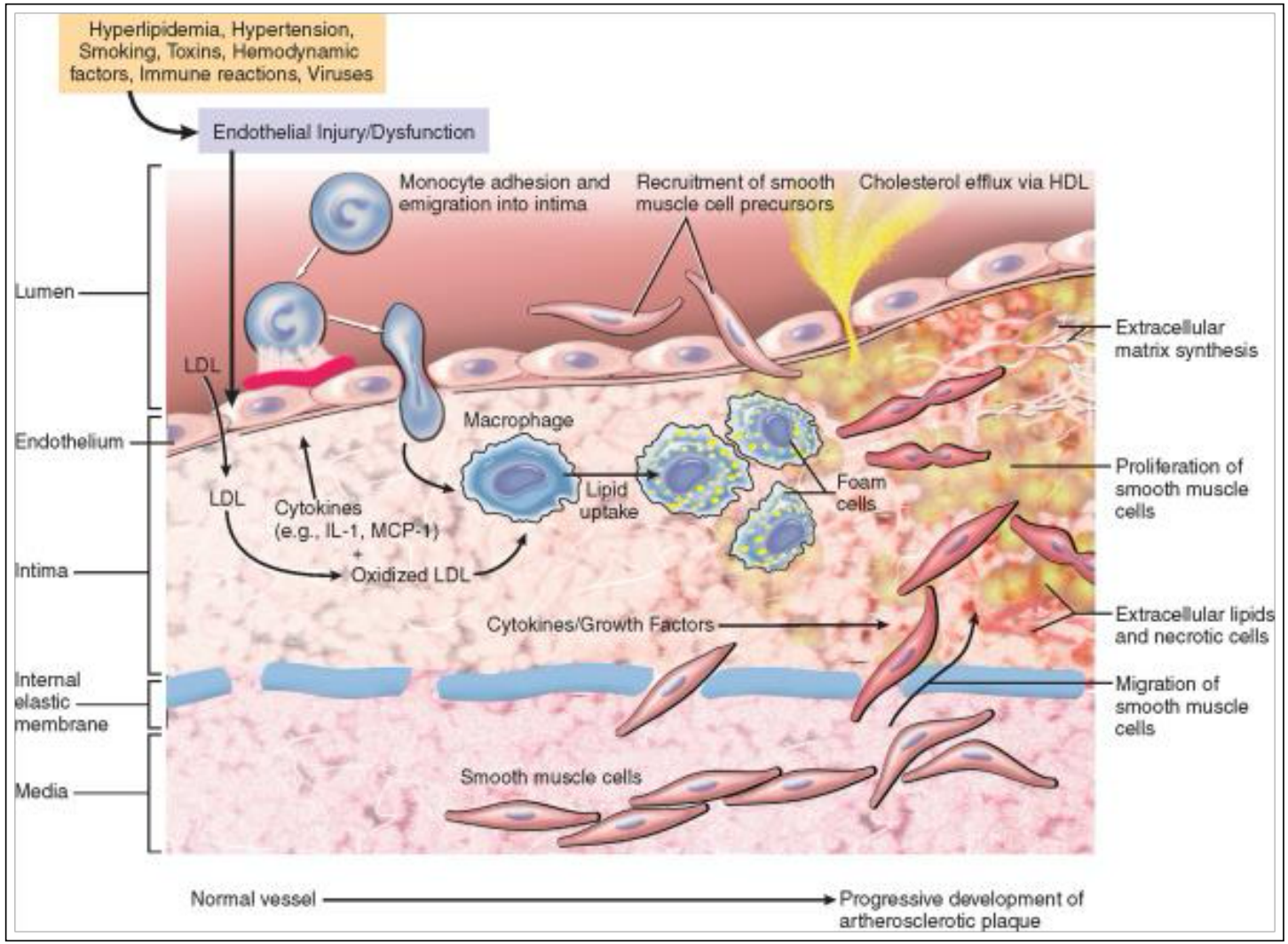
Which of the following is CORRECT about endothelial dysfunction?

1. ○ Endothelial permeability is reduced.
2. ○ Adhesion molecules are downregulated.
3. ○ Inflammation is reduced.
4. ✓ Monocyte's migration to subendothelial layer is increased.
5. ✗ B&D

- **Factor release from activated platelets, macrophages, and vascular wall cells,** inducing smooth muscle cell recruitment, either from the media or from circulating precursors.

- **Smooth muscle cell proliferation and ECM (extracellular matrix which contains lots of inflammatory mediators and growth factors) production**.

- **Lipid accumulation** both extracellularly and within cells (macrophages and smooth muscle cells).

