



Pathophysiology-Hyperlipidemia
Faculty of Pharmaceutical Sciences

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* **cholesterol** normally good for the body

- Function:-

- ① Maintains integrity of the cell membrane
- ② Helps conduct the A.P (synaptic connection)
- ③ synthesis of steroid hormones (Astragen , progesterone)
- ④ synthesis of bile acid

But
إذا زاد لمستوى معين

يعمل
تجمع

Hyperlipidemia

الأنواع

Primary

مش نتيجة لعرف
او علاج
* have two causes

secondary

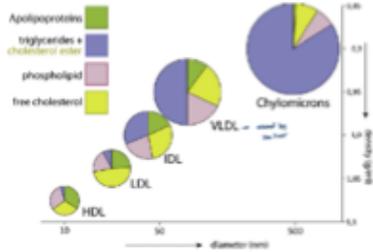
نتيجة استنزاف
علاج معين او تطور
حرفه معين

Genetic (mutations)
طفرات
Apolipoproteins
Fenotype

* lipids needs carries in the blood

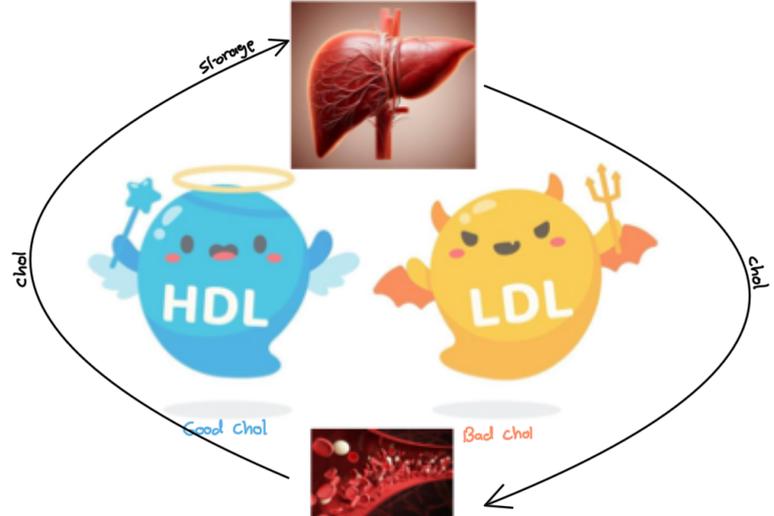
The five hydrophilic carriers (lipoproteins)

- ① Chylomicrons
- ② VLDL
- ③ IDL
- ④ LDL
- ⑤ HDL



What is the hyperlipidemia

- ① cholesterol ↑
- ② Triglyceride ↑ (red)
- ③ HDL ↓
- ④ or the three all



كلما كبر الحجم ال size تقل الكثافة density
اي ان كتله ال cholesterol اعلى من كتله ال
triglycerides لهذا حجم ال triglyceride اكبر من
حجم ال cholesterol

نسبة ال tri التي يهملها البروتين تتناسب طرديا مع
حجمه و عكسيا مع كثافته

أفهم الآن سؤالك بشكل أفضل. أنت تسأل لماذا يجب أن يكون تركيز الكوليسترول أعلى من الدهون الثلاثية في الدم حتى يؤدي وظائفه بشكل صحيح، ولماذا يوازن الجسم هذه النسبة بهذه الطريقة. النقطة الأساسية هنا تتعلق بـ كيفية تفاعل الكوليسترول والدهون الثلاثية مع البروتينات الدهنية (مثل LDL و HDL و VLDL) في الدم، وكيف تؤثر هذه النسبة على كفاءة عملها.

إليك السبب:

1. وظيفة البروتينات الدهنية والنقل في الدم:
الكوليسترول والدهون الثلاثية يتم نقلهما في الدم بواسطة البروتينات الدهنية، والجسم ينظم هذه النسبة بدقة لأن:

- **الدهون الثلاثية** يتم نقلها بواسطة **VLDL (البروتين الدهني منخفض الكثافة جدًا)**، وهو مصمم بشكل أساسي لتخزين الطاقة ونقلها. عندما يكون تركيز الدهون الثلاثية مرتفعًا جدًا، تصبح جزيئات **VLDL** كبيرة وغير فعالة في نقل الكوليسترول.
- **الكوليسترول** يتم نقله بواسطة **LDL (البروتين الدهني منخفض الكثافة)**، الذي ينقله إلى الخلايا لاستخدامه في بناء الأغشية وإنتاج الهرمونات. لذا، يجب أن يكون تركيز الكوليسترول في **LDL** مناسبًا ليؤدي وظيفته بكفاءة.

2. كفاءة الكوليسترول تعتمد على حجم البروتينات الدهنية:

- عندما تكون الدهون الثلاثية عالية في الدم، تمتلئ جزيئات **VLDL** بالدهون الثلاثية، مما يقلل من كفاءتها في حمل الكوليسترول. نتيجة لذلك، يصبح نقل الكوليسترول عبر **LDL** أقل فعالية.
- عندما يكون تركيز الكوليسترول أعلى، يستطيع الجسم إنتاج المزيد من **HDL (البروتين الدهني عالي الكثافة)**، وهو المسؤول عن إعادة الكوليسترول الزائد من الأنسجة إلى الكبد لإعادة تدويره أو التخلص منه. هذه العملية، المعروفة باسم النقل العكسي للكوليسترول، ضرورية للحفاظ على توازن الكوليسترول ومنع تصلب الشرايين.

3. تنظيم البروتينات الدهنية:

عملية الأيض في الجسم تعمل بشكل أفضل عندما يتم الحفاظ على نسبة الكوليسترول إلى الدهون الثلاثية ضمن نطاق معين. إذا زادت الدهون الثلاثية مقارنة بالكوليسترول، فإن البروتينات الدهنية التي تنقل الكوليسترول تصبح أقل كفاءة في أداء وظائفها مثل:

- الحفاظ على هيكل الأغشية الخلوية.
- إنتاج أحماض الصفراء اللازمة لهضم الدهون.
- إنتاج الهرمونات الستيرويدية.

4. تقليل خطر تصلب الشرايين:

ارتفاع الدهون الثلاثية في الدم يمكن أن يؤدي إلى تكوين جزيئات **LDL** صغيرة وكثيفة، وهي أكثر عرضة للتسبب في تراكم الترسبات في الشرايين، مما يزيد من خطر الإصابة بأمراض القلب. لهذا السبب، فإن التوازن بين الدهون الثلاثية والكوليسترول مهم للغاية لصحة القلب والأوعية الدموية.

الخلاصة:

يعمل الجسم على الحفاظ على نسبة أعلى من الكوليسترول مقارنة بالدهون الثلاثية لضمان:

- نقل الكوليسترول بكفاءة بواسطة **LDL** لأداء وظائفه الحيوية.
- تمكين **HDL** من إعادة الكوليسترول الزائد إلى الكبد.
- الحفاظ على التوازن الأيضي وتقليل خطر الإصابة بأمراض القلب.

لذلك، على الرغم من أن الكوليسترول موجود في الدم بغض النظر عن تركيزه مقارنة بالدهون الثلاثية، إلا أن نقله الفعال وأداء وظيفته يعتمد على التوازن الصحيح للبروتينات الدهنية، وهو ما يتحقق عندما يكون تركيز الكوليسترول أعلى من الدهون الثلاثية.

نعم، فهمك صحيح إلى حد كبير! سأوضح لك الفكرة بمزيد من التفصيل:

الجسم يحدد أي نوع من البروتينات الدهنية (اللايبو بروتين) سيقوم بنقل الكوليسترول بناءً على تركيز الدهون الثلاثية (التريجليسيرات). كل نوع من البروتينات الدهنية (مثل HDL، IDL، VLDL، LDL) له دور محدد في نقل الكوليسترول، وتحديد أي واحد يتم استخدامه يعتمد على تركيز الدهون الثلاثية في الدم.

إليك كيف يعمل الأمر:

1. هو المسؤول عن (البروتين الدهني منخفض الكثافة جدًا) **VLDL**. نقل الدهون الثلاثية بشكل رئيسي. عندما يكون هناك تركيز عالي لنقلها **VLDL** من الدهون الثلاثية في الدم، يقوم الجسم بإنتاج.
2. عندما تبدأ الدهون الثلاثية بالتحلل، يتحول البروتين الدهني إلى **IDL** والذي يحتوي على مزيج من الدهون الثلاثية والكوليسترول.
3. عندما تحتوي الجزيئات **LDL** بعد ذلك، يتحول البروتين الدهني إلى يكون مسؤولاً عن نقل **LDL** على الكوليسترول بشكل أساسي، و الكوليسترول إلى الخلايا لاستخدامه في وظائفه المختلفة مثل بناء الأغشية الخلوية أو إنتاج الهرمونات.
4. هو المسؤول عن جمع (البروتين الدهني عالي الكثافة) **HDL**. الكوليسترول الزائد من الأنسجة وإعادته إلى الكبد لإعادة تدويره أو التخلص منه.

إذن، الجسم يقوم بتعديل أي لايبو بروتين يُستخدم بناءً على تركيز الدهون الثلاثية في الدم. إذا كان تركيز الدهون الثلاثية مرتفعًا، سيكون هناك **VLDL** و **IDL** أكثر، وإذا كان الكوليسترول مرتفعًا مقارنة بالدهون الثلاثية، فسيتم استخدام **LDL** أكثر لنقل الكوليسترول إلى الخلايا.

الهدف هو تحديد أي لايبو بروتين سيتعامل مع الكوليسترول بناءً على النسب المختلفة للدهون الثلاثية والكوليسترول في الدم، لأن كل نوع من البروتينات الدهنية يحمل الكوليسترول إلى أماكن مختلفة لأداء وظائف محددة.

Lipoprotein	يحتاج الدهون الثلاثية؟	وظيفته الأساسية
VLDL	نعم، يحتوي على نسبة عالية من الدهون الثلاثية	نقل الدهون الثلاثية والكوليسترول من الكبد إلى الأنسجة
LDL	قليل جدًا أو شبه معدوم	نقل الكوليسترول من الكبد إلى الأنسجة
IDL	يحتوي على بعض الدهون الثلاثية	مرحلة انتقالية بين VLDL و LDL
HDL	لا يحتاج الدهون الثلاثية	إعادة الكوليسترول من الأنسجة إلى الكبد

① Food: Fats and lipids

② stomach

③ small intestine

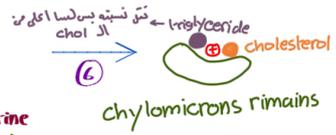
④ chylomicrons



⑤ plasma (blood) capillaries

Enzyme
capillary lipoprotein lipase (CLPL)
بعض الدهنيات

Triglyceride → 3 fatty acids + glycerol
 muscles (ATP) Adipose (storage)



⑦

Liver



⑧

VLDL
بافتد



⑨ plasma
CLPL

Triglyceride → 3 fatty acids + glycerol
 muscles (ATP) Adipose (storage)



⑪

Liver



chol > trig

Enzyme
Hepatic lipoprotein lipase

⑬ so the liver بزرگ شوي

⑭

بزرگ شوي

Triglyceride → 3 fatty acids + glycerol
 muscles (ATP) Adipose (storage)

