PATHOLOGY TEAM
439

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Risk factors & pathogenesis of atherosclerosis

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.

Index:
Important
NOTES
Extra Information

blood vessels

Arteries

- Large (elastic) arteries

e.g: aorta , common carotid, iliac
-lots of elastic fibers

- Medium (muscular) arteries

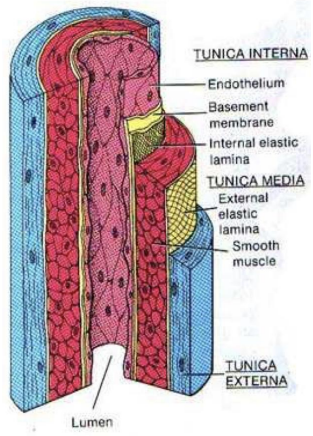
e.g: coronary, renal arteries
-mostly smooth muscle cells

- Small arteries Normal

-all smooth muscle cells Blood
-blood pressure controlled here.

Veins

-Large diameter.
-Thin walls.
- Compressible, penetrable by tumor.
- Have valves.



Normal blood vessels

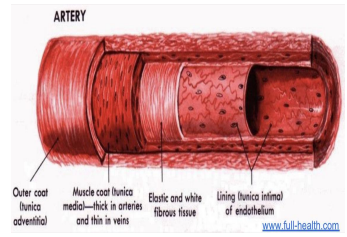
Capillaries

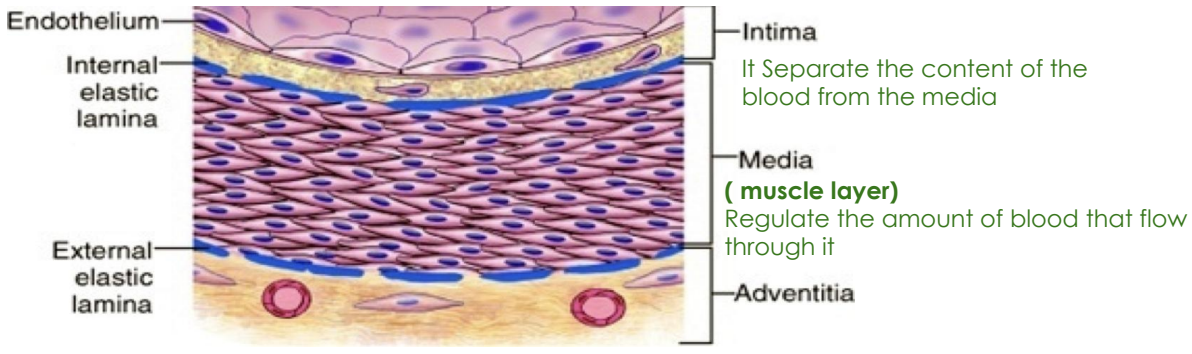
-Has same Diameter as RBC.
-Thin walls, slow flow (For gas exchange).

-Great for exchanging oxygen and nutrients.

Lymphatics

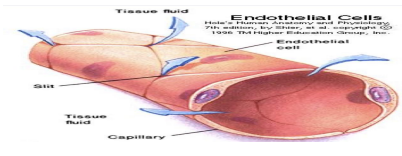
-Drains excessive interstitial fluid from the interstitial tissue.
-Passes through lymph nodes.
-End in the superior vena cava.



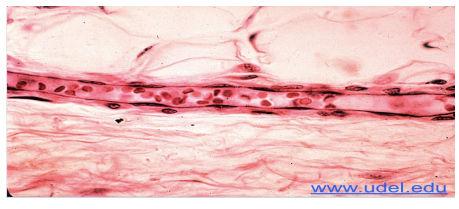


Endothelial cells

The endothelium is a single falt 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 covers the basement membrane completely.)



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 :

- maintenance of vessels wall homeostasis
- Normal circulatory function.

