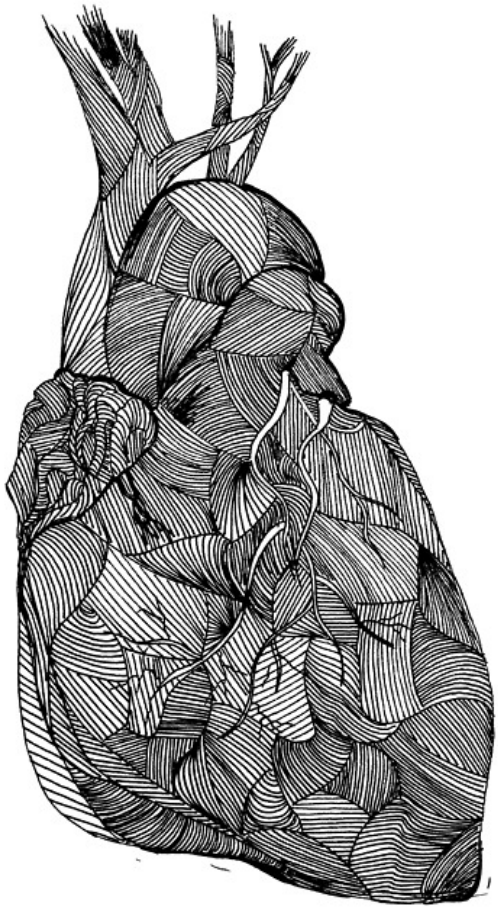
Risk factors & pathogenesis of atherosclerosis



Objectives:

(1) Understand the pathogenesis and clinical consequences of atherosclerosis.
(2) Risk factors of atherosclerosis.
(3) Pathogenesis of the fibrolipid atherosclerotic plaque.
(4) Clinical complications of atherosclerosis.
(5) Commonest sites for the clinically significant coronary atherosclerosis.

Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: **Pathology Edit**

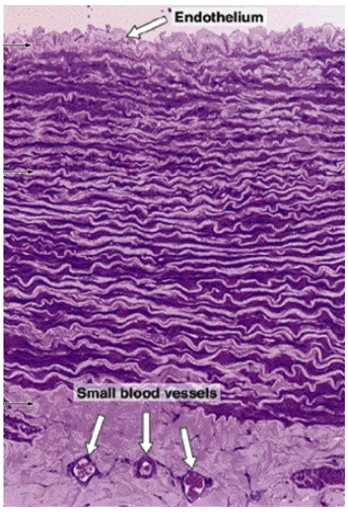
Histology of Normal Blood Vessels & Capillaries.

Arteries.

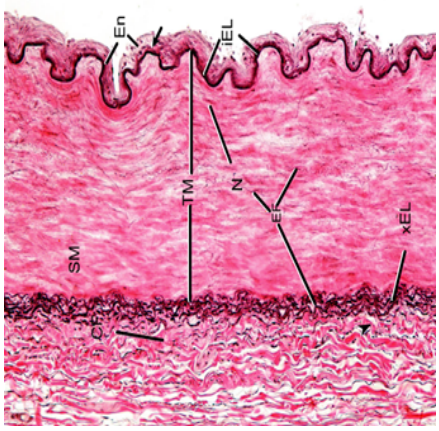
- **Large elastic arteries** (e.g., aorta, arch vessels,subclavian,common iliac and pulmonary arteries).
  - Have many elastic fibers & they are pulsatile.[1]

- **Medium-sized muscular arteries** (e.g., coronary, brachial,ulnar and renal arteries).
  - Here, the media is composed primarily of smooth muscle cells. Atherosclerosis occurs mainly in larger, muscular arteries.

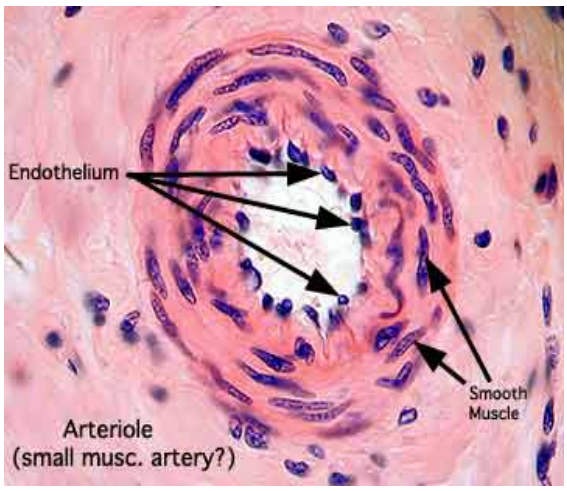
- **Small arteries & arterioles.** The media in these vessels is mostly composed of smooth muscle cells. Arterioles are where resistance is regulated, small changes in arteriolar lumen size have profound effects on blood pressure. Sympathetic nerve fibers modulate arterioles by vasoconstriction (mainly by alpha1 receptors). This has a profound effect on blood pressure.



Elastic artery



medium-sized muscular artery



arteriole

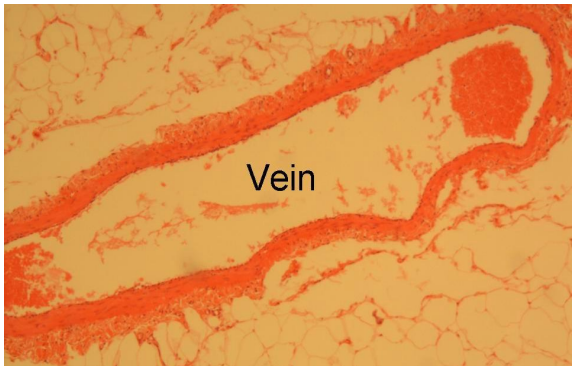
Capillaries.

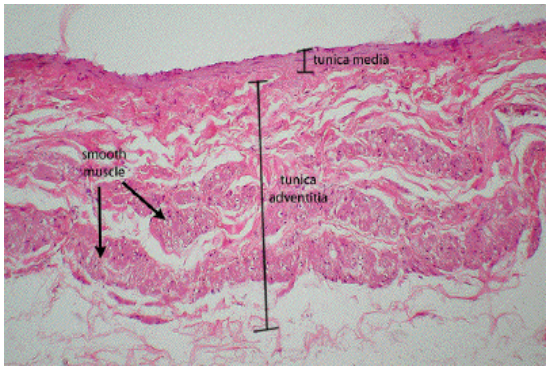
- Diameter of RBC. These vessels are lined by endothelial cells and partially surrounded by smooth muscle cell–like cells called *pericytes*.
- A single capillary has a very small radius & very slow blood velocity. This makes it an ideal place for exchange (of nutrients, wastes, & gases for example)

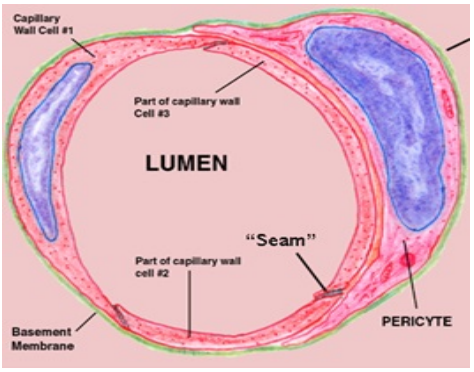
Venules/Veins.

Compared with arteries, veins have a larger diameter, larger lumen, and thinner walls; with less distinct layers. All adaptations to the low pressures found on the venous side of the circulation. Thus, veins are compressible, penetrable by tumor or inflammatory processes. In veins in which blood flows against gravity, backflow is prevented by **valves**.

[1] Undergoing pulsation.