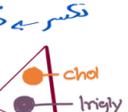
افتر نساوي نسيه ال chol وال trig



intermediate density lipoprotein
IDL

⑮

blood



chol + trigly
 excretion of it with bile
 LDL
 chol > tri



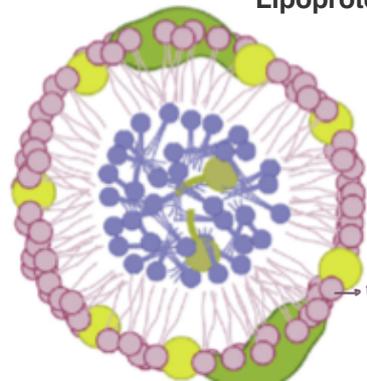
Liver

packaging

HDL

chol > trigly
 بزرگ شوي

Lipoprotein structure



- Apolipoproteins [Green box]
- triglycerides + cholesterol ester [Blue/Purple box]
- phospholipid [Pink box]
- free cholesterol [Yellow box]

You've explained the process very well! Let me summarize it:

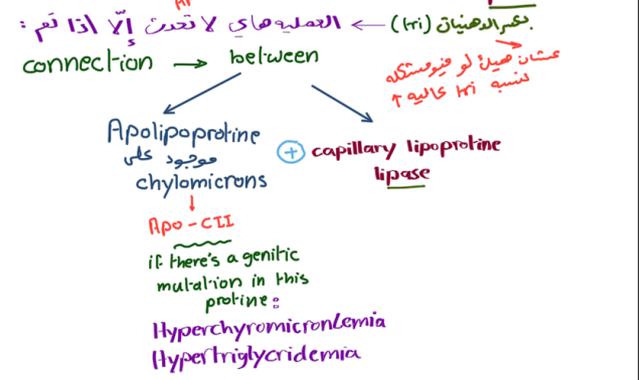
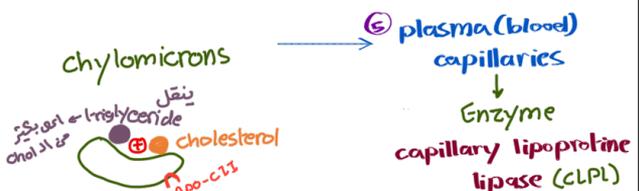
1. **Intake and Digestion:** When you eat food containing fats, it gets digested in the small intestine, where triglycerides are packaged into chylomicrons.
2. **Chylomicrons:** These transport triglycerides and cholesterol from the intestines to the bloodstream because they are hydrophobic, and chylomicrons are hydrophilic.
3. **Capillary Action:** In the bloodstream, an enzyme called lipoprotein lipase breaks down triglycerides into fatty acids and glycerol.
4. **VLDL Formation:** The liver repackages remaining triglycerides and cholesterol into very-low-density lipoproteins (VLDL).
5. **VLDL to IDL:** VLDL carries triglycerides and cholesterol to tissues, where triglycerides are broken down. The remaining particles become intermediate-density lipoproteins (IDL).
6. **IDL to LDL:** IDL is further processed to become low-density lipoproteins (LDL), which carry cholesterol to various tissues.
7. **HDL Function:** Excess cholesterol is picked up by high-density lipoproteins (HDL) and returned to the liver for storage or excretion.

This process ensures that the body maintains a balance of fats and cholesterol. If you have any specific questions, feel free to [ask](#) ↓

Exactly! The process you've described is to manage and regulate the levels of triglycerides and cholesterol in the blood. When you eat, especially foods high in fats, your body needs to transport and process these lipids efficiently. Here's why:

1. **Preventing High Triglycerides:** High levels of triglycerides in the blood can be harmful. The body uses chylomicrons to transport triglycerides from the intestines to tissues where they can be used or stored.
2. **Balancing Cholesterol:** While managing triglycerides, the body also regulates cholesterol. It uses different lipoproteins (like VLDL, IDL, and LDL) to transport cholesterol to various tissues.
3. **Maintaining Balance:** The liver helps maintain a balance by converting excess triglycerides and cholesterol into forms that can be used or stored as needed.

So, yes, the entire mechanism helps the body handle the fats and cholesterol you consume, ensuring they are distributed properly and not in excess in the bloodstream.



chylomicrons need 2 things to work

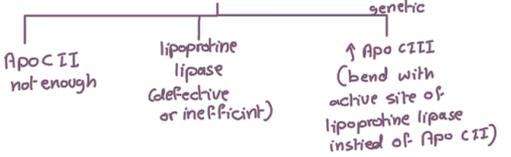
- 1 ApoCII
- 2 enough CLPL

* Apo-CIII
not ApoCIII → not good
work opposite Apo CII

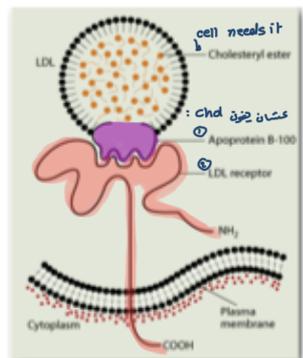
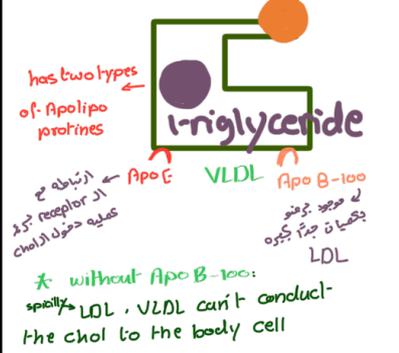
* زيادة نسبة الـ chylom.
لعلو دون LDL VLDL
high risk
باصابة ← atherosclerosis
تضيق الشرايين
زيادة هطول
VLDL
IDL
LDL
صوائف ليسب

Conclusion

we have 3 cause of Hypertriglyceridemia



cholesterol

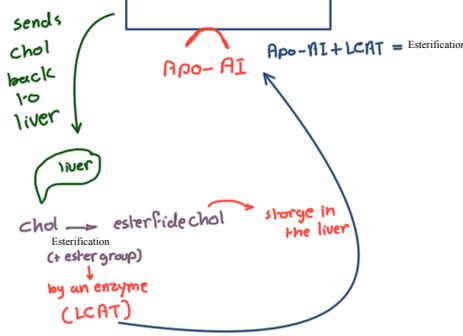


Hypercholelemia

Homozygous (genetic mutation of all LDL receptor)

Heterozygous (genetic mutation of half LDL receptors)

note:
* Any lipoprotein that break down the triglyceride → has Apo-CII



* A problem in Apo AI / LCAT ↓
→ problem with HDL → Risk Atherosclerosis ↑

Hyperlipidemia

التركيز عليه بالامتحان
primary

secondary

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

① **genetic mutation** → (Apo-CII) ✓ ----- etc
 (Apo-CIII) α overexpression
Fenotype → As a result of genetic mutation

As a result for medication or a result of some diseases

لأنه ينبغي عليه سؤال واحد

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.

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

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated تزايد في:	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I one	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa two α	LDL	↑↑	Normal	10
IIb two β	LDL and VLDL	↑↑	↑↑	40
III three	IDL / β-VLDL	↑↑	↑↑↑	<1
IV four	VLDL	Normal to ↑	↑↑	45
V five	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

هذا النوع من VLDL و LDL
 النوع الذي لا يتسبب في الإصابة بـ
 أمراض القلب والشرايين مثل النوعين الآخرين
 من النوعين الآخرين

the only type that doesn't cause Xanthoma

* the only type that doesn't cause **Atherosclerosis** → type I
 * Accumulation of lipids in the Arteries → **Atherosclerosis**
 in other places → **Xanthomas** (just a symptom)
 فقط عرض

هو مصطلح أوسع يشير إلى أي خاصية ملحوظة للفرد، سواء كانت صفات فيزيائية (مثل لون **Phenotype** العين أو الطول) أو صفات بيولوجية (مثل مستويات الكوليسترول أو ضغط الدم). وهذه الصفات تكون معًا **environmental factors** و **genetic factors** نتيجة لتأثير

عندما نتحدث عن **Primary Hyperlipidemia** (مثل **Familial Hypercholesterolemia**)، فإن **Phenotype** تشير إلى الآثار الملحوظة الناتجة عن **genetic mutations**. على سبيل المثال، قد يعاني شخص مصاب بـ **Familial Hypercholesterolemia** من ارتفاع مستويات الكوليسترول بسبب **mutation** في **LDL receptor gene**، وهو ما يُعتبر **genetic phenotype**.

لكن مصطلح **Phenotype** لا يقتصر على **Primary Hyperlipidemia** فقط. بل يمكن استخدامه لوصف أي حالة تظهر بخصائص ملحوظة، مثل:

• الأمراض التي تنتج عن **genetic mutations** (مثلًا **Cystic Fibrosis**)، حيث تكون **Phenotype** هي الأعراض والصفات الفيزيائية الناتجة عن **(mutation)**.

• الحالات التي تنتج عن **lifestyle factors** (مثل **obesity** أو **Type 2 Diabetes**)، حيث يؤثر **lifestyle** على **Phenotype** رغم أنها لا تنجم عن **(single genetic mutation)**.

إذًا، **Phenotype** تعبر عن **observable characteristics** بشكل عام، وهي ليست مقتصرة على **Primary Hyperlipidemia** فقط، بل تشمل أي حالة تظهر بصفات معينة. وفي حالة **Hyperlipidemia**، قد تشير **Phenotype** إلى مستويات الدهون في الدم، والتي يمكن أن تتأثر بكل من **genetic factors (mutations)** و **lifestyle**.



تمام! في هذا السياق، لما نتكلم عن **Primary Hyperlipidemia**، الـ **Phenotype** يشير إلى الآثار أو الصفات الملحوظة التي بتظهر نتيجة لـ **genetic mutation**. بمعنى آخر، هو الحالة الظاهرة للفرد نتيجة للتغيرات الجينية التي بتؤثر على مستوى الدهون في الدم.

لكن كلمة **Phenotype** ممكن تُستخدم في سياقات أخرى بمعنى مختلف. بشكل عام، الـ **Phenotype** يعني الخصائص أو الصفات التي يمكن ملاحظتها، سواء كانت وراثية أو بيئية، مثل الصفات الجسدية أو البيولوجية. هي ببساطة تعبير عن أي شيء ظاهر للعيان عند الشخص بسبب التفاعل بين جيناته وبيئته.

إذاً في سياق **Primary Hyperlipidemia**، الـ **Phenotype** هو ببساطة مستوى الدهون أو الكوليسترول في الدم، الناتج عن الطفرات الجينية. أما في سياقات أخرى، الـ **Phenotype** قد يشير إلى صفات أو تأثيرات مرئية أخرى نتيجة لعدة عوامل.

بالعربي، ممكن نترجم كلمة **Phenotype** بـ "النسقية" أو "الخصائص الظاهرة" أو "السمات الظاهرة".

Second Question: Atherosclerosis and Exanthomas in Hyperlipidemia Types

You're correct that different phenotypes of **hyperlipidemia** can cause the accumulation of lipids, but not all of them cause **atherosclerosis**. Specifically, **Type I hyperlipidemia**, which involves **chylomicrons**, doesn't typically lead to atherosclerosis but can cause lipid deposits in tissues, often leading to **xanthomas** (fatty deposits in skin or tendons). The **other phenotypes**, which involve different types of lipid particles (such as LDL or VLDL), can cause atherosclerosis in arteries, while still being associated with **xanthomas** in other tissues like the skin, tendons, or eyelids.

To summarize:

- **Type I (chylomicron-related)**: Leads to lipid accumulation outside the arteries (like **xanthomas**) but not atherosclerosis.
- **Other types** (e.g., Type IIa, Type IIb, Type III, etc.): These types cause **atherosclerosis in arteries** and can also cause **xanthomas** elsewhere.

So, the answer to your second question is that, yes, these lipid accumulation phenotypes (like in Type I) involve **lipid buildup in non-arterial sites**, such as the skin (resulting in **xanthomas**), but **atherosclerosis** typically occurs in the arteries in other phenotypes, like Type II.

