Pathophysiology-Hyperlipidemia

Faculty of Pharmaceutical Sciences

Dr. Amjaad Zuhier Alrosan, Dr. Abdelrahim Alqudah

Hyperlipidemia

مقدمة

AUD-20250322-WA0027

07:05

primary hyperlipidemia → phenotype
+ secondary hyperlipidemia.
Genetic
Genetic mutation في الـ apoliporoteins تتأدي لـ primary hyperlipidemia

phenotype → بزيد الـ triglyceride لحاله او الكوليسترول لحاله او Both

الدهنيات مابتمشي في الدم لوحدها بدها apolipoproteins عليه (Lipoproteins carrier)
لـ ما بتشتغل لإلا يكونوا عليها

Lipoproteins 5
- Chylomicron
- VLDL
- IDL
- LDL
- HDL

في الـ Small intestine يتم تجميع الـ Glycerol + Fatty acids على شكل triglyceride وفي الأمعاء الدقيقة يتم تصنيع اول Lipoprotein اليكو Chylomicrones هو الوحيد الذي يُصنع في الـ Small intestine والباقي في الـ Liver
بعدين بيجي عندنا الـ Chylomicron بيحلل الـ triglyceride من الـ Small intestine وبروح على الـ Capillary في عنا انزيم اسمه Capillary Lipoprotein Lipase يفرز من الـ Capillary بكسر الـ triglyceride اللي على شكل triglyceride وبتكون نسبة الـ Cholesterol + شوية Free Fatty acids و Glycerol
جزء من الـ Fatty acid بروح على الـ adipose tissue بتخزن وجزء بروح على الـ muscle والجزء المتبقي منها برجع على شكل triglyceride فقلت نسبتها لكن تبقى أعلى من الـ Cholesterol
فبصير اسم الـ lipoprotein ← Chylomicron remnants وبروح على الـ Liver و بيصنع Cholesterol الكبد لكن نسبة triglyceride أعلى من الكوليسترول
هيك بتصنع VLDL ← فيه نسبة triglyceride أعلى من الكوليسترول . وبروح تاني على الـ Blood فيجد الانزيم اللي في الدم بكسر الـ triglyceride لـ Fatty acids
وبتتوزع على الـ muscles والـ adipose tissue والباقي برجع على شكل triglyceride وبتصير نسبة الـ triglyceride قريبة على الـ Cholesterol فبرجع تاني مرة على الـ Liver ويكون اسمه VLDL remnants وفي الكبد في انزيم اسمه hepatic lipoprotein lipase بشتغل انزيم الـ Cappillary وبكسر الـ triglyceride
وبعمل على مناعة الكوليسترول كمان فبتصير كمية الـ Cholesterol مساوية للـ triglyceride والـ Liver بعملو packaging على شكل IDL
وبروح الـ Blood وبتكسر الدهون الثلاثية بنفس الوتيرة و بتصير نسبة الـ Cholesterol أعلى وهلا LDL بعمل Liver packaging على شكل LDL
الـ density

Cholesterol لـ triglyceride من أعلى

hyperlipidemia: زيادة بال triglycerides او ال cholesterol او الاثنين مع بعض وهون يجي عنا مبدأ ال phenotype

الـ cholesterol عبارة عن HDL + LDL

في اشي اسمه receptor endocytosis واحد من ال examples عليها

LDL receptor عبارة عن lipoprotein بيساعد على نقل ال cholesterol لداخل الخلية لأنه هاد

الـ LDL برتبط على الـ receptor LDL. واذا كان عند نا مشكلة بال receptor وما رح يرتبط ال LDL

ب LDL receptor ويدخل ال cholesterol على الخلايا.

او في نفس ال LDL

ناقلات للسيد عليها protien برتبط بال receptor أو ب enzyme بشتغل عليها

الـ Lipids والدهنيات بدهم ناقلات لأنهم hydrophopic اسماء الناقلات lipoprotiens بنقسموا لـ 5 اقسام هم

الـ Chylomicrons و VLDL و IDL و LDL و HDL.

الاختلاف بيناتهم بكون بين كمية الـ triglycerides و الـ Cholesterol اللي بتحملهم

الـ Lipids بدها ناقلات تنقلها عبر الدم تكون hydrophilic اسم الناقلات lipoprotiens.

ولما ناكل Fatty acide بروح على الـsmall intestine وبتجمع مع ال glycerol وبصير triglycerides

ومين بحمله ← اول Lipoprotien بتم تصنيعه هو ال chylomicrons لكن بشيل جزء

من ال cholesterol لكن ال triglycerides بكون أكثر وبروح الـ chylomicron على الدم

الـ lipoprotein الذي يتم تصنيعه الوحيد في الـsmall intestine هو ال chylomicron عادا ذلك يتم

تصنيعه بالكبد (Liver). ويروح الـ chylomicron على الـ Blood ويوجد هناك capillary lipoprotein lipase

و بحلل ال triglycerides وبتحلل لـ fatty acid جزء منها بروح لـ muscle والثاني بروح

لـ adipose tissue فبتقل نسبة الـ triglyceride لكن بضلها أعلى من نسبة ال cholesterol و بسميناه

chylomicron remenant.

الـ apo lipoprotein الموجود على سطح الـ chylomicron هو ال apo CII وبدونه ما بشتغل

الـchylomicrone هو اللي برتبط مع ال capillary lipoprotein lipase عشان يقدر الـ lipase يفوت جوه

الـ chylomicrone ويكسر ال tryglyceride.

capillary lipoprotein lipase

الناس لي عندهم مشكلة ب الانزيم أو ال apolipoprotein بكون عندهم الـ type I من الـ

hyperlipidemia phenotype هدول الناس بتكون نسبة ال chylomicron عالية فاسم المرض هو 1

hyperchylomicronemia انه عندهم ارتفاع ب chylomicron فيعني انه عندهم ارتفاع بالـ tryglycerides

وهنا هو الـ phenotype 1 وهو لا بزيد من الـ risk لل athero sclerosis ✓ ← hyper tryglycerimia

زيادة بالـ chylomicron فقط لحاله لا يرتبط بال arteriosclerosis لانه ال apolipoprotein ما الها علاقة ب تصلب الشرايين

ولبعد ما يخلص الـ chylomicrone من ال Blood بصير اسمه chylomicron remnant وبروح بعدين إلى Liver

وفيه انزيم اسمه hepatic lipoprotein lipase و VLDL يحتوي على apo CII وبعده يرجع الـ VLDL على الدم

ويرتبط مع capillary lipoprotein lipase عشان يحلل ال tryglycerides الموجود جواته. + يحتوي على apo E + apo B100

اذا كان عندنا over expression بالـ LDL receptor أو apo B100 هذا يعني نسبة الـ LDL في الدم بتكون أكبر نفسه موجود وهاد على ال LDL

وبالتالي كمية الـ cholesterol أكبر والـ risk بكون عالي لتصلب الشرايين لأن الـ LDL والـ cholesterol بحمل الكثير من الـ cholesterol ← الـ tryglycerides

بتركز والدم بعد ما تأخذ الـ cells حاجتها الزيادة برجع للدم.

وبعض الأشخاص عندهم مشكلة بالـ LDL receptor وفي ناس عندها نفس الكمية الطبيعية من الـ LDL ما عندها أي functional LDL receptor

وهون بيجي الـ phenotype 2 وبكون اسمه familial hypercholesterolemia الـ Two sections: الأول 2 a IIa ← هدول بزيد عندهم الـ LDL

بزيد عندهم ال arteriosclerosis

والثاني 2 II b ← بزيد عندهم VLDL و LDL ← عليه apolipoproteine اسمه apo B100

بزيد ال risk من تصلب الشرايين ← apo C2, apo B100

مثل الـ LDL بسبب وجود receptor خاص فيه لحتى يدخل الخلية

apo E ← بوجد على الـ VLDL

وفئة الشباب اذا صار عندهم حالة بكون بالأول صار عندهم تصلب بالشرايين وبكون اسمه عندهم premature arteriosclerosis ← قبل وقته الاصلي

وقته الطبيعي هو يصير عند الرجال أكبر من 45
والنساء أكبر من 50 سنة .

وجود و اسبب The premature arteriosclerosis هو الـ apoE الموجود على الـ VLDL ← فبزيد من الـ risk من تصلب الشرايين قبل وقته

بسبب الـ apoE و تصلب الشرايين العادي لأنه عليه apo100 عندنا الـ VLDL يروح على الدم بتحبث له عملية Degradation الـ triglycerides منتقل نسبة
الـ triglycerides بس بتضل أعلى شوي من الـ cholesterol وبرجع الـ Liver * يتم تصنيع الـ Cholesterol في الكبد

في الكبد يوجد Hepatic lipoprotein lipase وبرجع على شكل triglycerides = VLDL remnants
Aseel Sukkarieh

وبرجع للدم تبكس الـ ILDL ← بصير اسه

الدهون الثلاثية فبقيس نسبة الـ cholesterol عالية مقارنة بالدهون الثلاثية ودون اسمه بصير LDL

Liver → Blood الـ الكوليسترول بنقل
Bad Cholesterol
بجرين المخزون يوزعوا على الـ cells اذا الـ cells مش محتاجته اومشكلة

Lipid accumulation بصير عنا Blood بالـ receptor برجع بتجمع بالـ
في الدم وبصير تصلب الشرايين

والـ HDL بنقل الكوليسترول للكبد والكبد بضيف عليه ester group فبا بتخزن على شكل
esterified cholesterol عن طريق free cholesterol ← لأنه toxic على الجسم اذا زاد وصيانة بتحول
مساعدة الـ HDL عليه apo AI اسمه apolipoprotein هو اللي بترتبط مع الانزيم اللي بده يحول
الـ Cholesterol لـ cholesterol ester وبتخزن بالكبد على هذا الشكل واسم الانزيم اللي حولته LCAT