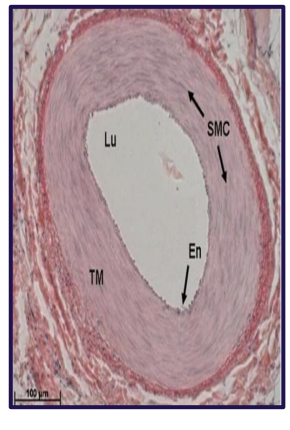
- If the endothelial cell gets injured, the basement membrane gets exposed. This exposure is a source of trouble and diseases. - Intact endothelial cells are very important for normal physiology.

blood vessels

Smooth muscle cells (SMC)

SMCs are present in the media of blood vessels that is responsible for vasoconstriction and vasodilation of blood vessel to regulate the amount of the blood in the vessel

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



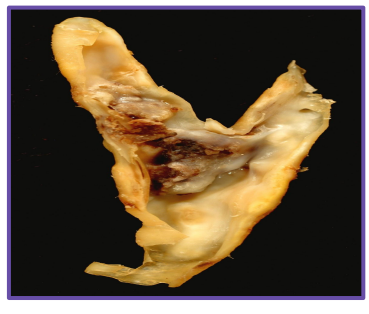
1. Migrate from the media to the intima.
2. In the intima the SMCs lose the capacity to contract and gain the capacity to divide. So they proliferate as intimal SMCs. (SMCs changed completely)
3. They synthesize collagen, elastin etc and deposit extracellular matrix (ECM).

Atherosclerosis

Definition

What is atheroma?
An atheroma, or atheromatous plaque ("plaque"), is an abnormal accumulation of material in the inner layer of the wall of an artery. The material consists of mostly macrophage cells, or debris, containing lipids, calcium and a variable amount of fibrous connective tissue. Atheroma is shown in the below gross pathological picture

Atherosclerosis is characterized by **intimal lesions** called atheromas (also known as atheromatous plaque or fibrofatty plaque), as it's growing ,which protrude into and obstruct vascular lumens and weaken the underlying media.
as the Atheroma grows the vessel became narrower and the blood flow decrease leading to atherosclerosis.



- The most commonly involved vessels are the **abdominal aorta** than **coronary arteries**, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis (3 arteries come together and meet to form a circle)

AS pulque grow leading to serious complications (depends on the location of AS)

In Coronary artery disease (angina & MI)	It blocks the blood flow to heart Leading to MI….etc
Carotid atherosclerotic disease (stroke)	

In boy's slide only,consider it extra information

Arteriosclerosis (hardening of the arteries) is a generic term for thickening and loss of elasticity of arterial walls.

1. Arteriosclerosis
2. Hypertension
3. calcific sclerosis , Mönckeberg medial
4. Atherosclerosis
5. Old age

The pathogenesis of atherosclerosis

the hypothesis is that AS is a response to injury

Accumulation of lipoproteins
(mainly LDL with its high cholesterol content) in the vessel wall and subtle chronic endothelial injury
It is the first and most important step in the pathogenesis of atherosclerosis and will lead to the next following steps.

Will lead to

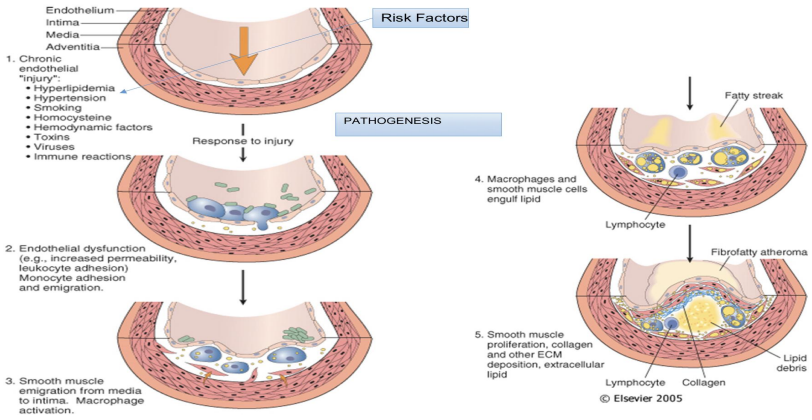
Increased permeability and leukocyte (monocyte) adhesion.