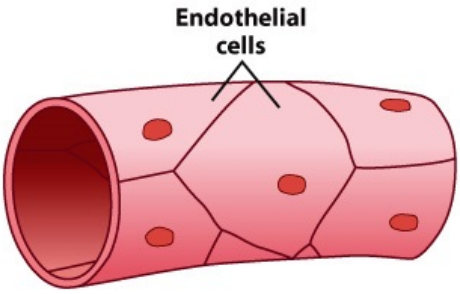






Lymphatics: Drain excess interstitial fluid & pass through nodes.

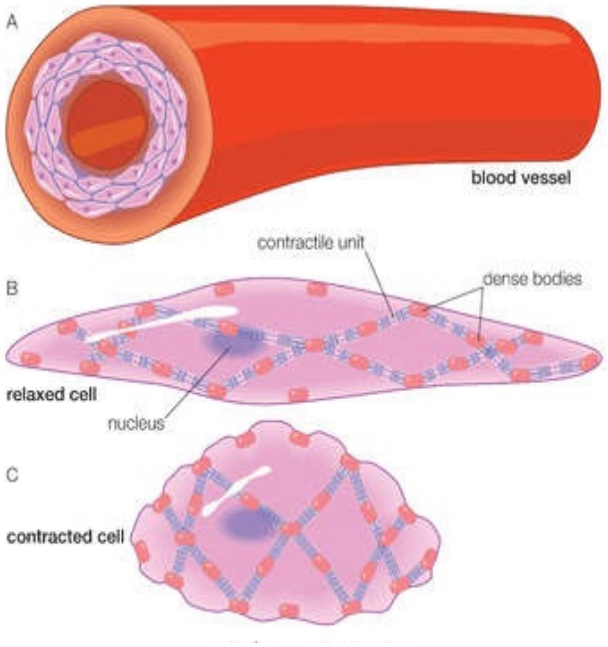
Endothelial cells.



The endothelium is a **single cell thick** lining of endothelial cells and it is the **inner** lining of the entire cardiovascular system (heart,arteries, veins and capillaries) and the lymphatic system.
It is in direct contact with the blood/lymph and the cells circulating in it.
Endothelial structural and functional integrity is fundamental to the maintenance of vessel wall homeostasis and normal circulatory function.

Smooth muscle cells (SMC).

SMCs are present in the **vascular media**. also they mediate the vasoconstriction or vasodilation* that occurs in response to physiologic or pharmacologic stimuli. Smooth muscle cells participate in both normal vascular repair and pathologic processes such as *atherosclerosis.*
* Decreased sympathetic stimulation is what causes vasodilation.



When SMCs are stimulated by any vascular injury or dysfunction, they:

1. Migrate from the media to the intima.
2. In the intima they lose the capacity to contract and gain the capacity to divide. So they multiply/proliferate as intimal SMCs.
3. They synthesize collagen, elastin and deposit extracellular matrix (ECM).

Atherosclerosis (AS).

[How cholesterol clogs your arteries (atherosclerosis)]

Atherosclerosis is characterized by intimal lesions called atheromas/ atheromatous/ fibrofatty plaques. Atheromatous plaques are raised lesions composed of soft grumous [2]lipid cores (mainly cholesterol and cholesterol esters, with necrotic debris) covered by fibrous caps, which protrude into and obstruct vascular lumen and weaken the underlying media. This may cause the formation of an aneurysm [3]or more dangerously, the rupture of the vessel leading to hemorrhage.

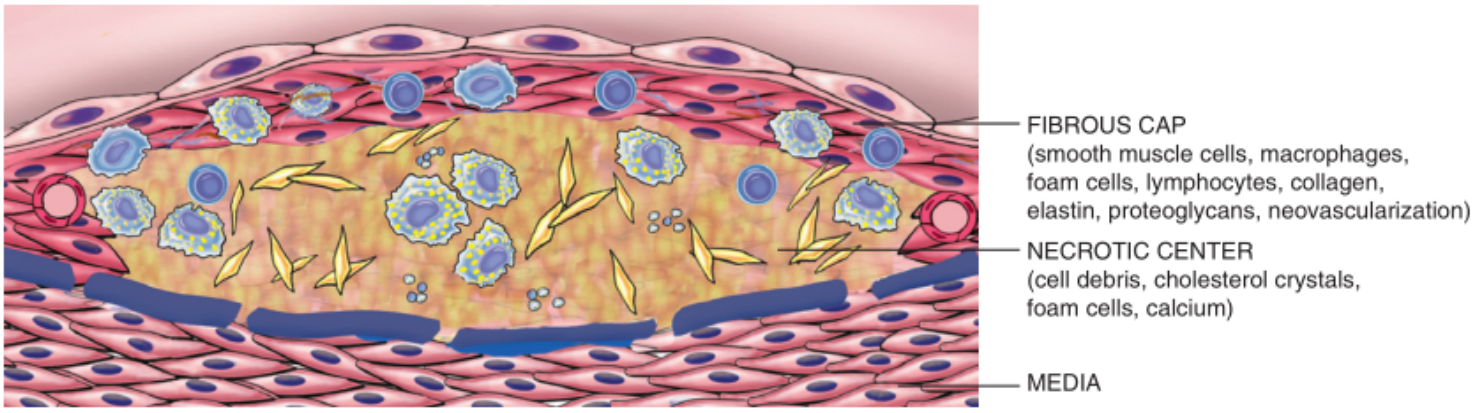


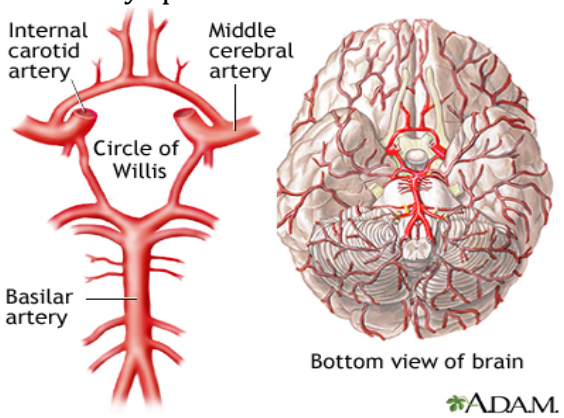
Figure 9–7 The basic structure of an atheromatous plaque.

Common sites of atherosclerosis

Large elastic arteries and *large and medium-sized muscular arteries* are the vessels most commonly involved by atherosclerosis, In descending order, the most extensively involved vessels are:

1. The abdominal aorta.
2. The coronary arteries.
3. The popliteal arteries.
4. The internal carotid arteries.
5. The vessels of the **Circle of Willis** (supplies blood to the brain and surrounding structures).

Vessels of the upper extremities are usually spared.



[2] Thick, clotted

[3] an excessive localized enlargement of an artery caused by a weakening of the artery wall.

RISK FACTORS. Robbins page 336 - 337

They are classified as major & minor.

Major risk factors: Classified into **Non-Modifiable** (*Constitutional)* & ***Modifiable*** (Potentially controllable).

Non-Modifiable (Constitutional) Major Risk Factors:

1. **genetics.** Certain mendelian disorders are strongly associated with atherosclerosis (e.g., familial hypercholesterolemia). Although most familial risk is related to polygenic traits that go hand-in-hand with atherosclerosis, such as hypertension and diabetes, as well as other genetic polymorphisms.
2. **age.**
3. **gender.** Premenopausal women are relatively protected against atherosclerosis (and its consequences) compared with age-matched men.This is because of the presence of estrogen. After menopause, unfortunately,, the incidence of atherosclerosis-related diseases increases and in old age, even exceeds that in men.

note that: clinical trials have shown no benefit of hormonal therapy for prevention of vascular disease. Indeed, postmenopausal estrogen replacement appears to increase cardiovascular risk.