* HDL ← apo AI عشان يترتبط مع الانزيم LCAT و يحط الكوليسترول الكوليسترول استر

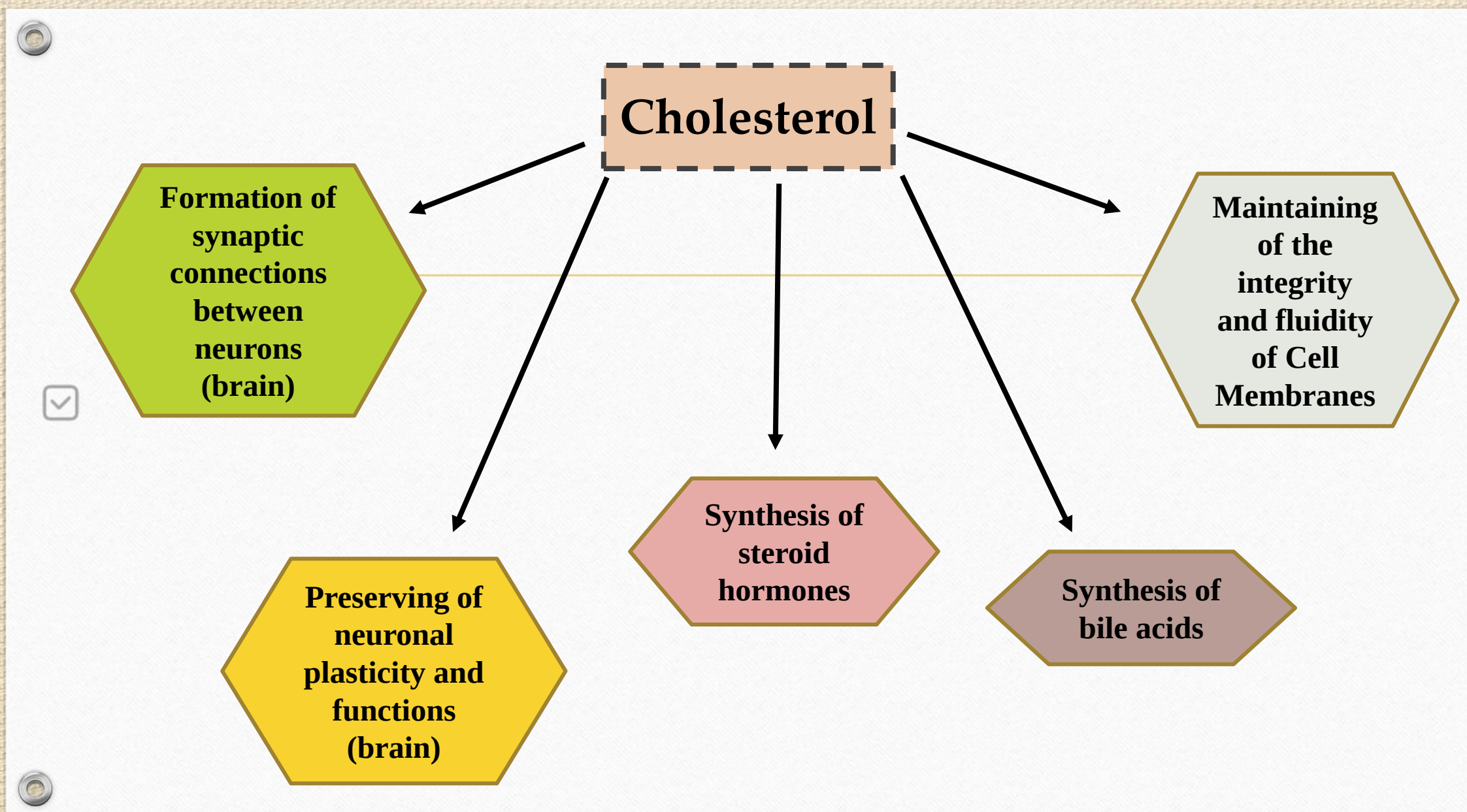
apoCII , apoE , apo100 VLDL*

apo100 LDL*

Introduction

- **Cholesterol is essential** for cell membrane formation & 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
Synthesis of steroid hormones
Preserving of neuronal plasticity and functions (brain)
Synthesis of bile acids

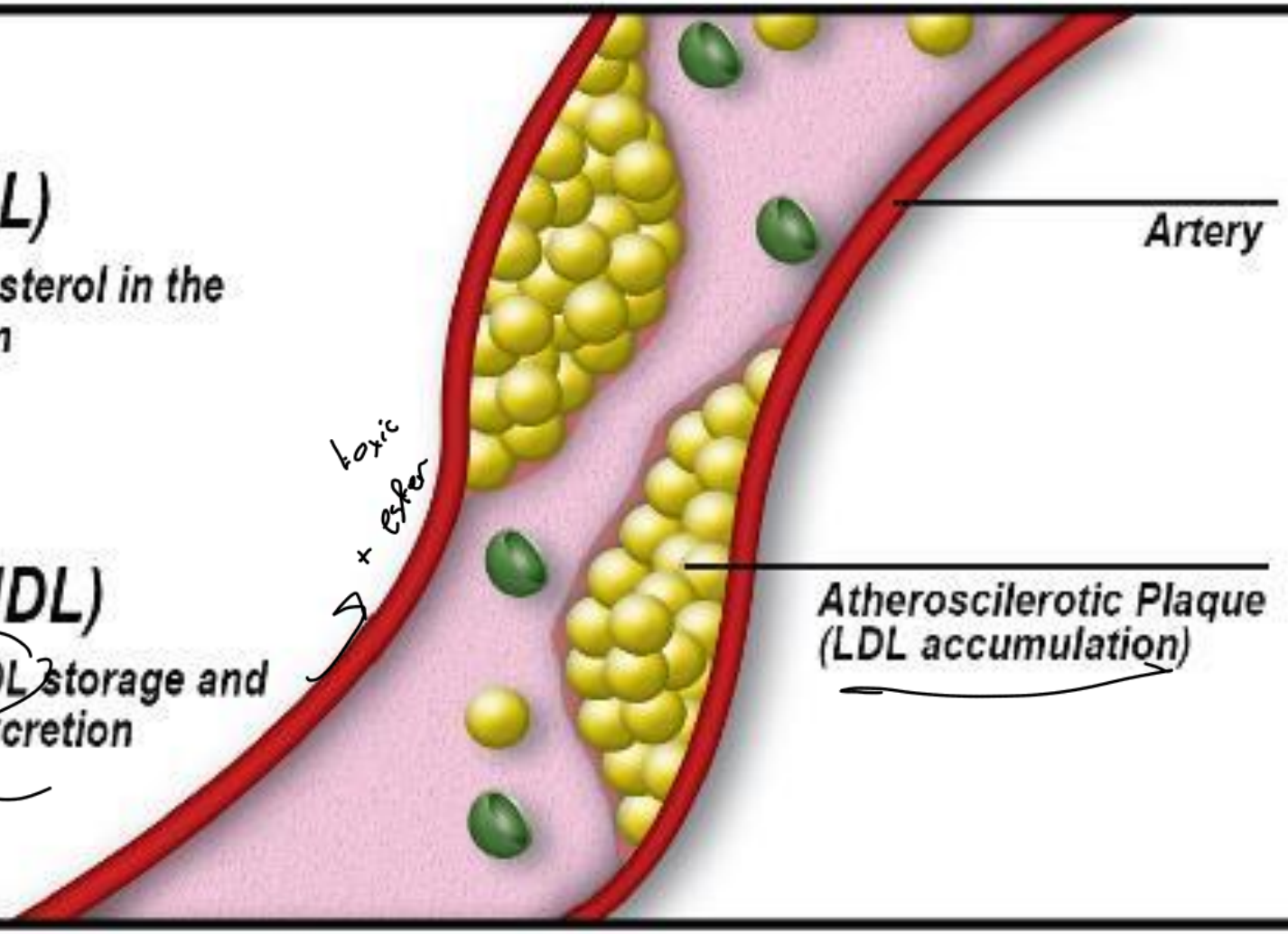
Bad vs. Good Cholesterol

Bad (LDL)

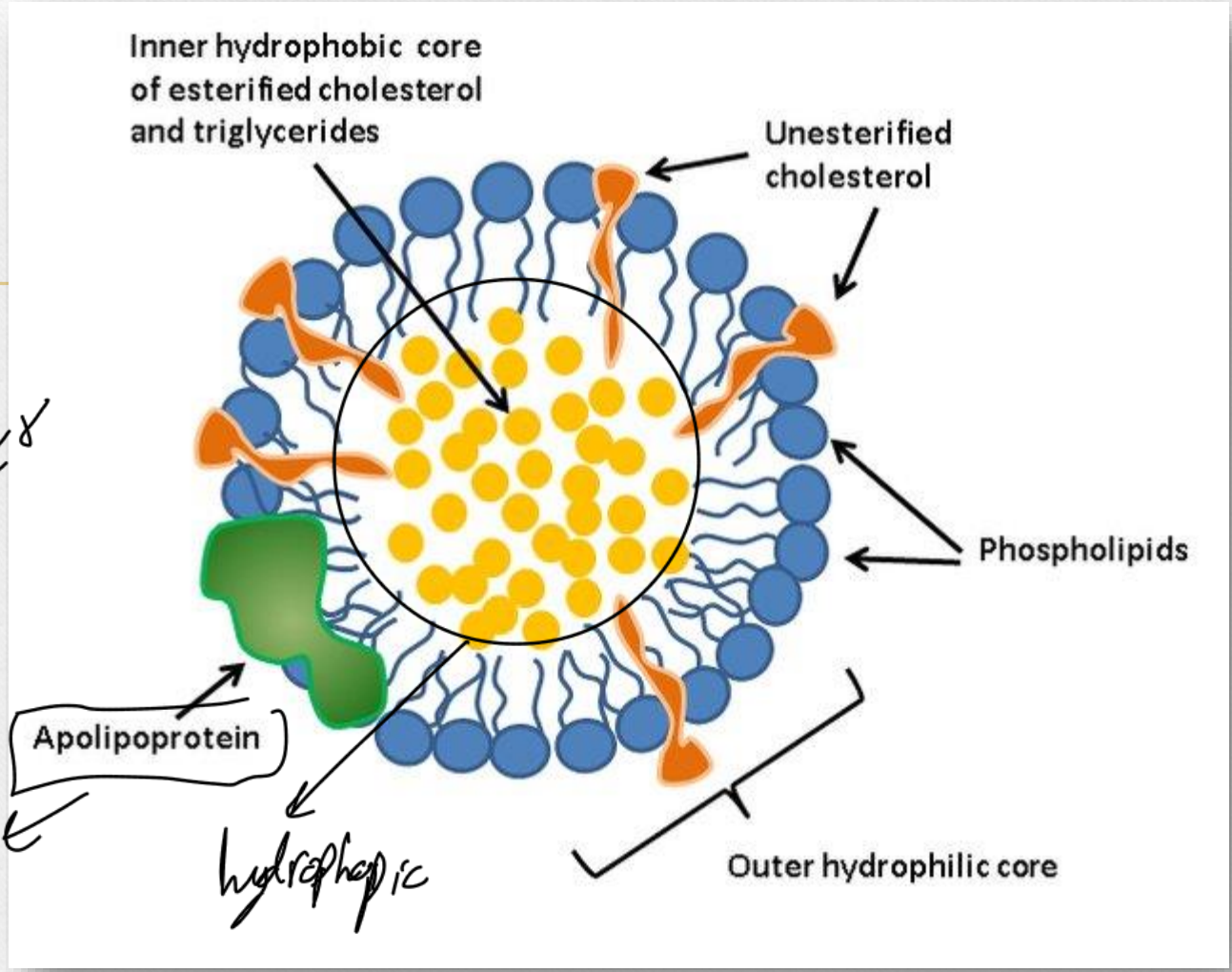
stores cholesterol in the blood stream

Good (HDL)