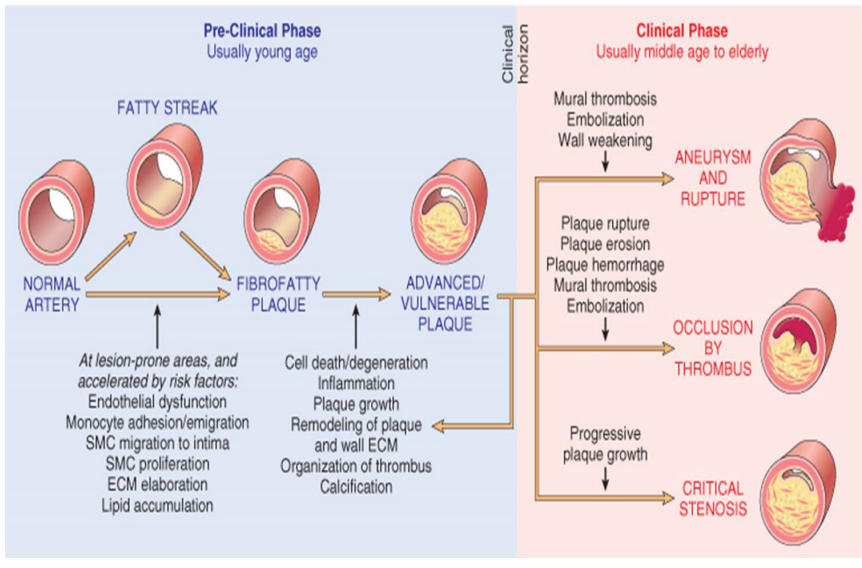
Adhesion of blood leukocytes to the endothelium, followed by migration of leukocytes into the intima & transformation into macrophages & foam cells

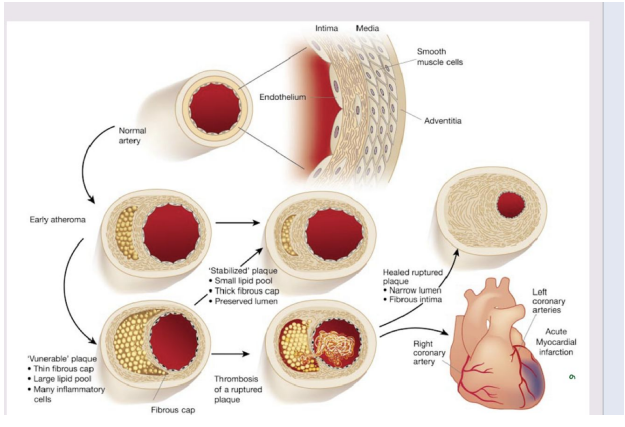
Adhesion of platelets

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.

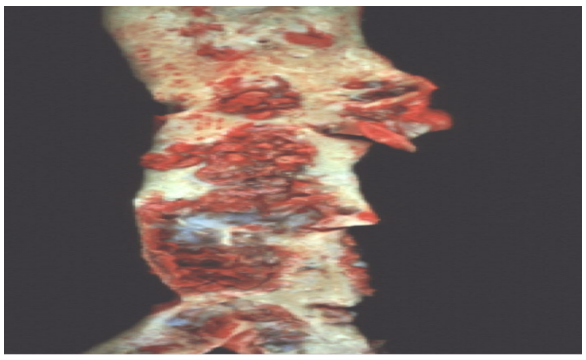






Briefly : fatty streaks taken place in some places on the blood vessel and then there's fibrofatty plaque which is growing bigger and bigger and the vessel became narrower (in this step the atheroma can rupture or formed thrombus causing complete occlusion or progressive growth leading to critical stenosis