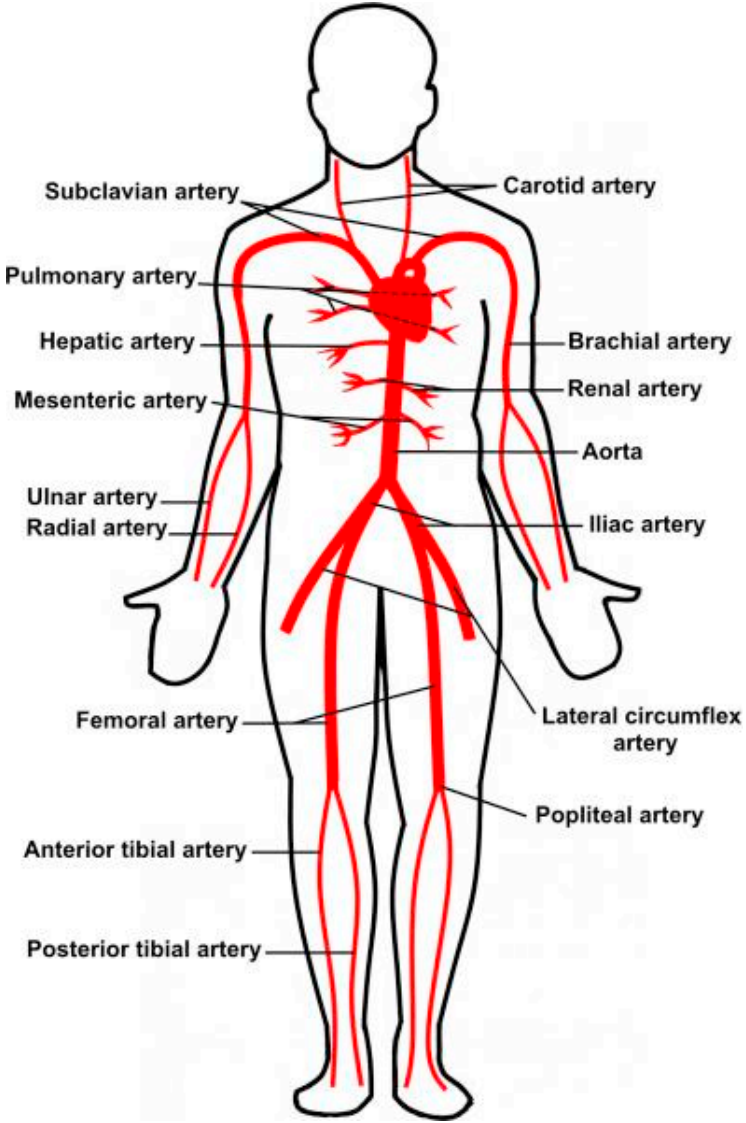

Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Recruitment of smooth muscle cell precursors
Cholesterol efflux via HDL
Lumen
Endothelium
Intima
Internal elastic membrane
Media
LDL
Macrophage
LDL
Cytokines (e.g., IL-1, MCP-1) + Oxidized LDL
Lipid uptake
Foam cells
Extracellular matrix synthesis
Proliferation of smooth muscle cells
Extracellular lipids and necrotic cells
Cytokines/Growth Factors
Migration of smooth muscle cells
Smooth muscle cells
Normal vessel
Progressive development of artherosclerotic plaque

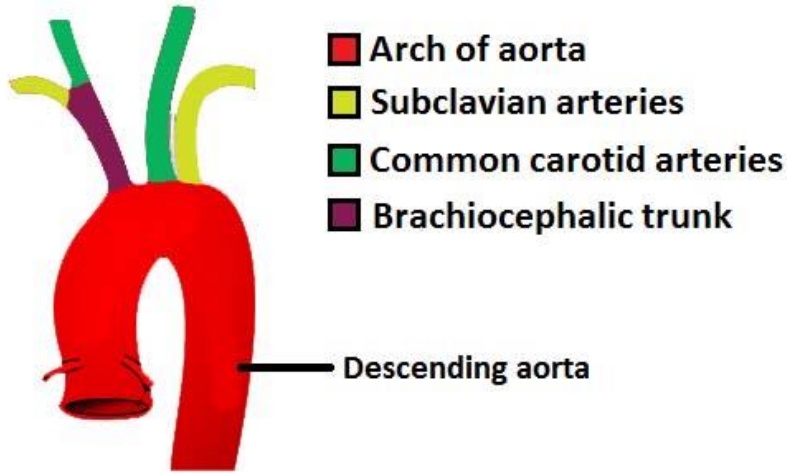
Consequences of Atherosclerosis

- The aorta, carotid, and iliac arteries (large elastic arteries) and coronary and popliteal (medium-sized muscular arteries) are targets for atherosclerosis.