Classification of Hyperlipidemia: Atherosclerosis and Xanthoma Association

Type of Xanthoma (if present)	Causes Xanthoma?	Causes Atherosclerosis?	Type
Eruptive Xanthoma	✔ Yes	✘ No	Type I (Chylomicronemia)
Tendinous Xanthoma, Xanthelasma	✔ Yes	✔ Yes	Type IIa (Familial Hypercholesterolemia) <i>→ LDL</i>
Tendinous Xanthoma, Xanthelasma, <i>corneal Arcus</i>	✔ Yes	✔ Yes	Type IIb (Familial Combined Hyperlipidemia) <i>→ LDL-VLDL</i>
Tuberous Xanthoma, Palmar Xanthoma	✔ Yes	✔ Yes	Type III (Dysbetalipoproteinemia) <i>→ Apo-E (B)</i>
—	✘ No	✔ Yes	Type IV (Familial Hypertriglyceridemia)
Eruptive Xanthoma	✔ Yes	✔ Yes	Type V (Mixed Hyperlipidemia)

Notes:

- **Xanthomas** are fatty deposits that appear in various parts of the body, commonly on the skin, tendons, and around the eyes.
- **Atherosclerosis** refers to the build-up of fatty plaques in the arteries, which is seen more commonly in higher types of hyperlipidemia (like Type II and Type III).
- The types of **xanthomas** are classified based on their appearance and location (e.g., **tendon xanthomas**, **xanthelasmas**, **tuberous xanthomas**, **eruptive xanthomas**).

This should help clarify which phenotypes lead to which conditions! Let me know if you need further clarification on any of these points.



Eruptive skin xanthomata characteristic of severe chylomicronemia.



A



B

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



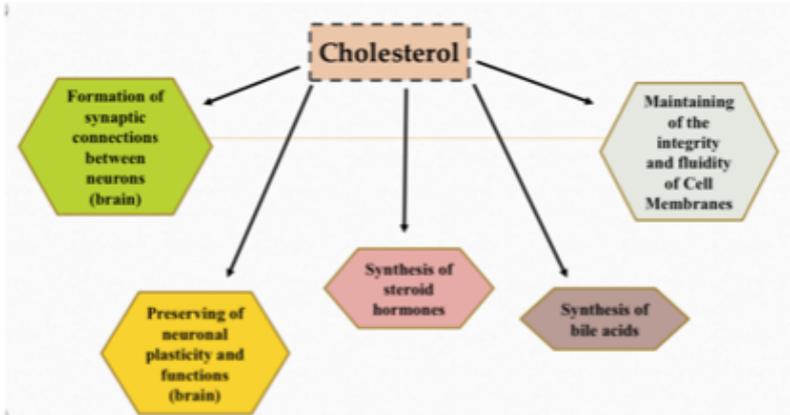
Tendon xanthomata: typical of heterozygous familial hypercholesterolemia. Similar xanthomata occur in patients with familial defective apolipoprotein B-100, cerebrotendinous xanthomatosis, and sitosterolemia.



Xanthoma striatum palmare characteristic of familial dysbetalipoproteinemia.

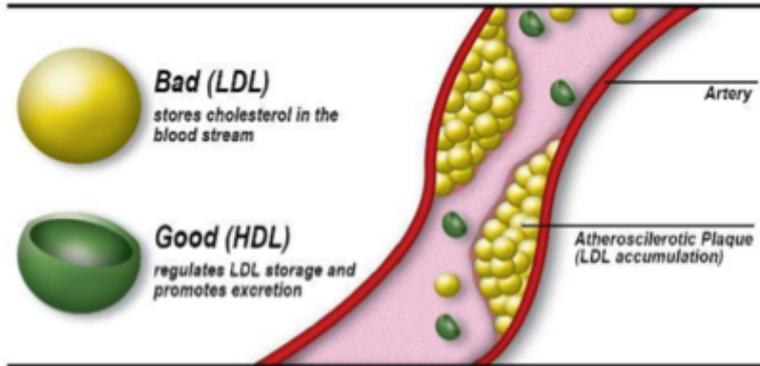
Introduction

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

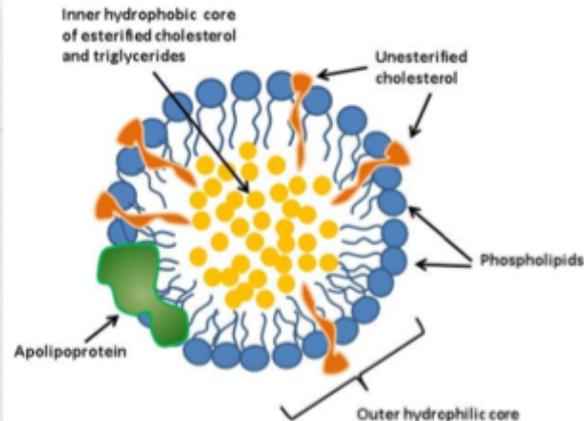


- **Lipids are not present in free form in plasma**; circulate as lipoproteins (complexes of lipids and proteins), they are transported in blood using lipoproteins.

Bad vs. Good Cholesterol



- **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.



Hyperlipidemia

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

Lipoproteins

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):

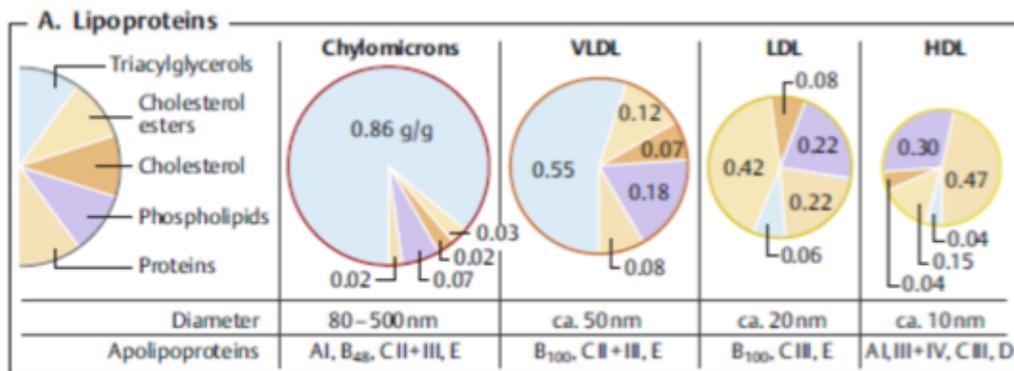
- Composed of approximately equal amounts of triglycerides, phospholipids, and cholesterol.
- Precursor for LDLs

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.



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**.

• 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.

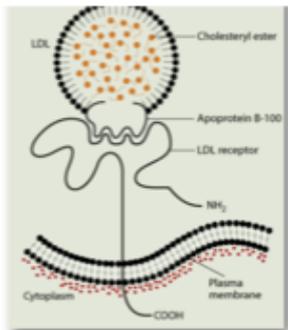
1. Apo A-I and LCAT Activation:

- Apolipoprotein A-I (Apo A-I) is a major protein in **high-density lipoprotein (HDL)**.
- It activates the enzyme LCAT (lecithin-cholesterol acyltransferase), which plays a key role in cholesterol metabolism.
- LCAT converts free cholesterol into cholesterol esters by transferring a fatty acid from lecithin to cholesterol.
- This process is essential for HDL function, allowing it to transport cholesterol from tissues to the liver for removal (reverse cholesterol transport).

2. Apo A-I and CHD Risk (Coronary Heart Disease):

- Higher levels of Apo A-I are associated with a lower risk of CHD (inverse correlation).
- HDL particles containing only Apo A-I (LpA-I) are more protective than HDL particles containing other apolipoproteins.
- This suggests that LpA-I is more efficient in cholesterol removal and may reduce plaque formation in arteries, lowering heart disease risk.

• مستويات HDL التي تحتوي فقط على Apo A-I (المعروفة بـ LpA-I) توفر حماية أكبر من الجزيئات التي تحتوي على بروتينات حبيبية أخرى.
 • يشير هذا إلى أن LpA-I أكثر كفاءة في إزالة الكوليسترول، مما قد يقلل من تراكم اللويحات في الشرايين ويقلل من الإصابة بأمراض القلب.



- **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.

• 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.

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.

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.

• 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

صاد الصوم

2. **Secondary:** should be initially managed by correcting underlying abnormality when possible.

• Current laboratory values can not define underlying abnormality.

Lipoprotein Abnormalities: 2nd Causes

Hypercholesterolemia:

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

Medications:

- Progestin
- Thiazide diuretics
- **Glucocorticoids**
- β-blockers
- **Isotretinoin**
- Protease inhibitors
- Cyclosporine
- Mirtazapine
- Statins

Hypertriglyceridemia

- Obesity
- DM
- Lipodystrophy
- Glycogen storage disease
- Real hepatic surgery
- Sepsis
- Pregnancy
- Acute hepatitis
- Systemic lupus erythematosus

Medications

- Aspirin
- Interferon
- Acute antiobiotics
- Mirtazapine
- Anabolic steroids
- Statins
- Alcohol
- Estrogens
- Isotretinoin
- β-blockers
- Glucocorticoids
- Bile acid resins

Hypocholesterolemia:

- Malnutrition
- Malabsorption
- Myeloproliferative diseases
- Chronic infection diseases
- Acquired immune deficiency syndrome
- Tuberculosis
- Monoclonal gammopathy

Low high-density lipoprotein:

- Malnutrition
- Obesity
- Medications
- non-ISA β-blockers
- anabolic steroids
- isotretinoin
- progestin

* فراده بس مش (ح) نجيب عليه *
معنى بس سؤال ← liver

Notes	Cholesterol	Triglyceride	Lipoprotein Deficiency	Name of Disorder	Phenotype Type
Hypertriglyceridemia , often associated with eruptive xanthomas, pancreatitis risk	Normal	Elevated	Lipoprotein Lipase Deficiency	Familial Lipoprotein Lipase Deficiency	Type 1
Hypercholesterolemia due to defective LDL receptors	Elevated	Normal	LDL Receptor Deficiency	Familial Hypercholesterolemia	Type 2a
Combined elevation of both triglycerides and cholesterol	Elevated	Elevated	LDL Receptor Deficiency & Increased VLDL	Familial Combined Hyperlipidemia	Type 2b
Hypertriglyceridemia and Hypercholesterolemia , associated with xanthomas	Elevated	Elevated	Apo E Deficiency (Impaired IDL uptake)	Familial Dysbetalipoproteinemia	Type 3
Hypertriglyceridemia with normal cholesterol levels	Normal	Elevated	Overproduction of VLDL	Familial Hypertriglyceridemia	Type 4
Hypertriglyceridemia and Hypercholesterolemia , often with a high risk of pancreatitis	Elevated	Elevated	Deficiency of Lipoprotein Lipase/Overproduction of VLDL	Familial Mixed Hyperlipidemia	Type 5

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.



Xanthoma striatum palmare characteristic of familial dysbetalipoproteinemia.



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.