Morphology of AS



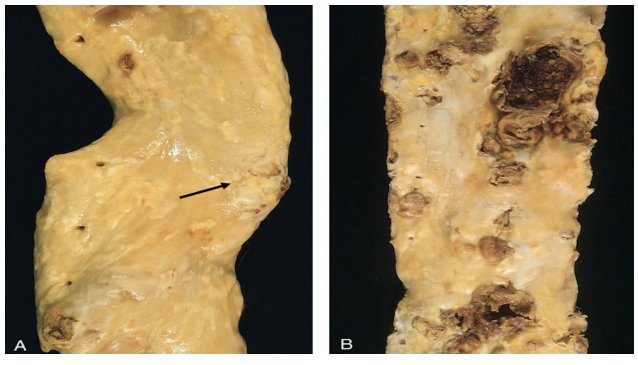
Gross morphology of atheroma / atheromatous plaque

- 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.**
- As plaques usually involve only a **partial circumference of the arterial wall ("eccentric"lesions)* and are patchy and variable along the vessel length .**

*eccentric = in the side , not involving the entire circle of the vessel .

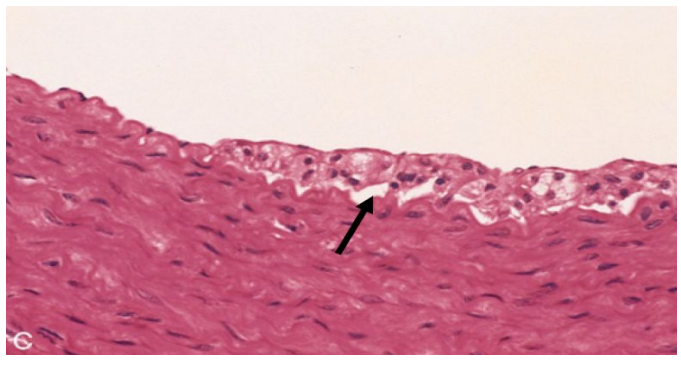
Fatty streaks

- **Fatty streaks are the earliest lesion of atherosclerosis,** they are a collection of **lipid and lipid laden foam cells in the intima .**
- The do not cause any disturbance in blood flow
- Fatty streaks begin as multiple yellow, flat spots less than 1mm 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 plaques .



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 .



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

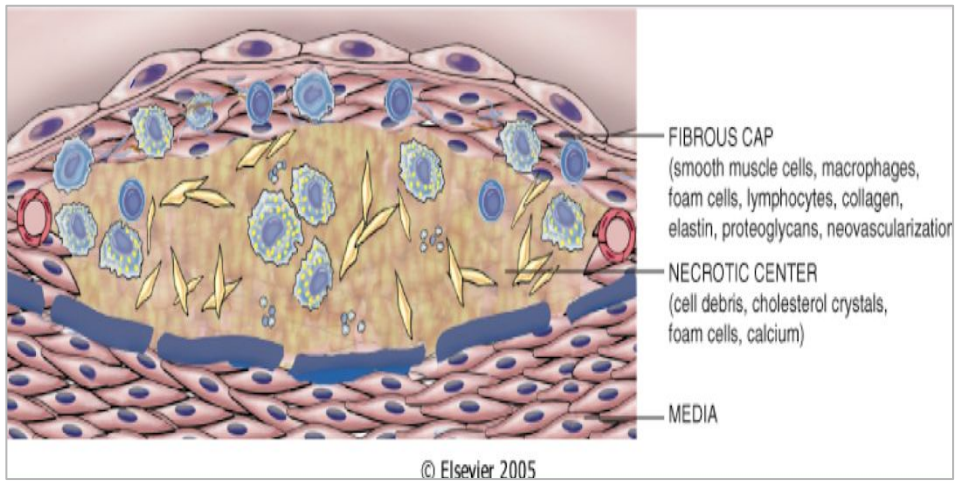
Morphology

Microscopic

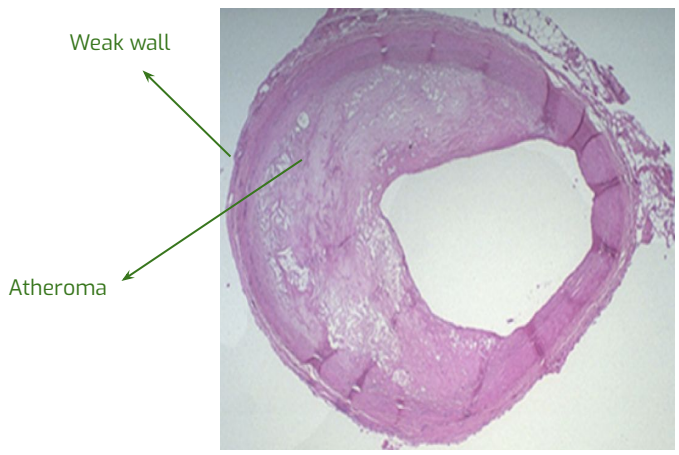
What are you going to see in the AQ pulaque ?

