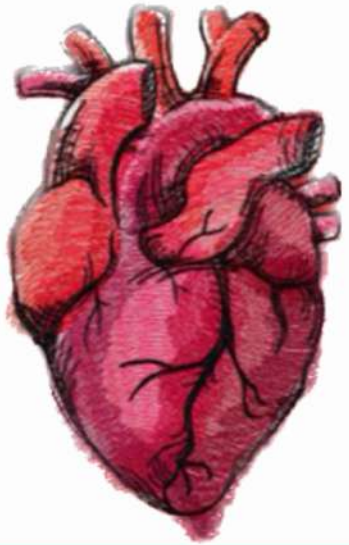
النادي الطبي

CARDIOVASCULAR SYSTEM

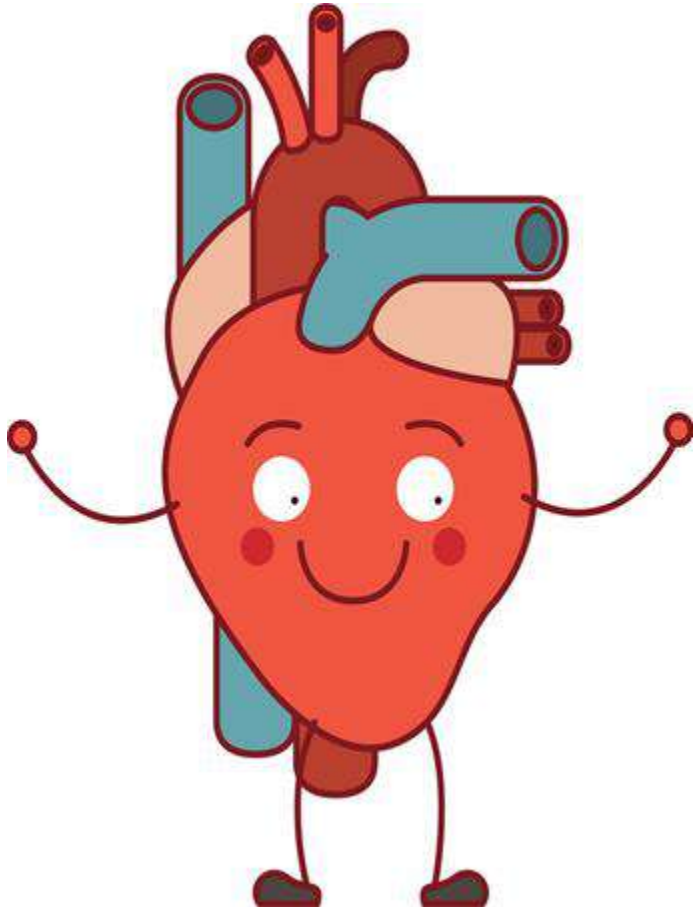


SUBJECT : Arteriosclerosis.

LEC NO. : 2

DONE BY : Shahd Abu-Tariah.

وقل رب زدني علماً



Arteriosclerosis
Cardiovascular Module 2024

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2024

مراجعة

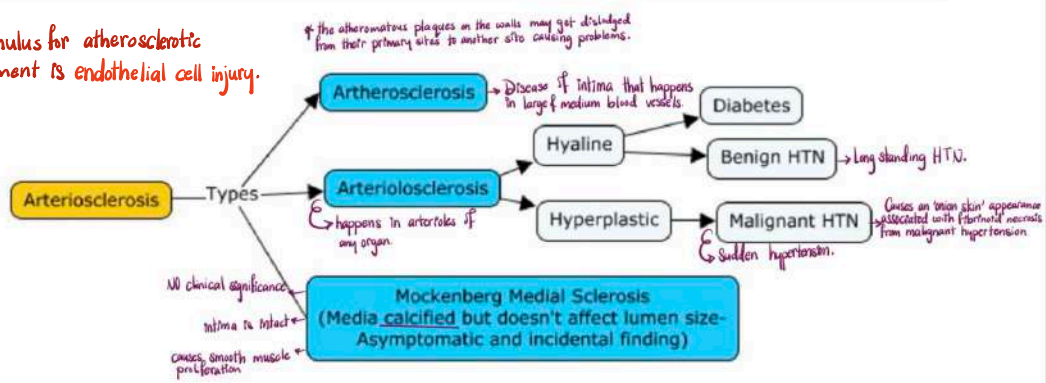
ARTERY + HARDENING

ARTERIO SCLEROSIS

*artery thicker, harder, less elastic *

Arteriosclerosis

Imp
- The main stimulus for atherosclerotic plaque development is endothelial cell injury.



Atherosclerosis takes place in:

1. Large blood vessels (aorta).
2. Medium sized blood vessels (Coronary blood vessels).
3. Popliteal artery → atherosclerosis of the popliteal artery causes peripheral arterial disease.
4. Carotid arteries → atherosclerosis of the carotid arteries cause stroke or cerebrovascular accident.
   - Supply blood to the brain & head.

* Endothelial cell lining is positioned as the first-line defense system to participate in immune responses.

ممكن يكون بسبب ال modifiable or non
modifiable causes مثل ما أخذنا بالمحاضرة الأولى.

Pathogenesis of atherosclerosis

.Endothelial cell "cracking" is due to the "shearing force" exerted by hypertension on endothelial cell lining. This mostly happens eothin the blood vessels branching.

Facilitates LDL entry. (Diabetes mellitus (leads to fat metabolism defect), obesity... etc lead to increased LDL accumulation.

➢ **Starts with chronic EC injury:** resulting in increased endothelial permeability. Also, dysfunctional injured endothelial cells **express adhesion molecules, e.g., (VCAM-1)** that binds **monocytes & T cells,** followed by their migration into the intima.

Endothelial cell injury > increased endothelial permeability> more LDL particles entry into the sub-intima> disease of intima (Atherosclerosis)

➢ **Accumulation of the lipoproteins**: **LDL and oxidized forms of LDL**

.Atherosclerosis is also called "Chronic inflammatory disorder/disease" because of the recruitment of chronic inflammatory cells like monocytes and lymphocytes.

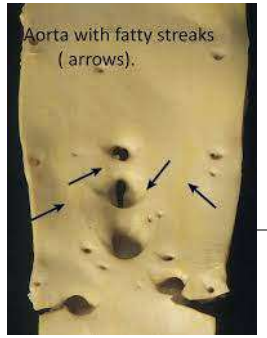
➢ **When monocytes** migrate into the intima, they transform into macrophages & foam cells (foam cells are macrophages engulfing oxidized LDL)

* للتذكير: بنسميهم monocytes بس بكونوا بالدم و بجيبوا macrophages بس يدخلوا بالـ tissue.

➢ Factors released during this process **induces SMC recruitment from media**

Monocytes release growth factor for smooth muscle cells recruitment from media to surround the area where the oxidized LDL & foam cells are present (in sub-intima).

بالإضافة لكل هذه المعلومات هو انه بس يصير في damage of EC رح يصير في عندي expression of VWF بالsub-endothelial collagen عشان يصير في adhesion of platelets بعدين activation of platelets و بعدين aggregation of platelets عشان يغطي مكان الdamage.
الplatelets رح تفرز مادة اللي هي Platelet derived growth factor عشان يصير في عندي overproduction of ECM و كمان الPlatelet derived growth factor يساعد بالmigration of smooth muscle cells من الmedia إلى الintima عشان يحيط الfoam cells and the inflammatory cells الموجودين بالمنطقة.



Pathogenesis of atherosclerosis

patches و plaques يعني early stages بالـ Fatty streaks بتصير .
و الـ atheroma لسا ما ظهرت.

- Lipid (oxidized LDL) accumulation in both cells macrophages & SMCs → **fatty streaks**
  - → Fatty streaks is one of the gross appearances of atherosclerosis (نستطيع رؤيته بالعين المجردة).
  - → Fatty streaks consist of foam cells (macrophages) & smooth muscle cells.
- Some of which die, releasing lipid & necrotic debris
  - → ROS that are released from activated macrophages cause LDL oxidation.

تذكروا بأنه بس يصير في LDL oxidation ، الـ LDL ما رح تقدر تطلع من الـ intima.
عشان هيك الـ macrophages لازم تدخل عشان تاكل الـ oxLDL و تتخلص منه.

- Activated macrophages produce **free radicles**, thus, aggravating LDL oxidation

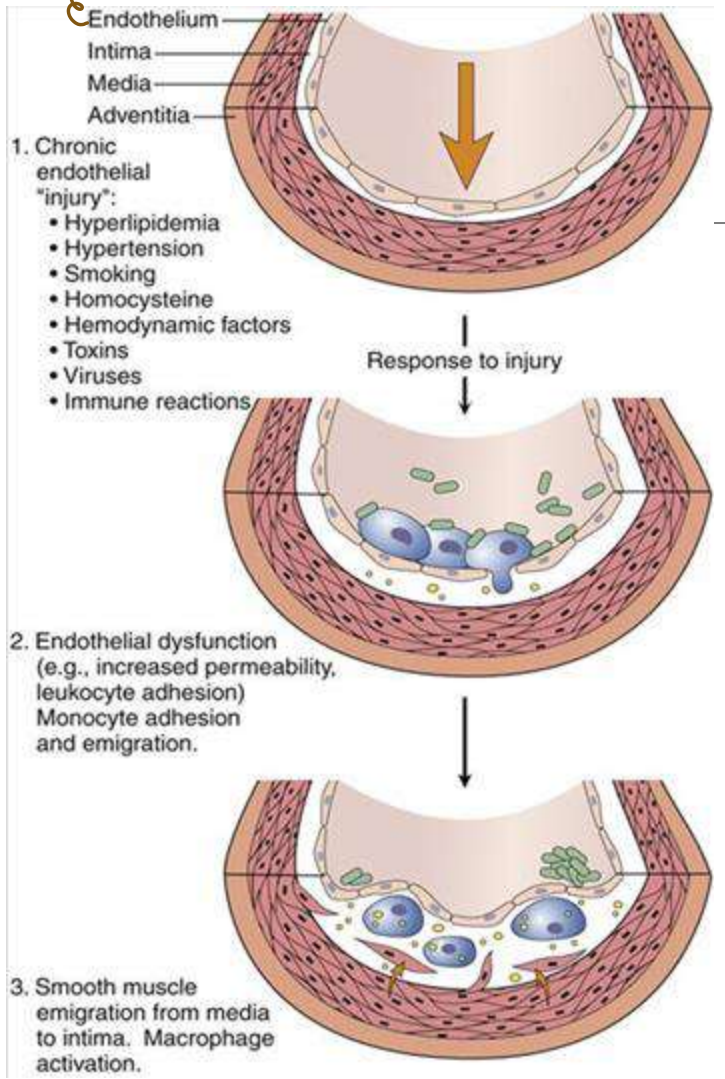
- The **activated T lymphocytes** elaborate INF-γ, which → **stimulate macrophages, ECs & SMCs** to release **growth factors GF**

- **GF** promote ? SMC proliferation ① & ECM synthesis (mainly collagen) ② → ① **stabilizes the atheroma**, and ② **produces a fibrous cap** covering the central core of lipid-laden cells & fatty debris

بصير في عندي زيادة بالـ collagen deposition
و بتتحول إلى صفائح متصلبة مكونة من نسيج ليفي و نسيج دهني.

central core : Lipid-laden cells, fatty debris, inflammatory cells & ECM.