- Heart attack, stroke, aneurysm, and gangrene in the legs are potential consequences of the disease.

- The principal outcomes depend on:
  - The size of the involved vessels.
  - The relative stability of the plaque itself.
  - The degree of degeneration of the underlying arterial wall.

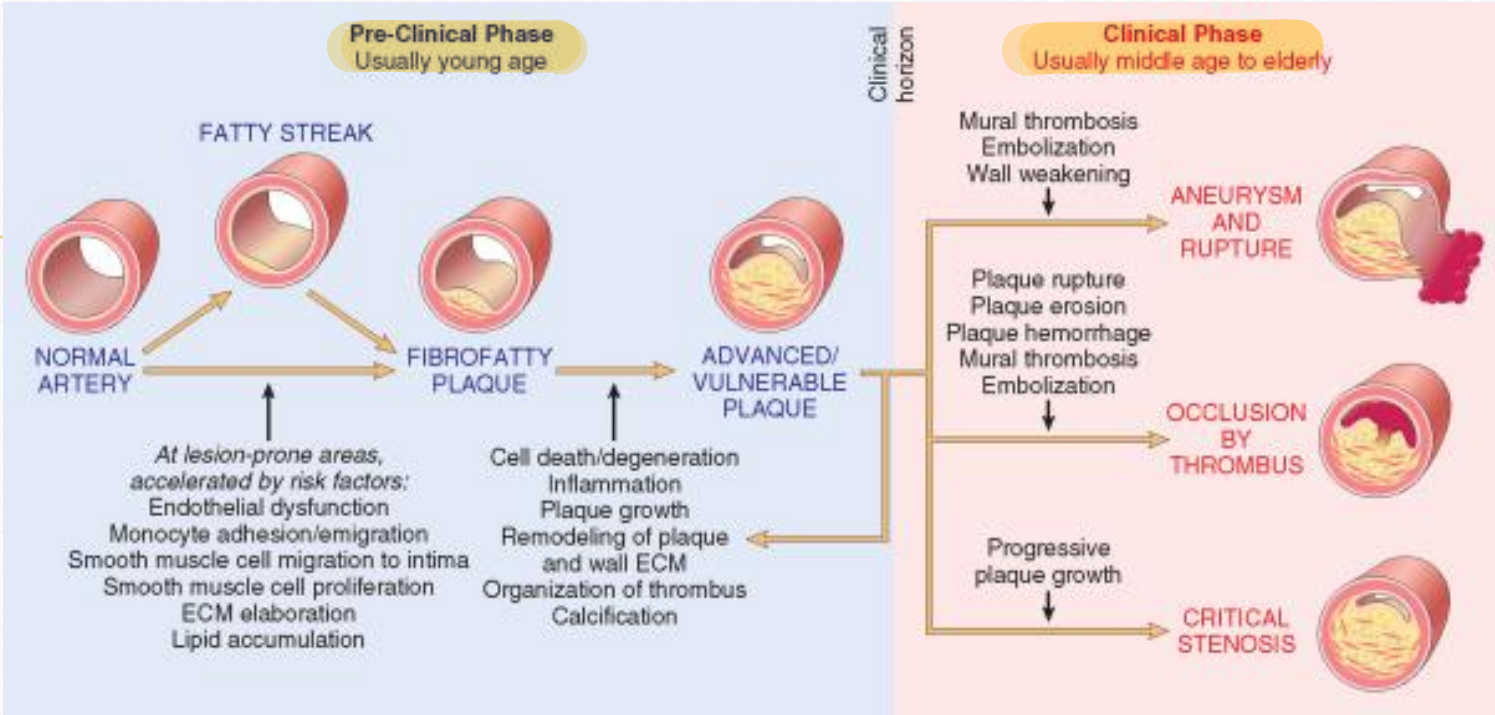




- The aorta, carotid, and iliac arteries (large elastic arteries) and coronary and popliteal (medium-sized muscular arteries) are targets for atherosclerosis.