Modifiable Major Risk Factors:

1. **Hyperlipidemia**. specially **hypercholesterolemia**: The main cholesterol component associated with increased risk is low-density lipoprotein (LDL) cholesterol "bad cholesterol".
2. **Hypertension.** Hypertension also is the major cause of left ventricular hypertrophy (LVH).
3. **Cigarette smoking.**
4. **Diabetes mellitus.** It is associated with raised circulating cholesterol levels and markedly increases the risk of atherosclerosis. This disorder is also associated with an increased risk of stroke and a 100-fold increase in atherosclerosis-induced gangrene of the lower extremities.

Major	Lesser, Uncertain, or Nonquantitated
Nonmodifiable	
Increasing age	Obesity
Male gender	Physical inactivity
Family history	Stress ("type A" personality)
Genetic abnormalities	Postmenopausal estrogen deficiency
	High carbohydrate intake
Potentially Controllable	
Hyperlipidemia	Alcohol
Hypertension	Lipoprotein Lp(a)
Cigarette smoking	Hardened (trans)unsaturated fat intake
Diabetes	*Chlamydia pneumoniae*

Minor risk factors (Additional Risk Factors):

1. **Inflammation.** Inflammatory cells are present during all stages of atheromatous plaque formation and are intimately linked with plaque progression and rupture. Measures of systemic inflammatory mediators have become important risk factors. Determination of C-reactive protein (CRP) has emerged as one of the simplest and most sensitive ways to determine this.

Note that: CRP secreted by cells within atherosclerotic plaques can activate endothelial cells, increasing adhesiveness and inducing a prothrombotic state.

Note that: statins[4] reduce CRP levels independent of their LDL cholesterol-lowering effects.

2. **Hyperhomocysteinemia.** Serum homocysteine levels correlate with coronary atherosclerosis, peripheral vascular disease, stroke, and venous thrombosis.
3. **Metabolic syndrome.** This clinical entity is characterized by insulin resistance, hypertension, dyslipidemia (elevated LDL and depressed HDL), hypercoagulability, and a pro-inflammatory state. The dyslipidemia, hyperglycemia, and hypertension are all cardiac risk factors, while the systemic hypercoagulable and pro-inflammatory state may contribute to endothelial dysfunction and/or thrombosis.
4. **Lipoprotein(a) levels. "an LDL-like particle".**
5. **Elevated levels of procoagulants.**
6. **lack of exercise and living a competitive, stressful lifestyle ("type A personality").**

LDL Vs. HDL (low-density lipoprotein and high-density lipoprotein). Robbins page 336

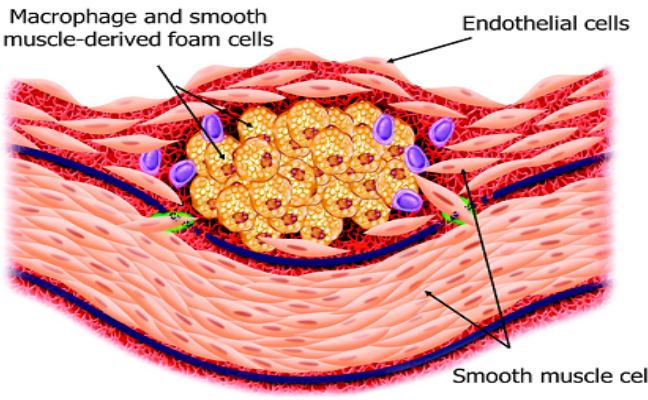
Hyperlipidemia and, more specifically, hypercholesterolemia is a major risk factor for development of atherosclerosis and is sufficient to induce lesions in the absence of other risk factors. Chylomicrons also promote atherosclerosis.

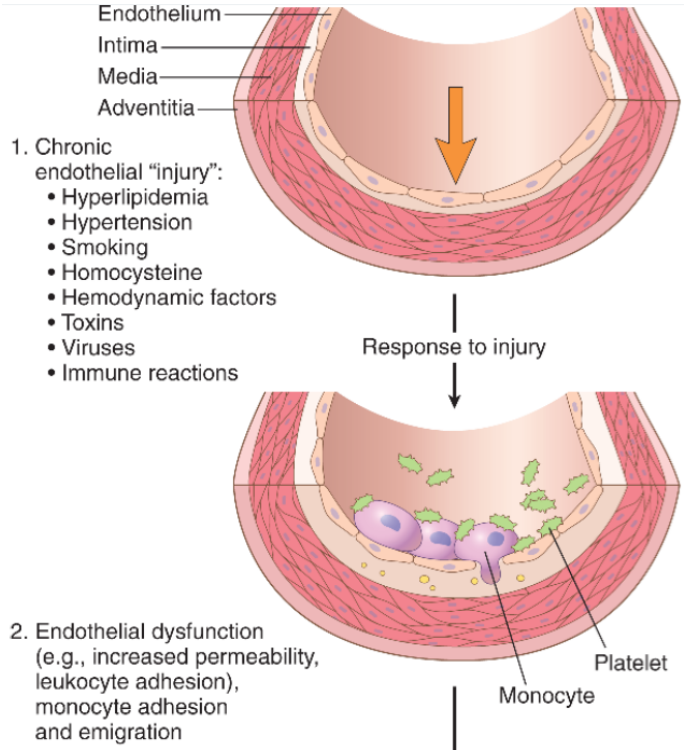
High Density Lipoprotein (HDL)	Low Density Lipoprotein (LDL)
Known as "good" cholesterol, because high levels of HDL protects against heart attack. Low levels of HDL also increase the risk of heart disease. HDLs help to reverse the effects of high cholesterol.	When too much LDL "bad" cholesterol circulates in the blood, it promote atherosclerosis and therefore contributes to heart disease.
Exercise and moderate consumption of ethanol raise HDL levels	Very-low-density lipoproteins (VLDLs): is also considered to be a type of bad cholesterol and it promotes atherosclerosis

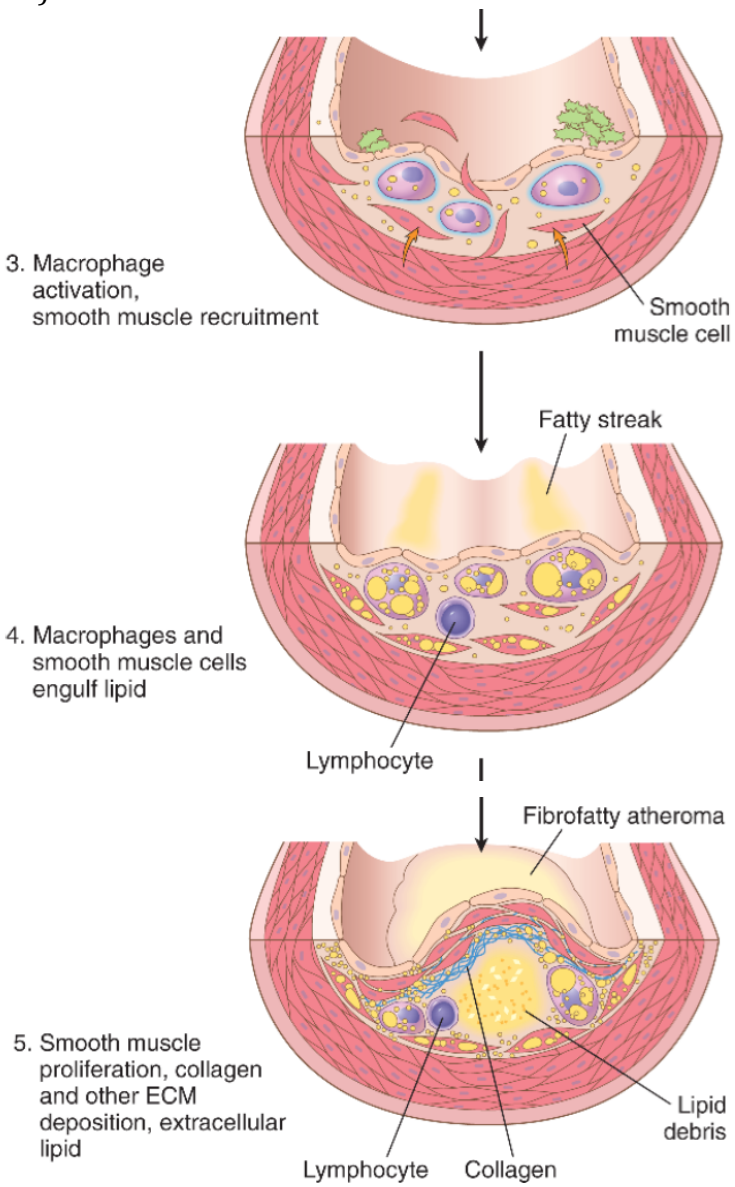
[4] *Statins* are a widely used class of drugs that lower circulating cholesterol levels by inhibiting hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis.