لازم تكون smooth بدون أي تشققات أو مشاكل عشان يسهّل الـ blood flow ويمنع أي adhesion of platelets.



Atherosclerosis

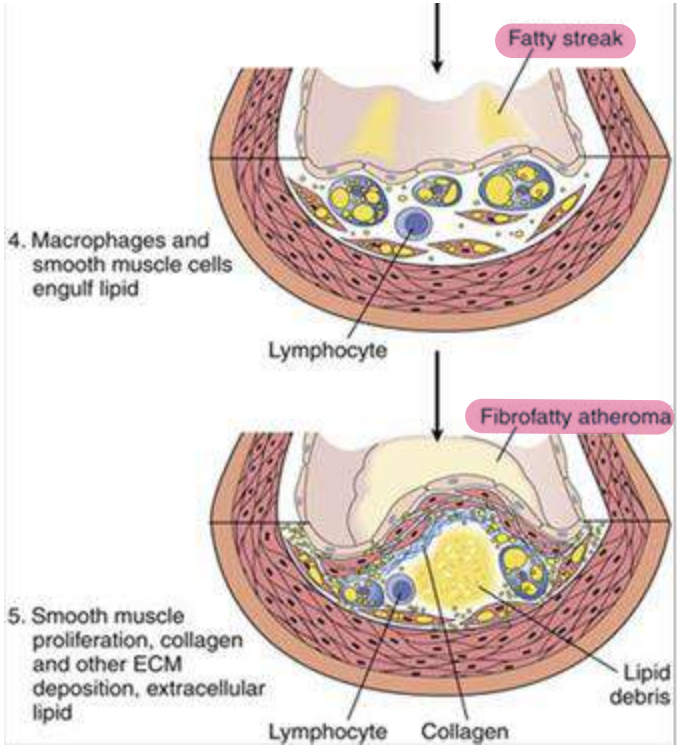
Evolution of arterial wall changes in the **response to injury hypothesis**.

1 Normal. → Endothelial cells have to be smooth to prevent platelet or monocytes adhesion & to facilitate the blood flow.

2. Endothelial injury with adhesion of monocytes & platelets to sites where endothelial has been lost

3. Migration of monocytes & smooth muscle cells (SMC) into intima.

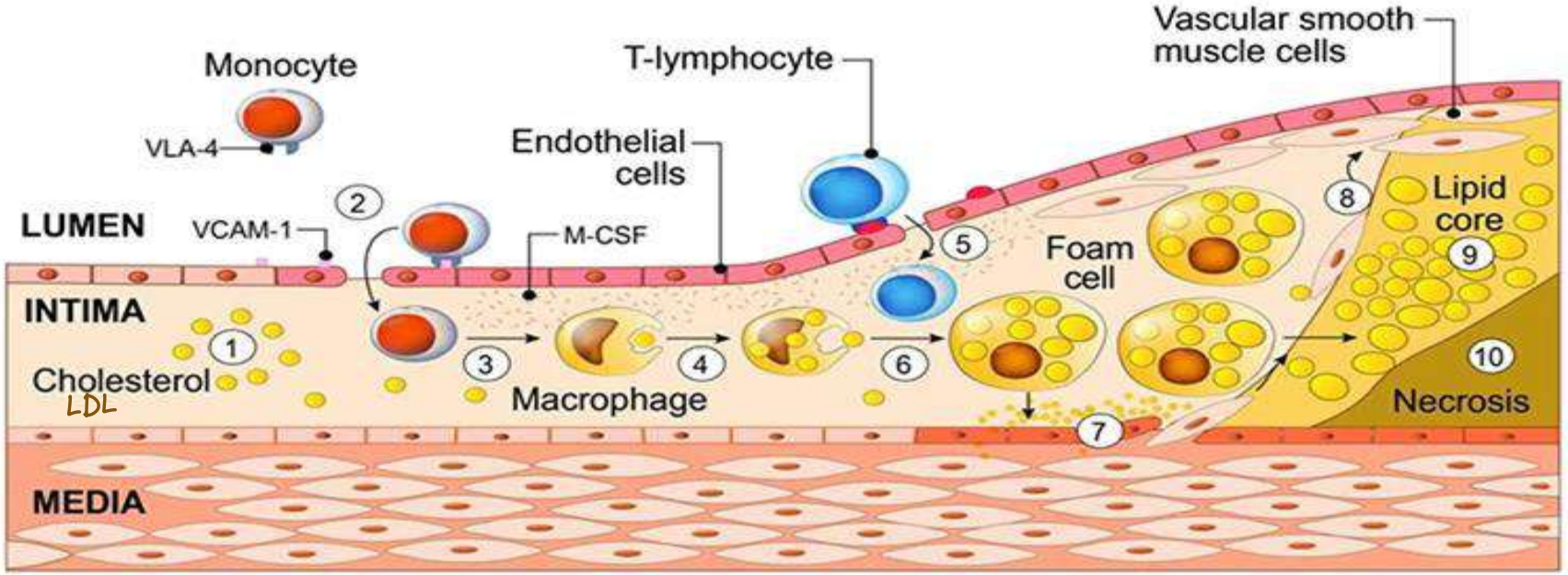
Atherosclerosis



4. SMC proliferation in intima with extracellular matrix (ECM) elaboration

5. Well-developed atheromatous plaque

Pathogenesis of atherosclerosis



Pathogenesis of atherosclerosis

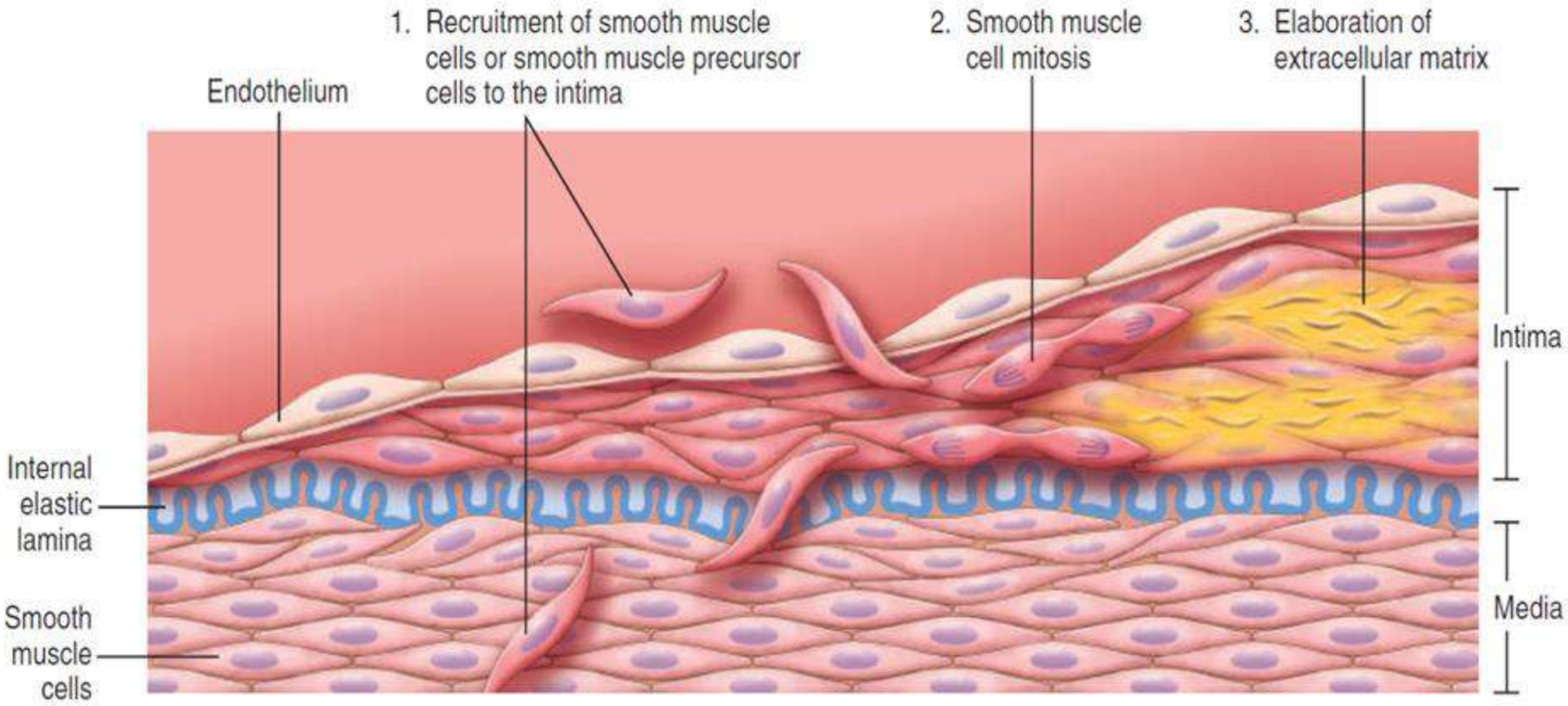
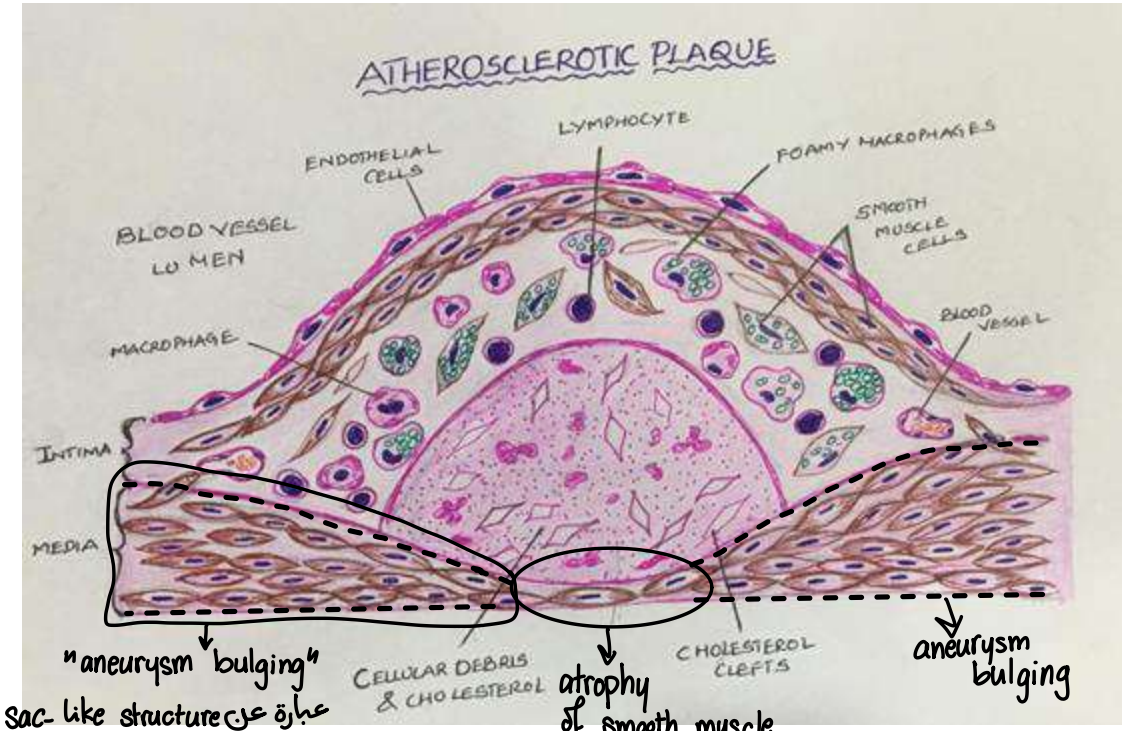


