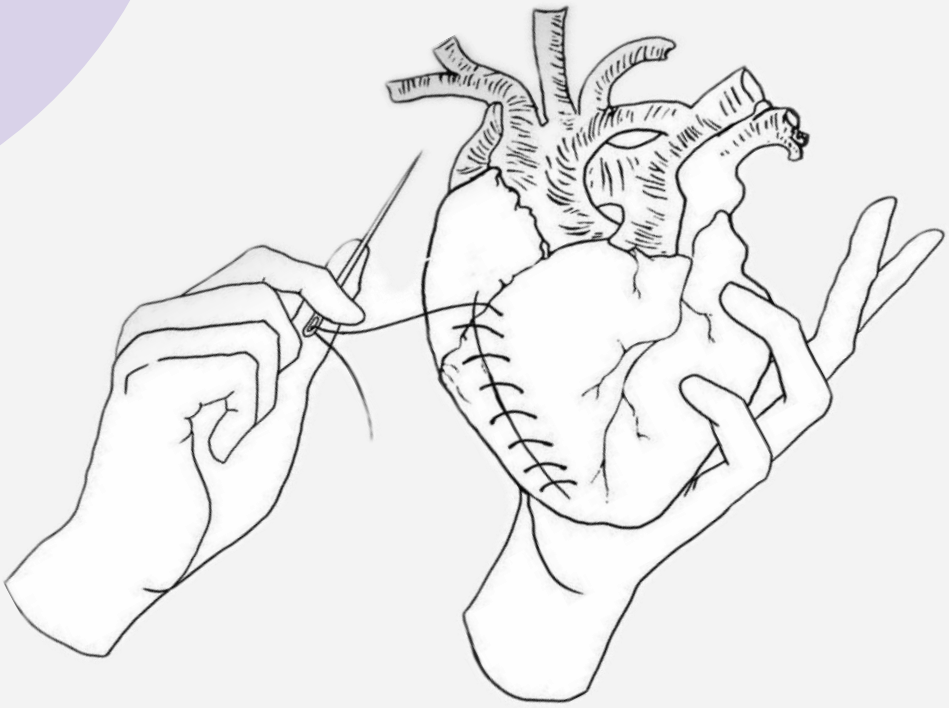
Risk Factors & Pathogenesis of Atherosclerosis



Editing file:

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

EXTRA INFO (GREY)

Objectives

- Understand the pathogenesis and clinical consequences of atherosclerosis.
- Be able to discuss pathology and complications of ischemic heart diseases with special emphasis on myocardial infarction.
- Know how lifestyle modifications can reduce the risk of ischemic heart diseases.

Key principles to be discussed:

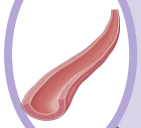
- Risk factors of atherosclerosis.
- Pathogenesis of the fibro lipid atherosclerotic plaque.
- Clinical complications of atherosclerosis.
- Commonest sites for the clinically significant coronary atherosclerosis.
- Macroscopic and microscopic changes in myocardial infarction.
- Biochemical markers of myocardial infarction.
- Complications of myocardial infarction: immediate and late.

If you want to read the lecture from Robbins click here

اللهمّ انفعنا بما علّمتنا، وعلّمنا ما ينفعنا، وزدنا علمًا وبارك لنا فيه

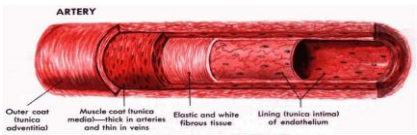
Normal Blood Vessels

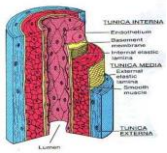
FEMALES SLIDES

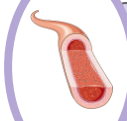


Large (elastic) arteries

- aorta, common carotid, iliac
- lots of elastic fibers





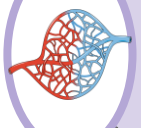


Medium (muscular) arteries

- coronary, renal arteries
- mostly smooth muscle cells

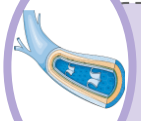
Small arteries/arterioles

- all smooth muscle cells
- blood pressure controlled here



Capillaries

- diameter of RBC
- thin walls, slow flow
- great for exchanging O2, nutrients



Venules/veins

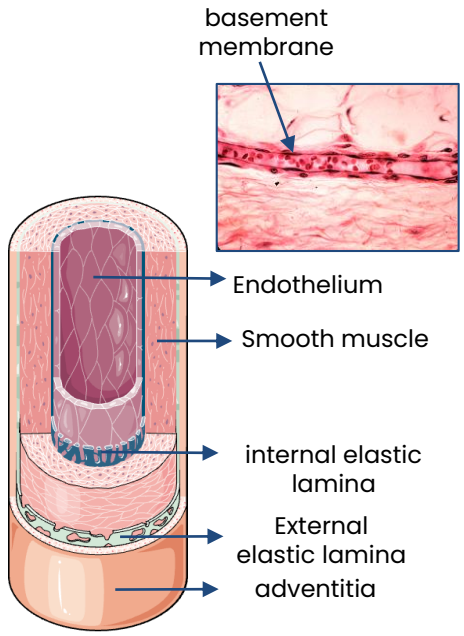
- large diameter,thin walls
- compressible,penetrable by tumor
- have valves

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 (arteries, veins and capillaries) and the lymphatic system.
- It is in direct contact with the blood/lymph and the cells circulating in it.
- A normal structure and function of endothelium is essential for the maintenance of vessel wall homeostasis and normal circulatory function.
- Endothelial cells are very sensitive so if they get injured, the basement membrane gets exposed leading to trouble and diseases.



Smooth Muscle Cells

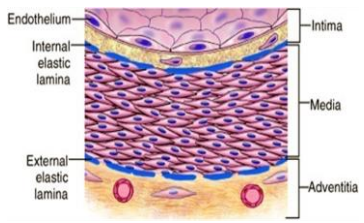
- SMCs are present in the media of blood vessels.
- SMCs are responsible for vasoconstriction (causes peripheral resistance) and vasodilation of blood vessel.

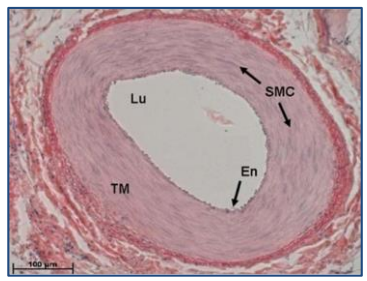
Any vascular injury or dysfunction stimulates SMCs. On stimulation,the SMCs:

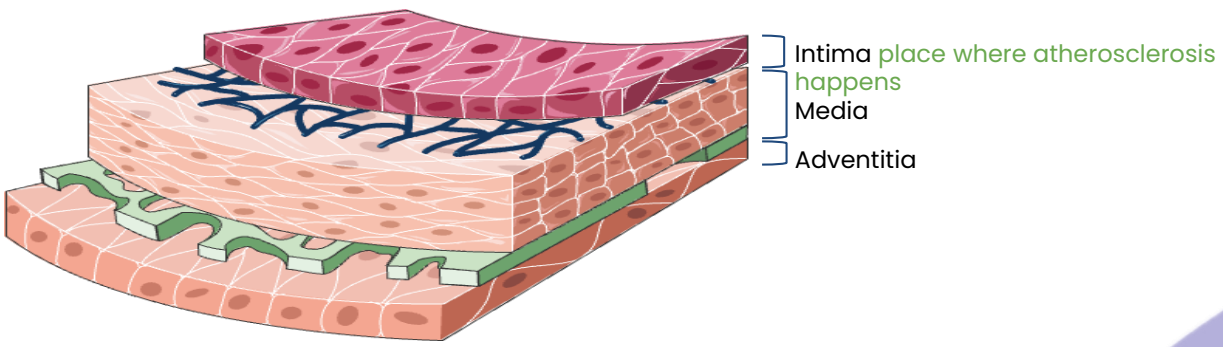
1.Migrate from the media to the intima.

2. In the intima, the SMCs lose the capacity to contract and gain the capacity to divide. So they proliferate as intimal SMCs.