PATHOGENESIS. Robbins page 338

1. chronic Endothelial injury (resultant endothelial dysfunction) leading to increase permeability, leukocyte adhesion, and thrombosis
2. accumulation of lipoprotein (mainly oxidized LDL and cholesterol crystal).
3. macrophage infiltrate the intima.
4. inflammatory cell release cytokines and growth factors.
5. smooth muscle migrate to intima.
6. LDL enters SM and macrophages produce foam cells.
7. smooth muscle produces extracellular matrix forming the fibrous plaque, overlies a necrotic center consisting of (cell debris, cholesterol crystal, foam cells, & calcium).

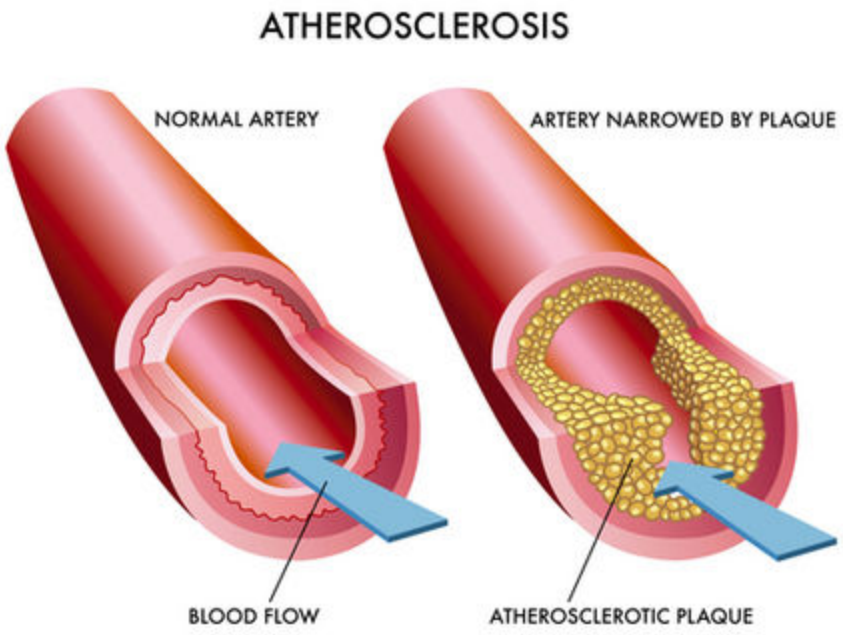






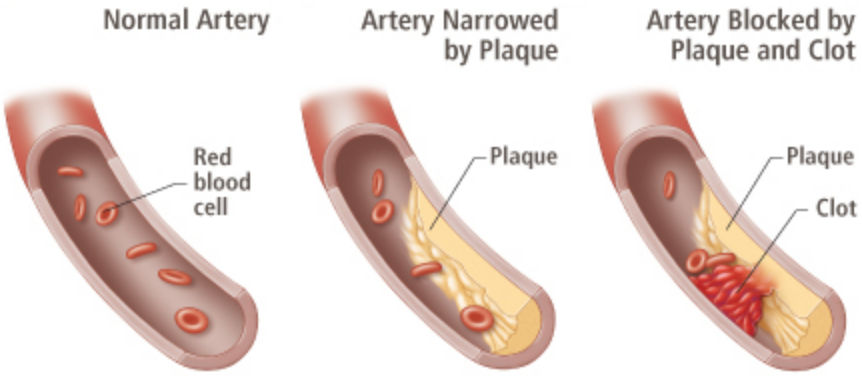
Morphology. Robbins page 340

Gross morphology.



Fatty streaks: The earliest lesion of atherosclerosis they are flat yellow lesions of the intima consisting of lipid filled foamy macrophages; and don't cause any significant flow disturbance.
The relationship of fatty streaks to atherosclerotic plaques is uncertain, although fatty streaks may evolve into plaques, not all do.

Atherosclerotic plaques: The key features of these lesions are intimal thickening and lipid accumulation. Atheromatous plaques are white to yellow raised lesions. They range from 0.3 to 1.5 cm in diameter but can fuse to form larger masses.
Atheromatous plaques are **patchy**, usually involving only a portion of any arterial wall, therefore the lesions appear **eccentric**[5].



[5] not placed centrally or not having its axis or other part placed centrally.

Microscopic morphology.

[Histopathology Aorta - Atherosclerosis with fatty streak.]

An atheroma[6] consists of a raised focal lesion, with a soft, yellow, grumous [7]core of lipid (mainly cholesterol and cholesteryl esters[8]) located in the **intima**. It is covered by a firm, white fibrous cap.

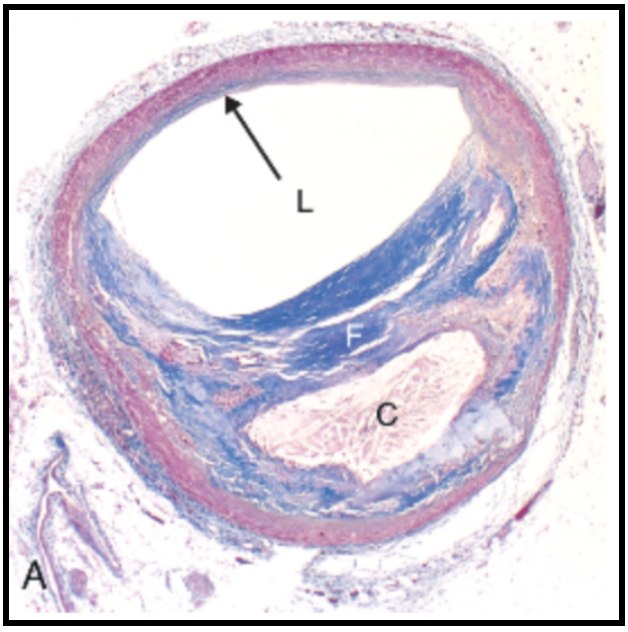
What are the three principal components of atherosclerotic plaques ?

- **Cells:** smooth muscle cells (SMCs), macrophages, lymphocytes and foam cell.
- **Extracellular matrix:** collagen, elastic fibers, and proteoglycans.
- **Lipid:** Typical atheromas contain relatively abundant lipid of both intracellular and extracellular lipid.