regulates LDL storage and promotes excretion



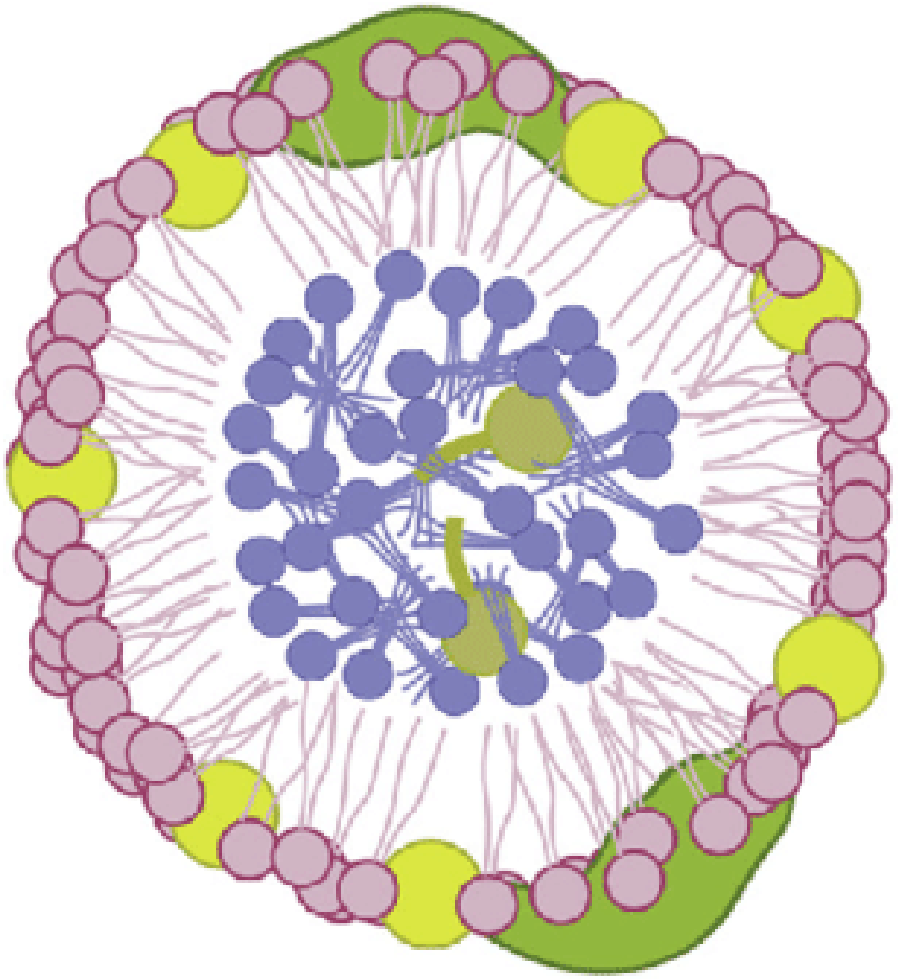
- **Lipoproteins:** spherical macromolecular complexes with **SURFACES** that consist largely of "phospholipid, free cholesterol, and apolipoprotein" and **CORES** composed mostly of "triglyceride and cholesterol ester".
- **Function:** To keep the **lipid-soluble** for *transporting* them between organs and also 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

Hyperlipidemia

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



Lipoprotein

Apolipoproteins

triglycerides +
cholesterol ester

phospholipid

terol

Chylomicrons

VLDL

IDL

LDL

HDL

0,85

0,9

0,95

1,0

1,05

1,1

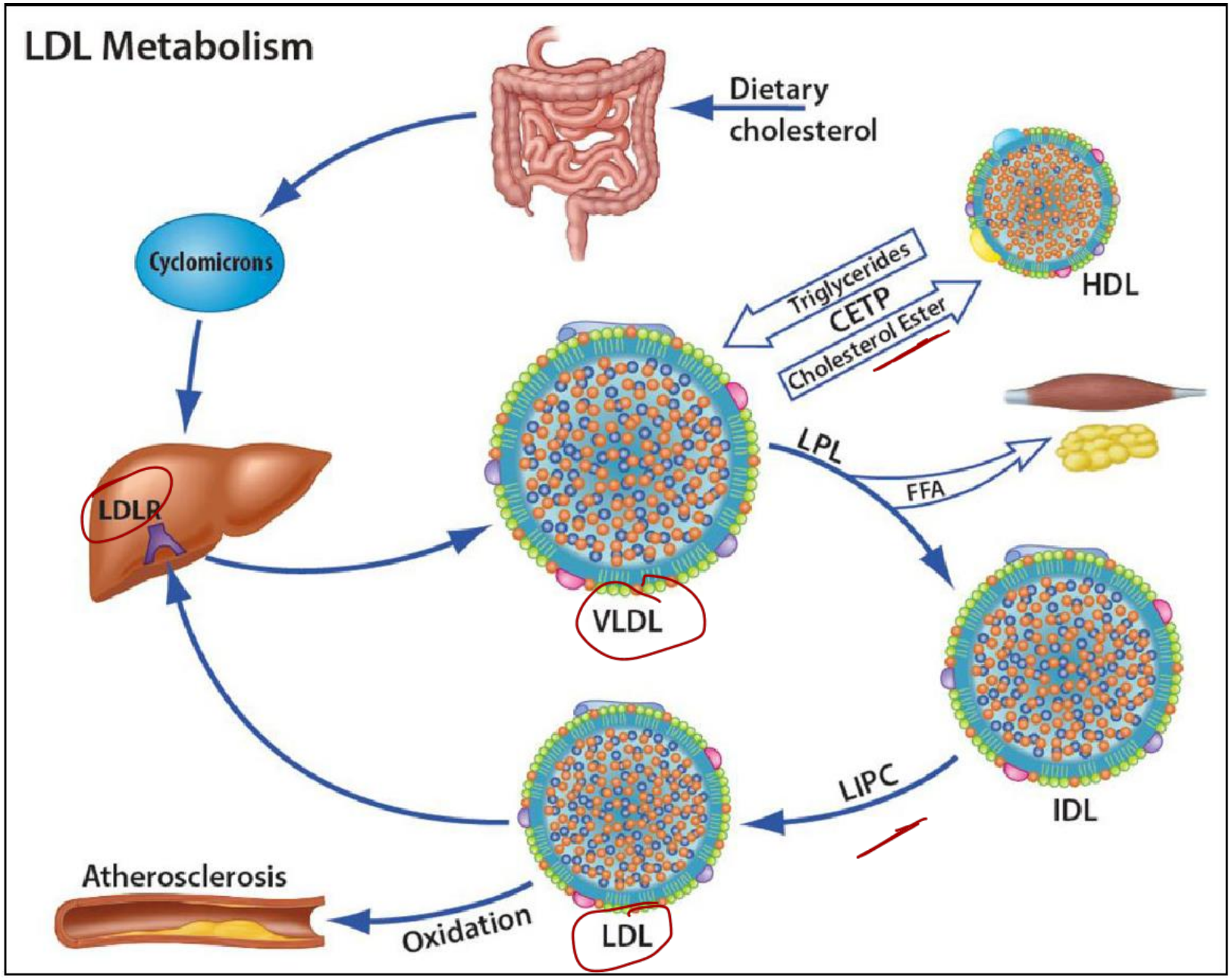
density (g/ml)

10

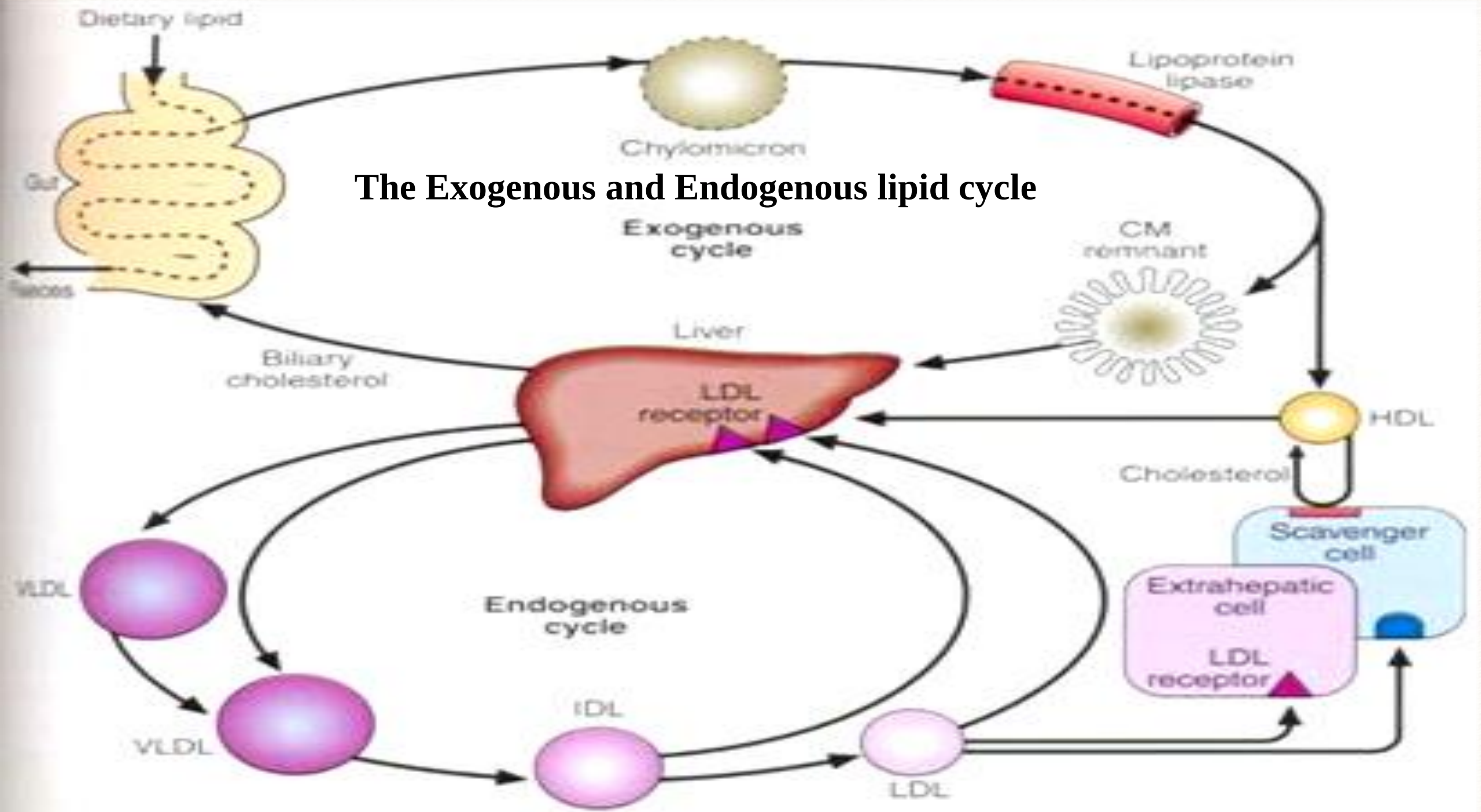
50

500

diameter (nm)