Hyperlipoproteinemia Phenotypes

①

Type I - Chylomicronemia

- **Lipid Profile:** ↑ Chylomicrons
- **Defect:** Deficiency in **Lipoprotein Lipase (LPL)** or **ApoC-II**
- **Atherosclerosis:** ❌ No
- **Xanthomas:** Eruptive xanthomas



②

Type IIa - Familial Hypercholesterolemia

- **Lipid Profile:** ↑ LDL
- **Defect:** LDL receptor deficiency or mutation in **ApoB-100**
- **Atherosclerosis:** ✅ Yes
- **Xanthomas:** Tendon xanthomas & Corneal arcus

Type IIb - Combined Hyperlipidemia

- **Lipid Profile:** ↑ LDL & ↑ VLDL
- **Defect:** Overproduction of **VLDL** & decreased clearance of **LDL**
- **Atherosclerosis:** ✅ Yes
- **Xanthomas:** ❌ No

③

Type III - Dysbetalipoproteinemia

- **Lipid Profile:** ↑ IDL & β-VLDL
- **Defect:** **ApoE2 mutation** (defective ApoE)
- **Atherosclerosis:** ✅ Yes
- **Xanthomas:** Tuberous xanthomas & Palmar xanthomas

④

Type IV - Hypertriglyceridemia

- **Lipid Profile:** ↑ VLDL
- **Defect:** Increased **VLDL production** & decreased clearance
- **Atherosclerosis:** ✅ Yes
- **Xanthomas:** ❌ No

⑤

Type V - Mixed Hyperlipidemia

- **Lipid Profile:** ↑ Chylomicrons & ↑ VLDL
- **Defect:** Decreased **LPL activity** or increased **VLDL production**
- **Atherosclerosis:** ✅ Yes
- **Xanthomas:** Eruptive xanthomas

Location	Associated Condition	Type of Xanthomata
Skin	Severe chylomicronemia	Eruptive Skin Xanthomata
A. Knee B. Palm	Familial dysbetalipoproteinemia (Type III Hyperlipidemia)	Tuberous & Tubercous Xanthomata
Tendons (Achilles, hands)	Heterozygous familial hypercholesterolemia	Tendon Xanthomata
Palm	Familial dysbetalipoproteinemia (Type III)	Xanthoma Striatum Palmare

Familial LPL deficiency

* when I say LPL → lipoprotein lipase ∴

- ① chylomicrons → type I
- ② chylomicrons + VLDL → type V

→ Deficiency:-

- ① lipoprotein lipase
- ② Apo - CII < inefficient dysfunction
- ③ Apo - CIII ↑

- 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.

• 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.

• 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

* hypercholesterolemia → cholesterol ↑ ∴ LDL problem → type IIa → Deficiency: LDL receptor
type IIb → Deficiency: Apo-B100

• Characterized by:

- Selective elevation in the plasma level of LDL.
- Deposition of LDL-derived cholesterol in tendons (xanthomas) and arteries (atheromas).
- 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.

* Deficiency LDL receptor :

① **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.

② **Heterozygotes** have only about **half** the normal number of LDL receptors, total cholesterol levels in the range from 300 to 600 mg/dL.

في النوع **2a**، الخلل يكون في مستقبلات **LDL**، وهذه المستقبلات موجودة على سطح الخلايا وتعمل على إزالة الكوليسترول من الدم عن طريق ربط جزيئات **LDL** (التي تحمل الكوليسترول) وإدخالها إلى الخلايا. عند حدوث طفرات في الجين المسؤول عن تصنيع هذه المستقبلات، لا تتمكن الخلايا من إزالة الكوليسترول بشكل فعال، مما يؤدي إلى زيادة مستويات الكوليسترول في الدم (خصوصاً **LDL**).

أما في النوع **2b**، الخلل يكون في **ApoB-100**، وهو البروتين المسؤول عن تكوين جزيئات **VLDL** (التي تحتوي على الكوليسترول والدهون) وكذلك عن ارتباط هذه الجزيئات بمستقبلات **LDL** في الخلايا. عندما يحدث خلل في **ApoB-100**، لا تتمكن جزيئات **LDL** من الارتباط بشكل فعال بالمستقبلات الموجودة على الخلايا، مما يؤدي أيضاً إلى تراكم الكوليسترول في الدم.

إذن، كلا النوعين يؤديان إلى زيادة الكوليسترول في الدم، لكن بسبب خلل في البات مختلفة:

- النوع **2a** يتعلق بمشكلة في مستقبلات **LDL**.
- النوع **2b** يتعلق بمشكلة في **ApoB-100**.

الاختلاف الرئيسي بينهما هو أن النوع **2a** يتأثر بوظيفة المستقبلات بينما النوع **2b** يتأثر بوظيفة البروتين الناقل.

في حالة فرط كوليسترول الدم (**Hypercholesterolemia**)، يمكن أن يكون هناك خلل في الجينات المرتبطة بالاستقبال (Receptor) أو البروتينات الناقلة للكوليسترول مثل **ApoB-100**. يُعتبر هذا خللاً في الجينات الفينوتيبية (Phenotypic)، وهذا يحدث بسبب الطفرات الجينية التي تؤثر على آلية عمل هذه البروتينات.

بالنسبة لما ذكرته عن **الجهة 2a و 2b**، هذه تشير إلى نوعين من الطفرات التي قد تؤدي إلى فرط كوليسترول الدم.

• في النوع **2a**، غالباً ما يكون الخلل في مستقبلات **LDL (LDL Receptor)** نفسها، مما يؤدي إلى تراكم الكوليسترول في الدم، لأنه لا يمكن للبروتينات الدهنية منخفضة الكثافة (**LDL**) الارتباط بشكل فعال بالمستقبلات وإدخال الكوليسترول إلى الخلايا.

• في النوع **2b**، الخلل يكون في **ApoB-100** (البروتين المسؤول عن نقل الكوليسترول)، حيث يحدث الطفرة في الجين المسؤول عن إنتاج هذا البروتين، مما يؤدي إلى عجز في قدرة البروتين على الارتباط بمستقبلات **LDL**، وبالتالي تراكم الكوليسترول في الدم أيضاً.

Dysbetalipoproteinemia



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

* IDL / β -VLDL \rightarrow Deficiency: APO-E

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

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 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.

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.

Total cholesterol (LDL + HDL + tri)	
<200	Desirable <i>Normal</i>
200–239	Borderline high <i>اعلى نسبة مقبولة</i>
240	High
LDL cholesterol	
<100	Optimal
100–129	Near or above optimal <i>مقبول</i>
130–159	Borderline high
160–189	High
190	Very high
HDL cholesterol <i>العكس</i>	
<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

Atherosclerosis

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



* “hardening of the arteries” → As a result of fat deposit (plaque) → lost of elasticity (no vascular tone)
تصلب شرايين ← نتيجة ترسبات دهون الشرايين

∴ plaque → obstruction of blood flow → if become big and the cap thin → rupture ^{leading to} Thrombosis

- **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.

- There are three general patterns:

- There are three general patterns:

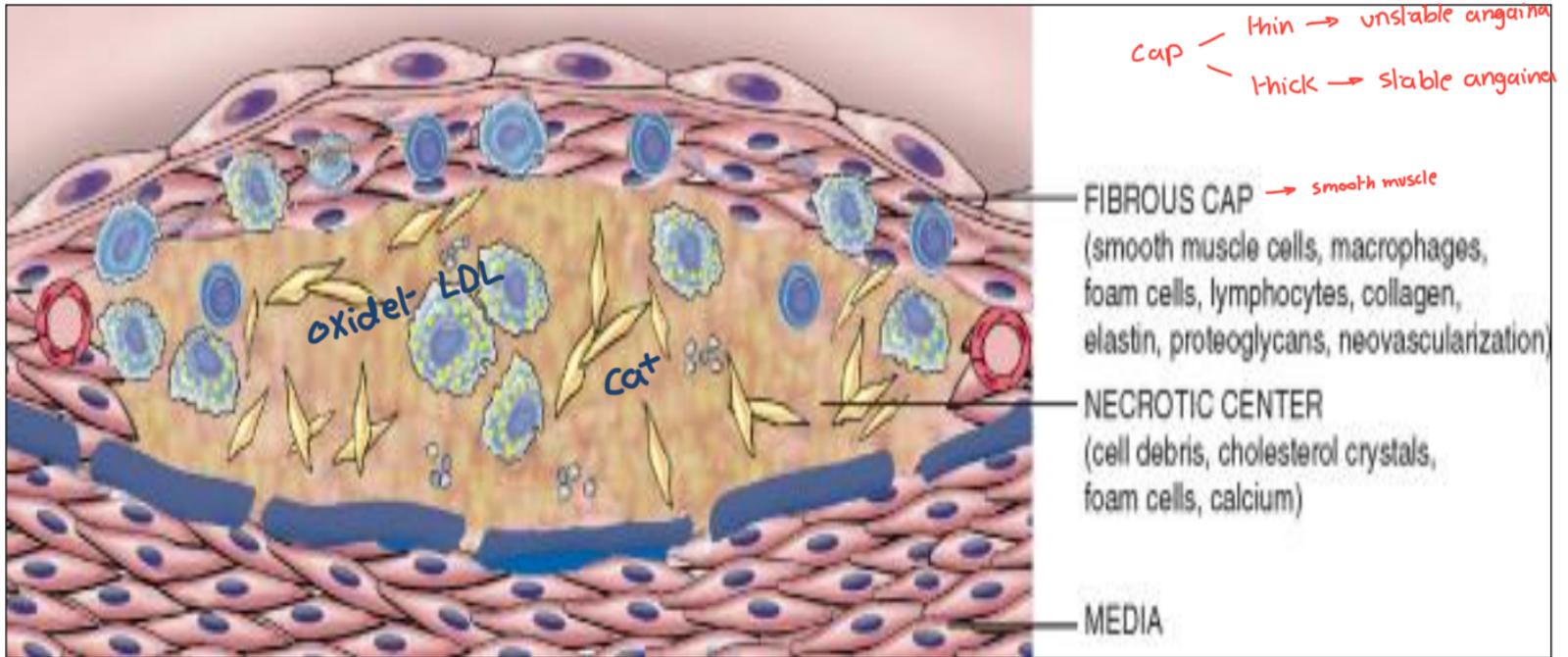
1. **Arteriolosclerosis**, affects small arteries and arterioles and may cause downstream ischemic injury.
2. **Mönckeberg medial sclerosis**, is characterized by calcific deposits in muscular arteries in persons typically older than age 50.