Fig. 10.6 Stereotypical response to vascular injury. Schematic diagram of intimal thickening, emphasizing intimal smooth muscle cell migration and proliferation associated with extracellular matrix synthesis. Intimal smooth muscle cells may derive from the underlying media or may be recruited from circulating precursors; they are depicted in a color different from that of the medial smooth muscle cells, to emphasize their distinct phenotype.

Pathogenesis of atherosclerosis Summary



A **plaques have three principal components**;

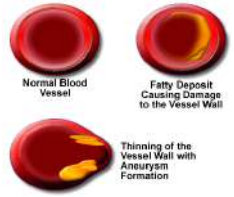
- ✓ **Cells** = SMCs + macrophages + T lymphocytes cells;
- ✓ **ECM** = collagen + elastic fibers
- ✓ **Lipids**: mainly oxidized LDL

AND COMPOSED MAINLY OF

(1) **Fibrous cap** (SMCs & collagen).

(2) **Necrotic core**, deep to the fibrous cap containing lipids + foam cells + debris from dead cells

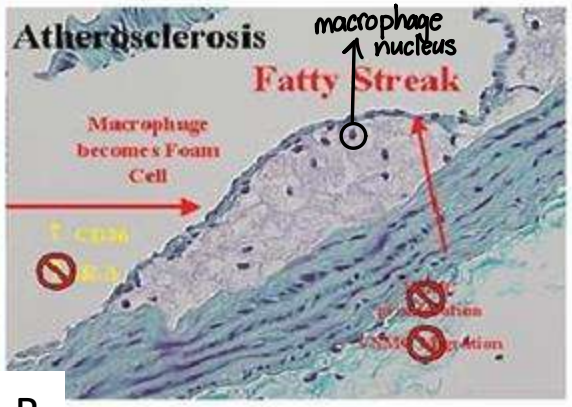
. **Aneurysm**: an abnormal swelling or bulge in a weakend blood vessel wall.



MORPHOLOGY OF ATHEROMAS
Fatty Streaks

Fatty streak
↳ the first grossly visible lesion in atherosclerosis.

A



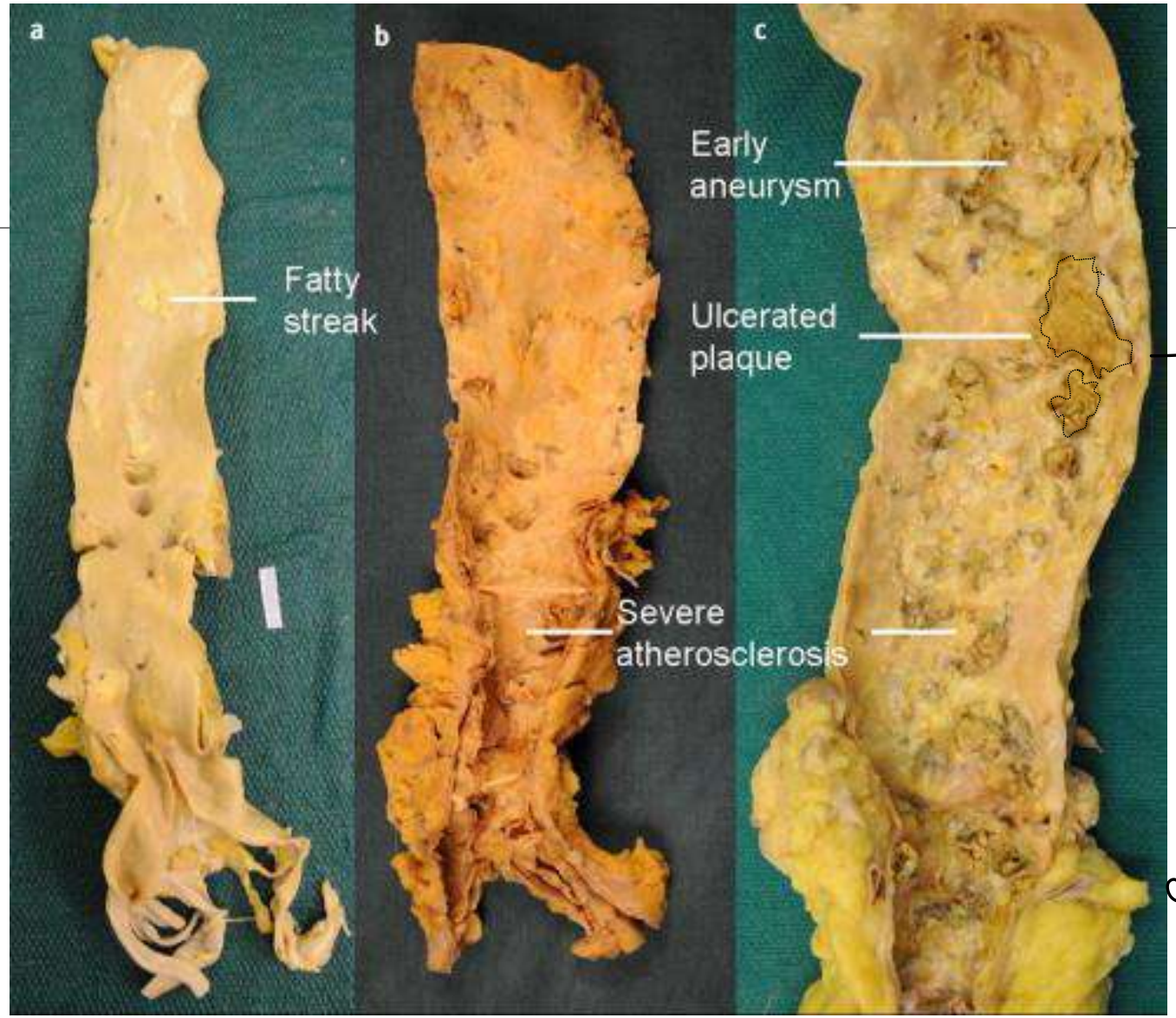
B

A. Grossly, the fatty streaks are multiple, minute **yellow flat spots**

B. Histology, fatty streaks are composed of **lipid-filled foam cells only**

!! مهم

الـ Fatty streak هو مجرّد.
بس لما يصير في inflammatory reaction و plaque formation ح يصير في خرز



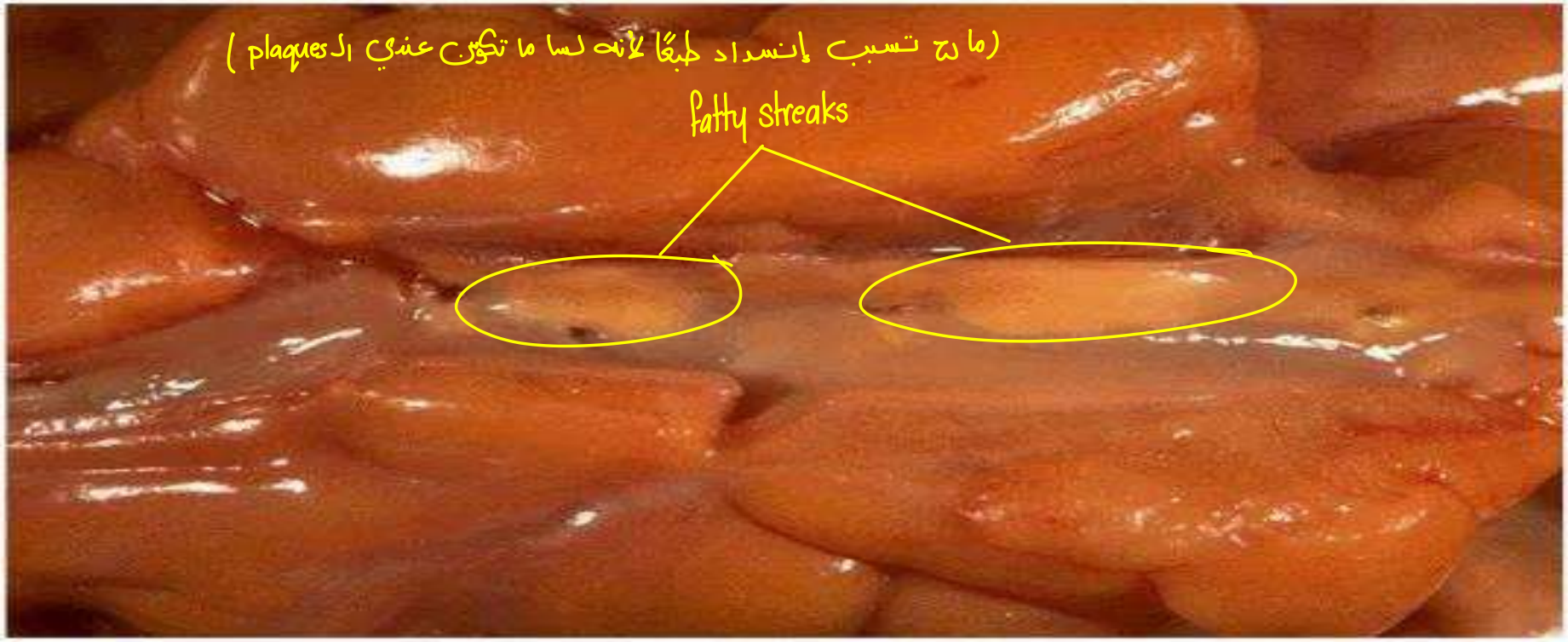
→.Plaques form due to the accumulation of inflammatory cells & foam cells.