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

The Exogenous and Endogenous lipid cycle



1. Chylomicrons:

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

---

2. VLDL (very low-density lipoproteins):

- 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

4. LDL (low-density lipoprotein):

- 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.

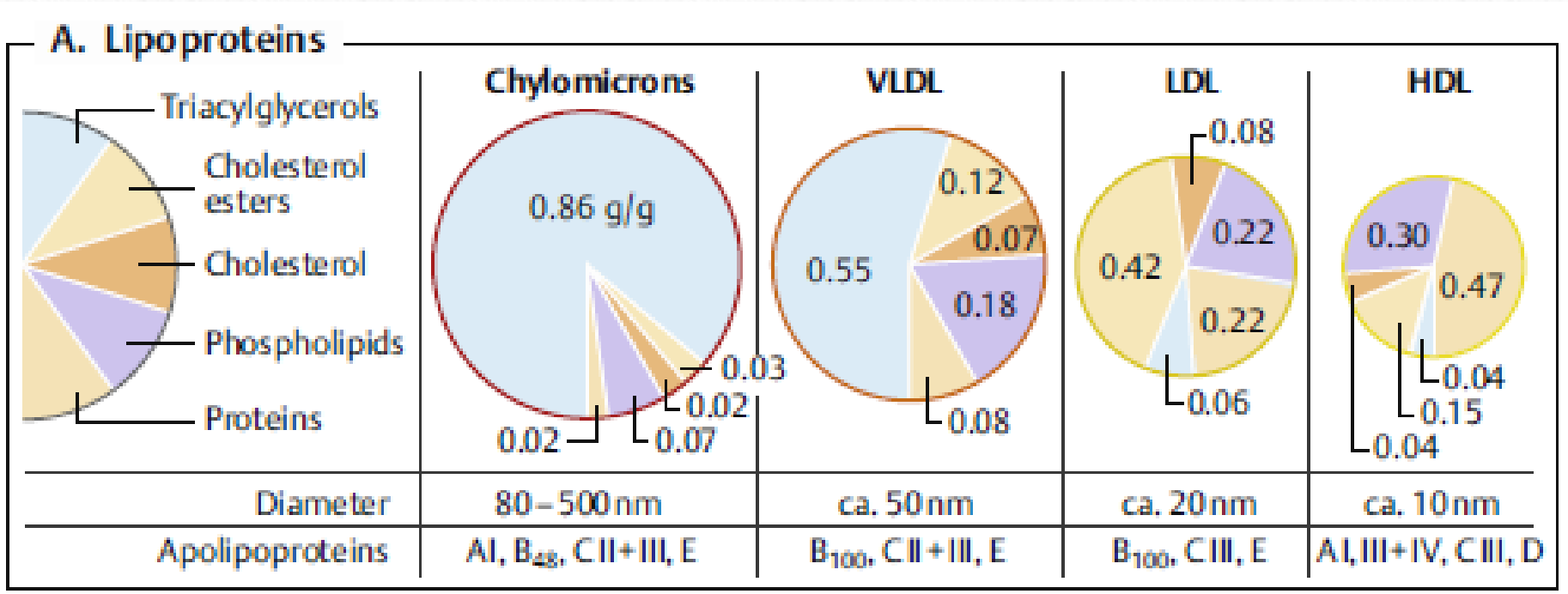
5. HDL (high-density lipoprotein):

- 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.

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

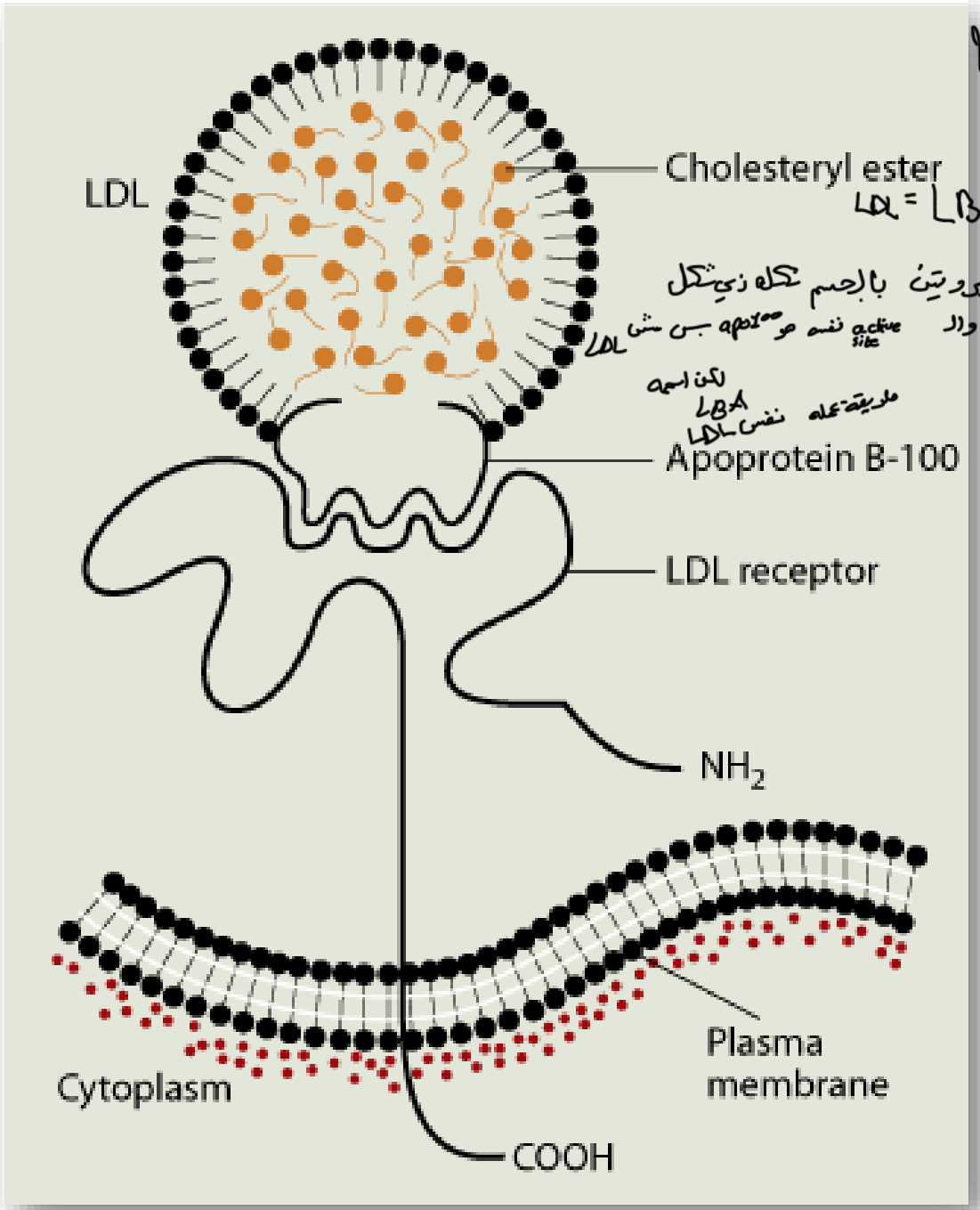
- **These proteins have three functions:**
  - Provide structure to the lipoprotein, activate enzyme systems, bind with cell receptors.
- **The five most clinically relevant apolipoproteins are A-I, A-II, B-100, C, and E:**
  - **Apo B and E** proteins are ligands for LDL receptors:
    - **The blood 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 C-II** is a cofactor for lipoprotein lipase, which releases fatty acids and glycerol from chylomicrons, VLDL and IDL.
- **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).
- **Apo A-I** protein activates LCAT (lecithin-cholesterol acyltransferase), which catalyzes the esterification of free cholesterol in HDL particles.
  - 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.

	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
- 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 cholesterol levels inhibits HMG-CoA reductase & decreases LDL receptor synthesis.



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.