3. They synthesize collagen, elastin etc and deposit extracellular matrix (ECM).





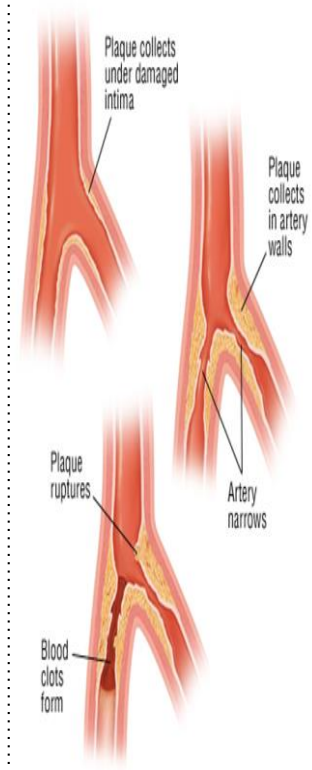


Atherosclerosis (AS)

✦ **Atherosclerosis** (a type of arteriosclerosis , is a chronic inflammatory response in the walls of arteries , is slowly progressive, and includes build up of fat (cholesterol) within the artery wall) is characterized by **intimal lesions** called **atheromas** (also known as **atheromatous plaque or fibrofatty plaque**), which protrude into and obstruct vascular lumens and **weaken** the underlying media.

✦If the plaque was big , it'll obstruct the flow of blood leading to problems in the organ it's supplying causing irreversible cell injury →ischemia /necrosis .

✦AS can lead to serious complications like Coronary artery disease (angina & MI) and Carotid atherosclerotic disease (stroke) or cerebrovascular accidents/paralysis resulting in brain hemorrhage.

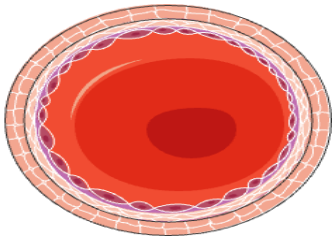


The most commonly involved vessels are (from most to least common):

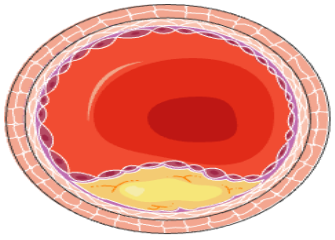
1- abdominal aorta (most common)
2- coronary arteries (2nd most common)
3- popliteal arteries
4- internal carotid arteries
5- the vessels of the circle of Willis

Mnemonic to memorize in order: *A CoPy Cat Named Willis*

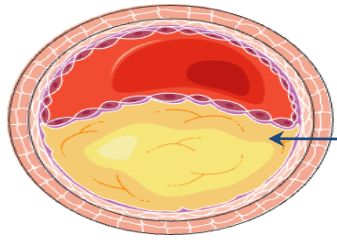
Abdominal Aorta > Coronaries > Carotid > Popliteal > Circle of Willis



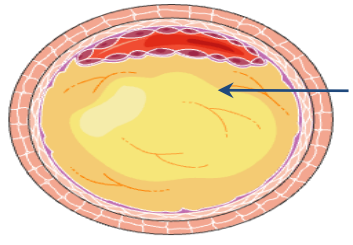
1. Normal cut section of artery



2.Tear in artery wall



3.Fatty material is deposited in vessel wall
partial block →angina/pain

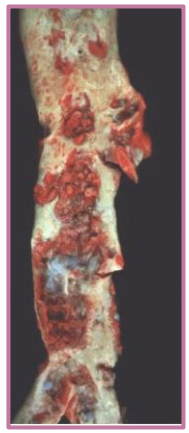


4.Narrowed artery becomes blocked by a blood clot
If thrombus developed→total blockage

Gross Morphology of Atheroma/ Atheromatous (AS) Plaque

FEMALES SLIDES

- The key processes in AS is intimal thickening and lipid accumulation
- AS plaques impinge on the lumen of the artery.
- AS plaques vary in size & shape
- AS plaques usually involve only a partial circumference of the arterial wall ("eccentric" lesions)(occupy the sides) and are patchy and variable along the vessel length.

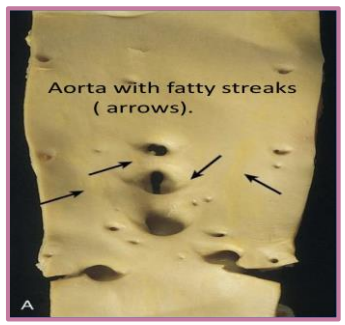


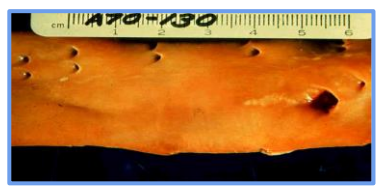
Fatty Streaks

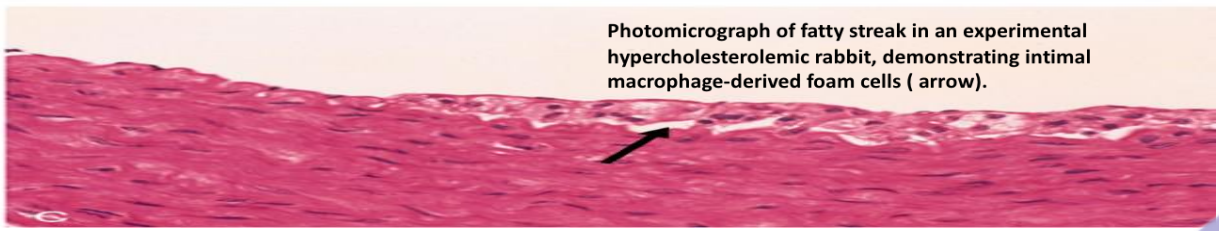
Fatty streaks are present in most teenagers. Atherosclerosis doesn't happen in one day, it's a process of decades. so please take care of your health and those around you <3

How does atherosclerosis start? as fatty streaks/yellow lines at a very young age

1. Fatty streaks are the earliest lesion of atherosclerosis they are a collection of l**ipid and lipid laden foam cells in the intima.**
2. They do not cause any disturbance in blood flow.
3. Fatty streaks begin as multiple yellow, flat spots less than 1 mm in diameter that coalesce into elongated streaks, 1 cm long or longer. They contain T lymphocytes, extracellular lipid in smaller amounts and rare **lipid laden foam cells** than in plaques.



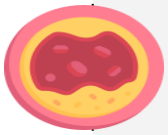




Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal macrophage-derived foam cells (arrow).

Atherosclerosis : Microscopic Morphology

FEMALES SLIDES



A well established atheroma/AS plaque consists of a raised focal lesion in the intima, with a soft, yellow, grumous/granular **core of lipid** (mainly cholesterol and cholesteryl esters), covered by a firm, white fibrous cap. **Atherosclerotic plaques have three principal components:**

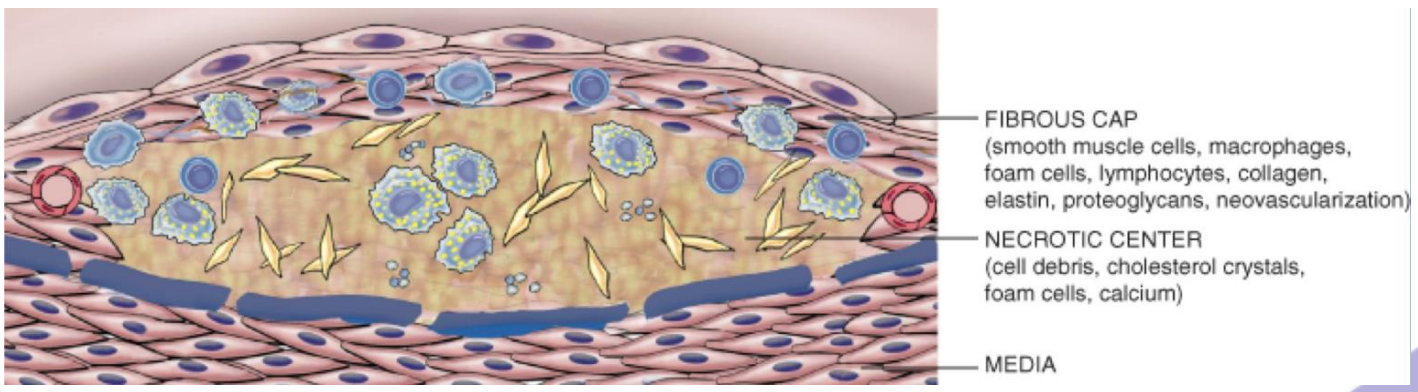
1. **Cells:** SMCs(they attract inflammatory cells), macrophages, lymphocytes and foam cell, proliferating smooth muscle cells
2. **Extracellular matrix:** including collagen, elastic fibers, and proteoglycans.
3. **Lipid:** Typical atheromas contain relatively abundant lipid both intracellular and extracellular lipid .