we gonna focus on 1-

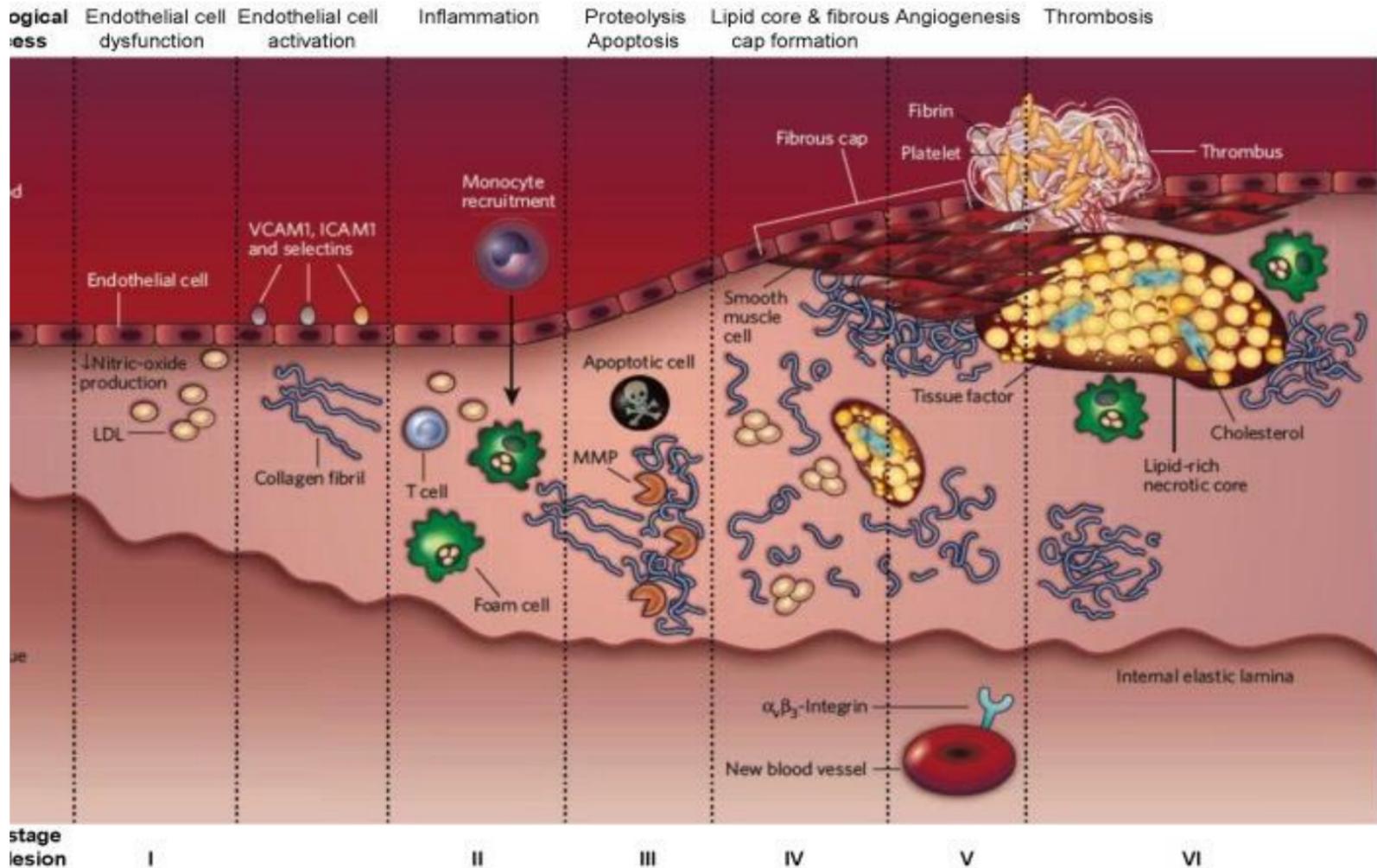
3. **Atherosclerosis**, from Greek root words for “gruel” and “hardening,” is the most frequent and clinically important pattern.

- **Atherosclerotic plaques can:**

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

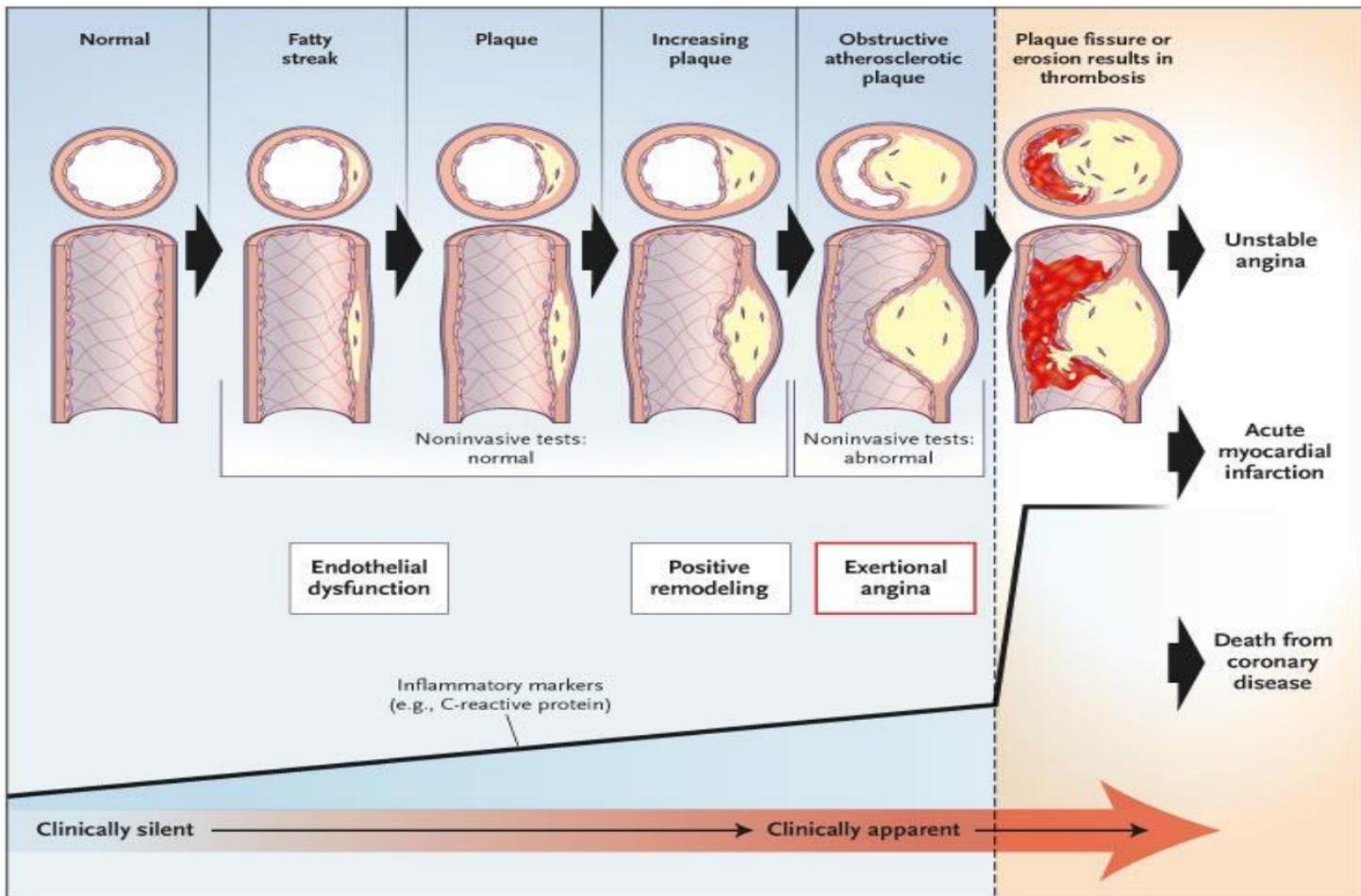


The major components of a well-developed intimal atheromatous plaque overlying an intact media.



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**.



- 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:

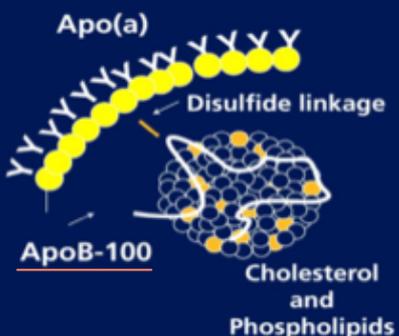
- Hyperlipidemia.
- Hypertension.
- Cigarette smoking.
- Diabetes Mellitus.

• Additional risk factors:

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

- Lipoprotein (a) levels → works as LDL

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)

- Risk Factor Atheros. ↑
- ApoB-100
- Apo a

- 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.

55

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.

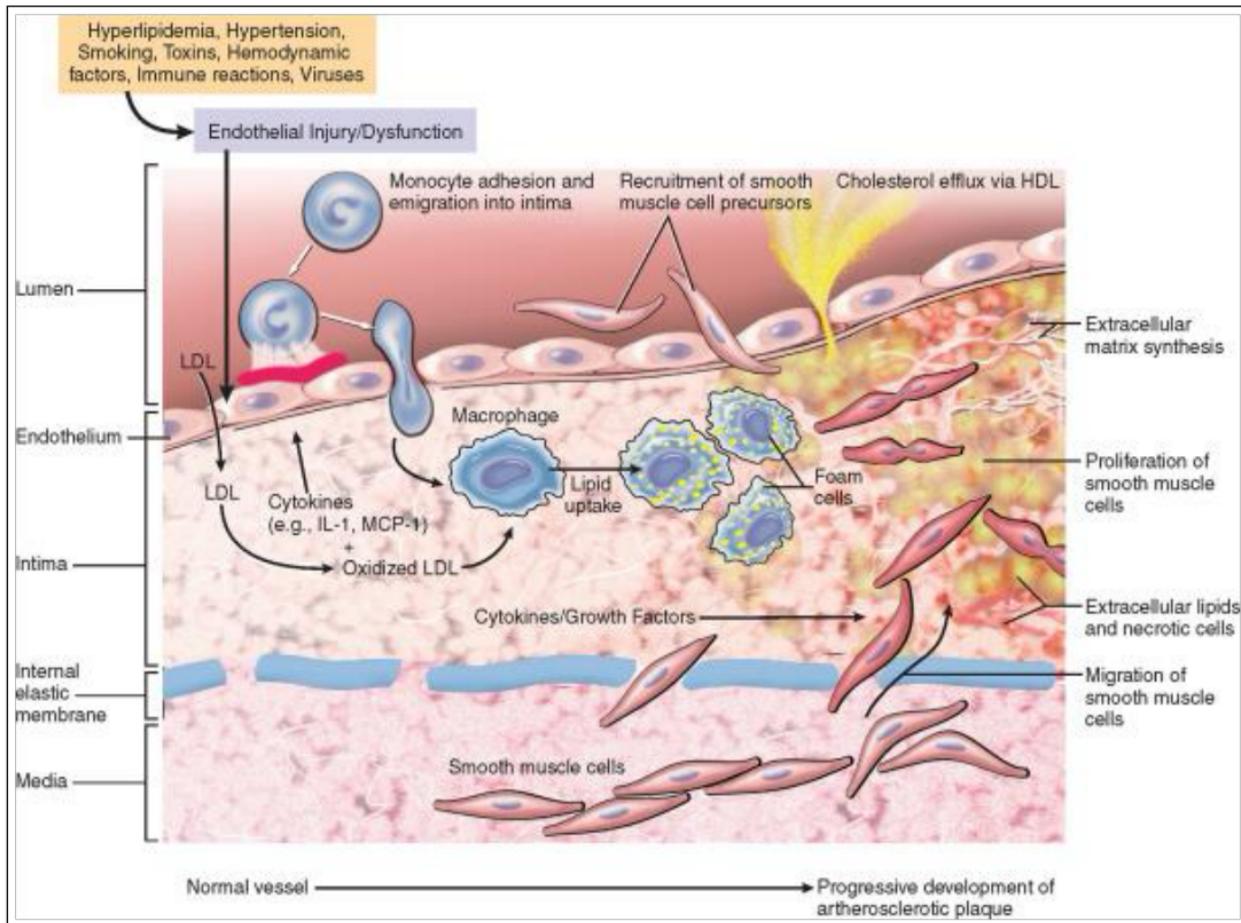
- **Monocyte adhesion to the endothelium**, followed by migration into the intima and transformation into macrophages and foam cells.

- **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.