Etiology

- **There are two major ways in which dyslipidemia are classified:**

---

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

- **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

- **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)

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

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

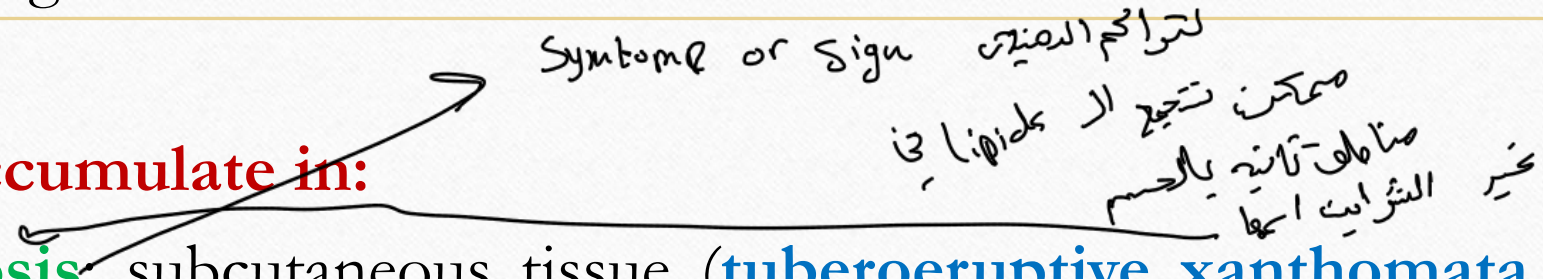
Frederickson	Classification	Lipid Profile
Type		
I	Familial lipoprotein lipase deficiency (hyperchylomicronemia, hypertriglyceridemia)	TG++, C normal, CM++, HDL–/normal
IIa	Familial hypercholesterolemia	TG normal, C+, LDL+
IIb	Familial combined hyperlipidemia	TG+, C+, LDL+, VLDL+
III	Familial dysbetalipidemia (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:**

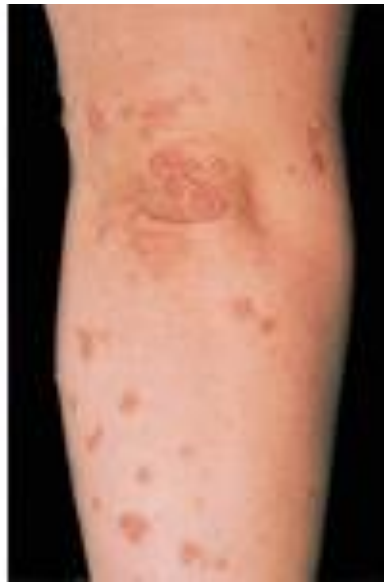
a. **Xanthomatosis**: subcutaneous tissue (**tuberoeruptive xanthomata** (over knees and elbows- **type III hyperlipidemia**)-triglyceride), tendons (**tendon xanthomas**-familial hypercholesterolemia- **type II hyperlipidemia**), palm (**palmar xanthomata-type III hyperlipidemia**), the cornea (**corneal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

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

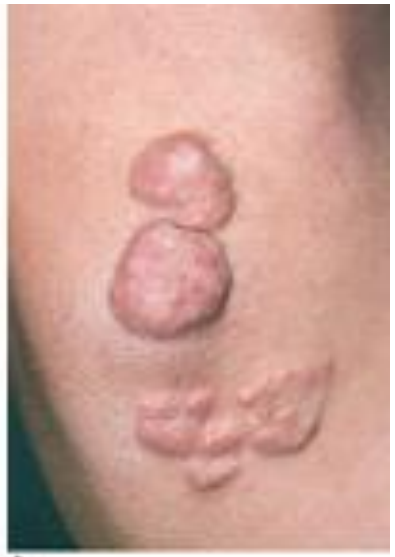
Xanthomas

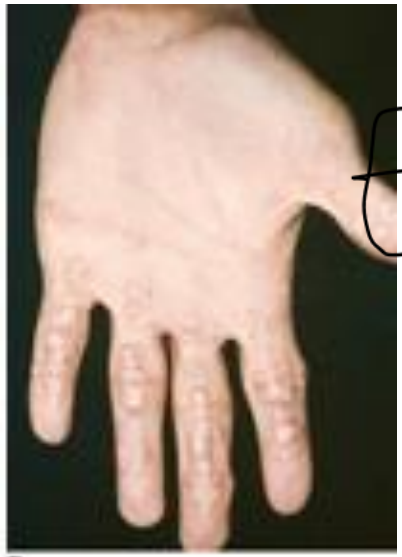
- **Xanthomas are plaques or nodules consisting of abnormal lipid deposition and foam cells. They do not represent a disease but rather are symptoms of different lipoprotein disorders or arise without an underlying metabolic effect.**
- **Clinically, xanthomas can be classified as:**
  - **Eruptive,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

- There are characteristic clinical phenotypes associated with specific metabolic defects.

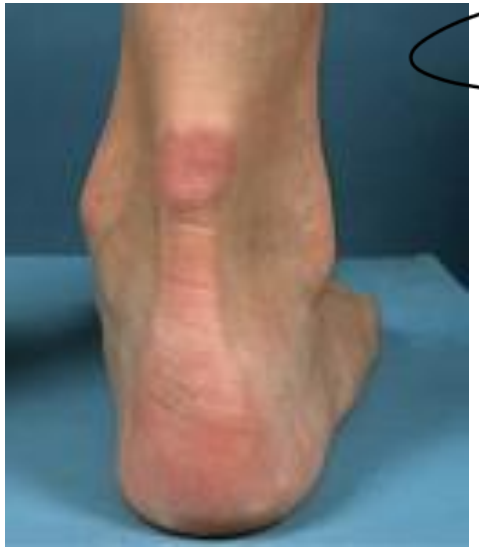


Eruptive skin xanthomata characteristic of severe chylomicronemia.

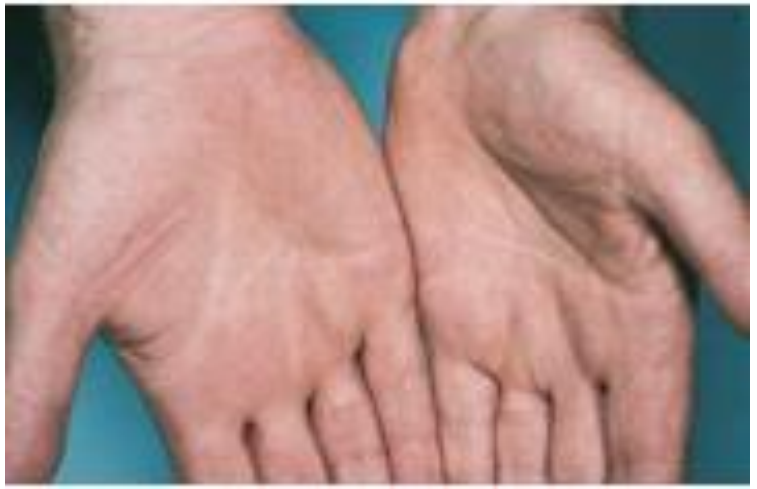




Tuberoeruptive and tuberous xanthomata typical of familial dysbetalipoproteinemia.
A. Knee B. Palm.



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



Xanthoma striatum palmare characteristic of familial dysbetalipoproteinemia.

phenotype 2 بزيد

عند الناس obese والـ pregnant او الناس اللي عندهم Diabetes او الـ uric acid عالي

5 الانسولين بزيد عند الناس obese واللي عندهم سكري بحب pregnant

واللي عندهم ارتفاع باليوريك اسيد و

او الناس اللي بتشرب بحول

Dominant trait	Recessive trait
النوع الثاني بزيد فيه LDL	apoE مشكلة الـ بهي جينات حتى يظهر
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.	4. The presence of another similar allele is required to produce its phenotype.

27

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**.

Familial hypercholesterolemia

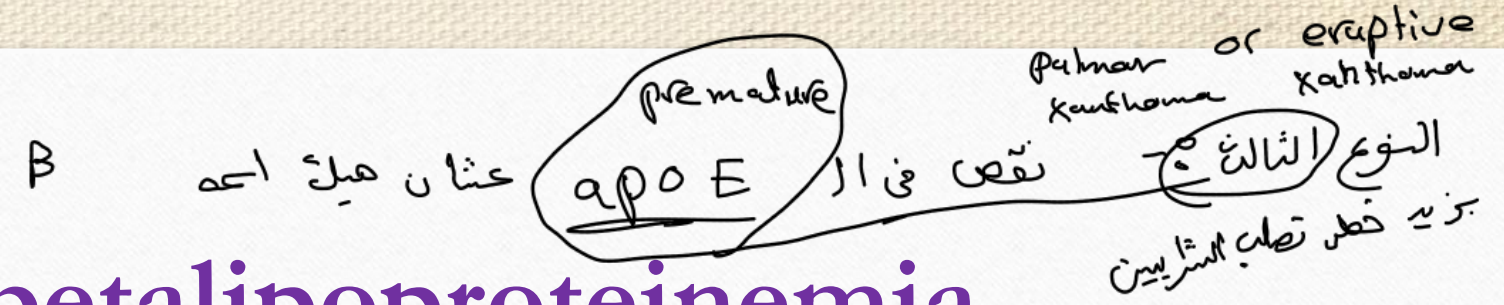
النوع الثاني هو مايكون عندهم LDL receptor اي

- **Characterized by:**
  a. Selective elevation in the plasma level of LDL.
  b. Deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas).
  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.



Dysbetalipoproteinemia

- **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);
  - **Tuberous or tuberoeruptive xanthomas** (bulbous cutaneous xanthomas);
  - **Severe atherosclerosis** involving the coronary arteries, internal carotids, and abdominal aorta.

ApoE has a very high affinity for the LDL receptor, actually much superior to that of apoB 100; hence, apoE in VLDL and LDL may influence the plasma concentration and metabolic destination of these lipoproteins, with potential implications for atherogenesis and the occurrence of cardiovascular disease (CVD).

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).

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

Premature AS (PreAS) has been referred to by various names, but it is typically defined as atherosclerotic associated pathology diagnosed before the age of 50 to 55 years and accounts for approximately 10% of patients with AS symptoms.

Premature AS (PreAS) has been referred to by various names, but it is typically defined as atherosclerotic associated pathology diagnosed before the age of 50 to 55 years and accounts for approximately 10% of patients with AS symptoms.

Familial combined hyperlipidemia

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

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

Type IV hyperlipoproteinemia

- Two genetic patterns:
  - **Familial hypertriglyceridemia**, which does not carry a great risk for premature CVD,
  - **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.

Lipoprotein Abnormalities: 2° Causes

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

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

Hypertriglyceridemia

- Obesity.
- DM.
- Lipodystrophy.
- Glycogen storage disease.
- Ileal bypass surgery.
- Sepsis.
- Pregnancy.
- Acute hepatitis.
- Systemic lupus erythematous.

Medications

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

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

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

Total cholesterol	
<200	Desirable
200–239	Borderline high
240	High high risk
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]

حسبي قديه الله برحنا

[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

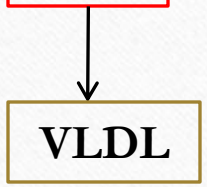
[a]Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL cannot be achieved by **therapeutic lifestyle changes (TLC).** Others prefer to use drugs that primarily modify triglycerides and high-density lipoprotein, e.g., nicotinic acid or fibrates. Clinical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

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.