In both slides but details were only in females' slides

NOTE: Foam cells are large, lipid-laden macrophages derived from blood monocytes, but SMCs can also imbibe lipid to become foam cells.

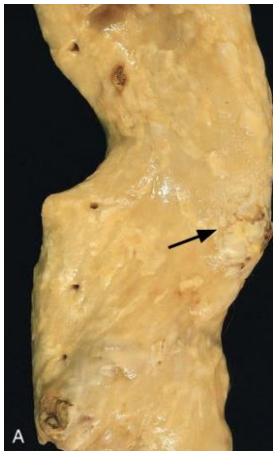
✦Typically, the superficial fibrous cap is composed of SMCs and extracellular matrix. With some macrophages and T lymphocytes.

✦Below the fibrous cap is a necrotic core, containing a lipid deposits (primarily cholesterol and cholesteryl esters), cholesterol clefts/crystals, debris from dead cells, foam cells, fibrin.



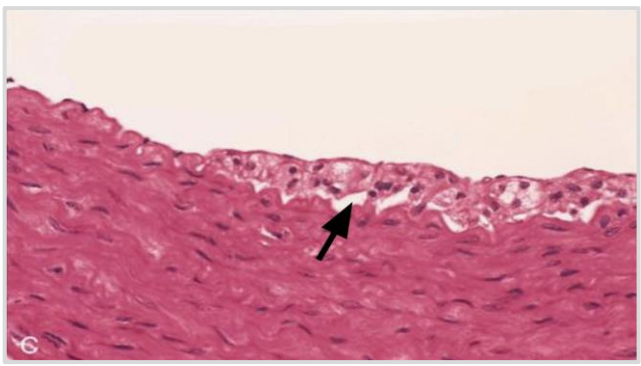
Gross Views of Atherosclerosis in the Aorta

FEMALES SLIDES

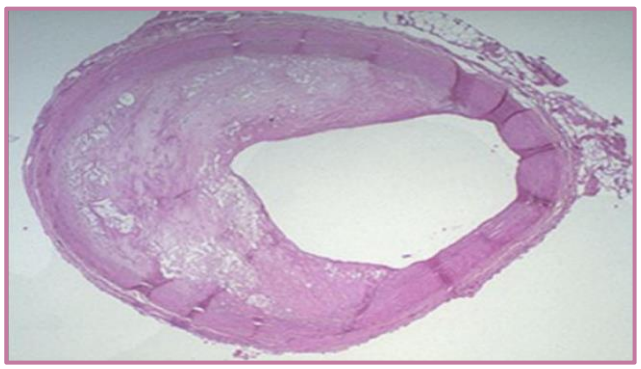


Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the arrow.

Severe disease with diffuse and complicated lesions.



Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal macrophage-derived foam cells (arrow).



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

Clinical note :

Stable plaques cause symptoms of reversible ischaemia in the supplied organ, e.g. angina pectoris, chronic lower limb ischaemia. Unstable plaques cause acute ischaemic events, e.g. acute coronary syndromes, stroke, acute lower limb ischaemia.

Pathological / Morphological Changes that are seen on Macro and Microscopic levels in/of Atherosclerosis

Advanced lesion of AS is at risk for the following:

1 Plaque rupture/ ulceration/ fissure/ erosion

of the AS plaques induce thrombus formation **OR** the AS plaque may discharge debris into the bloodstream, producing **cholesterol microemboli** composed of plaque lipid (**cholesterol emboli or atheroemboli**).Larger plaques have more chance of rupture. same concept of thrombosis (blood clotting) in foundation block except that the physiological thrombosis is for protection but this is pathological →plaque rupture + thrombus = blockage either partial or complete

2 Superimposed thrombosis (thromboembolism)

Usually occurs on top of ruptured or ulcerated plaques. The thrombus can lead to partial or complete occlusion of the lumen.It can also embolize and lead to myocardial infarction, or cerebral infarct or gangrene. It is the most feared complication.This thrombus is friable like cookie crumbs and the blood is pushing it, it can break into small pieces and these pieces embolize and go to different places of the body and block blood supply to that area.**Exposed endothelial membrane is prothrombotic.**

3 Weakening of the blood vessel wall with aneurysmal dilation

Atheroma can induce atrophy of the underlying media, causing weakness, aneurysm and potential rupture. Atheroma narrows the lumen and weakens the wall → dilation of the vessel and plugging out (aneurysm)→ rupture →internal bleeding.

4 Hemorrhage

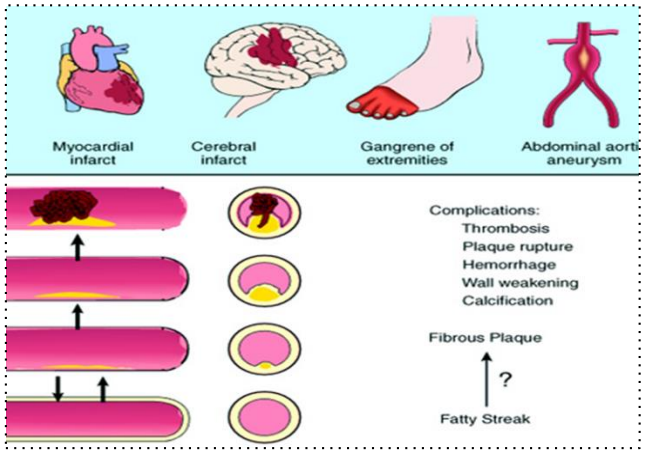
into a plaque due to rupture of the overlying fibrous cap or the capillaries in the plaque.The hematoma may expand the plaque or induce plaque rupture

5 Neovascularization & Medial thinning

Neovascularization: is the process by which new vascular structures assemble

6 Calcification

Atheromas often undergo calcification.(harmless)
439: Atheroma is a dead tissue can undergo Dystrophic calcification

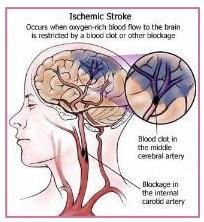


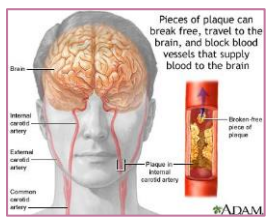
- the size of the plaque matters/ makes a difference
- In case of an aneurysm,wall becomes weak→rupture→internal bleeding

Pathological Complications of Atherosclerosis

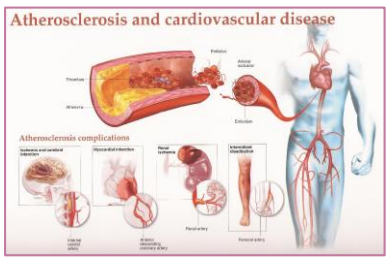
Atherosclerosis Clinical Complications

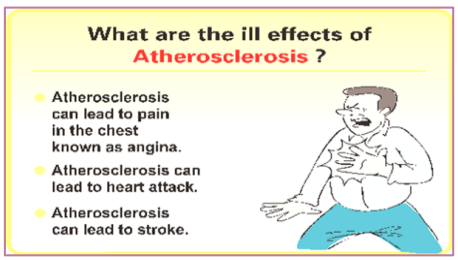
- **Aortic aneurysms**
- **Peripheral arterial/ vascular disease**
  - Intermittent claudication is muscle pain that happens when you're active and stops when you're at rest
  - Leg blood clot
  - Gangrene of the legs
- **Mesenteric occlusion**
- **Cerebrovascular stroke/ Cerebral infarction(stroke)**





- **Coronary artery disease**
  - Heart disease
  - Angina
  - Heart attack (myocardial infarction)