Foam cells: are large, lipid-laden macrophages derived from blood monocytes. infact, SMCs can also gain lipids to become foam cells.
Typically, the superficial fibrous cap is composed of **SMCs, dense collagen** and **extracellular matrix** with some **macrophages** and **T lymphocytes**.

Below the fibrous cap is a **necrotic core**, containing a lipid deposits (mainly cholesterol and cholesterol esters), cholesterol clefts, debris from dead cells, foam cells, fibrin, variably organized thrombus.

- ➔ The periphery of this lesions shows **neovascularization**. (proliferating small blood vessels).
- ➔ The plaques continue to change and enlarge through cell death and degeneration, synthesis and degeneration of the extracellular matrix and thrombus organization.

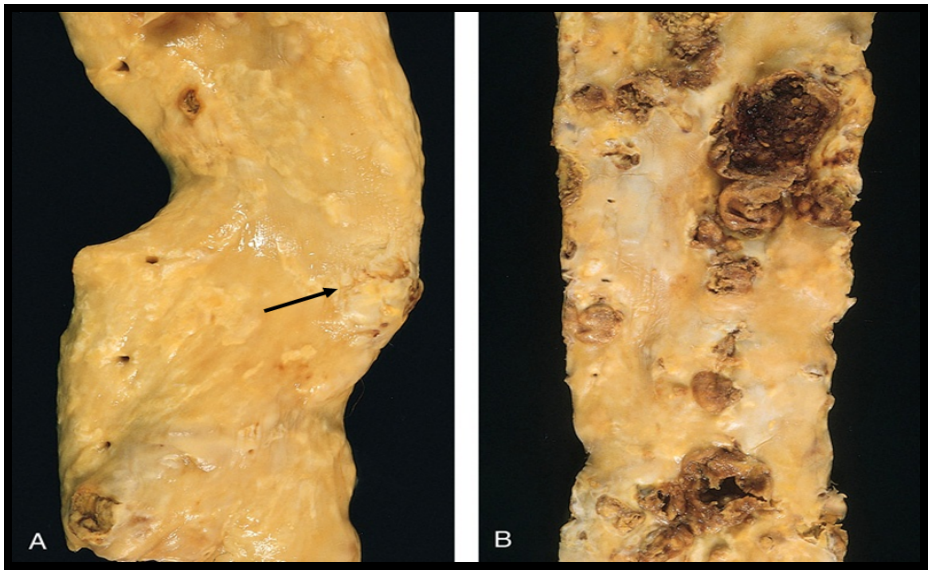


This microscopic picture shows an atherocclerotic plaque in a coronary artery:
F: fibrous cap
C: central necrotic core
L: lumen is moderately narrowed by the lesion which is the part of the artery wall uneffected

[6] An **atheroma** is an accumulation of degenerative material in the tunica intima (inner layer) of artery walls. The material consists of (mostly) macrophage cells, or debris, containing lipids, calcium and a variable amount of fibrous connective tissue.

[7] مخثوثر : متخثر clotted

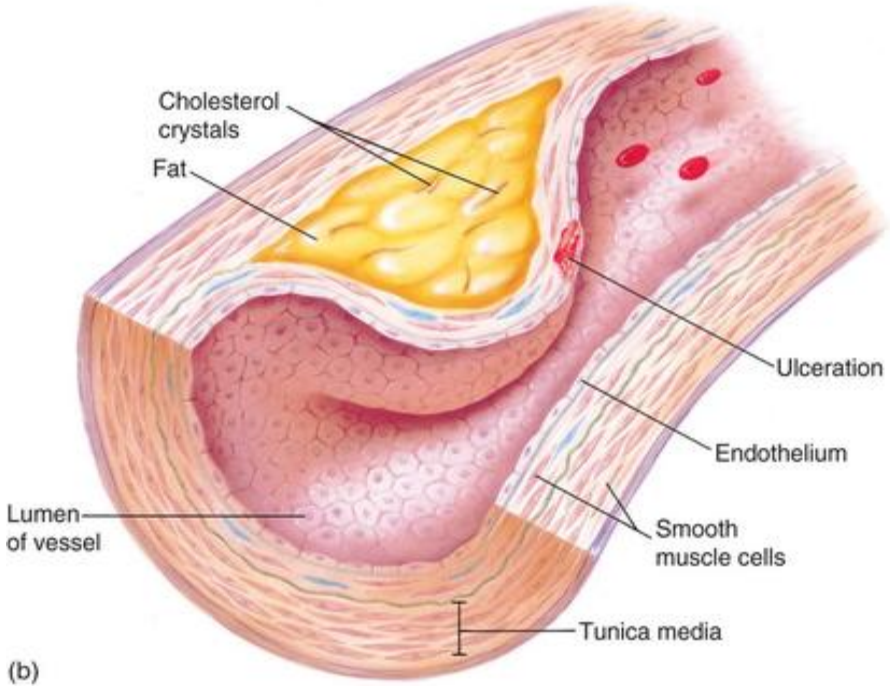
[8] **Cholesteryl ester**, a dietary lipid, is an ester of cholesterol. Cholesteryl esters have a lower solubility in water than cholesterol and are more hydrophobic. They are hydrolyzed by pancreatic enzymes, cholesterol esterase, to produce cholesterol and free fatty acids. They are associated with atherosclerosis.



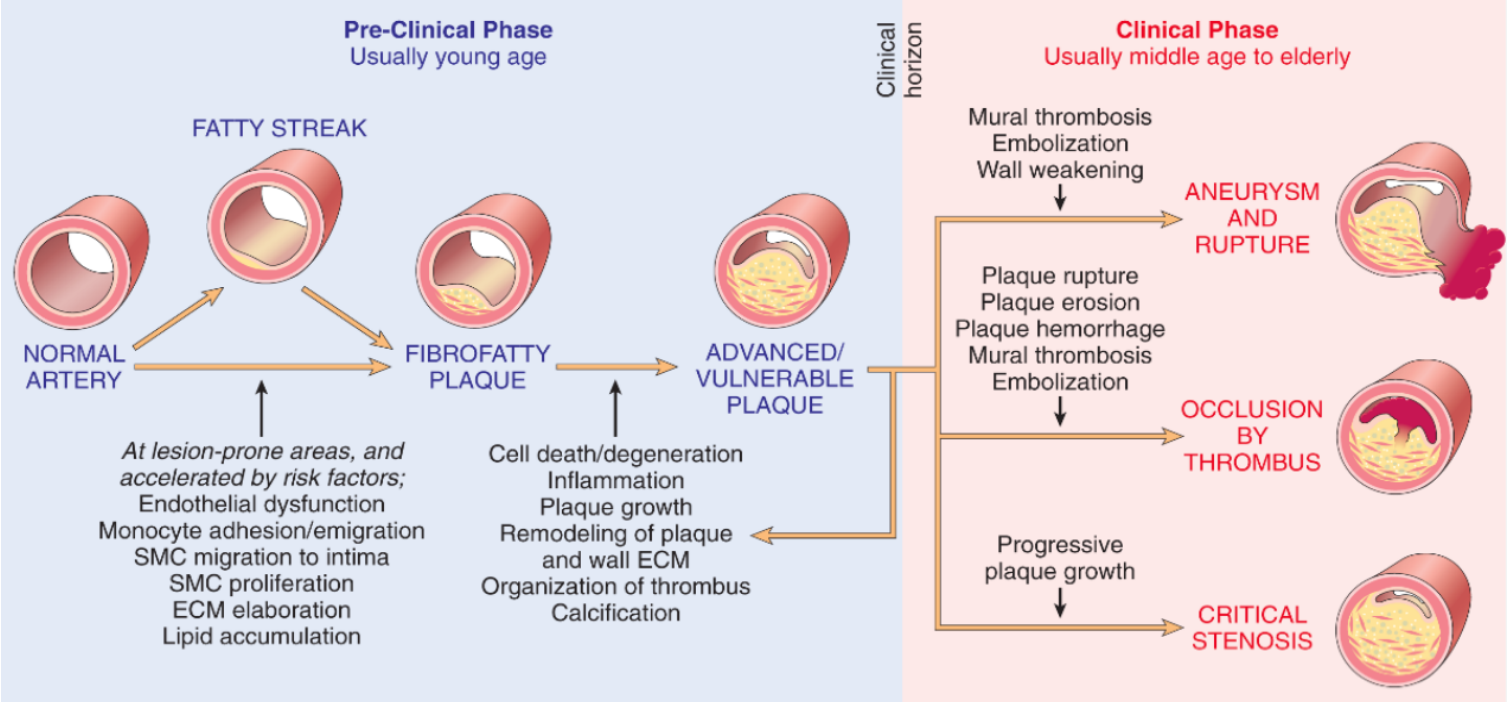
Gross views of atherosclerosis in the aorta.

A. Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the arrow.
B. Severe disease with diffuse and complicated lesions.

Overall architecture demonstrating an eccentric lesion with a fibrous cap and a central lipid core with typical cholesterol clefts. The lumen is moderately narrowed.



PATHOLOGICAL COMPLICATIONS.

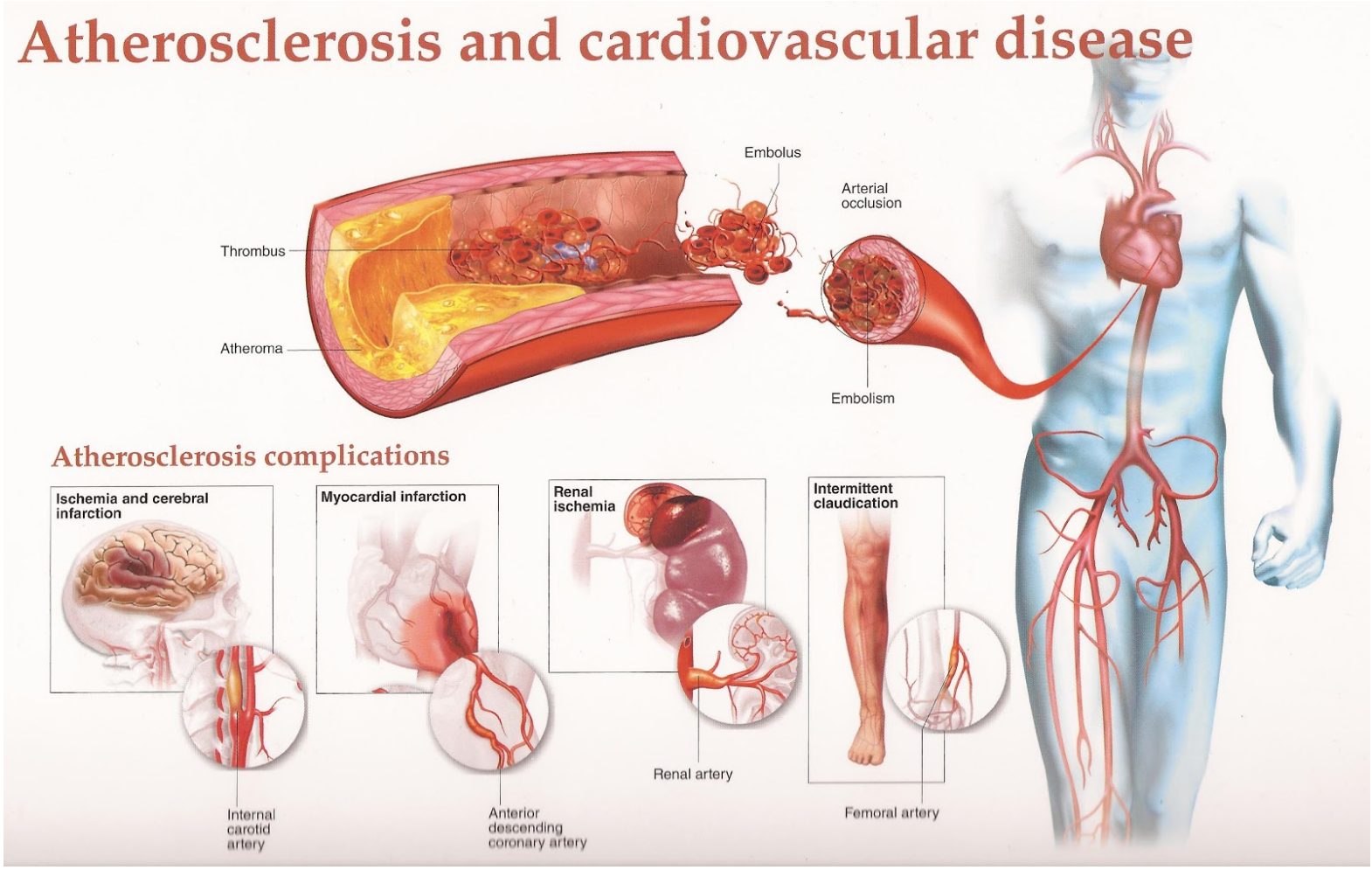


- **Coronary artery disease (angina & MI) and Carotid atherosclerotic disease (stroke)**
- **gangrenous extremities**
- Focal rupture, ulceration, or erosion of the luminal surface of atheromatous plaques which may induce **thrombus formation or atheroembolism**
- **Hemorrhage into a plaque** due to rupture of the overlying fibrous cap. The hematoma may cause plaque expansion or the plaque rupture
- **Aneurysm formation**: atherosclerosis induced pressure or ischemic atrophy with loss of elastic tissue cases structural weakening that can lead to aneurysm dilation or rupture
- **Calcifications**: Atheromas often undergo calcification.
- **Mesenteric occlusion.**

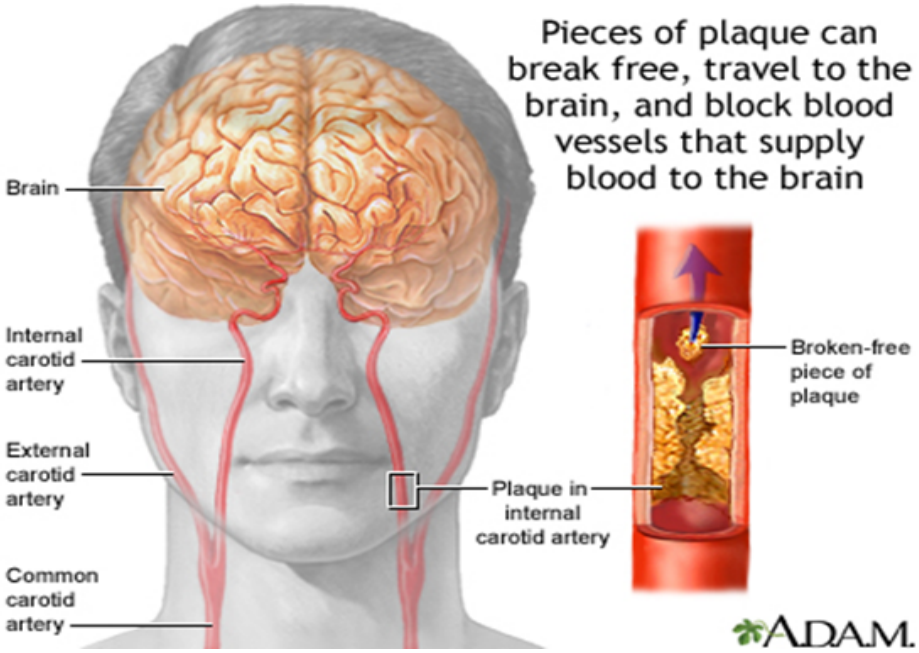
Natural history of atherosclerosis.