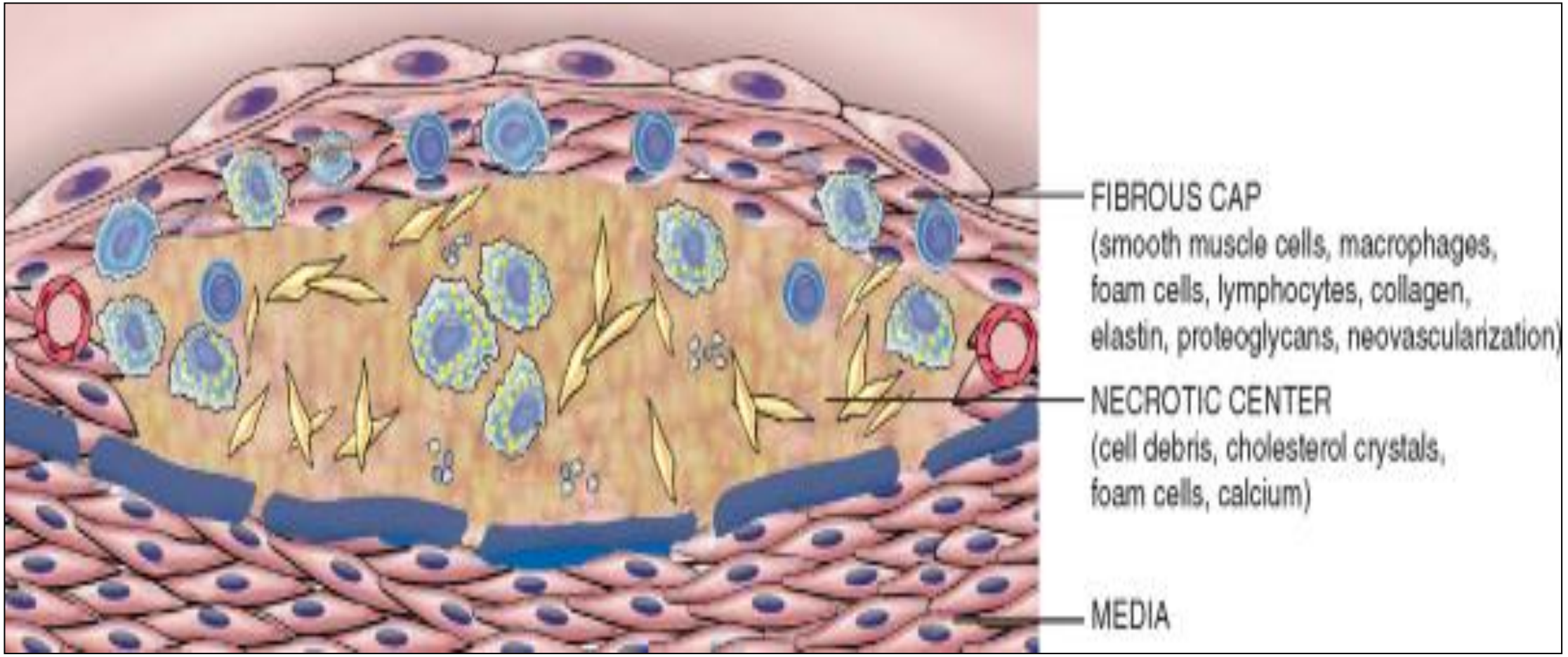
2. **Mönckeberg medial sclerosis**, is characterized by calcific deposits in muscular arteries in persons typically older than age 50.

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

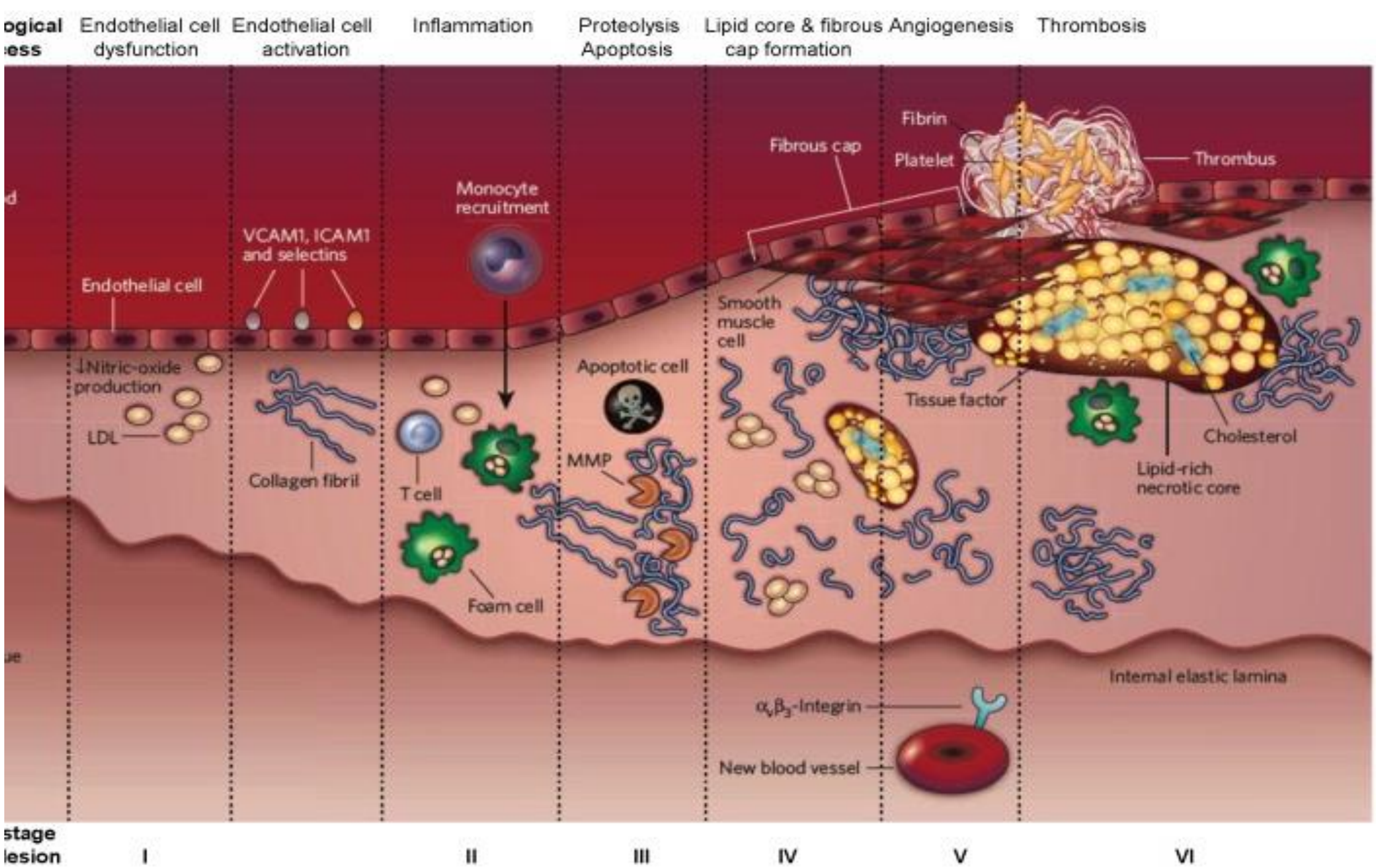
- **Atherosclerosis** is characterized by intimal lesions called *atheromas* (also called *atheromatous* or *atherosclerotic plaques*) that protrude into vessel lumens.

- 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.

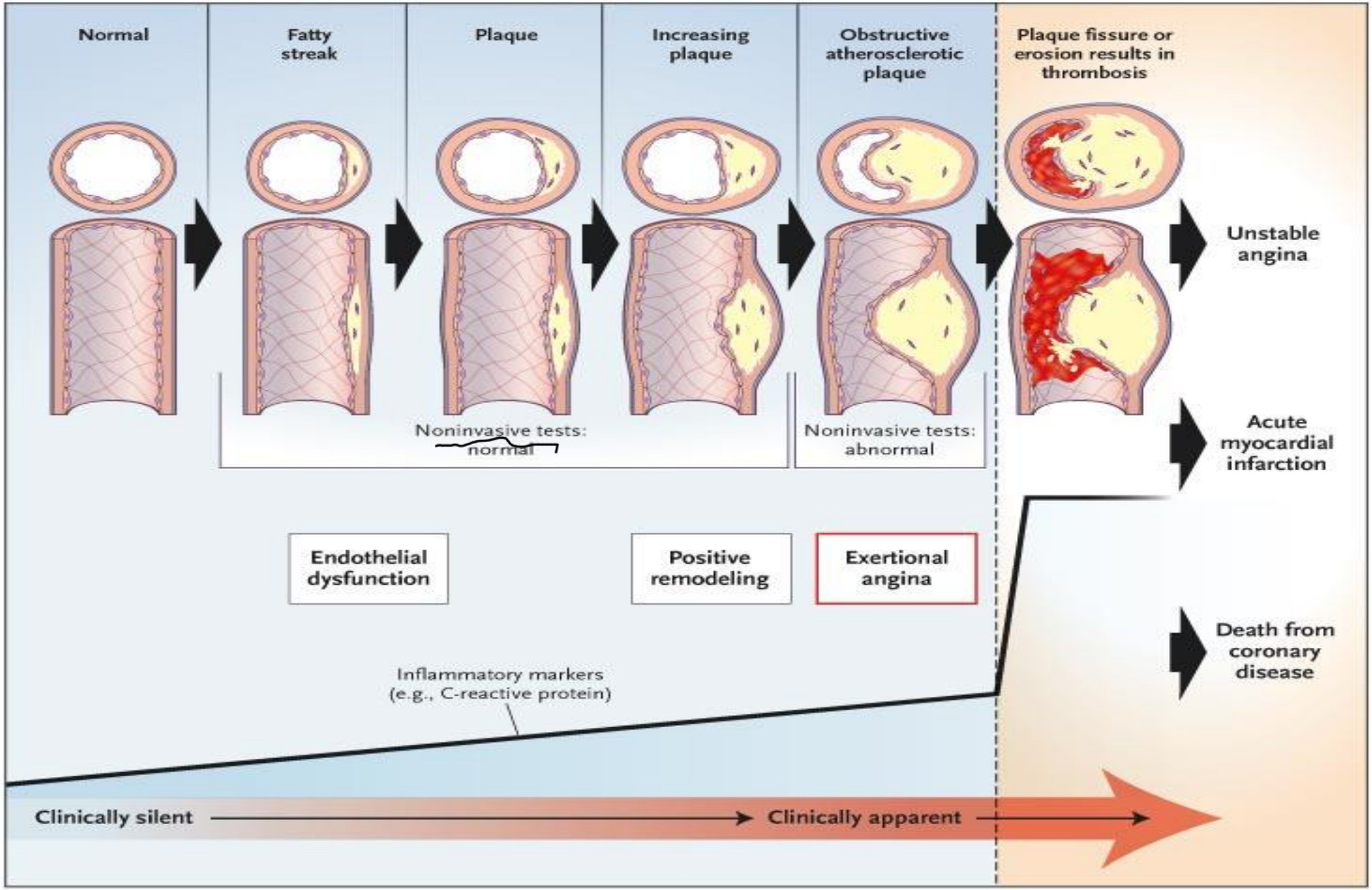


The major components of a well-developed intimal atheromatous plaque overlying an intact media.