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 cholesterol esters), covered by a firm, white fibrous cap. Atherosclerotic plaques have **three principal components :**
1- Cells : SMCs "smooth muscle cells", macrophages & foam cells .
2-Extracellular matrix : including collagen, elastic fibers and proteoglycans
3- Lipid : Typical atheromas contain relatively abundant lipid both intracellular & extracellular lipid .

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



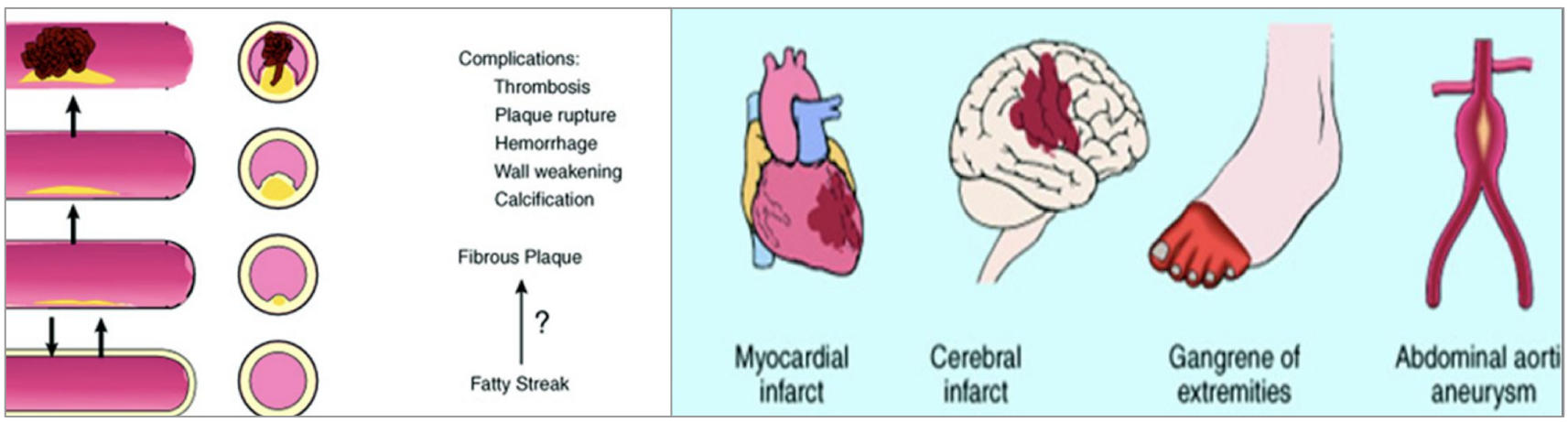
- Typically, the **superficial fibrous cap** is composed of SMCs and extracellular matrix,With some macrophages and T lymphocytes .
- Below the fibrous cap is a **necrotic core,** containing a lipid deposits (primarily cholesterol and cholesterol esters), cholesterol clefts, debris from dead cells, foam cells and fibrin .
- **Note:make sure you know the contents of (cap + necrotic core)**