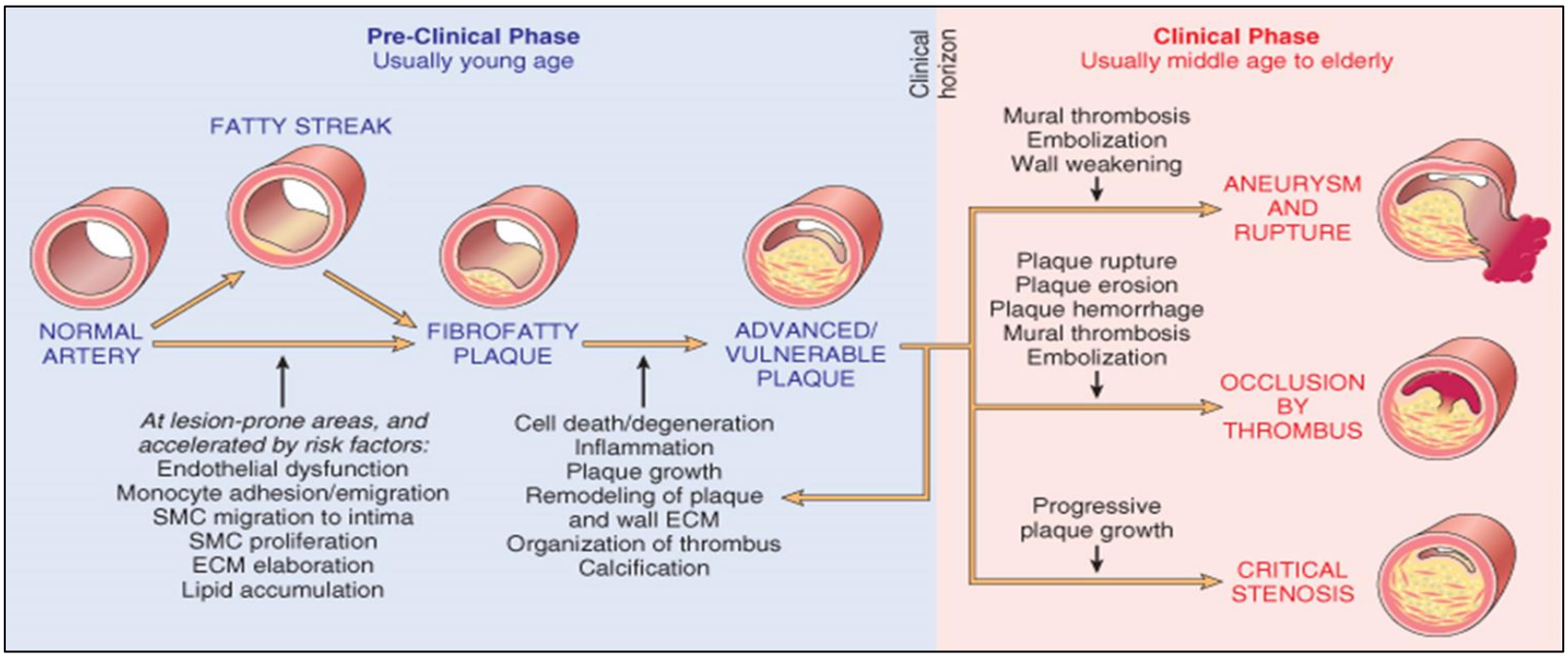


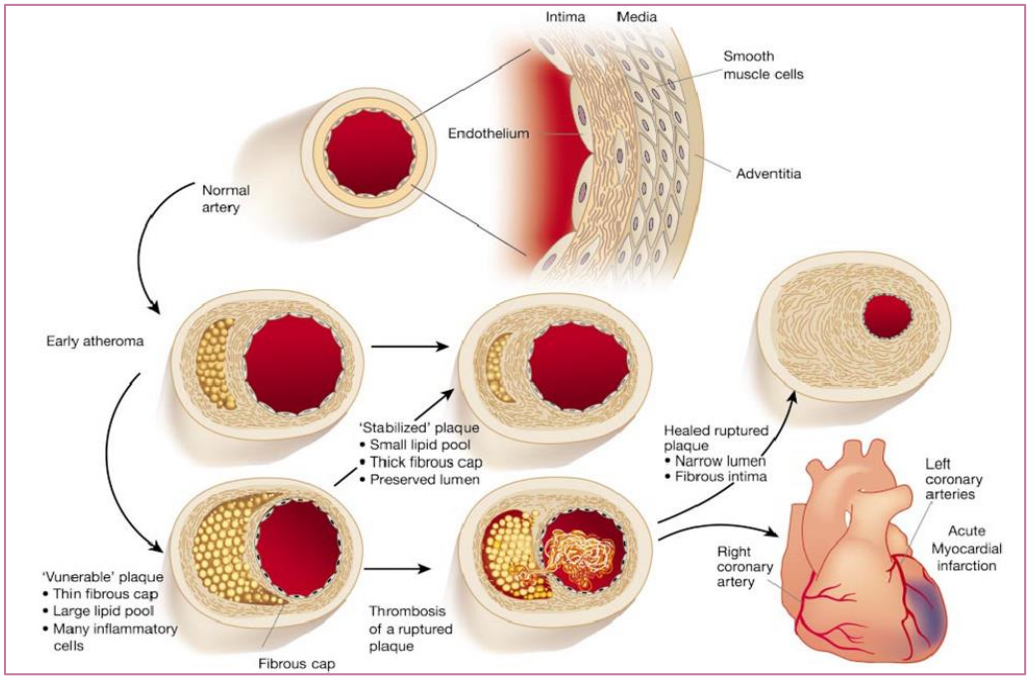


Pathological Complications of Atherosclerosis

Atherosclerosis Consequences

439 : fatty streaks taken place in some places on the blood vessel and then there's fibrofatty plaque which is growing bigger and bigger and the vessel became narrower (in this step the atheroma can rupture or formed thrombus causing complete occlusion or progressive growth leading to critical stenosis





Within 15-20 min→ the thrombus either leads to:

1. **Complete occlusion→** ischemic infarct
2. **Partial occlusion → t**he damage depends on the demand of blood supply & the location.

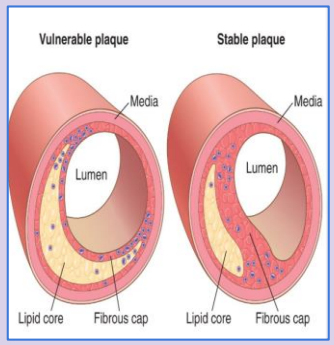
So give the patient thrombolytics such as streptokinase first before performing procedures.