ogical
ess
Endothelial cell dysfunction
Endothelial cell activation
Inflammation
Proteolysis Apoptosis
Lipid core & fibrous cap formation
Angiogenesis
Thrombosis
Fibrin
Platelet
Thrombus
Fibrous cap
Monocyte recruitment
VCAM1, ICAM1 and selectins
Endothelial cell
Smooth muscle cell
↓Nitric-oxide production
LDL
Collagen fibril
T cell
Foam cell
Apoptotic cell
MMP
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

Due to endothelial dysfunction,

- **LDL particles migrate** from the blood and accumulate in the arterial intima, forming pro-inflammatory particles.
- This results in the **activation of endothelial cells**, which secrete **adhesion molecules.**
- **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.**


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

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

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

- Age
- Gender
- Genetics

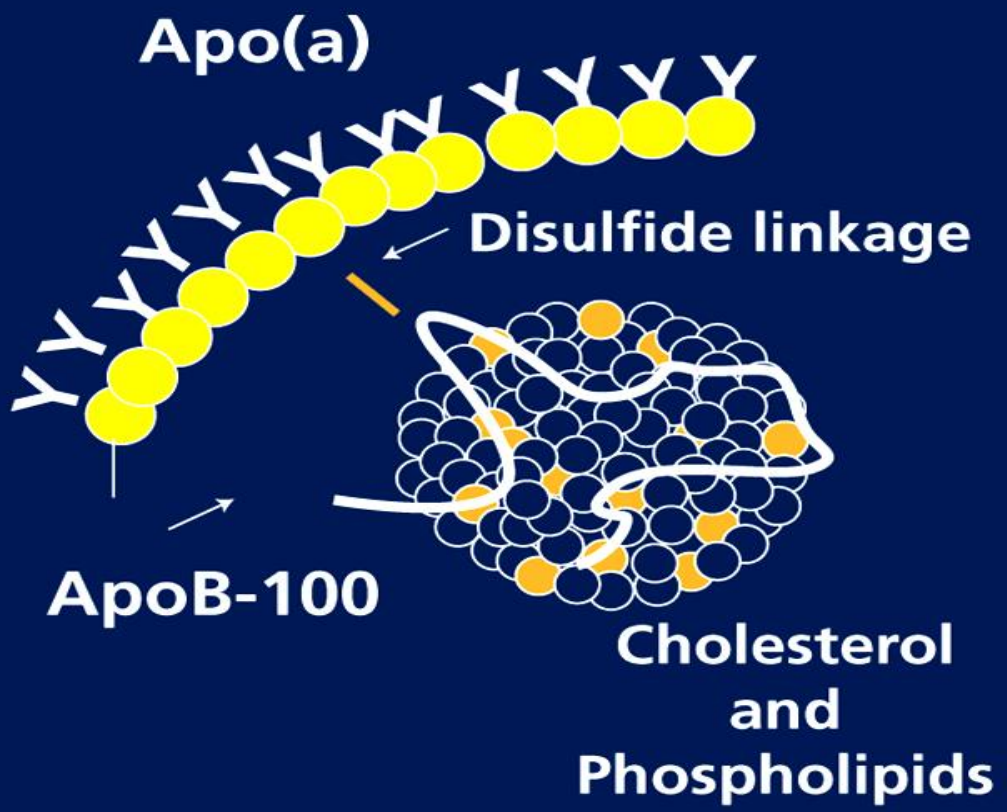
II. Acquired (Modifiable) risk factors in IHD:

- 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
- 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.*

arteries
higher risk
انواع ال

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.

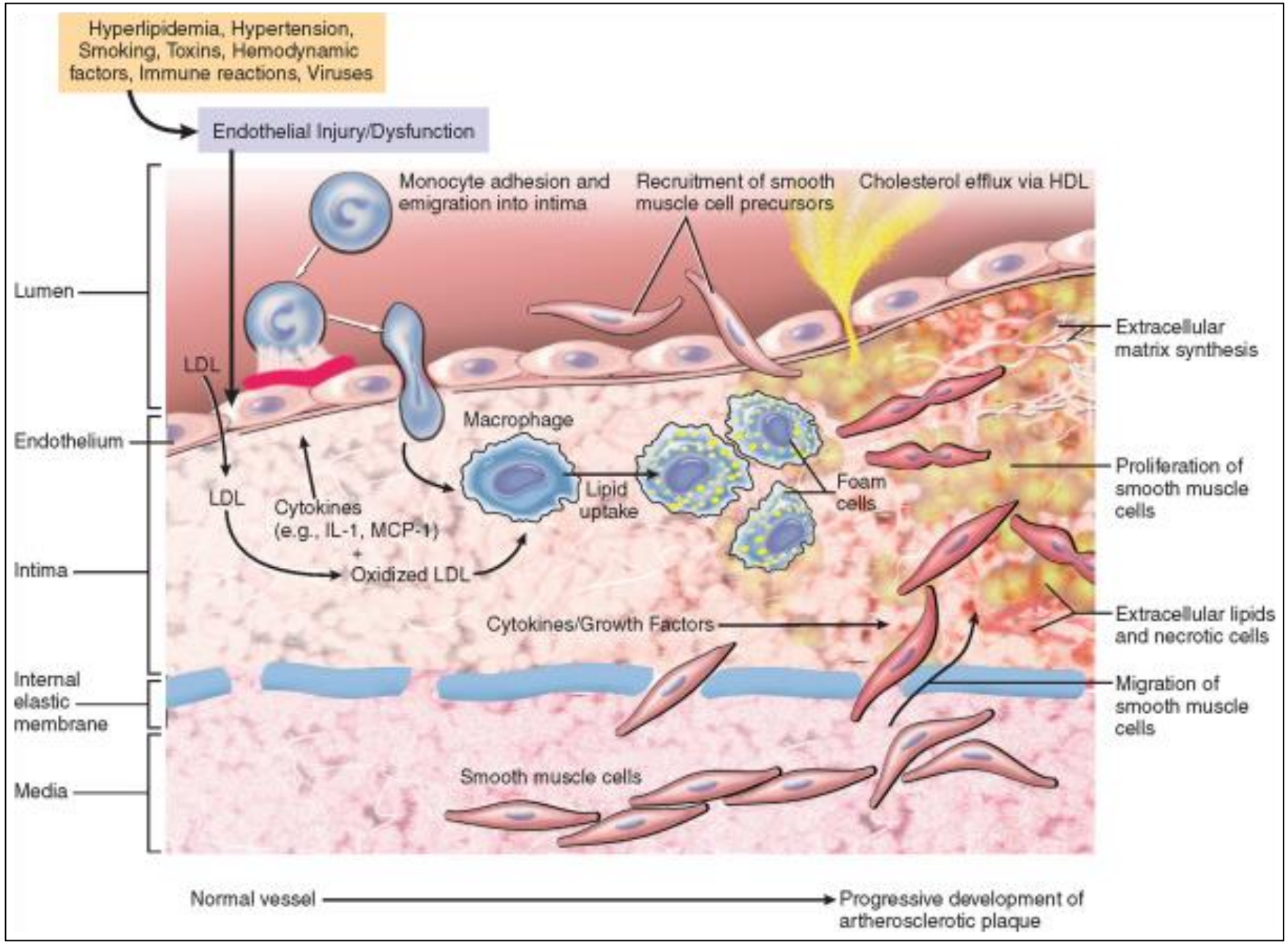
- **Monocyte adhesion to the endothelium**, followed by migration into the intima and transformation into macrophages and foam cells.

- **Platelet adhesion.**

- **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).