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

Complications of AS

Advanced AS Plaque	
1-**Plaque rupture/ ulceration/ erosion (disruption)** Of the AS plaques (The blood vessel is weak so it may ruptur)	induce thrombus formation **OR** the AS plaque may discharge debris into the bloodstream, producing microemboli composed of plaque lipid (cholesterol emboli or atheroemboli)
Hemorrhage **(It can start bleeding inside the the atheroma itself)**	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 .
Superimposed thrombosis (and thromboembolism) endothelial cell gets injured, the basement membrane gets exposed=thrombosis There's 2 masses now = total or sub blocked the vessel = ischemia	which usually occurs on top of ruptured or ulcerated plaques . It is the most feared complication . The thrombus can lead to partial or complete occlusion of the lumen . The thrombus can also **embolize** .
Weakening of the blood vessel wall with aneurysmal dilation **(Normally the blood vessel is straight but it may dilate and plugging out which we call it aneurysm = ultimately can rupture)**	Atheroma can induce atrophy of the underlying media, causing weakness, aneurysm and potential rupture .
Calcification Atheroma is a dead tissue can undergo Dystrophic calcification	Atheromas often undergo calcification .



The location of Atheroma determines the the size of the damage and the chance of surviving

Risk factors

Risk factors for atherosclerosis

Major
Non-modifiable risk factors Cannot be changed

- (Increased age)Aging[1]
- Male gender[2]
- Family history
- Genetic abnormalities

Major
Modifiable risk factors
Can be changed

- Hyperlipidemia
- Hypertension
- Cigarettes smoking
- Diabetes

Minor risk factors

- Obesity
- Physical inactivity
- Stress ("type A" personality)
- Postmenopausal estrogen deficiency
- High carbohydrate intake
- Alcohol
- Lipoprotein Lp(a)
- Hardened (trans)unsaturated fat intake
- Chlamydia pneumoniae

Importance of lipoproteins in hyperlipidemia

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

- Low-density lipoproteins (LDLs)
- Very-low-density lipoproteins (VLDLs)
- Chylomicrons
- increased levels of lipoprotein(a)

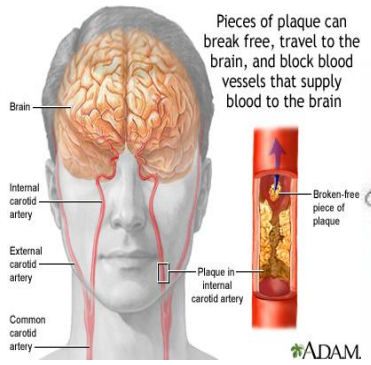
High density lipoproteins (HDL):

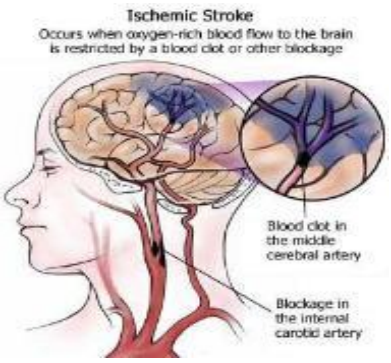
Known as "**good**" cholesterol, high levels of HDL protects against heart attack.
Low levels of HDL also increase the risk of heart disease. HDLs help to reverse the effects of high cholesterol.

[1] Because women's estrogen levels decrease after menopause .
[2] Because women have higher estrogen levels which protect against atherosclerosis.

Stroke / cerebrovascular accident

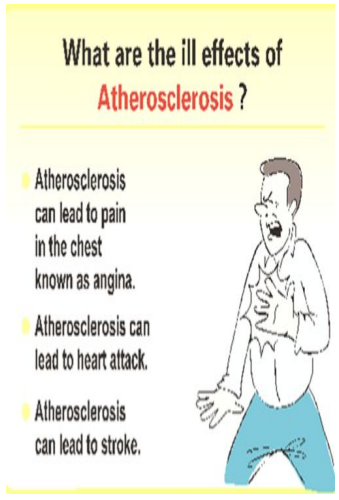
Ischemic stroke occurs when oxygen-rich blood flow to the brain is restricted .
(Type of stroke depend on the involved site)





atherosclerosis

- Coronary artery disease
  - Angina
  - Heart disease
  - heart attack
- cerebrovascular stroke
- peripheral arterial disease
  - Leg blood clot
  - Intermittent claudication