.Atheromatous plaques: atheroma mass-like lesion projecting from the blood vessel wall to the lumen.

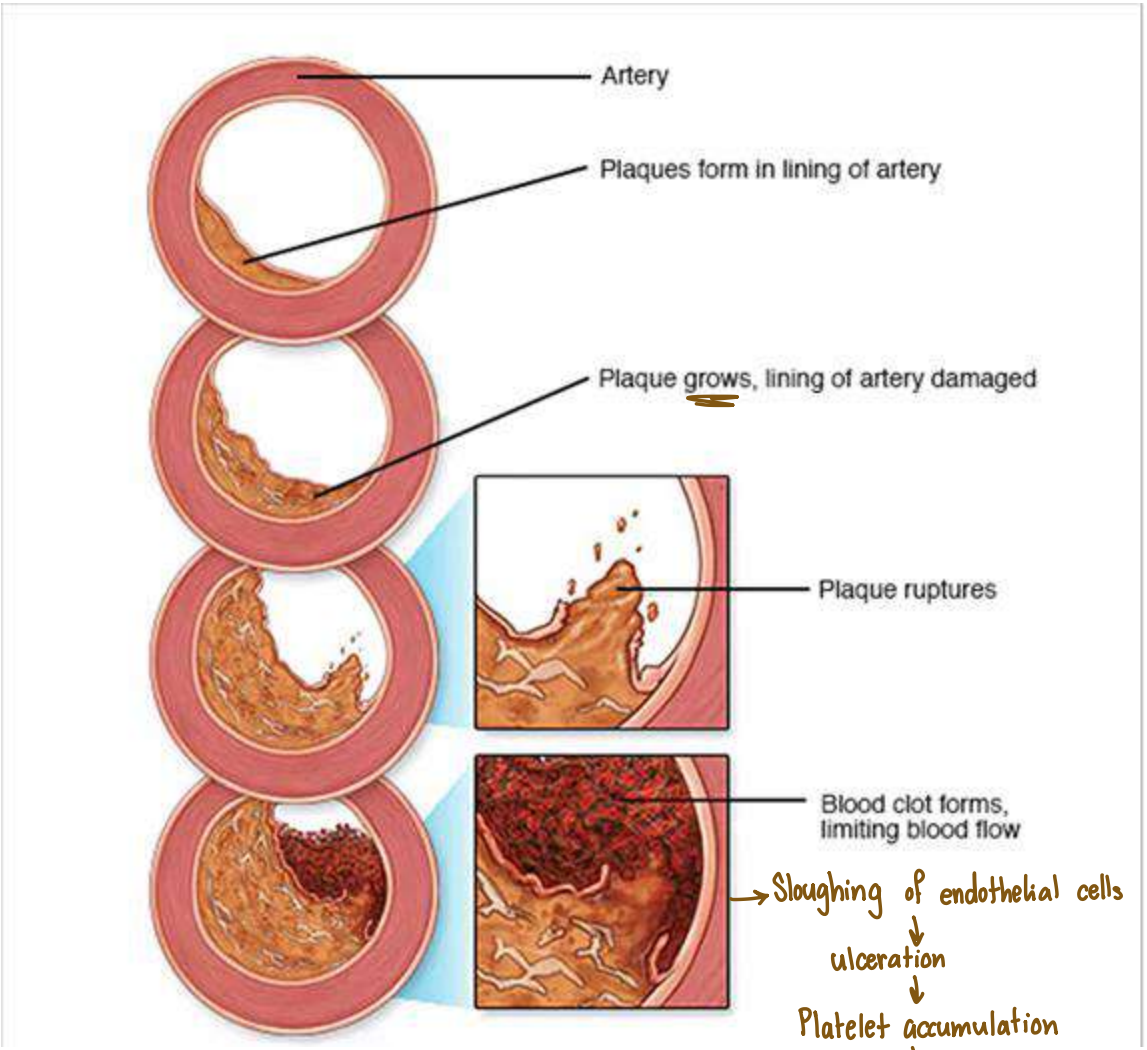
. فهذا رح يسبب تحرجات بالaorta و من أسبابها هي الـ pressure effect و الـ accumulation of inflammatory cells فبالتالي رح يصير في Sloughing للـ endothelial cell.

. لازم تعرفوا إنه الـthrombosis بالaorta ما بيقفل الـ aorta بسبب كبر حجم الaorta بس يمكن يصير لها dislodge و تتحول لـ emboli و تعمل مشاكل.

Fatty Streaks, Coronary Artery with Increased Fat

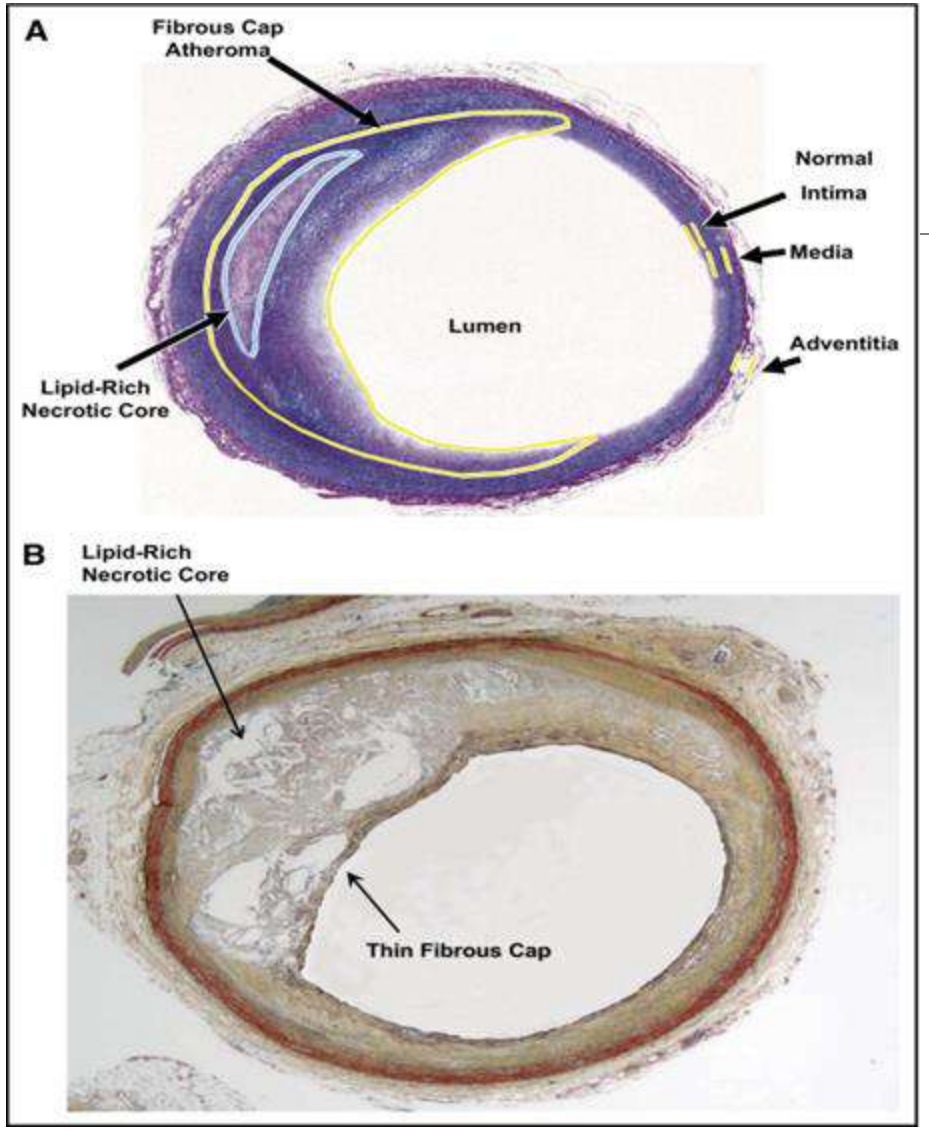


Pathogenesis of atherosclerosis



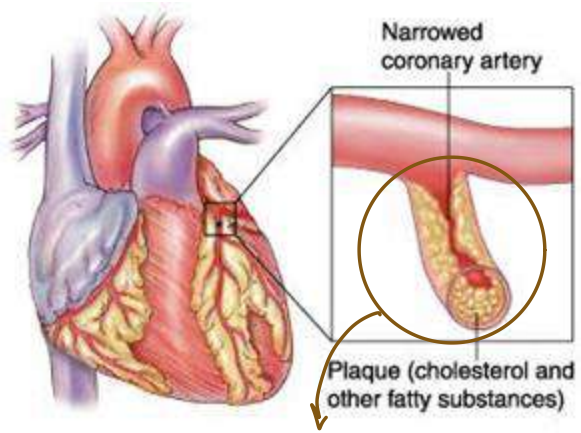
Rupture of the fibrous cap → superimposed thrombus → leads to catastrophic consequences (sudden occlusion of the vessel or thromboembolism)

.Rupture of the fibrous cap leads to ulceration.