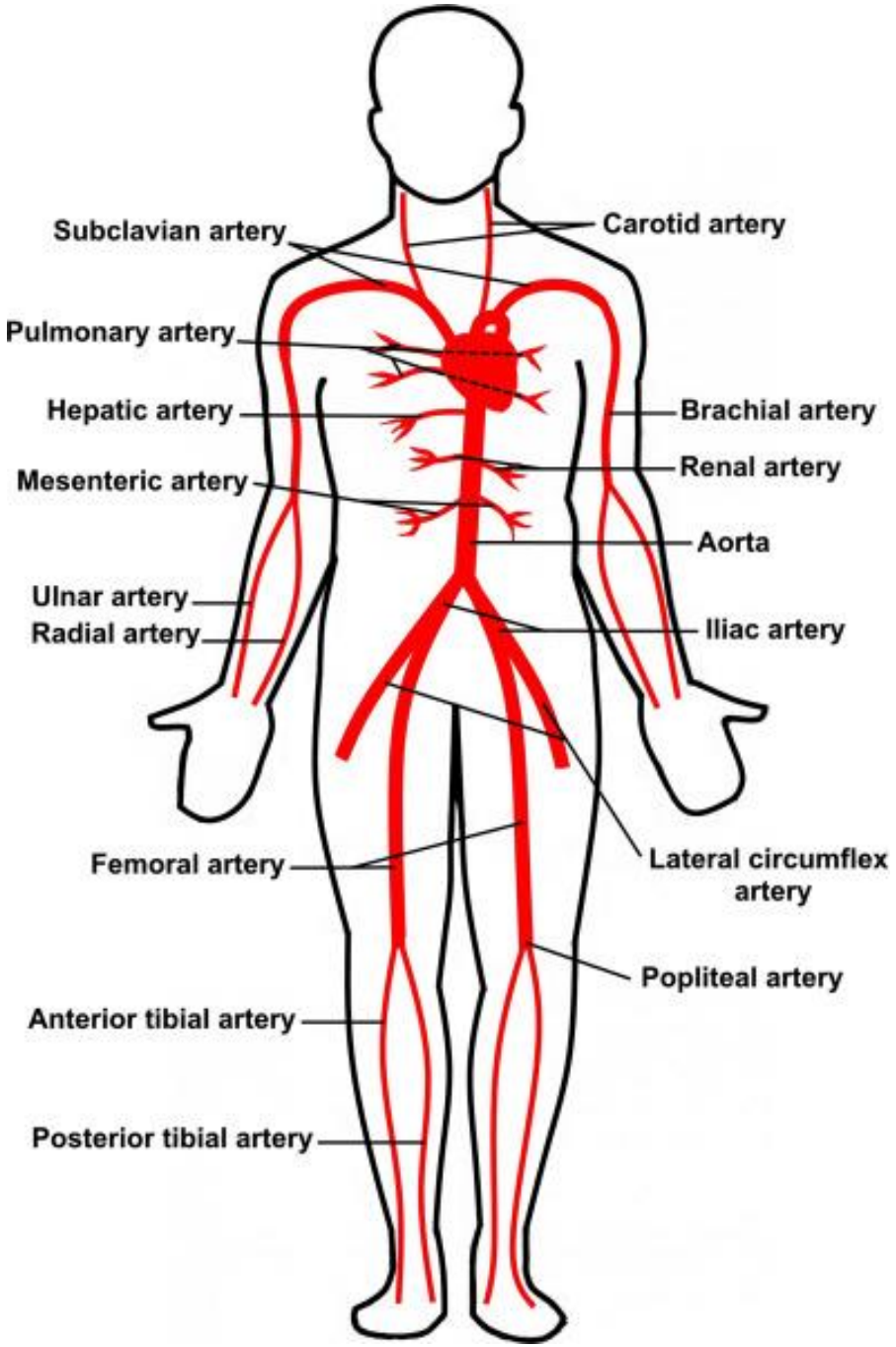

Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Recruitment of smooth muscle cell precursors
Cholesterol efflux via HDL
Lumen
Endothelium
Intima
Internal elastic membrane
Media
LDL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

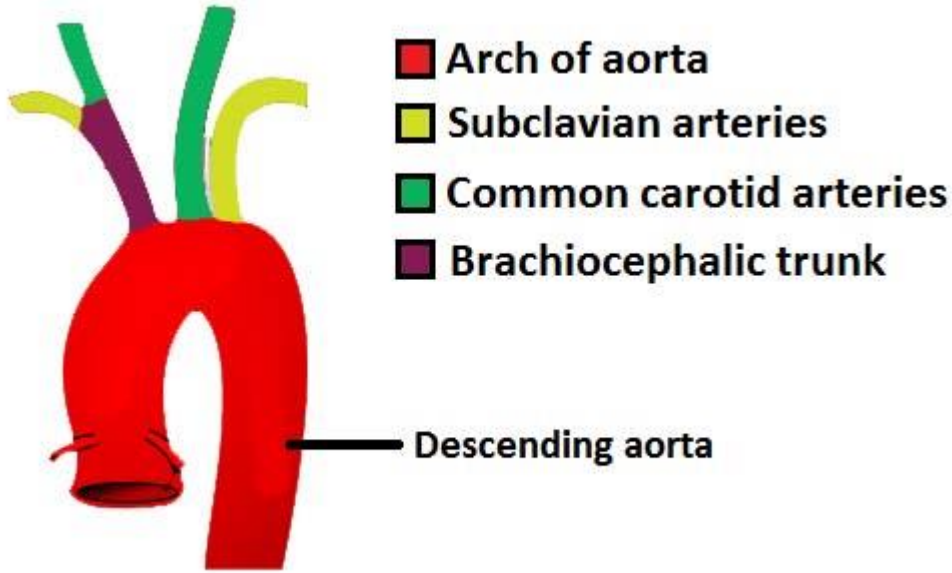
Consequences of Atherosclerosis

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

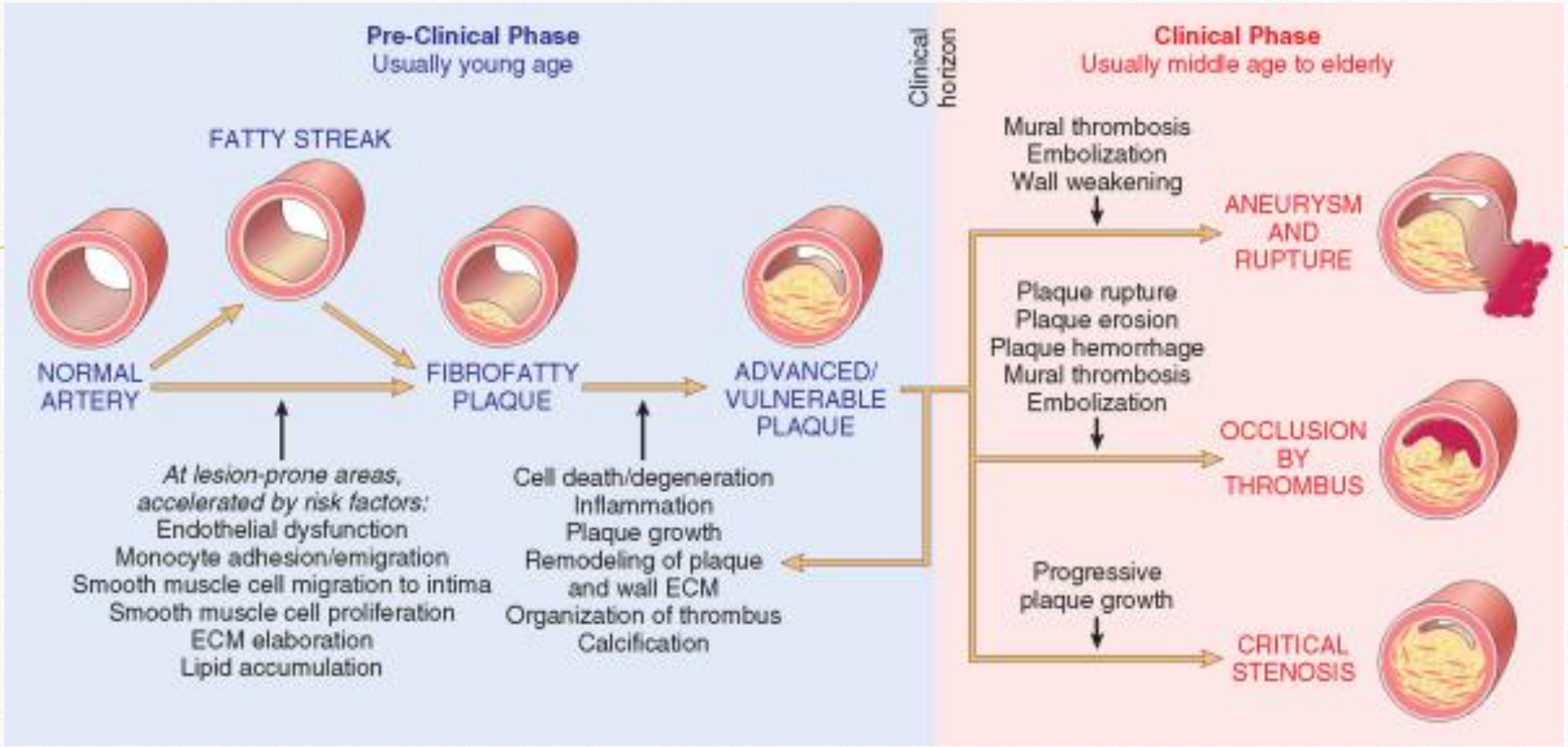
- Heart attack, stroke, aneurysm, and gangrene in the legs are potential consequences of the disease.

- 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.


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).**

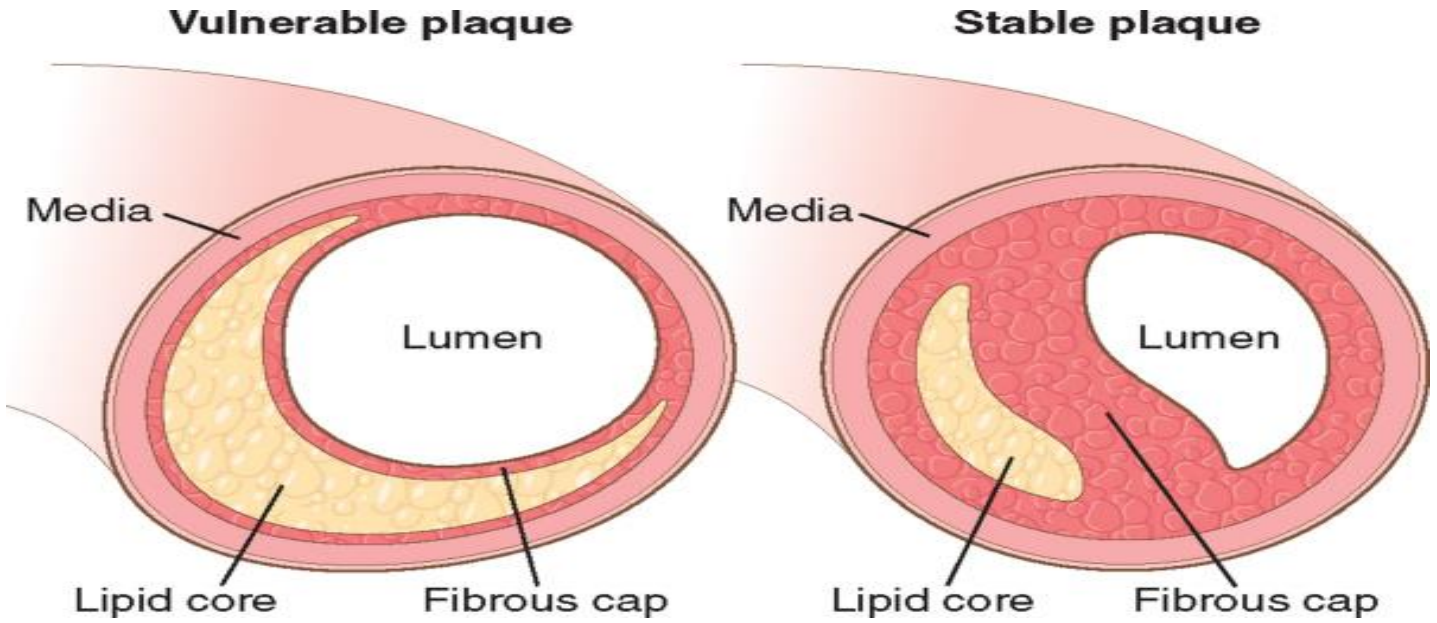
- **Plaque changes fall into three general categories:**

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

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

  - **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

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

(1) circulating adrenergic agonists

(2) locally released platelet contents

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

(4) mediators released from perivascular inflammatory cells.

Thank You