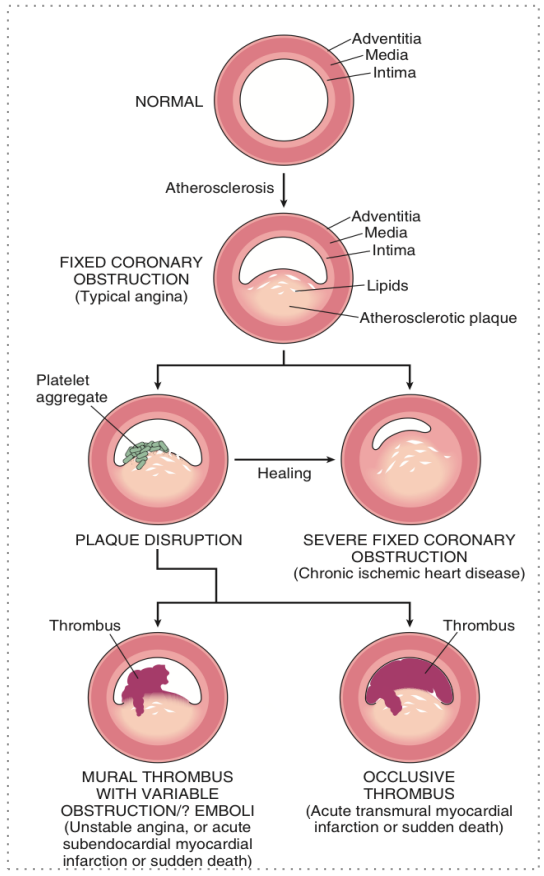
Extra from med443

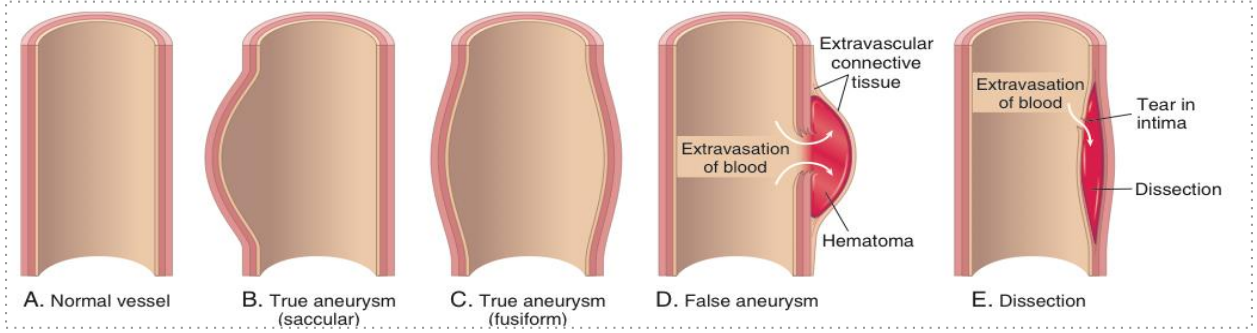
Highly thrombogenic constituents or underlying subendothelial basement membrane, leading to rapid thrombosis. In addition, hemorrhage into the core of plaques can expand plaque volume, thereby acutely exacerbating the degree of luminal occlusion.

- Plaques that contain large atheromatous cores or have thin overlying fibrous caps are more likely to rupture and are therefore termed vulnerable.

Vulnerable plaque	Stable plaque
More Lymphocytes	Less lymphocytes
Bigger lipid core	Smaller lipid core
Thinner fibrous cap	Thicker fibrous cap







Aneurysms are congenital or acquired dilations of blood vessels or the heart aneurysms involve all three layers of the artery (intima, media, and adventitia) or the attenuated wall of the heart; these include athero- sclerotic and congenital vascular aneurysms, as well as ventricular aneurysms resulting from transmural myocardial infarctions. By comparison, a false aneurysm (pseudoaneurysm) results when a wall defect leads to the formation of an extravascular hematoma that communicates with the intravascular space (“pulsating hematoma”).

Risk Factors of Atherosclerosis

Important for MCQs

Major risk factors .

Non-modifiable :

- Increasing age
- Male gender(post menopausal women are at as much = risk as male population since they lack estrogen which protects them from atherosclerosis)
- Family history
- Genetic abnormalities
  Ex:hypercholesterolemia

Potentially modifiable:

- Hyperlipidemia
- Hypertension
- Cigarette smoking
- Diabetics
- Inflammation
  Ex:RA,Crohn's disease,ulcerative colitis , SLE or autoimmune diseases

Minor uncertain , lesser, non quantitative factors .

- Obesity
- Physical inactivity
- Stress ("type A" personality)
  when you are stressed all the time.
- Postmenopausal estrogen deficiency
- High carbohydrate intake
- Alcohol
- Lipoprotein Lp(a)
- Hardened (trans) unsaturated fat intake
- Chlamydia pneumoniae

Importance of Types of Lipoproteins in Hyperlipidemia (LDL Vs. HDL)

Types of cholesterol in the body

Good Cholesterol

High-density lipoproteins (HDLs):

- known as “good” cholesterol.
- 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.
- mobilizes cholesterol from developing and existing atheromas and transports it to the liver for excretion in the bile.

Bad Cholesterol

High blood levels of the following promotes AS and therefore heart disease:

Low-density lipoproteins (LDLs):

- It is “bad cholesterol”.
- deliver cholesterol to peripheral tissues.

Very-low-density lipoproteins (VLDLs).

Chylomicrons.

Pathogenesis

FEMALES SLIDES

The steps are as follows:

Starts as a subtle chronic endothelial injury at the sight of fatty streaks

Accumulation of lipoproteins (mainly LDL with its high cholesterol content) in the vessel wall and subtle chronic endothelial injury

Increased permeability and leukocyte (monocyte) adhesion.

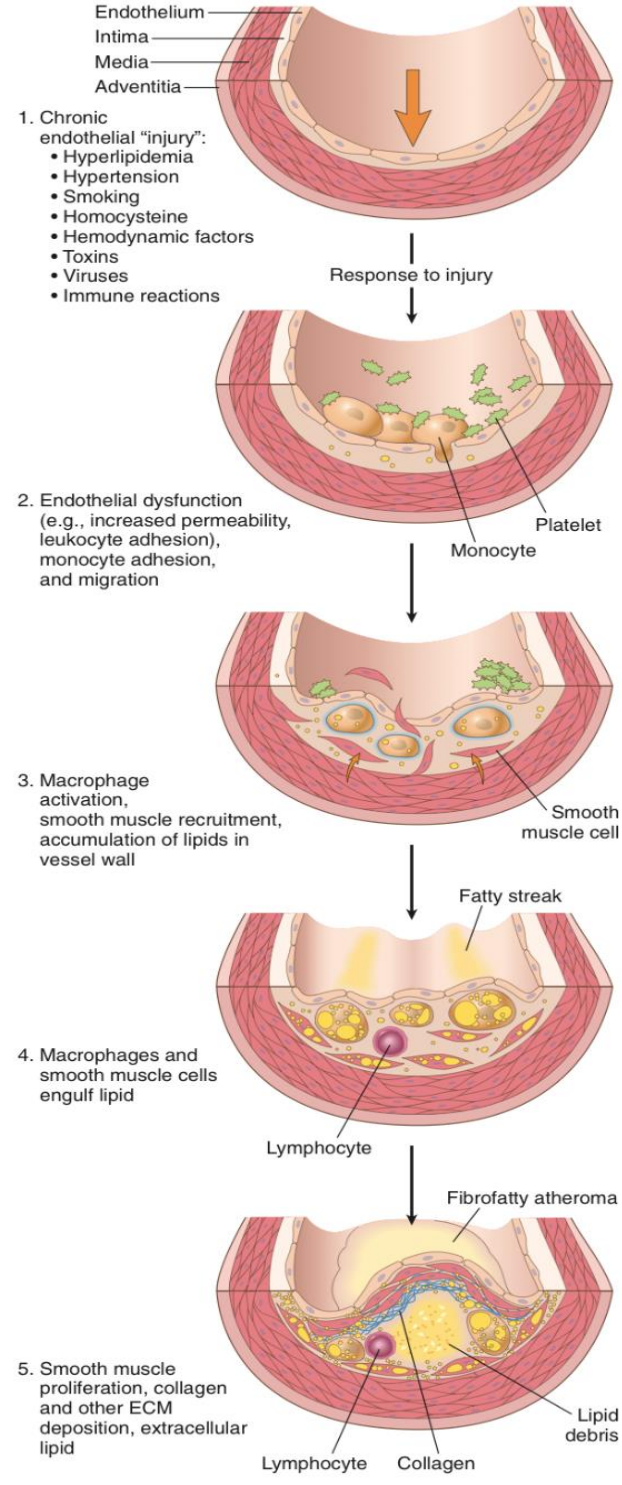
Adhesion of blood leukocytes to the endothelium, followed by migration of leukocytes into the intima & transformation into macrophages & foam cells

Adhesion of platelets

Release of factors from activated platelets, macrophages, or vascular cells that cause migration of SMCs from media into the intima.

Proliferation of smooth muscle cells in the intima, and production of extracellular matrix (e.g. collagen & proteoglycans).

Enhanced accumulation of intracellular (macrophages and SMCs) and extracellularly lipids.