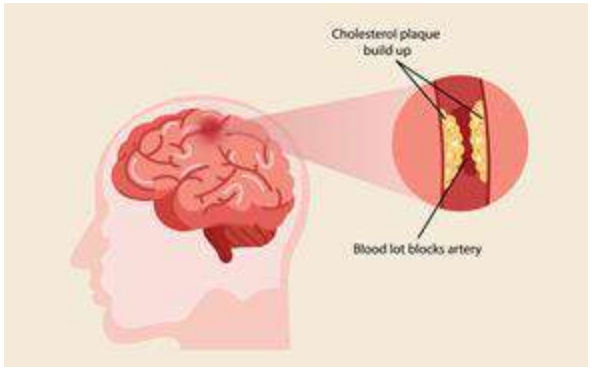


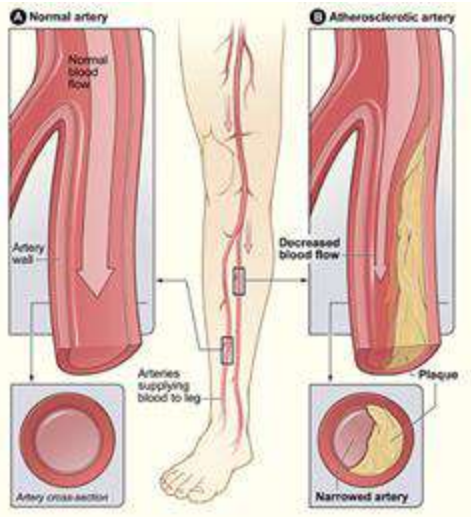
ماحكت شي إجاني ، بس
قرأت الصور.

Atheromas: histology



تصلب الشرايين حارت بال branching
لأنه لما توصل الدم بهذه المنطقة ح
تضغط بشكل قوي على ال endothelial cell
فبصير له damage.





Atherosclerosis (Vessels involved)

Most common vessels involved by atherosclerosis are:

Atherosclerosis first happens in the site of blood vessel branching. الدكتورة حكتها اكثر من خمس مرات

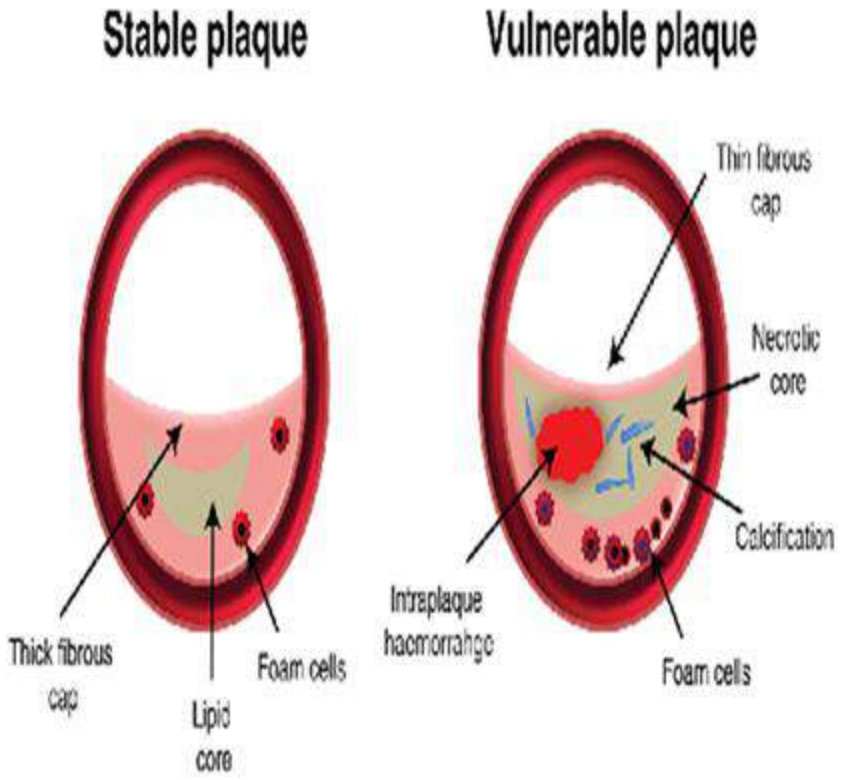
1. Coronary arteries (IHD)
2. Infrarenal abdominal aorta (aneurysms)
3. Popliteal arteries (gangrene)
4. Internal carotid arteries (stroke)
5. The vessels of the circle of Willis (stroke)

infrarenal abdominal aorta هي aneurysm أكثر مكان يصير فيها

vessels that supply the legs get clogged leading to gangrene.

both supply the brain.

Types of Plaque



easily ruptured.

Vulnerable plaques: leads to dramatic and fatal ischemic complications

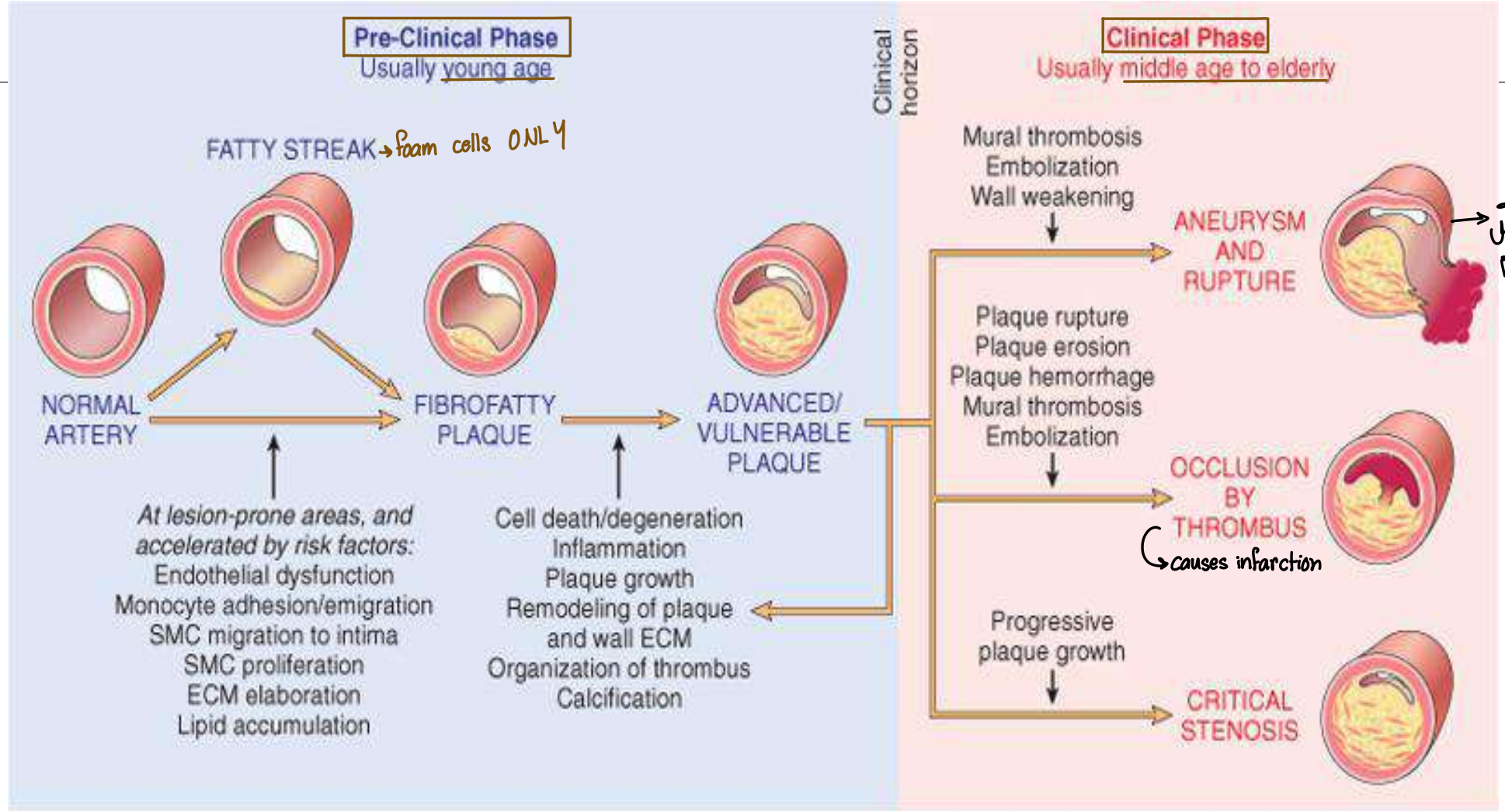
- Large numbers of foam cells and abundant extracellular lipid
- Thin fibrous caps
- Clusters of inflammatory cells. → Cause thin fibrous cap & increase the plaque's vulnerability.

stronger & more stable than vulnrable plaques.

Stable Plaques: leads to chronic ischemia

- Minimal lipid accumulation
- Dense collagen, thick fibrous cap
- Minimal inflammation
- **The factors involved to promote either a vulnerable plaque or a stable plaque are not clear yet, however, the major differences between a vulnerable and stable plaque are that vulnerable plaques have a "rich-lipid core" and a "thin fibrous cap" in comparison with the "thick fibrous cap" and the "poor lipid** → stable plaque الدهنات البرتقالي الفاتح
- **Whereas stabilized atherosclerotic lesions progress slowly, vulnerable plaques suddenly rupture and cause thrombosis, resulting in acute coronary syndrome (ACS).**

Natural history, morphologic features, main pathogenic events, & clinical complications of atherosclerosis.



جدًا جدًا خطيرة لدرجة إنه المريض يمكن ما يلحق يوصل المستشفى لأنه رح يصير الدم كله مجتمع بالبطن.