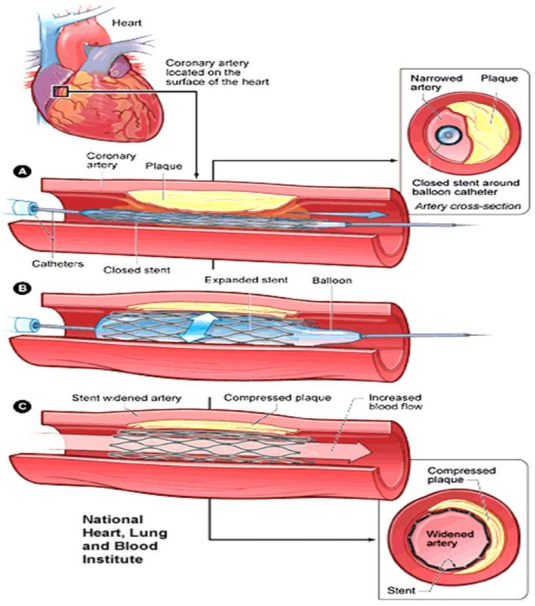


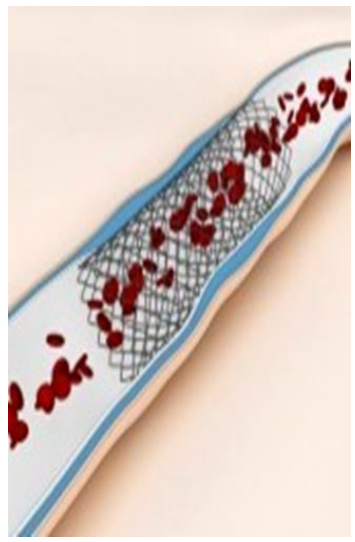
Atherosclerosis in

- **Internal carotid** *may lead to* **Ischemia,stroke and cerebral infarction.**
- **Middle cerebral & Internal carotid** *may lead to* **stroke and cerebral atrophy.**
- **Anterior descending coronary artery** *may lead to* **myocardial infarction.**
- **Renal artery** *May lead to* **renal ischemia.**
- **Femoral Artery** *may lead to* **intermittent claudication.**
- **Popliteal artery** *may lead to* **peripheral ischemia which may lead to gangrene and claudication (cramping pain in the leg induced by exercise).**
- **Superior mesenteric** *may lead to* **infarction of the small intestines.**

Angioplasty

It is a procedure to restore blood flow through the artery. You have angioplasty in a hospital.
(treatment of Atherosclerosis)





Qulz

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- HDL	B- Chylomicrons	C- Oxidized LDL	D- VLDL
2- 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
3- A group of pathologists are analyzing tissue samples of adolescents age 13-18 to study the aging process. Autopsy of a 14-year-old boy who died in a motor vehicle accident shows several minimally raised yellow spots on the inner surface of the abdominal aorta. The rest of the cardiovascular findings during the autopsy are unremarkable. He had no known medical problems. There was no family history of cardiovascular disease or sudden cardiac death. Which of the following is most likely to be the predominant cell type in these lesions on light microscopy?			
A- Macrophages	B- Fibroblasts	C- Neutrophils	D- Mast cells
4-:A 42-year-old man is found dead at home. His medical problems included hypertension and dyslipidemia, but he had been noncompliant with his medications. The patient had a lengthy smoking history and, despite constant urging from his physicians to stop smoking, he had only quit recently. An autopsy is requested by the family. Pathological examination shows complete thrombotic occlusion of the left main coronary artery and diffuse atherosclerotic vascular disease characterized by multiple atheromas. Along with a lipid core, these atheromas have a fibrous cap formed from dense deposition of collagen. Which of the following cells are directly responsible for synthesizing this fibrous cap?			
A- Interstitial fibroblasts	B- Macrophages	C- Smooth muscle cells	D- Endothelial cells