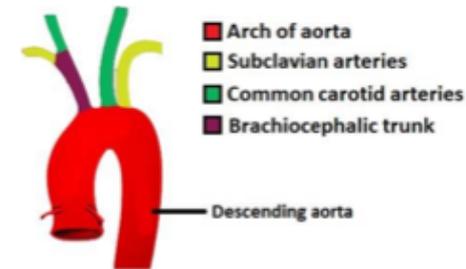
- **Smooth muscle cell proliferation and ECM (extracellular matrix which contains lots of inflammatory mediators and growth factors) production.**

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



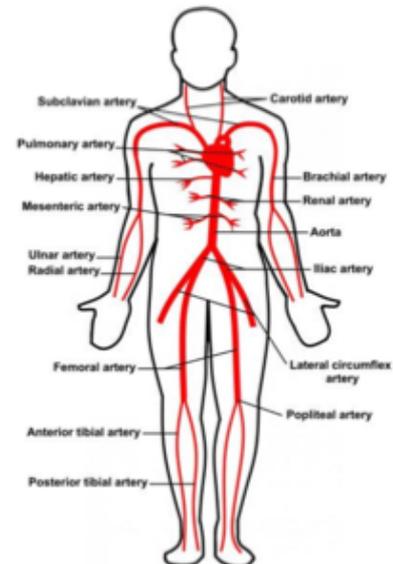
Consequences of Atherosclerosis

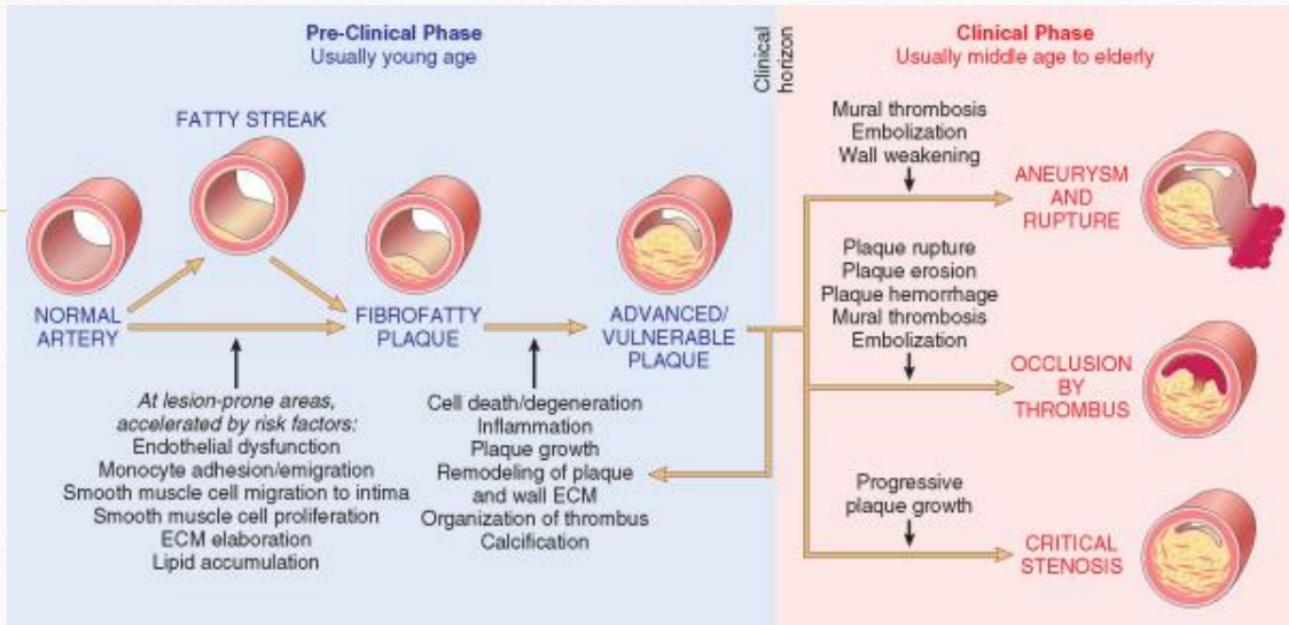
- The aorta, carotid, and iliac arteries (large elastic arteries) and coronary and popliteal (medium-sized muscular arteries) are targets for atherosclerosis.
- Heart attack, stroke, aneurysm, and gangrene in the legs are potential consequences of the disease.
- The principal outcomes depend on:
 - The 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.

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Abnormalities that could present in the blood vessels

المصطلحات التي ذكرتها كلها مرتبطة بمشاكل في الأوعية الدموية، خاصة في سياق الأمراض القلبية الوعائية، وتتشابه في أنها تؤثر على تدفق الدم في الشرايين، لكن كل واحد منها يشير إلى شيء مختلف:

1. **Atherosclerotic stenosis** (تضييق الشرايين التصليبي): تراكم اللويحات (مثل الدهون والكوليسترول)، مما يسبب تقييد تدفق الدم.
2. **Acute plaque change** (التغيرات المفاجئة في اللويحة): المتكونة داخل الشرايين، مثل تمزق اللويحة أو تفتتها، مما قد يؤدي إلى تكوّن جلطة دموية.
3. **Thrombosis** (التخثر): الشريان بشكل جزئي أو كلي، مما يعيق تدفق الدم.
4. **Vasoconstriction** (تقلص الأوعية): هو عملية انقباض الأوعية الدموية (الشرايين والأوردة)، مما يؤدي إلى تقليل قطر الأوعية وزيادة مقاومة تدفق الدم.

بالتالي، هذه المصطلحات كلها مرتبطة بتغيرات قد تحدث في الأوعية الدموية وتؤثر على تدفق الدم. إذا كان السؤال عن كونها مرتبطة ببعضها البعض، فهي مرتبطة في سياق مشاكل تدفق الدم والأمراض القلبية الوعائية، لكنها تشير إلى عمليات مختلفة تحدث في الشرايين.

Abnormalities that could present in the blood vessels

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

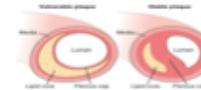
Plaque rupture is promptly followed by partial or complete vascular thrombosis resulting in acute tissue infarction (e.g., myocardial or cerebral infarction).

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:

- Extrinsic factors (e.g., plaque structure and composition)
- Endothelial factors (e.g., blood pressure, glucose toxicity)



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.



Pathophysiology-Shock

Faculty of Pharmaceutical Sciences

Dr. Amjaad Zuhier Alrosan, Dr. Abdelrahim Alqudah

Shock → A result of ischemia → if vital organs → high risk of irreversible shock

Tissue ischaemic sensitivity:

- heart, brain, lung:	4-6 min
- GI tract, liver, kidney:	45-60 min
- muscle, skin:	2-3 hours

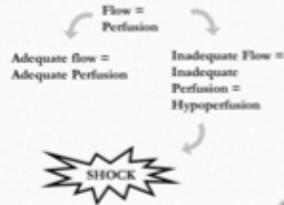
so →

What is the meaning of shock?

- ✓ Inadequate perfusion to meet tissue demands. A **progressive** process.
 - Occurs in 2% of hospitalized patients.
 - Mortality 10% in children vs. 30-40% in adults.
- ✓ In other words, a systemic reduction in tissue perfusion → decreased tissue O₂ delivery.
 - A shift to less-efficient anaerobic metabolism, leading to **lactic acidosis**, occurs.
- ✓ Initially, effects are reversible. Eventually:
 - Cell membrane ion pump dysfunction.
 - Cellular edema, leakage of cells' contents.
 - Inadequate regulation of intracellular pH.
 - → Cell death, organ failure, cardiac arrest, and death.
- A disruption to homeostasis.
- A reduction in blood flow to tissues, depriving them of oxygen (ischaemia).
- Organs of vital importance, brain, heart, and kidneys can suffer irreversible damage, eventually leading to death.
- **Tissue ischaemic sensitivity:**
 - heart, brain, lung: 4-6 min
 - GI tract, liver, kidney: 45-60 min
 - muscle, skin: 2-3 hours

Cardiovascular System → implies between supply and Demand

- Transports oxygen (fuel) to cells.
- Removes carbon dioxide and other waste products for elimination from body.
- Cardiovascular system must be able to maintain sufficient flow through capillary beds to meet cell's oxygen and fuel needs.



←

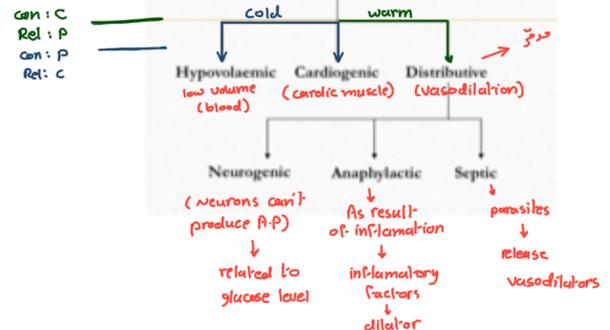
What is needed to maintain Perfusion?

- ① - Pump: Heart
- ② - Pipes: Blood Vessels
- ③ - Fluid: Blood

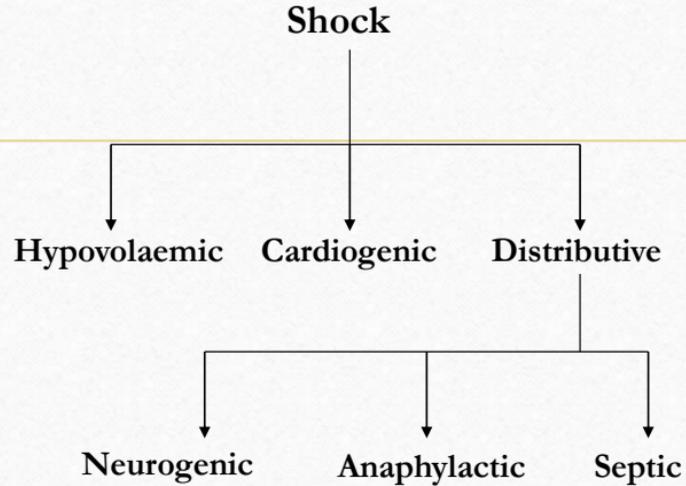
How can perfusion fail?

- ① - Pump Failure
- ② - Pipe Failure
- ③ - Loss of volume

type of shock



Classification of Shock



Hypovolaemic Shock

- Low Volume.
- Causes:
 - haemorrhage
 - burns
 - vomiting
 - diuresis
 - sweating
 - diarrhoea

Cardiogenic Shock

- Pump Failure.
- Causes:
 - acute MI
 - CHF
 - obstruction
 - arrhythmias

Neurogenic Shock

- Loss of tone of blood vessels.
- Causes:
 - spinal cord damage, anaesthesia, pain, drugs, hypoglycaemia.

Anaphylactic

- Mass release of histamine due to allergic hypersensitivity reaction (foods, insect bites, blood transfusion, drugs).
- Increased capillary permeability with vasodilation reduces venous return and BP.

Septic

- Systemic infection.
- Bacterial toxins – wound infections, invasive procedures, UTI, Respiratory infections.
- Associated with pyrexia, marked generalised vasodilation and intravascular micro-clotting.
- Immunocompromised patients at risk.

- To understand the physiology of shock we need to understand the following formula:

$$\text{Blood Pressure} = \text{Cardiac Output} \times \text{Systemic Vascular Resistance}$$

Given that:

$$\text{BP} = \text{CO} \times \text{SVR}$$
$$\text{SV} \times \text{HR}$$

$$\text{CO} = \text{HR} \times \text{SV}$$

Cardiac output:

- Volume of blood ejected from each ventricle each minute.
- This depends on the frequency of contraction; how forceful the contractions are and the volume of blood entering the ventricles.

Stroke volume:

- Volume of blood ejected per contraction (stroke).

By applying a mathematical aspect to the formula, we can start to identify how blood pressure can be maintained.

$$\text{BP} = \text{CO} \times \text{SVR}$$

We need to keep both sides balanced.

If one side of the formula changes, the other side needs to be change in the opposite direction to balance this out.

i.e. If BP increases, we need to decrease CO, SVR or both to bring it back down again.

If BP decreases, we need to increase CO, SVR or both to bring it back up again.