Effects and complications of atherosclerotic plaques

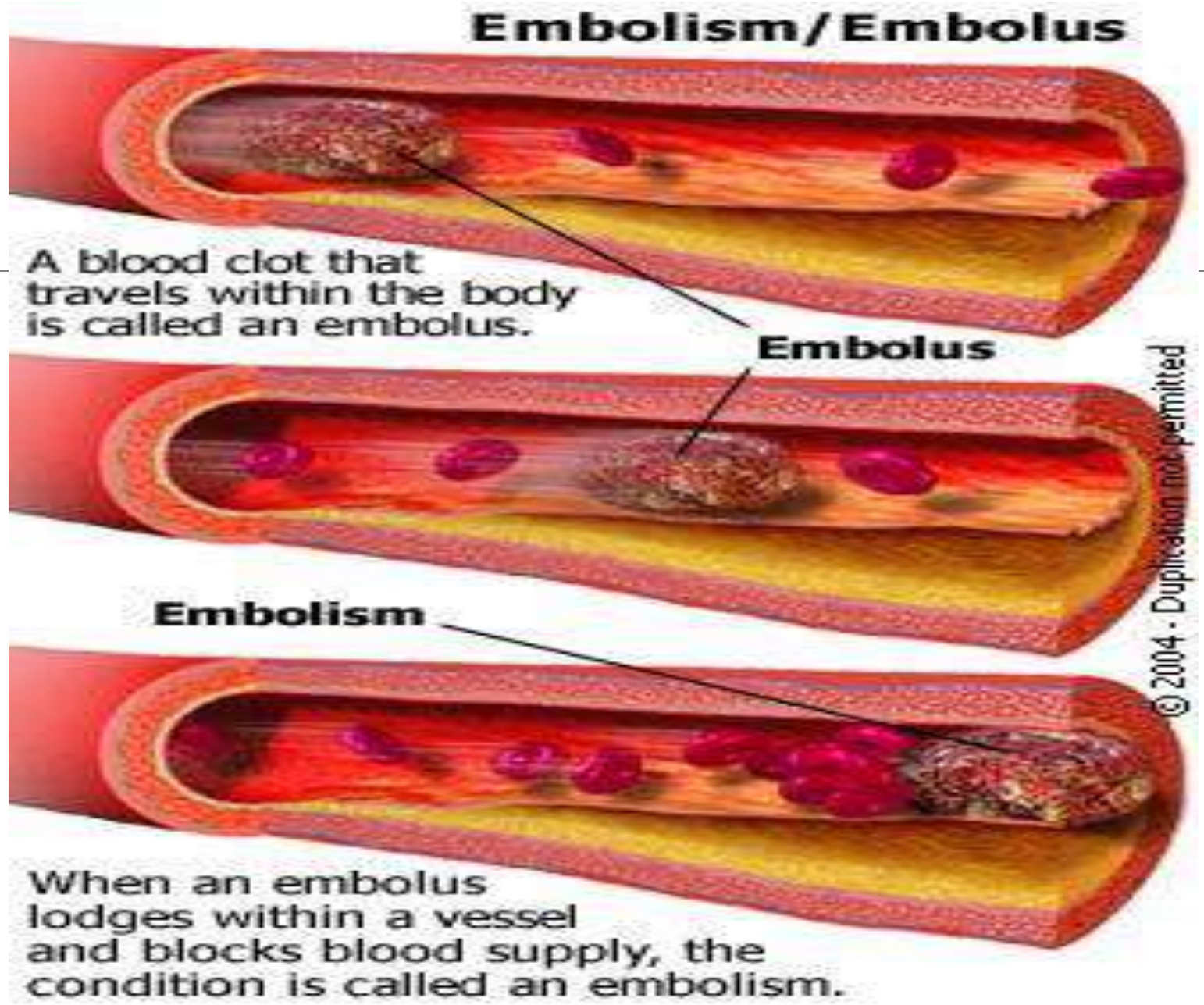
- **Narrowing**, or even complete occlusion of the arterial lumen, by progressively enlarging plaque causing ischemic injury → Poor perfusion → Poor blood supply → ischemia → infarction → death of tissue.

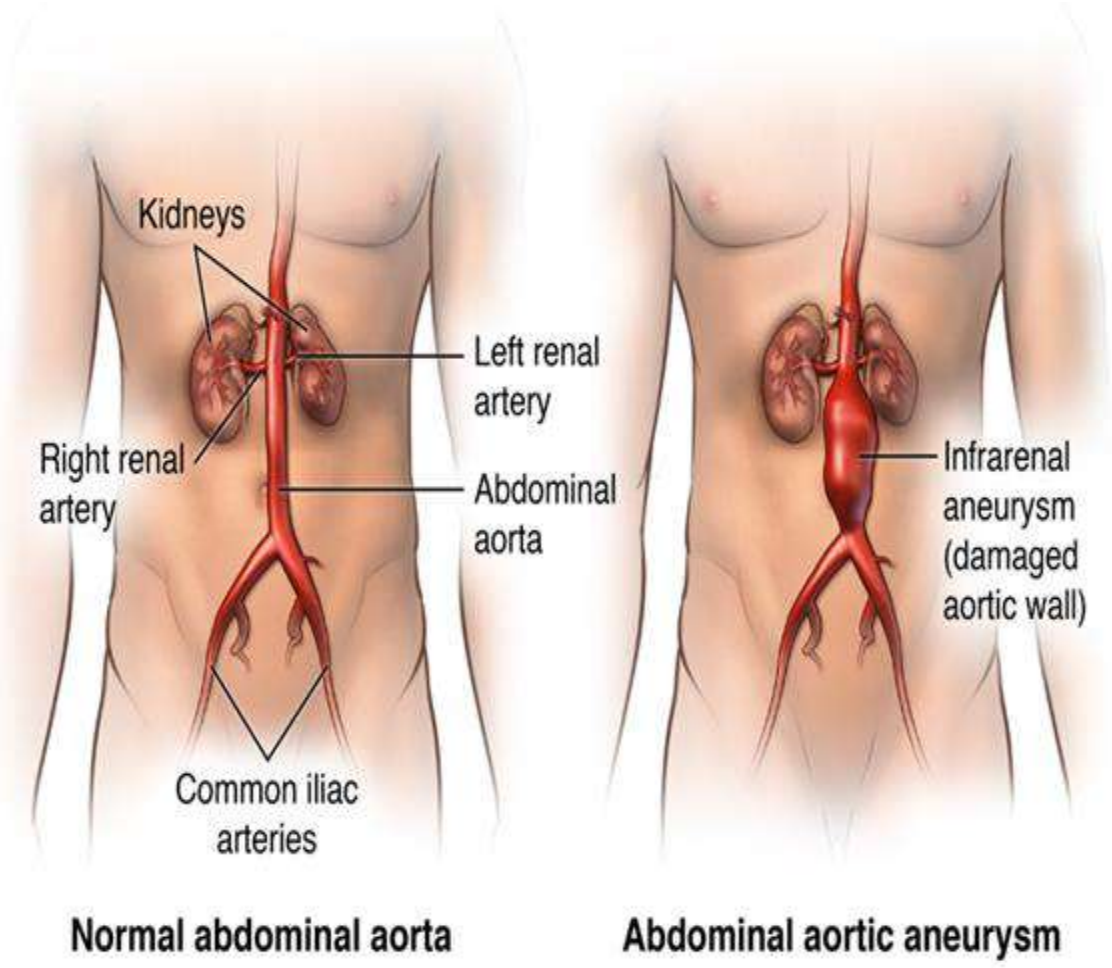
- **Ulceration, fissuring, erosion or rupture**, of the plaques fibrous cap exposes the bloodstream to highly thrombogenic substances and causes **thrombus formation**.
  - ↳ because of the plaque rupture, endothelial cells will get sloughed, attracting highly thrombogenic substances like platelets which will form a thrombus.

Such thrombi can: (I) occlude the lumen, partially or completely (II) dislodged, resulting in systemic thromboembolism.
- ↳ mainly happens in coronary arteries which causes ischemia or MI.

Note: If the patient survives the initial vascular occlusion, the thrombi may become organized & incorporated into the growing plaque.
- ↳ organized: fibrosis
- ↳ incorporated into the growing plaque: الـ thrombus رح تندمج مع الـ plaque فحجمها رح يكبر
- → infarction هون ما رح يصير في لأن الـ organization ما رح تسد الوعاء بس رح يصير في ischemia . كامل

- **Intra-plaque hemorrhage**


Embolism/Embolus
A blood clot that travels within the body is called an embolus.
Embolus
Embolism
When an embolus lodges within a vessel and blocks blood supply, the condition is called an embolism.
© 2004 - Duplication not permitted



Effects and complications of atherosclerotic plaques

very dangerous bcz it can get ruptured any time causing fatal consequences.

- **Aneurysm formation: atheroma** induce **pressure or ischemic atrophy of the underlying media**, with loss of elastic tissue in large arteries, this causes **weakness** of the arterial wall & development of **atheromatous aneurysms (commonest type of aneurysm) that may rupture.**

Lipid accumulation in intima → migration of SMC → atheroma → pressure effect of the underlying media → atrophy → loss of elastic tissue → blood vessel wall weakening → aneurysm.

Clinical Consequences of Atherosclerotic Disease

Ischemia in the heart > myocardial infarction > severe chest pain> fainting> severe hypotension.
Chest pain is the main symptom of ischemic heart disease caused by atherosclerosis or occlusion of blood vessels by thrombus.

✓Signs and symptoms related to ischemia in the heart, brain, kidneys, and lower extremities → حكينا قبل كم سلايد عن الأوعية الأكثر عرضة للـatherosclerosis فالـorgans اللي يعتمدوا على هذول الأوعية رح يصيرلهم مشاكل.

✓Myocardial infarction (heart attack), cerebral infarction (stroke), aortic aneurysms, and peripheral vascular disease (gangrene of extremities)
↳ dry gangrene is caused by atherosclerosis.

.sudden severe pain in the abdomen associated with hypovelmic shock due to aortic aneurysm rupture of the abdomen.
.Urgent surgery & treatment are needed.

✓**Atheroembolism:** ruptured plaque can discharge debris into the blood, producing microemboli composed of plaque contents.

✓Outcomes depends on **size of the affected vessel, size and stability of the plaques**

Atherosclerotic Stenosis

Positive remodeling feedback: widening or increasing the blood vessel's diameter in response to LDL accumulation.

بدنا نوسّع الـ blood vessel المتجمع فيها الدهون عشان تقدر الدم تحمل flow داخلها و بتأخر ظهور الـ atherosclerosis.

- **At early stages:** remodeling of the media tends to preserve the luminal diameter by increasing the vessel circumference.

بعدين رح يصير fibrosis.

الـ elastic tissue لساته بخير هون.

- **Critical stenosis:** chronic occlusion limits flow so severely that tissue demand exceeds supply.

- **Arterial remodeling** is currently being recognized as an important determinant in vascular pathology in which narrowing of the lumen is the predominant feature. Not only expansive remodeling (enlargement), but also constrictive remodeling (shrinkage) is observed.