Aorta , carotid , ilic artery , feet artery , small arteriols , small venouls
atheroscalarosis عالية نسبة يصير فيهم

true or false اتوقع هيك كانت صيغة السؤال


Pre-Clinical Phase
Usually young age
Clinical horizon
Clinical Phase
Usually middle age to elderly
FATTY STREAK
NORMAL ARTERY
FIBROFATTY PLAQUE
ADVANCED/ VULNERABLE PLAQUE
At lesion-prone areas, accelerated by risk factors:
Endothelial dysfunction
Monocyte adhesion/emigration
Smooth muscle cell migration to intima
Smooth muscle cell proliferation
ECM elaboration
Lipid accumulation
Cell death/degeneration
Inflammation
Plaque growth
Remodeling of plaque and wall ECM
Organization of thrombus
Calcification
Mural thrombosis
Embolization
Wall weakening
ANEURYSM AND RUPTURE
Plaque rupture
Plaque erosion
Plaque hemorrhage
Mural thrombosis
Embolization
OCCLUSION BY THROMBUS
Progressive plaque growth
CRITICAL STENOSIS

1. Atherosclerotic stenosis:

- Compromised blood flow WILL lead to ischemic injury secondary to *critical* occlusion of a small vessel.

- Total circumference expansion due to outward remodeling of vessel media is an adaptive mechanism before an injury commences.

- At 70% fixed occlusion, clinical symptoms surface (Stable angina).

- The effects of vascular occlusion ultimately depend on arterial supply and the metabolic demand of the affected tissue.

2. Acute plaque change

- **Plaque rupture** is promptly **followed by partial or complete vascular thrombosis** resulting in acute tissue infarction **(e.g., myocardial or cerebral infarction).**

- **Plaque changes fall into three general categories:**

  - **Rupture/fissuring**, exposing highly thrombogenic plaque constituents

  تشقق

  تآكل تقرح

  - **Erosion/ulceration**, exposing the thrombogenic subendothelial basement membrane to blood

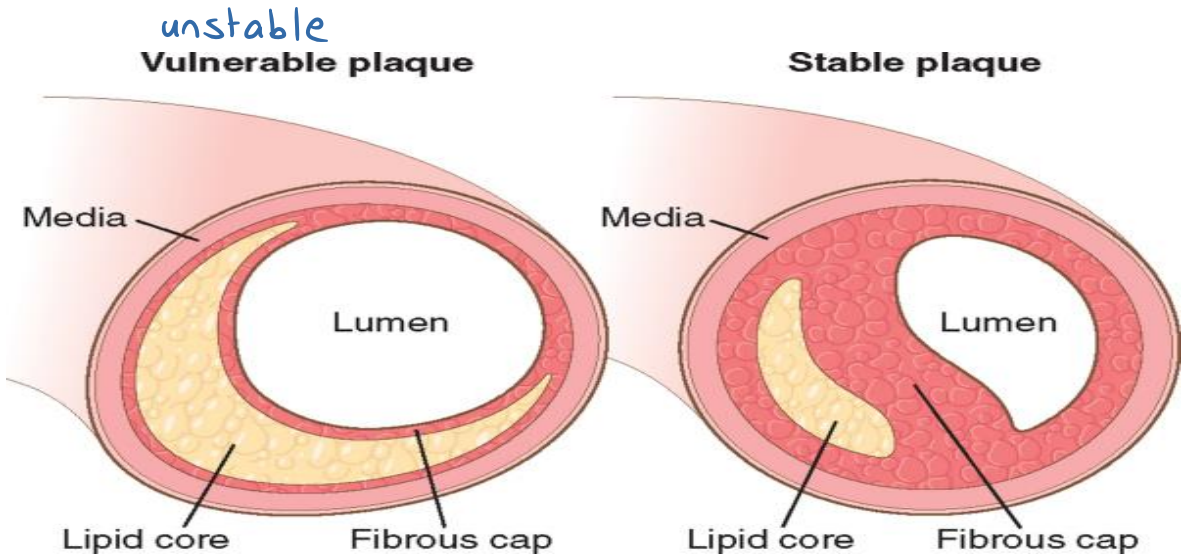
  نزيف

  - **Haemorrhage** into the atheroma, expanding its volume

- The events that trigger abrupt changes in plaque configuration are complex and include:

  - Intrinsic factors (e.g., plaque structure and composition)

  - Extrinsic factors (e.g., blood pressure, platelet reactivity)



3. Thrombosis

- **Thrombosis (partial/total)** associated with a disrupted plaque is critical to the pathogenesis of the acute coronary syndromes.

- **Thrombus superimposed on a disrupted partially stenotic plaque converts it to a total occlusion.**

- **In other coronary syndromes luminal obstruction by thrombosis is usually incomplete and will disappear with time.**

- **Mural thrombus in a coronary artery can also embolize.**

4. Vasoconstriction

تصلب الشرايين

- **Vasoconstriction at sites of atheroma is stimulated by:**

(1) circulating adrenergic agonists

(2) locally released platelet contents

خلل

NO

(3) impaired secretion of endothelial cell relaxing factors (nitric oxide) relative to contracting factors (endothelin) as a result of endothelial cell dysfunction

حول

(4) mediators released from perivascular inflammatory cells.

مشكلة