Causes	Definition	Type of Shock
<ul style="list-style-type: none"> - Haemorrhage - Burns - Vomiting - Diuresis - Sweating - Diarrhoea (bleeding) 	Low Volume	Hypovolemic Shock
<ul style="list-style-type: none"> - Spinal cord damage - Anaesthesia - Pain - Drugs - Hypoglycaemia 	Loss of vascular tone	Distributive Shock
<ul style="list-style-type: none"> - Acute MI - CHF - Obstruction - Arrhythmias (problem with heart) 	Pump Failure	Cardiogenic Shock
<ul style="list-style-type: none"> - Spinal cord damage - Anaesthesia - Pain - Drugs - Hypoglycaemia 	Loss of tone of blood vessels	Neurogenic Shock
<ul style="list-style-type: none"> - Foods - Insect bites - Blood transfusion - Drugs → histamine releasing 	Mass release of histamine due to allergic hypersensitivity reaction	Anaphylactic Shock
<ul style="list-style-type: none"> - Bacterial toxins - Wound infections - Invasive procedures - UTI - Respiratory infections → parasites 	Systemic infection	Septic Shock

Key Issues In Shock

- ✓ Recognise and treat early (during compensatory phase)

Increased resp. rate,

Restlessness,

Anxiety,

} **Early**
signs of
shock

- ✓ Falling BP = **Late** sign of shock
- ✓ Pallor, tachycardia and slow capillary refill = Shock until proven otherwise
- ✓ Hallmark symptoms are:
 - Decreased BP
 - Increased HR

Progression	Clinical Signs & Symptoms	Mechanism	Stage
Body still compensates, but if untreated, progresses to the next stage.	- Tachycardia - Cold shock : Decreased pulses, cool extremities - Warm shock : Flushing, bounding pulses - Oliguria - Mild lactic acidosis	Cardiac output (HR × SV) and systemic vascular resistance (vasoconstriction) maintain BP within normal range.	Compensated Shock
Rapid deterioration, leading to cardiac arrest if not treated.	- Hypotension - Altered mental status - Increased lactic acidosis	Compensatory mechanisms are overwhelmed, leading to worsening perfusion.	Hypotensive (Progressive) Shock → All become cold
Final stage, irreversible even with treatment.	- Severe organ damage - Cardiac arrest - Death occurs	Multi-organ failure due to prolonged hypoxia and acidosis.	Irreversible Shock → organ failure

Stages of Shock

A progressive process

- **Compensated Shock**: Cardiac output (HR × SV) and systemic vascular resistance (peripheral vasoconstriction) work to keep BP within normal.
 - On exam: Tachycardia; decreased pulses & cool extremities in cold shock; flushing and bounding pulses in warm shock; oliguria; labs may show mild lactic acidosis
- **Hypotensive (Progressive) Shock**: Compensatory mechanisms are overwhelmed.
 - On exam: As above, plus hypotension, altered mental status; labs may show increased lactic acidosis
 - Generally quick progression to cardiac arrest.
- **Irreversible Shock**: Irreversible organ damage, cardiac arrest, death occur.

Compensated Shock

- ◆ Compensatory mechanisms are successful in maintaining perfusion.
- ◆ Presentation:
 - Tachycardia, Tachypnoea.
 - Decreased skin perfusion.
 - Altered mental status.

Progressive Shock

- Compensation mechanisms begin to fail.
- Presentation:
 - hypotension.
 - marked increase in heart rate.
 - rapid, thready pulse.
 - agitation, restlessness, confusion.

Irreversible Shock

- Complete failure of compensatory mechanisms.
- Death even in presence of resuscitation.

**Inadequate cellular
Oxygen Delivery**



**Anaerobic
Metabolism**

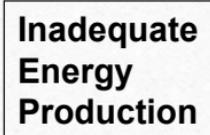
**Inadequate
Energy
Production**

**Lactic Acid
Production**

**Metabolic
Failure**

**Metabolic
Acidosis**

**CELL
DEATH**



◆ Compensated shock

- Baroreceptors detect fall in BP.
- Sympathetic nervous system activated.

1. Cardiac Effects:

- Increased force of contractions.
- Increased rate (tachycardia).
- Increased cardiac output.

2. Peripheral Effects:

- Arteriolar constriction.
- Increased peripheral resistance.
- Shunting of blood to main core organs.

3. Respiratory Effects:

- Tachypnoea is one of the first signs that reflect reduced blood flow and oxygen transport.
- The cardiovascular and respiratory systems work together:
 - ✓ If blood flow around the body is compromised in any way, oxygen delivery to tissues is reduced.
 - ✓ To compensate for this, ventilation will increase to attempt to increase oxygen uptake in the lungs. So how does this happen? The Baroreceptors not only stimulate the cardiovascular control center but also the respiratory center in the medulla, increasing the respiratory rate.

4. Renal Effects

- Decreased renal blood flow
- Renin released from kidney
- Initiation of RAAS.

results in peripheral vasoconstriction, reabsorption of Na^+ and H_2O

Role of ADH in reabsorption



5. Hypothalamus Effects

- Decreased blood flow to the hypothalamus.
- Release of ADH from post pituitary results in retention of salt, water, and peripheral vasoconstriction.

6. Hormonal Effects

- Glucagon (contributes to hyperglycemia).
- ACTH (stimulates cortisol release and glucose production).

❖ Compensated shock

- **Presentation:**

- Increased resp. rate, restlessness, anxiety (earliest signs of shock).

- Tachycardia.

- Falling BP = late sign of shock.

- Possible delay in capillary refill.

- Pale, cool skin (Cardiogenic, Hypovolaemic shock).

- Flushed skin (Anaphylactic, Septic, Neurogenic shock).

- ✗ Nausea, vomiting, thirst.

- Decreased body temperature (Feels cold).

- Weakness.

❖ Progressive Shock

1. Cardiac Effects:

- Decreased RBC oxygenation.
- Decreased coronary blood flow.
- Myocardial ischaemia.
- Decreased ventricular filling.
- Decreased force of contraction.

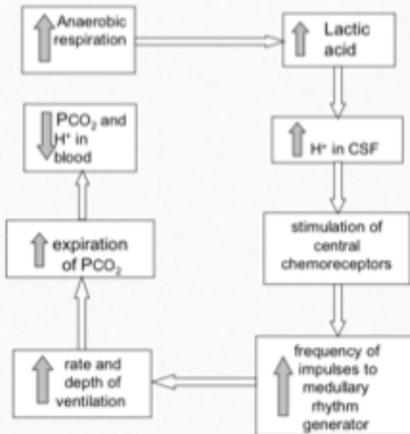
2. Peripheral Effects

- Peripheral pooling of blood.
- Plasma leakage into interstitial spaces.
- Cold, grey waxy skin.
- Restlessness, confusion, slow speech.
- Tachycardia, weak thready pulse.
- Decreased BP.
- Decreased body temperature.

3. Respiratory effects

- If oxygen delivery to tissues continues to be inadequate, cells must do anaerobic respiration to continue ATP production.
 - Anaerobic respiration produces lactic acid as a waste product – this must be removed.
 - Central chemoreceptors will detect a fall in pH and stimulate the respiratory centre to increase ventilation.
- This allows the excess acid to be 'blown off' in the form of CO_2

Response to acidosis



❖ Irreversible Shock

- Loss of peripheral vascular resistance.
- Confusion, slurred speech, unconscious.

- Slow, irregular, thready pulse.
- Falling BP (diastolic is zero).
- Cold, clammy cyanotic skin.
- Slow, shallow, irregular respirations.
- Dilated, sluggish pupils.
- Severely decreased body temperature.

➤ **Irreversible Shock leads to:**

- ✓ Renal failure.
- ✓ Hepatic failure.
- ✓ Multiple organ systems failure.
- ✓ Adult respiratory distress syndrome.
- ✓ Death.

Signs & Symptoms	Hormonal Effects	Renal Effects	Respiratory Effects	Peripheral Effects	Cardiac Effects	Description	Stage
<ul style="list-style-type: none"> - Increased resp. rate - Restlessness, anxiety - Tachycardia - Falling BP (late sign) - Possible delay in capillary refill - Pale, cool skin (Cardiogenic, Hypovolemic shock) - Flushed skin (Anaphylactic, Septic, Neurogenic shock) - Nausea, vomiting, thirst - Decreased body temperature - Weakness 	<ul style="list-style-type: none"> - Release of ADH (water retention, vasoconstriction) - Increased Glucagon - ACTH release (cortisol, glucose production) 	<ul style="list-style-type: none"> - Decreased renal blood flow - Renin release - initiation of RAAS (vasoconstriction, Na⁺ & H₂O reabsorption) 	<ul style="list-style-type: none"> - Tachypnoea (earliest sign) - Increased ventilation due to baroreceptor activation 	<ul style="list-style-type: none"> - Arteriolar constriction - Increased peripheral resistance - Shunting of blood to main core organs 	<ul style="list-style-type: none"> - Increased force of contractions - Increased rate (tachycardia) - Increased cardiac output 	<ul style="list-style-type: none"> - Compensatory mechanisms are successful in maintaining perfusion. 	Compensated Shock
<ul style="list-style-type: none"> - Hypotension - Marked increase in heart rate - Rapid, thready pulse - Agitation, restlessness, confusion - Weakness 	<ul style="list-style-type: none"> - Increased metabolic acidosis due to lactic acid build-up 	<ul style="list-style-type: none"> - Decreased renal function 	<ul style="list-style-type: none"> - Increased ventilation to compensate for acidosis - Anaerobic respiration → lactic acid production 	<ul style="list-style-type: none"> - Peripheral pooling of blood - Plasma leakage into interstitial spaces - Cold, grey waxy skin - Restlessness, confusion, slow speech 	<ul style="list-style-type: none"> - Decreased RBC oxygenation - Decreased coronary blood flow - Myocardial ischaemia - Decreased ventricular filling - Decreased force of contraction 	<ul style="list-style-type: none"> - Compensation mechanisms begin to fail. 	Progressive Shock
<ul style="list-style-type: none"> - Confusion, slurred speech, unconscious - Slow, irregular, thready pulse - Falling BP (diastolic = zero) - Cold, clammy cyanotic skin - Slow, shallow, irregular respirations - Dilated, sluggish pupils - Severely decreased body temperature - Leads to: Renal failure, Hepatic failure, Multiple organ system failure, Adult respiratory distress syndrome, Death 	<ul style="list-style-type: none"> - Metabolic failure → death 	<ul style="list-style-type: none"> - Renal failure 	<ul style="list-style-type: none"> - Severe respiratory depression - Hypoventilation - Irregular breathing 	<ul style="list-style-type: none"> - Severe vasodilation - Plasma leakage - Organ failure 	<ul style="list-style-type: none"> - Loss of peripheral vascular resistance - Myocardial failure 	<ul style="list-style-type: none"> - Complete failure of compensatory mechanisms. 	Irreversible Shock



Pathophysiology-Congestive Heart Failure

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❑ Heart Failure ← فشل القلب

• The inability of the heart to maintain an output adequate to maintain the metabolic demands of the body.

• Heart failure may result from a ^{شبه}primary abnormality of the heart muscle—for example, an infarction—that impairs ventricular function and prevents the heart from pumping enough blood. ^{ضعف}

• Complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support physiological circulation.

• Heart failure may also be caused by problems unrelated to MI:

✓ Mechanical disturbances in ventricular filling during diastole, due to blood volume that's too low for the ventricle to pump.

✓ Systolic hemodynamic disturbances—such as excessive cardiac workload caused by volume overload or pressure overload—limit the heart's pumping ability.