Plaques usually develop slowly and insidiously over many years, beginning in childhood or shortly after. They may progress from a fatty streak to a fibrous plaque and then to a complicated plaque that is likely to lead to clinical effects **like**:

- **Stroke / cerebrovascular accident.**



Stroke / cerebrovascular accident.



SUMMARY

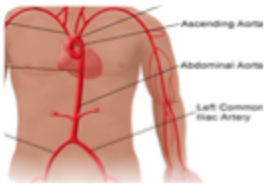
Atherosclerosis

- Atherosclerosis is an intima-based lesion composed of a fibrous cap and an atheromatous (literally, “gruel-like”) core; the constituents of the plaque include smooth muscle cells, ECMs, inflammatory cells, lipids, and necrotic debris.
- Atherogenesis is driven by an interplay of vessel wall injury and inflammation. The multiple risk factors for atherosclerosis all cause endothelial cell dysfunction and influence smooth muscle cell recruitment and stimulation.
- Atherosclerotic plaques develop and grow slowly over decades. Stable plaques can produce symptoms related to chronic ischemia by narrowing vessels, whereas unstable plaques can cause dramatic and potentially fatal ischemic complications related to acute plaque rupture, thrombosis, or embolization.
- Stable plaques tend to have a dense fibrous cap, minimal lipid accumulation, and little inflammation, whereas “vulnerable” unstable plaques have thin caps, large lipid cores, and relatively dense inflammatory infiltrates.

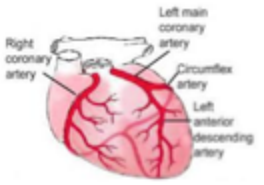
Summary.

Atherosclerosis: Characterized by intimal lesions called: atheromas, atheromatous or fibrofatty plaques.

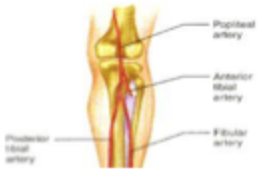
Common sites of Atherosclerosis:



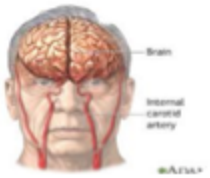
Abdomenal aorta



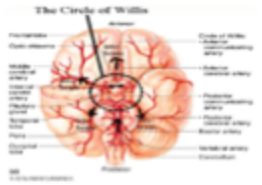
Coronaries



Popliteal artery

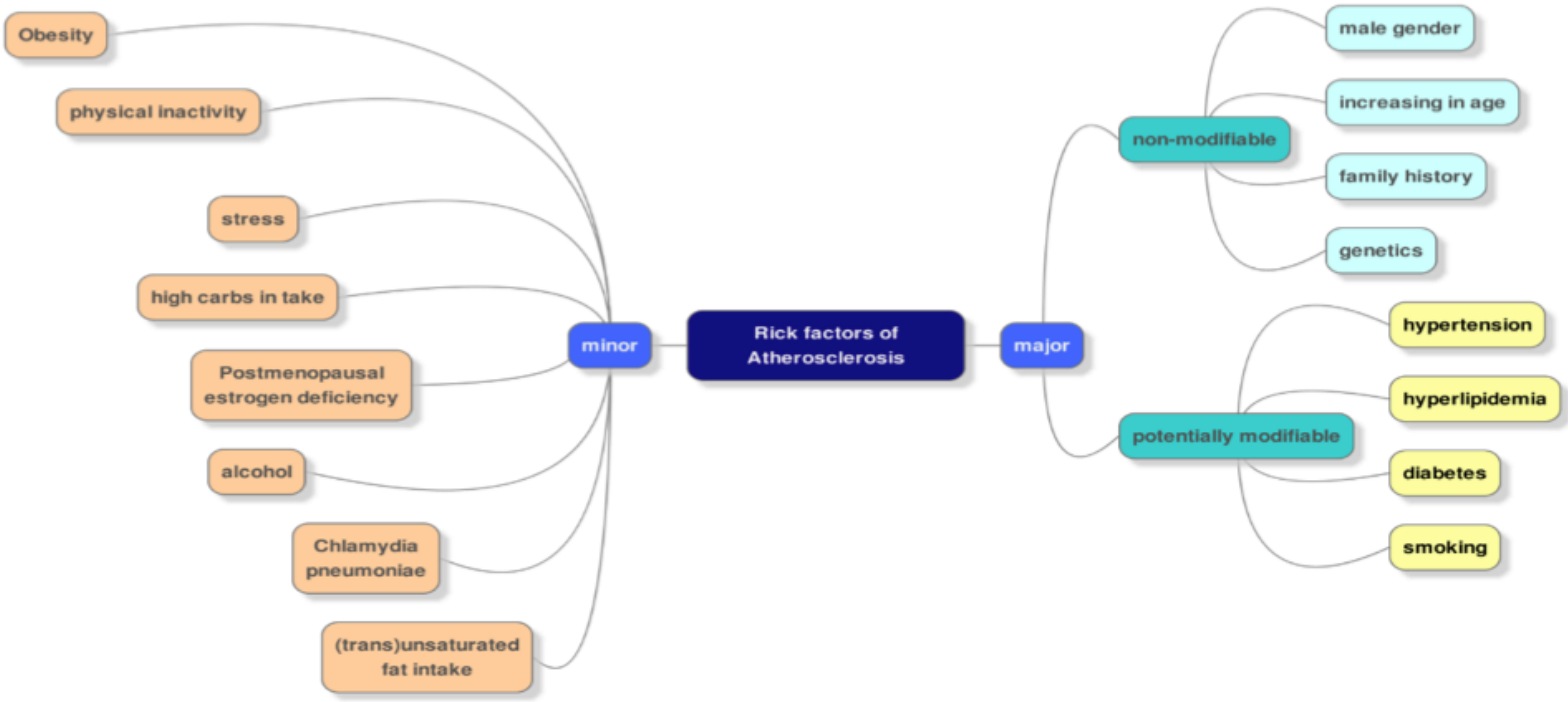


internal caroted artery



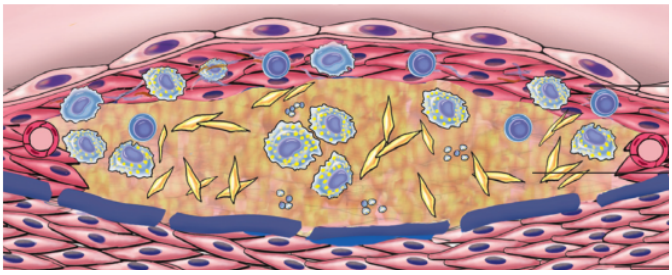
vesseles of circle of willis

Risk factors of Atherosclerosis:



Low-density lipoproteins (LDLs) / bad cholesterol	High-density lipoproteins (HDLs) / Good cholesterol
Deliver cholesterol to peripheral tissues.	Mobilizes cholesterol from developing and existing atheromas and transports it to the liver for excretion in the bile.

- Higher levels of HDL correlate with reduced risk of VLDL.



<u>Atherosclerosis is described as:</u> Fibrous cap & Necrotic center.