Pathogenesis

MALES SLIDES

Response-to-injury hypothesis

- Endothelial injury

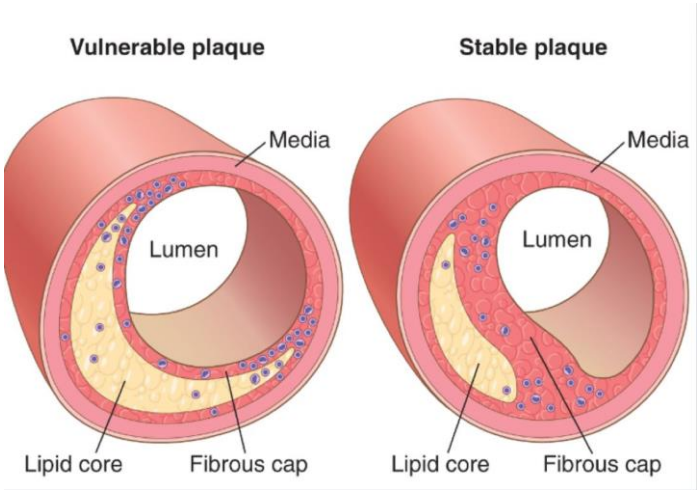
– Not completely understood

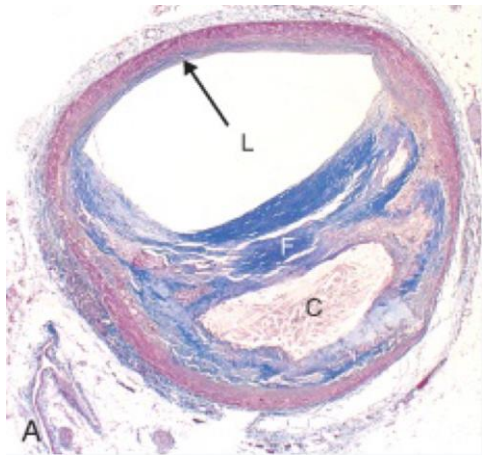
– Nevertheless, the two most important causes of endothelial dysfunction are:

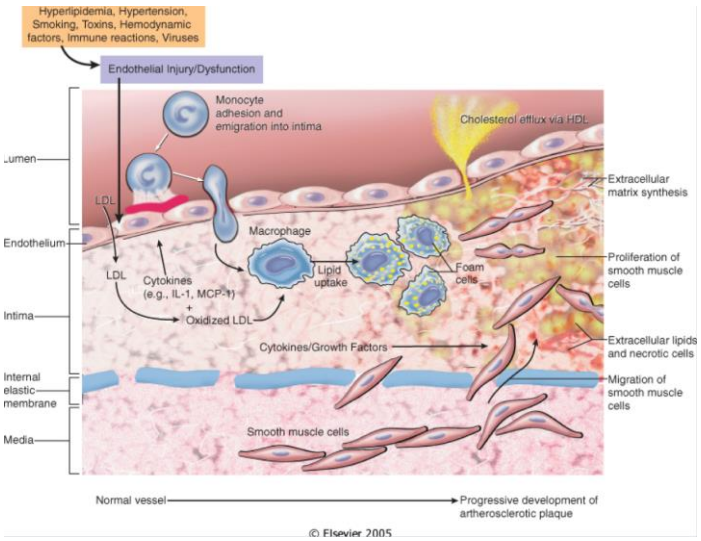
- Hemodynamic disturbances
- Hypercholesterolemia

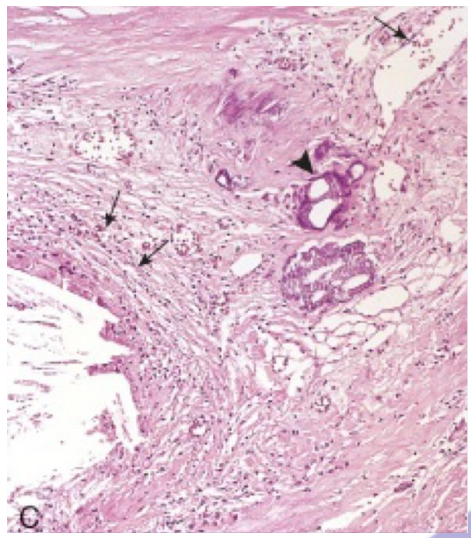
– Inflammation is also an important contributor.

- Smooth muscle cell proliferation





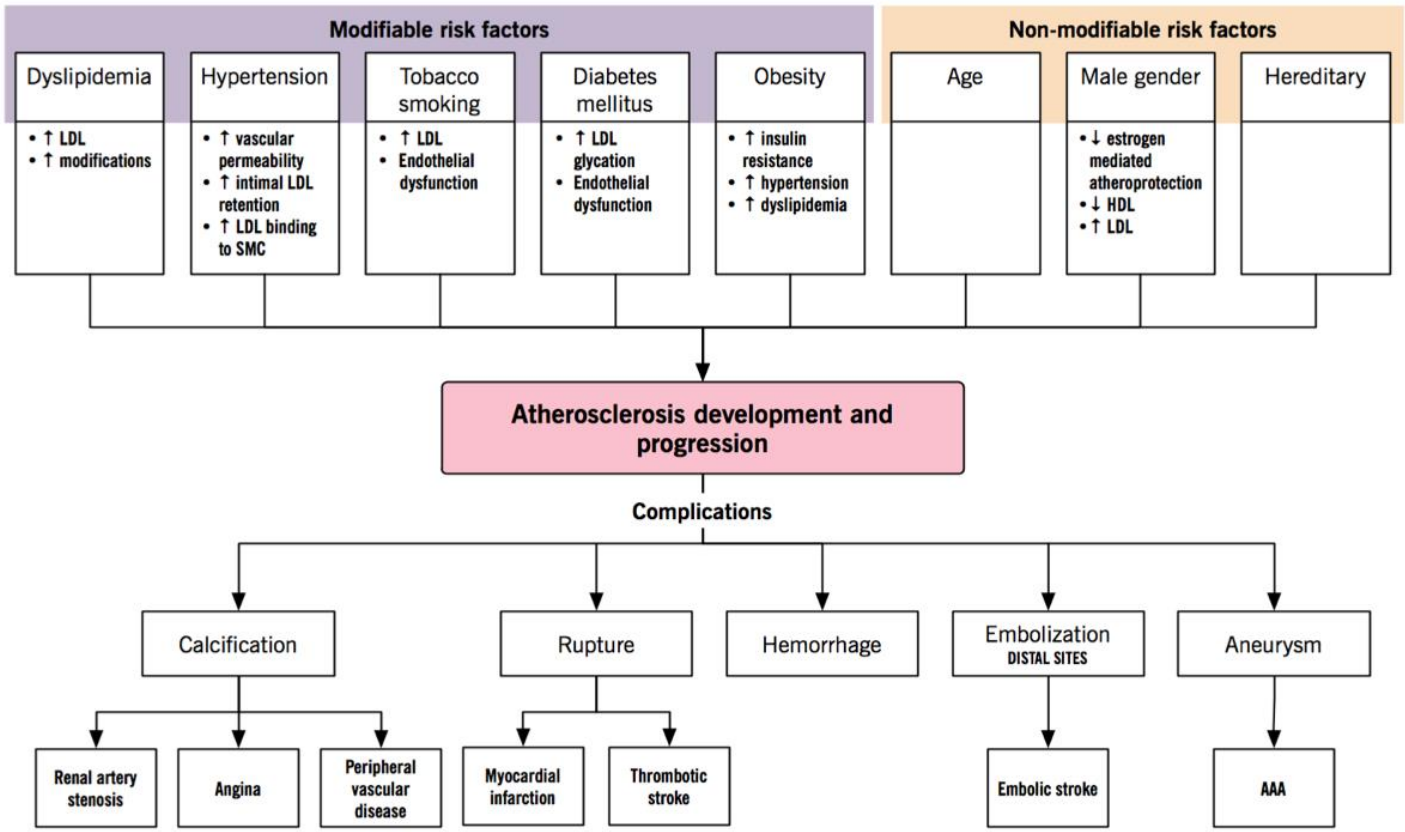




Summary

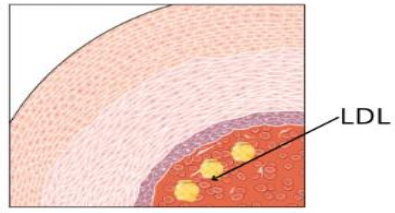
FEMALES SLIDES

ATHEROSCLEROSIS | Risk factors and complications of atherosclerosis

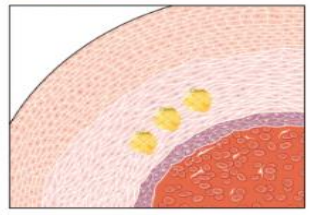


Pathogenesis Extra

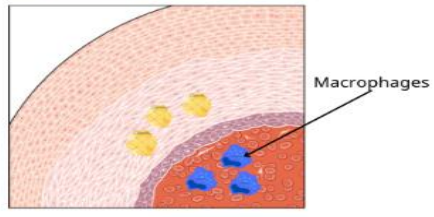
1. Normally LDL pass through endothelial cells then enter body cells by receptor mediated endocytosis