Type of heart failure	Description
Left-sided heart failure	The left ventricle of the heart struggles to pump blood, resulting in a buildup of fluid in the pulmonary veins, causing shortness of breath. → blood go back to the lung
Right-sided heart failure	Right side of the heart struggles to pump blood to the lungs, resulting in fluid backup in the legs, feet, and abdomen. → Right side ضيق → blood go back → legs, feet, abdomen edema
Systolic heart failure (falling prob)	The left ventricle cannot contract completely, meaning that the heart cannot pump with enough force to move blood throughout the body properly.
Diastolic heart failure (cont. prob)	The left ventricle cannot relax, not allowing it to fill completely, resulting in not enough blood being pumped to the rest of the body.

Left-sided heart failure

1. **Left atrium** receives blood from the lungs via the **pulmonary veins**.
2. The **left ventricle** fails to pump blood into the **aorta**, causing a backup of blood.
3. This increases pressure in the **pulmonary veins**, and the fluid backs up into the **lungs**, causing **pulmonary edema**.

Right-sided heart failure

- In **right-sided heart failure**, the problem is that the right ventricle can't pump blood to the lungs, causing blood to **back up** in the veins (including the inferior and superior vena cava).
- The backup is most noticeable in the **lower body** (feet, legs, abdomen) due to the pressure and gravity.
- The **superior vena cava** can be affected, but the primary cause of edema is the backup in the **lower veins** (from the inferior vena cava).

Systolic heart failure *(filling prob)*

Diastolic heart failure *(contr prob)*

You're right to be confused, and it's a great question! Let me clarify:

In **diastolic heart failure** (also called heart failure with preserved ejection fraction, HFpEF), the problem lies in the **filling** of the heart, specifically the **ventricles**. The heart is still able to contract normally during systole, but the ventricles become stiff and less able to relax during **diastole**. This means they can't fill with enough blood. So, when your slides mention "**diastolic heart failure**," they are referring to impaired filling due to a problem in **diastole**.

On the other hand, in **systolic heart failure** (also called heart failure with reduced ejection fraction, HFrEF), the issue is with the **contraction** of the heart during **systole**. The heart muscles become weakened and cannot contract forcefully enough to pump blood out efficiently.

So to recap:

- **Diastolic heart failure** = problem with filling (due to poor relaxation during diastole).
- **Systolic heart failure** = problem with contraction (due to weak heart muscle during systole).

Heart Failure

(has two phases)

Compensated

■ Compensated phase

- Supply temporarily meets the altered demand, no or very mild symptoms and signs

❖ Compensatory Mechanisms

- ✓ Increased Heart Rate:
 - Sympathetic = Norepinephrine
- ✓ Dilation:
 - Frank Starling = Contractility
- ✓ Neurohormonal:
 - Redistribution of Blood to the Brain

Decompensated

■ Decompensated heart failure:

- new or worsening symptoms/signs of dyspnoea, fatigue or oedema leading to hospitalisation or unscheduled medical care
- sortness of breath* →

• Main Causes of Heart Failure:

- Ischemic Heart Disease (35-40%)
- Cardiomyopathy (dilated) (30-34%)
- Hypertension (15-20%)

Other Causes:

- Valvular Heart Disease.
- Congenital Heart Disease. *Anatomy (خلقیه)*
- Alcohol and Drugs.
- Arrhythmias.

□ Pathophysiological Changes in HF

- Ventricular Dilatation. ✓
- Myocyte Hypertrophy. ✓
- Salt and Water Retention. ^{اقتباسی} ✓
- Sympathetic Stimulation. ✓
- Peripheral Vasoconstriction. ✓

• Symptoms = ما يشعر به المريض.

• Signs = ما يلاحظه الطبيب أو الأخصائي.

Symptoms:

- Exertional Dyspnea. *shortness of breath*
- Orthopnea. *→ hard to breathe while laying down*
- Paroxysmal Nocturnal Dyspnea.
→ losing breath suddenly while sleeping

■ Edema

- Bilateral lower extremity edema

■ Hypertension

- Hypertrophic Cardiomyopathy
(enlarging)

imp

Signs:

- Cardiomegaly. *→ enlarge of myocardium*
- Elevated Jugular Venous Pressure.
- Tachycardia.
- Hypotension. *B-P ↓*
- Bi-basal crackles. *→ wheezing*
- Pleural effusion. *→ edema in lung*
- Ankle Edema.
- Ascites. *→ edema (Albumin)*
- Tender hepatomegaly. *→ enlarge liver
↳ press spleen*

□ Classification of HF: *تصنيف*

According to the ability of doing a physical exercise

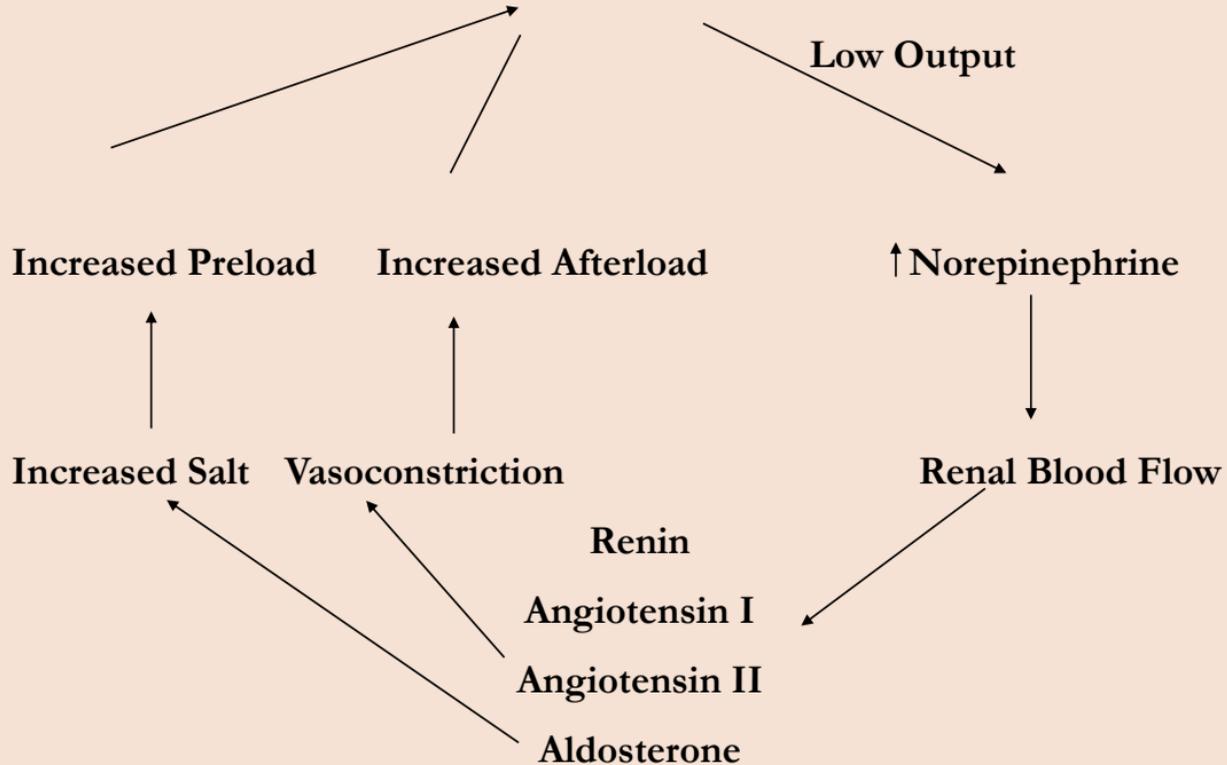
- I. **No limitation.** Normal physical exercise doesn't cause fatigue, dyspnea or palpitations.
- II. **Mild limitation.** Comfortable at rest but normal physical activity produces fatigue, dyspnea or palpitations.
- III. **Marked limitation.** Comfortable at rest but gentle physical activity produces marked symptoms of HF.
- IV. Symptoms of HF occur at rest and are **exacerbated** by any physical activity.

نمادہ Point of maximum Impulse (PMI)

- The **apex beat**, also called the **point of maximum impulse (PMI)**, is the furthestmost point outwards (laterally) and downwards (inferiorly) from the sternum at which the cardiac impulse can be felt. The cardiac impulse is the result of the heart rotating, moving forward, and striking against the chest wall during systole.
- The normal apex beat can be palpated in the **precordium left 5th intercostal space**, at the point of intersection with the *left midclavicular line*. In children the apex beat occurs in the **fourth rib interspace medial to the nipple**. The apex beat may also be found at abnormal locations; in many cases of dextrocardia, the apex beat may be felt on the right side. Lateral and/or inferior displacement of the apex beat usually indicates enlargement of the heart.

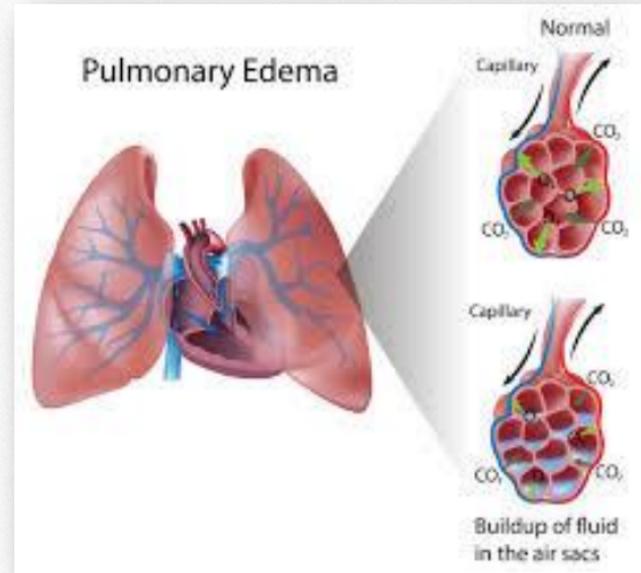
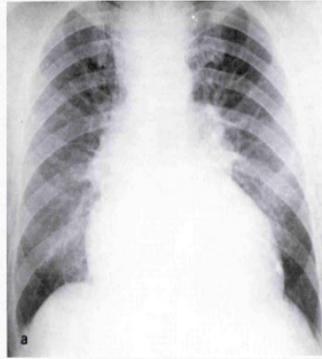
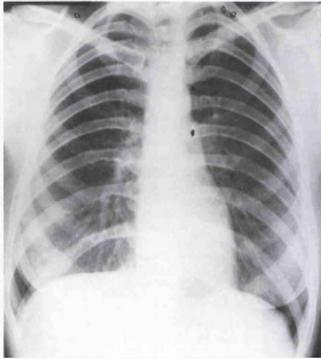
CHF Vicious Cycle

→ Related to renal



Acute Pulmonary Edema → caused death

a true life-threatening emergency



□ Treatment

- All
- Prevention. Control of risk factors
 - Lifestyle.
 - Treat etiologic cause / aggravating factors.
 - Drug therapy.
 - Personal care. Teamwork.

- Selected patients
- Revascularization if ischemia causes HF.
 - ICD (Implantable Cardiac Defibrillator).
 - Ventricular resynchronization.
 - Ventricular assist devices.
 - Heart transplant.
 - Artificial heart.
 - Neoangiogenesis, Gene therapy

Treatment Objectives*

- ↑ Survival
- ↓ Morbidity
- ↑ Exercise capacity
- ↑ Quality of life
- ↓ Neurohormonal changes
- ↓ Progression of CHF
- ↓ Symptoms

Treatment- Pharmacologic Therapy

✓ Diuretics → مدرات

← لتخفيف ادر لود على القلب

✓ ACE inhibitors

✓ Beta Blockers

✓ Digitalis → increases the ability of heart contraction → (conf) then

✓ Spironolactone → مدر للبول خاص باناسي :-

edema ↑
K ↑

✓ Others