Pathogenesis of Atherosclerosis:

<u>1-Endothelial injury</u> → Endothelial dysfunction by:

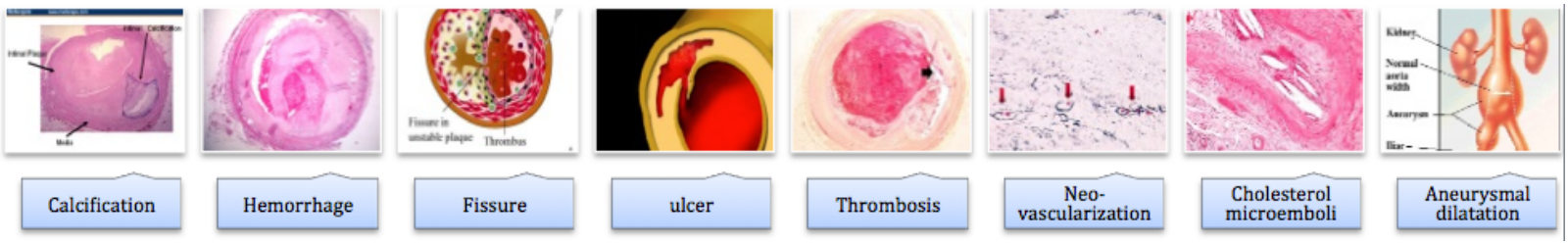
- Hemodynamic disturbances
- Hypercholesterolemia
- Inflammation (important contributor).

<u>2- Smooth muscle cell proliferation</u>

Clinical Complications of Atherosclerosis: What can happen if the block in:

- In Coronary artery → **Myocardial infarction.**
- In leg (**peripheral vascular disease) → gangrene.**
- In brain → **Cerebral infarction** (stroke).
- In the abdominal aorta → (**aneurysm**) **Mesenteric occlusion.**

Morphological changes that are seen on macro and microscopic levels in atherosclerosis:



What is the management of atherosclerosis? Angioplasty.

MCQs.

1- A 66-year-old woman has sudden paralysis of the left side of her body. She has been smoking a pack of cigarettes daily for the past 45 years. Vital signs: temp: 37.1 C. heart rate 80/minute, respiratory rate 16/minute, and BP 160/100 mm Hg. A cerebral angiogram reveals occlusion of a branch of her middle cerebral artery. Laboratory findings include a hemoglobin A1C of 9%.
- Which of the following components of blood lipids is most important in contributing to her disease?

A) Chylomicrons
B) HDL cholesterol
C) Oxidized LDL
D) VLDL

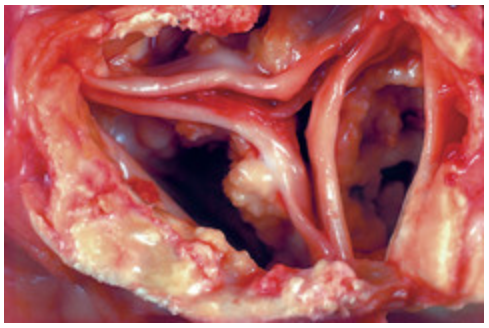
Answer: C) CORRECT. She has had a 'stroke' which is most often a consequence of cerebral atherosclerosis or embolic disease from the heart as a consequence of ischemic heart disease from atherosclerosis. LDL brings cholesterol to arterial walls, and when increased LDL is present or when there is hypertension, smoking, or diabetes, there is more degradation of LDL to oxidized LDL which is taken up into arterial walls via scavenger receptors in macrophages to help form atheromas.

2- An autopsy study reveals that atheromas can begin forming during childhood. The gross appearances of the aorta are recorded and compared with microscopic findings of atheroma formation.
- Which of the following is most likely to be the first visible gross evidence for the formation of an atheroma?
A) Thrombus
B) Fatty streak
C) Calcification
D) Hemorrhage

Answer: (B) CORRECT. This is the first sign. It is benign and reversible, but it may be the precursor to more severe plaques.

3- A 49-year-old woman with atherosclerosis came to the clinic. She complained of experiencing marked pain in her lower extremities on ambulation (moving) for more than 300 meters for the past 5 months. On physical examination, her lower extremities are cool and pale, without swelling or erythema. No dorsalis pedis or posterior tibial pulses are palpable. Her body mass index is 32 and she is a smoker.
- Which type of atherosclerosis complication is most likely responsible for these symptoms?
A) MI
B) Peripheral vascular disease
C) Aortic aneurysms
D) Cerebral stroke
Answer (B)

4- A 72-year-old man died suddenly from congestive heart failure. At autopsy, the heart weighed 580 g and showed marked left ventricular hypertrophy and minimal coronary arterial atherosclerosis. A serum chemistry panel ordered before death showed no abnormalities. Which of the following pathologic processes best accounts for the appearance of the aortic valve seen in the figure?



A. Amyloidosis
B. Dystrophic calcification
C. Lipofuscin deposition
D. Fatty change

Answer (B) The idea from this question is aortic calcification narrows the aortic valve & the LV must generate more pressure leading to LV hypertrophy.

5- A 56-year-old man reports reduced exercise tolerance over the past 5 years. Occasionally, he has been having chest pain after ascending a flight of stairs over the past year. He smokes 2 packs of cigarettes per day. He is found to have a blood pressure of 155/95 mm Hg. His body mass index is 30. Laboratory findings include a total serum cholesterol of 245 mg/dL with an HDL cholesterol that is 22 mg/dL. Which of the following vascular abnormalities is most likely his underlying pathology?

A. Hyperplastic arteriolosclerosis
B. Deep venous thrombosis
C. Medial calcific sclerosis
D. Atherosclerosis

Answer (D)

6- A 63-year-old man has had insulin dependent diabetes mellitus for over two decades. The degree of control of his disease is characterized by the laboratory finding of a hemoglobin A1C of 10.1%. He has noted episodes of abdominal pain following meals. These episodes have worsened over the past year. On physical examination, there are no masses and no organomegaly of the abdomen, and he has no tenderness to palpation.
- Which of the following pathologic findings is most likely to be present in this man?
A) Ruptured aortic aneurysm
B) Chronic renal failure
C) Mesenteric artery occlusion
D) Acute pancreatitis

(C) CORRECT. He has 'abdominal angina' from diminished blood flow to the bowel as a consequence of severe atherosclerosis. Persons with diabetes mellitus may have this, because all branches of major arteries to the bowel are affected by atherosclerosis

1- The following are true about atherosclerosis:

a) Males are at lower risk than females
b) raised HDL is associated with atherosclerosis
c) Atherosclerosis is a form of arteriosclerosis
d) In the natural history of atherosclerosis, the order of conditions is clean artery → fatty streaks → fibrous plaque → clinical lesion
e) The smooth muscles move from the intima to the media
f) The fibrous cap is comprised of calcium

2- The excess deposition of lipid in the ⋯⋯⋯ of an artery in Atherosclerosis
A) Intima
B) Media
C) Adventitia

3- platelets and macrophages release factors that result in :
a) Inflammation
B) Oxidation
C) Fibrous cap
D) Smooth muscle proliferation

4- LDL cholesterol deliver cholesterol to :

A. peripheral tissues
B. heart
C. liver

1)
a. F
b. F
c. T
d. T
e. F
f. T
2) A
3) D
4) A

Contact us on: Pathology434@gmail.com
Twitter: **@Pathology434**

Good Luck!

عمر الرهبيني	مها الربيعة
محمد الخراز	منى المتعب
حسين الكاف	رزان الصبحي
أحمد الصالح	نورة الهلالي
عبدالرحمن المزعل	رغد العتيبي
مشهور الزارعي	Najla2020
فيصل أبو نهية	هديل السلمي