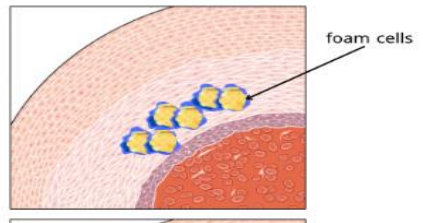
2. When endothelial layer is injured LDL Particles leak into the intimal layer and gets oxidised



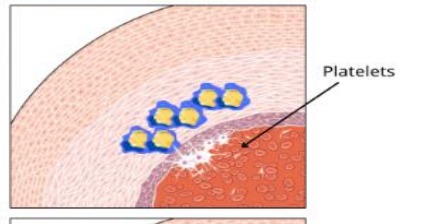
3. When LDL is oxidised it becomes pro inflammatory antigen triggering immune response and macrophages come to fight the LDL



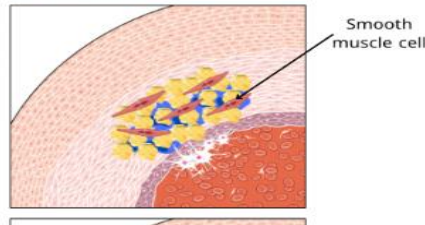
4. Macrophages engulfs LDL creating'"foam cells " and accumulation of foam cells underneath the endothelium layer forms "fatty strikes" which is the first marker of atherosclerosis



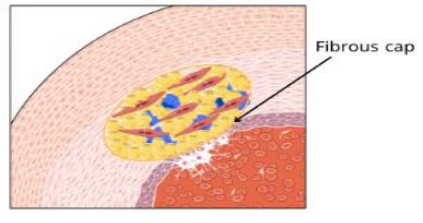
5. Damage to the endothelium cells trigger platelets and platelets & endothelial cells release many factors



6. Factors stimulates smooth muscle migration from tunica media to tunica intima



7. Smooth muscles proliferate and and stimulates production of extra cellular matrix like collagen & proteoglycans resulting in formation of fibrous cap overlying a lipid core called" plaque"



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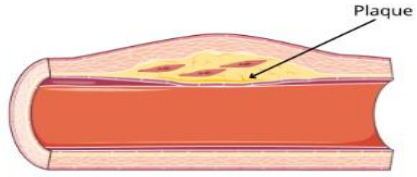
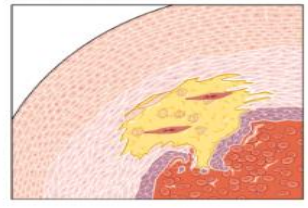
Pathogenesis Extra

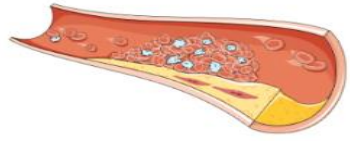
8.Plaque can obstruct the lumen



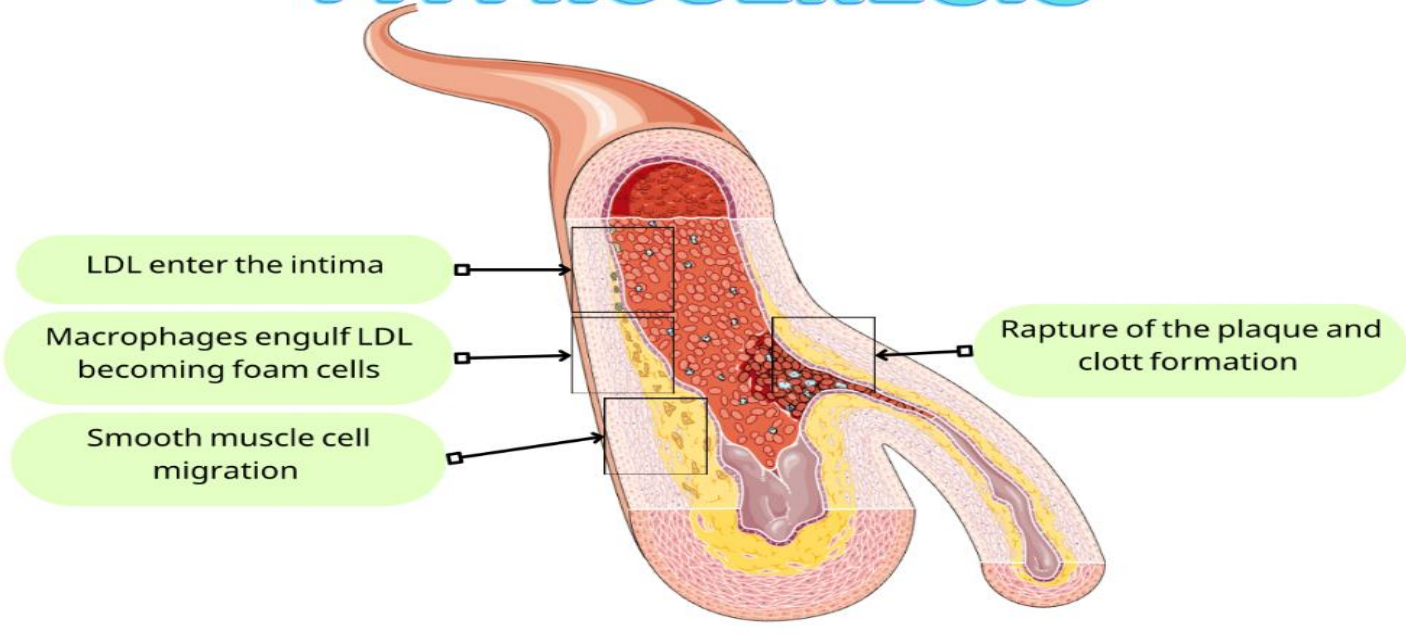
9.foam cells undergo necrosis releasing enzymes make the fibrous cap bigger and bigger till it raptures



10. Platelets forms a clot at the site of rapture



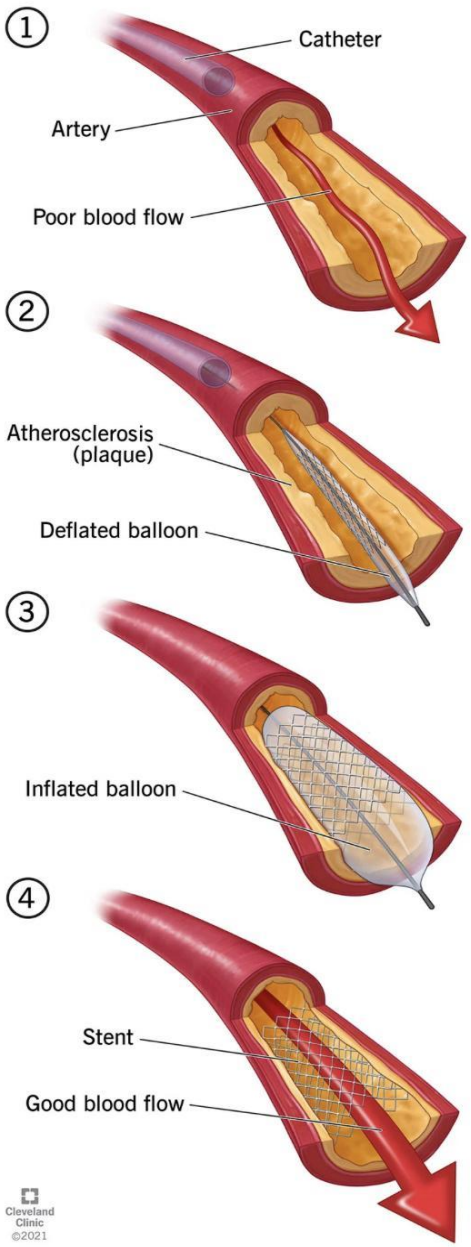
SUMMARY PATHOGENESIS

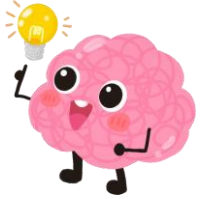


Made by : Lama Alotaibi

Angioplasty Dr's explanation

- **How to know if a patient has atherosclerosis ?** You test for blood cholesterol , blood pressure , ask if he has DM …
- Then send the patient to a "Treadmill test " where he will be put on a treadmill for a particular time and if he got breathless check his ECG results.
- If the treadmill test indicates that his cardiac function is abnormal, then you need to send him for an "Angiography" .
- Angiography : an imaging procedure where you will inject a dye that goes into/travels in the blood vessels.This will help you identify the areas that have atherosclerosis since they will not be picked up be the dye.The results will be shown in the images.
- Then if atherosclerosis is progressive, you will do an " Angioplasty".
- Angioplasty : you insert a needle with a stent/mesh that is later inflated or dilated in the blood vessel . When the stent expands, the plaque is pushed or squeezed to the sides and the lumen gets wider so blood can flow more easily .Later, the needle is pulled out but the stent is left there.
- The stent is coated with antithrombotic agents which prevent the rupture of the plaque and formation of blood clots .
- The plaque can't be ripped off because it's inside the vessel wall in the intima , if so it'll result in more damage.