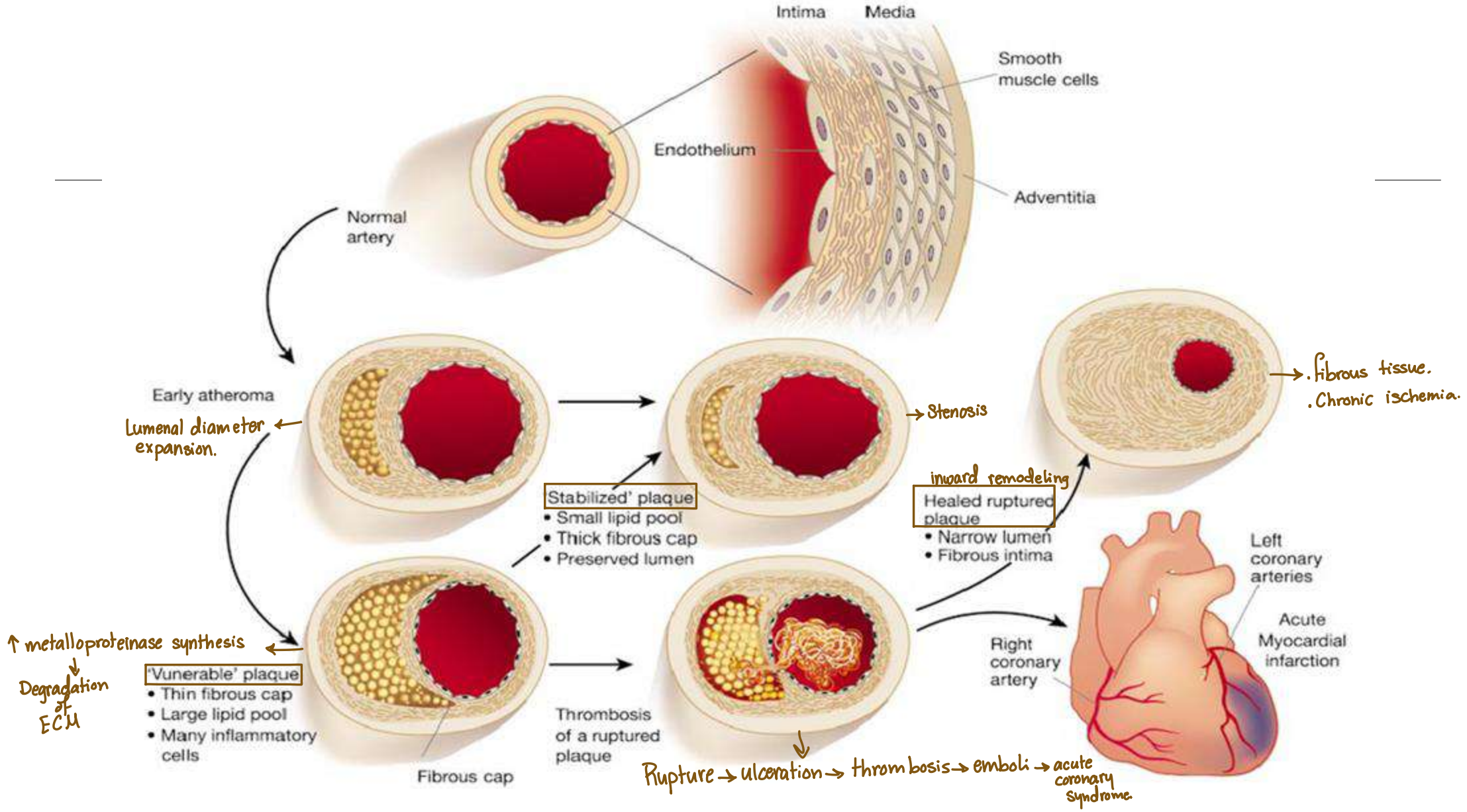
- **What is Remodeling in atherosclerosis?**

- Vascular remodeling is an active process of structural change that involves changes in at least four cellular processes: cell growth, cell death, cell migration, and the synthesis or degradation of extracellular matrix. → The blood vessel will undergo positive remodeling mechanism to preserve the blood flow.

- With development of atherosclerotic plaque, outward remodeling may preserve size of lumen. However, necessary degradation of matrix by metalloproteinases may increase risk of plaque rupture. Healing process after plaque rupture may result in inward remodeling → aneurysm.

→ vulnrable plaque

- Mechanisms involved in arterial remodeling include: ① fibrosis, ② hyperplasia of the arterial intima and media, ③ changes in vascular collagen and elastin, ④ endothelial dysfunction, and ⑤ arterial calcification. Migration and proliferation of vascular smooth muscle cells (VSMCs) contribute to thickening of the arterial intima.


Intima
Media
Smooth muscle cells
Endothelium
Adventitia
Normal artery
Early atheroma
Lumenal diameter expansion.
Stabilized' plaque
• Small lipid pool
• Thick fibrous cap
• Preserved lumen
Stenosis
inward remodeling
Healed ruptured plaque
• Narrow lumen
• Fibrous intima
. fibrous tissue.
. Chronic ischemia.
↑ metalloproteinase synthesis
Degradation of ECM
'Vunerable' plaque
• Thin fibrous cap
• Large lipid pool
• Many inflammatory cells
Fibrous cap
Thrombosis of a ruptured plaque
Left coronary arteries
Acute Myocardial infarction
Right coronary artery
Rupture → ulceration → thrombosis → emboli → acute coronary syndrome.

Prevention of atherosclerosis

Primary prevention programs:

Aim to delay atheromatous plaque formation in persons who have not yet suffered a serious complication. These involve cessation of cigarette smoking + control of hypertension + weight loss + exercise, & lowering total & LDL blood cholesterol levels while increasing HDL

Secondary prevention programs: → for non-modifiable causes & persons with past history of IHD or stroke.

It aims to **prevent recurrence** of IHD or stroke in symptomatic patients, involving medications (**aspirin** antiplatelet agent), **statins**, & **beta-blockers** (to limit cardiac demand).

↓ cholesterol

imp. **What is the gold standard diagnostic test for atherosclerosis?**

It is invasive coronary angiography (ICA) قسطرة has remained the gold standard upon which other diagnostic tests are measured. →

لما الدكاترة يبلشوا يحكوا إنه عند الشخص ischemic heart disease، دح يعملوا قسطرة (ICA) حتى يشوفوا مدى تضيق الـcoronary blood vessels عن طريق تدخيل شبكة أو بالون عشان يحافظوا على الـ blood flow in the Lumen وبنفس الوقت بيعطوا anti-coagulant حتى يمنعوا أي thrombosis.

Arteriosclerosis

Arteriosclerosis **is hardening of arterial wall**

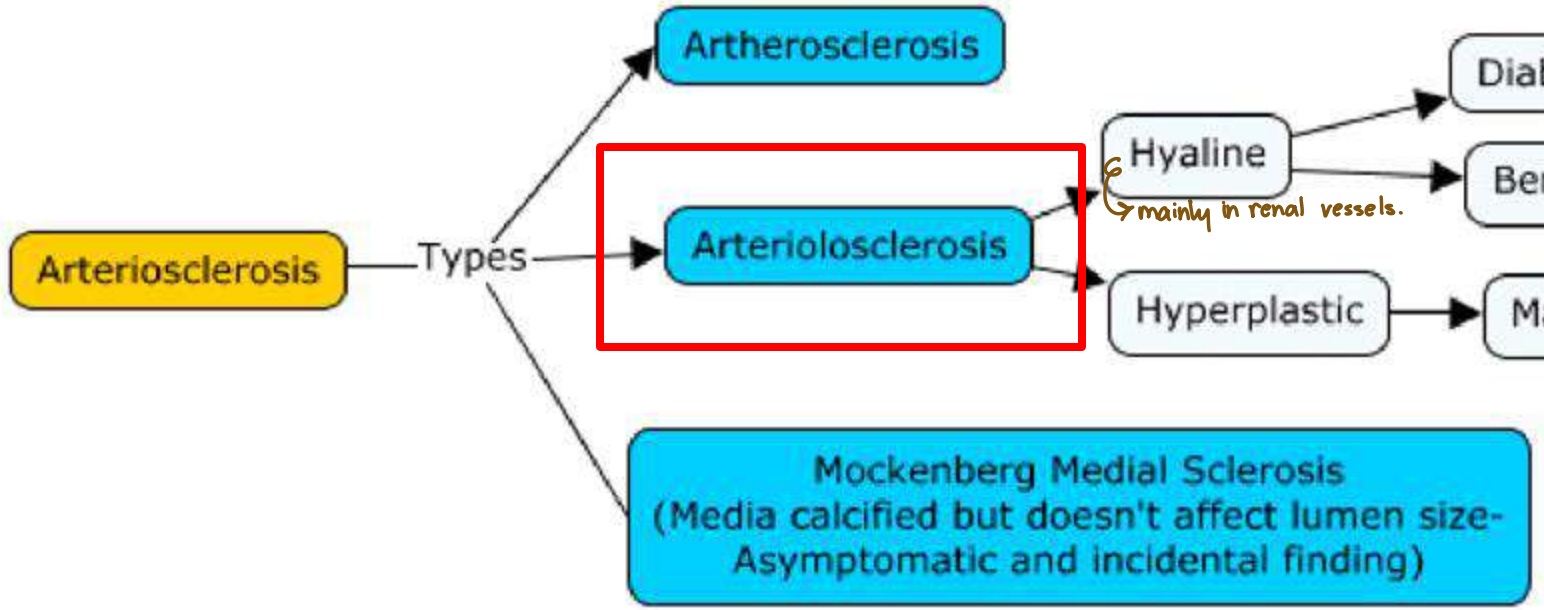
Three patterns

Done ☑ 1. Atherosclerosis

1. **Arteriolosclerosis - thickening of small vessels. Why? Wall thickens due to ① protein deposition (hyaline arteriolosclerosis) or ② hyperplasia of smooth muscle (hyperplastic arteriolosclerosis)**
   - Seen in malignant hyperplasia.

1. Monckeberg medial sclerosis

Arteriosclerosis



→Long standing hypertension.
يعني المريض بعاني منها لفترة طويلة.