KEYWORDS

Atherosclerosis	• Chest pain upon exertion • Troponin and CK-MB levels are normal • Atherosclerotic plaque with Necrotic debris with cholesterol cleft in the Center • Fatty streaks made of Foam cells and lymphatic cells • High level of LDL • lipid-laden macrophages • Aneurysm • Lipid accumulation

Summary extra from med443

Atherosclerosis

- **Definition**: Is a type of arteriosclerosis, a build-up of fat (cholesterol) within the artery wall, Slowly progressive. is characterized by intimal lesions called atheromas (also known as atheromatous plaque or fibrofatty plaque), which protrude into and obstruct vascular lumens and weaken the underlying media.
- **Sites**: Abdominal Aorta > Coronary Arteries > Popliteal Artery > Internal Carotid > Vessels of the circle of Willis
- **Risk Factors**
  - **Major**: Non-Modifiable: Age + Male gender + Family history + Genetic abnormalities
    Potentially Modifiable: Hyperlipidemia + Hypertension + Smoking + Diabetes + Inflammation
  - **Minor**: Obesity + Physical inactivity + stress + postmenopausal + high carbohydrate intake + Alcohol +Lipoprotein Lp (a) + Trans unsaturated fat intake + Chlamydia pneumonia
- **Pathogenesis**: Hemodynamic disturbances or Hypercholesterolemia > Endothelial injury > LP accumulation > Increased permeability > Adhesion of blood leukocyte > Transform into macrophages and foam cells > Adhesion of platelets > release factors > migration of SMCs into intima > proliferation and production of EC matrix > Enhanced accumulation of IC and EC lipids
- **Morphology**
  - **Gross**:
    - intimal thickening and lipid accumulation
    - SA plaques impinge on the lumen of the artery
    - AS plaques usually involve only a partial circumference of the arterial wall ("eccentric" lesions") and are patchy and variable along the vessel length. (vary in shape)
    - AS plaques vary in size
  - **Microscopic**:
    - Cells: SMCs, Macrophages, Lymphocytes and foam cells
    - Extracellular matrix: collagen, elastic fibers and proteoglycans
    - Lipid: typical atheromas contain relatively abundant lipid both extracellular and intracellular lipid
- **Complications**: Calcification + Hemorrhage + Plaque rupture + Superimposed thrombosis Complication (thromboembolism) + weakening of BV with aneurysmal dilation + Myocardial infarction + Cerebral infarction + Mesenteric occlusion + peripheral vascular disease

Answers:
1- C 2-D 3-A 4-A 5-A

MCQ

1- What is the earliest lesion of atherosclerosis?			
A) Fibrofatty plaque	B)Atheroma	C)Fatty streak	D)Cholesterol emboli
2-Which of the following is a non-modifiable risk factor for the development of atherosclerosis?			
A)Obesity	B)Hypertension	C)Smoking	D)Family History
3- Which of the following protects against a heart attack?			
A)HDL	B)LDL	C)VLDL	D) None
4- Atherosclerosis affecting the abdominal aorta can lead to the formation of:			
A)Aortic aneurysm	B)Myocardial hypertrophy	C)Chronic kidney disease	D)Pulmonary hypertension
5- Atherosclerosis involving the arteries supplying the lower extremities can lead to which of the following complications?			
A)Intermittent claudication	B)Ischemic colitis	C)Portal hypertension	D)Pleural effusion

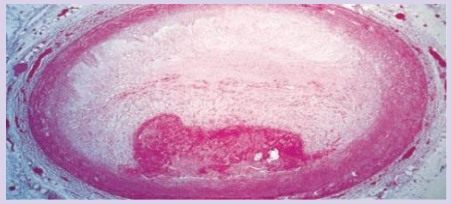
Answers:
6-D 7-B 8-A 9-B 10-C

MCQ

6- Which of the following is a modifiable major risk factors of Atherosclerosis?			
A)Increasing age	B)Gender	C)Family history	D)Cigarette smoking
7- The most serious complication of atherosclerosis?			
A)Aneurysmal dilation of the blood vessels	B)Superimposed thrombosis (Thromboembolism)	C)Calcification	D)Hemorrhage
8- During atherosclerotic plaque formation , what happens after Adhesion of platelets?			
A)Release of factors from activated platelets and other cells that cause migration of SMC from media to intima	B)Enhance accumulation of extracellular and intracellular lipids	C)Platelets form a clot at the site of ruptured plaque	D)Macrophages engulf LDL creating foam cells
9- Fatty streaks are mainly made of?			
A)Foam cells with necrotic debris.	B)T-lymphocytes with lipid Foam cells.	C)Smooth muscle cells	D)LDL
10- Which of the following can be seen when a surgeon opens an artery with atherosclerotic plaque?			
A)Blue complete circumference of the wall of artery	B)Blue spots with yellow lines of fatty streaks	C)Yellow partial circumference of the wall of artery	D)Multiple red polyps with cheasous necrosis

Answers:
1-A 2-C 3-A 4-B

Cases

1-A 60-year-old man is brought to the emergency department due to acute onset of chest pain. Medical history is significant for smoking 1 pack per day for the past 30 years, diabetes mellitus type 2, and hypertension. An ECG shows ST-segment elevation on V1-V4 leads. Cardiac catheterization is performed and shows 80% occlusion of the left anterior descending artery. The first step in the pathogenesis of this patient's condition most likely involves which of the following cell types?			
A)Endothelial Cells	B)Smooth muscle cells	C)Platelets	D)Monocytes
2- A 69-year-old woman presents with crushing substernal chest pain and nausea. Laboratory studies show elevated serum levels of cardiac proteins(CK-MB = 8.5 ng/mL; troponin-I =3.2ng/mL) A diagnosis of myocardial infarction is confirmed by ECG. Despite treatment, the patient becomes hypotensive, and resuscitation attempts are unsuccessful. A cross section of the patient's right coronary artery at autopsy is shown in the image. Which of the following pathologic changes are evident in this autopsy specimen? 			
A)Microaneurysm and canalization	B)Thrombosis and calcification	C)Atherosclerosis and thrombosis	D)Vasodilation and arteritis
3- A 60-year-old mildly obese woman is admitted to the hospital with a chief complaint of recurrent chest pain on exertion. The patient reports several episodes of chest pain over the past several years and painful leg cramps when walking. Fasting blood glucose (160 mg/dL) and total serum cholesterol (370 mg/dL) are high. The ECG is normal and blood tests for cardiac-specific proteins are negative. Chest pain in this patient likely due to which of the following underlying conditions?			
A)Atherosclerosis of coronary artery	B)Congenital anomalous origin of coronary artery	C)Coronary arteritis	D)None
4- A 62-year-old man is discovered to have hyperlipidemia on screening tests after a routine physical examination. Laboratory studies show total serum cholesterol of 285 mg/dL, LDL of 215 mg/dL, HDL of 38 mg/dL, and triglycerides of 300 mg/ dL. This patient is most at risk of developing an aneurysm in which of the following anatomic locations?			
A)Ascending aorta	B)Abdominal aorta	C)Circle of Willis	D)Coronary artery

رب أشرح لي صدري ويسر لي أمري وأحلل عقدة من لساني ..

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