→SUDDEN increase of BP or the patient has a pre-existing HTN that's developed into a malignant HTN.
(Diastole >120)

→Fibrinoid necrosis can take place in the arterioles OR hyperplastic (proliferation) changes of the SMC of the media leading to changes of the blood vessel constriction

Artherosclerosis

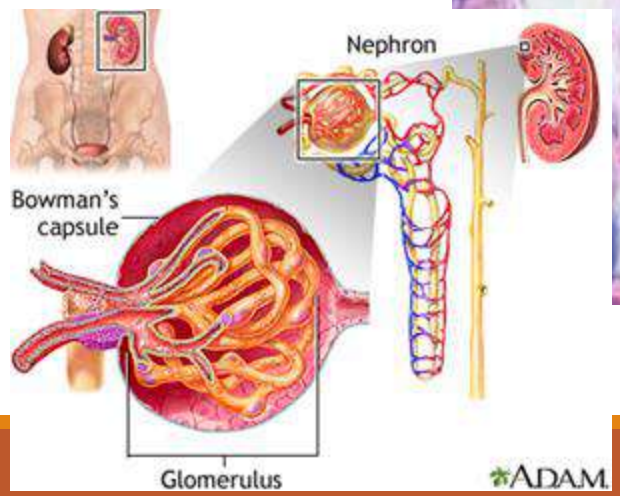
Arteriolosclerosis

1. Hyaline arteriolosclerosis:

- Seen in benign hypertension and DM. → They cause contracted fibrotic kidney. (مشروحة بالمخطط اللي بالنقطة الثالثة بهاي الصفحة)
- Pink hyaline thickening of the arteriolar walls, and luminal narrowing
- In the kidneys: narrowing leads to diffuse vascular compromise and **nephrosclerosis (glomerular scarring).** → ↓ blood supply to the kidney → ischemia → nephrotic sclerosis → interstitial fibrosis

Contracted fibrotic kidney ← tubular atrophy ↑

- Seen in **elderly** patients (normo- or hypertensive)
- Common in **diabetic microangiopathy**

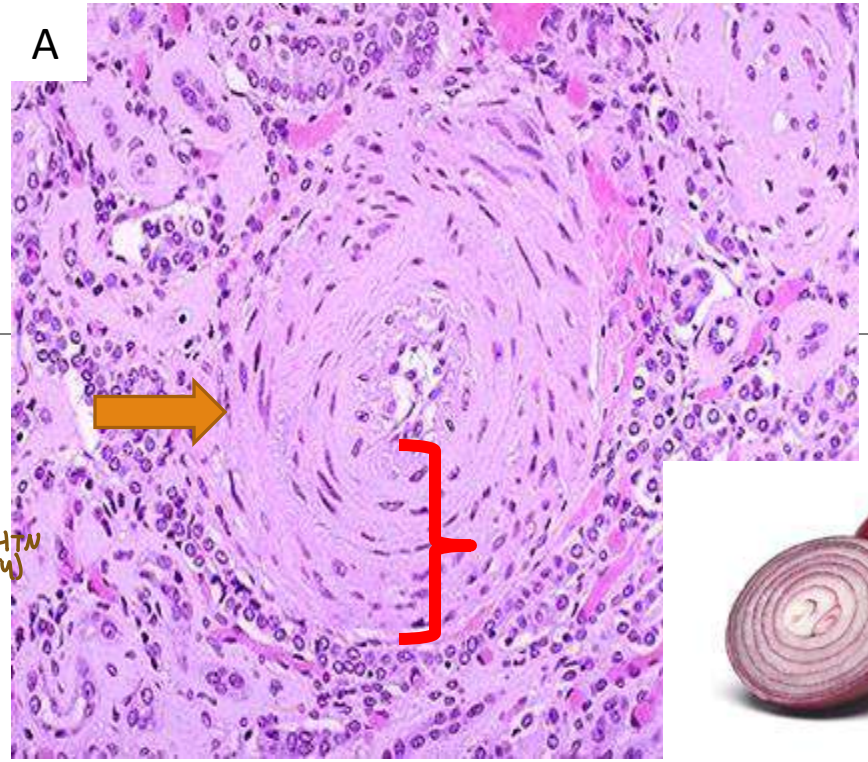


Arteriolosclerosis

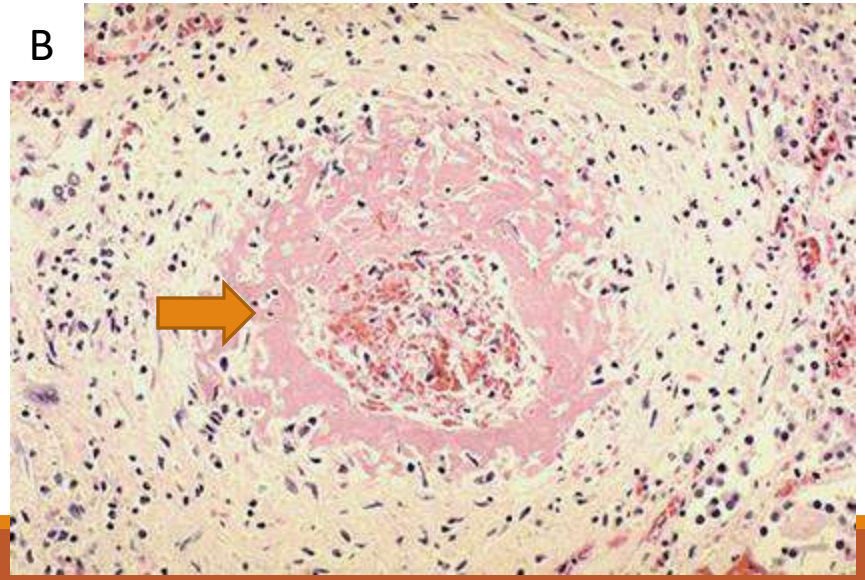
2. Hyperplastic arteriolosclerosis:

- **Seen in severe (malignant) hypertension.** → happens de-novo (without HTN history) or in pre-existing HTN.
- Onionskin concentric, laminated thickening of walls and luminal narrowing (figure A)
- The laminations consist of smooth muscle cells and thickened, reduplicated BM
- In malignant hypertension: accompanied by fibrinoid deposits and vessel wall necrosis **(necrotizing arteriolitis)**, prominent in the kidney (figure B)

A



B



Arteriosclerosis

Arteriosclerosis **is hardening of arterial wall**

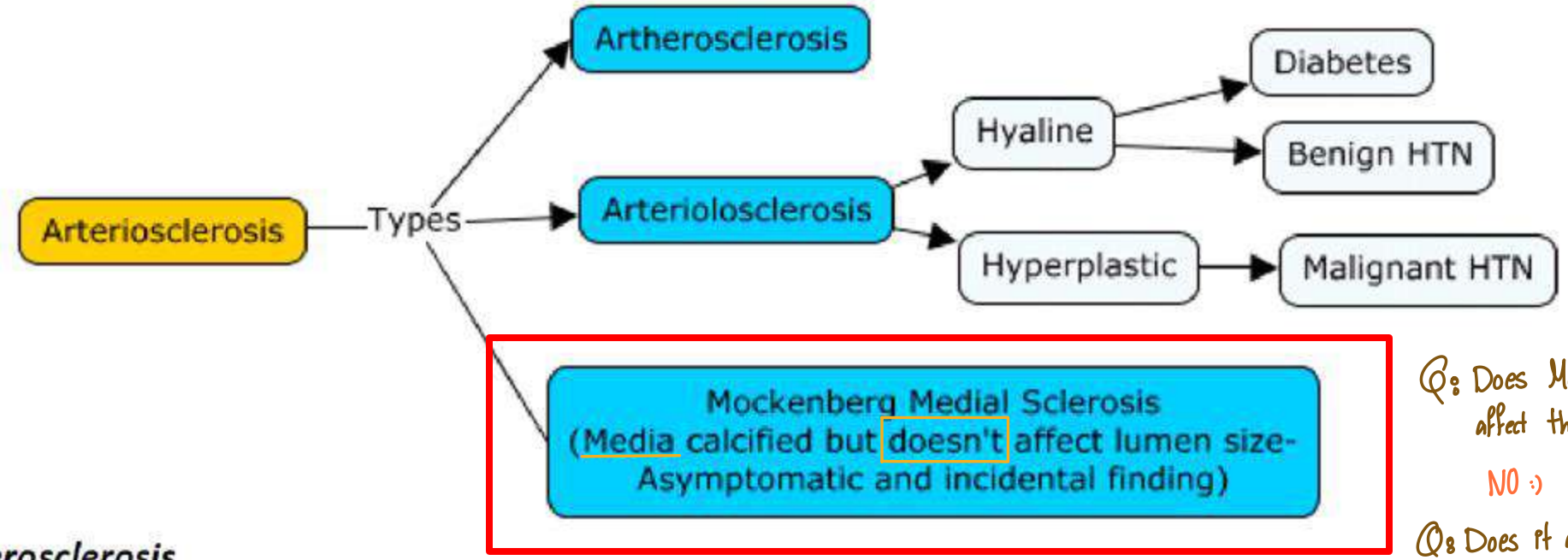
Three patterns

Done ☑ 1. Atherosclerosis

Done ☑ 2. Arteriolosclerosis

1. **Monckeberg medial sclerosis - calcification of media. Not very clinically significant** → بنسميها M-disease because it involves: media - muscular blood vessels - medium sized blood vessels - in males - Pipe stem appearance.

Arteriosclerosis



Q: Does Monckberg medial sclerosis affect the lumen size?

NO :)

Q: Does it affect the intima?

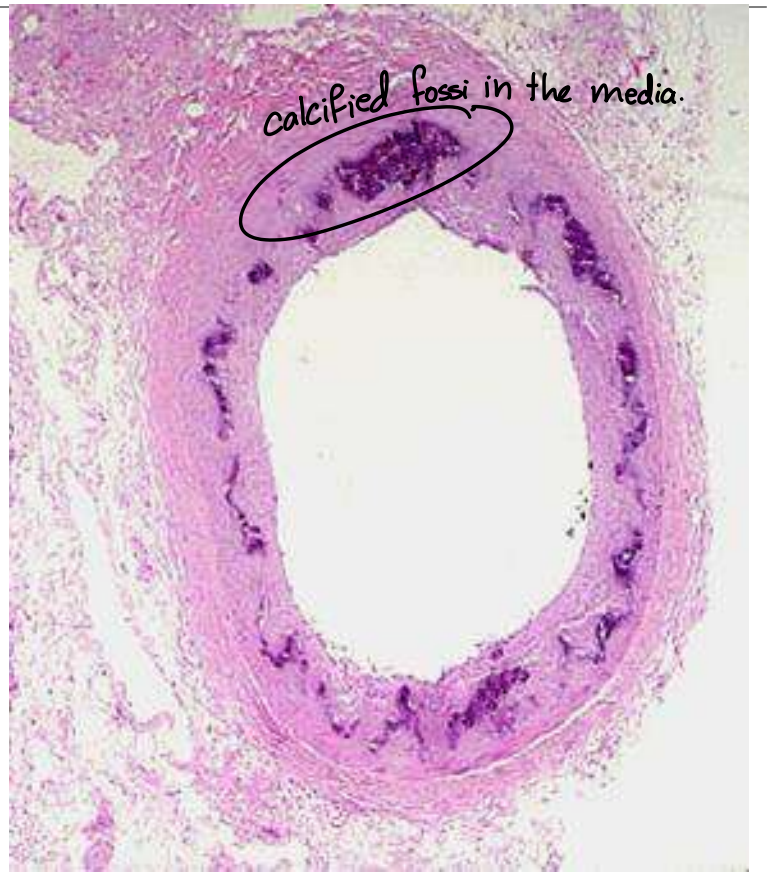
NO :)

Artherosclerosis

Monckeberg medial sclerosis

Monckeberg medial sclerosis:

- Calcified deposits in muscular arteries
- Seen in adults (older than 50 years)
- Not clinically significant



Monckeberg medial sclerosis

Monckeberg medial sclerosis