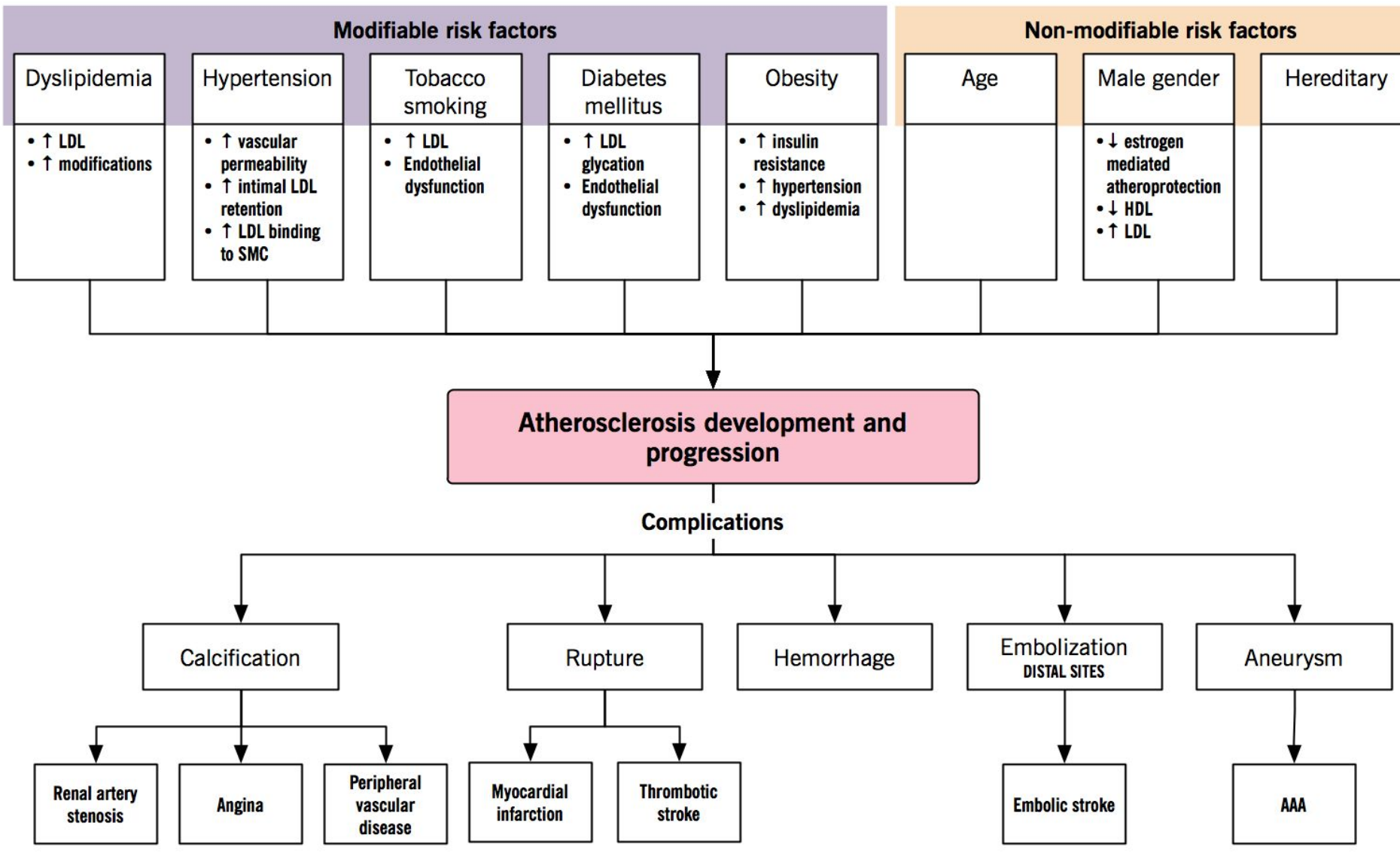
4-C
3-A
2-C
1-C

Summary

	Atherosclerosis	
Definition	**characterized by atheromas (intimal thickening + lipid accumulation), which protrude into and obstruct vascular lumens and weakens the underlying media**	
Morphology	**Microscopic** **:Components of Atherosclerotic plaques** **cells: SMCs, macrophages, lymphocytes and foam .cell** **Extracellular matrix: including collagen, elastic .fibers, and proteoglycans** **. Lipid: intracellular and extracellular lipid** **.Fibrous cap -** **.Central Necrotic core -**	**Gross** • **Early lesion → Fatty streaks** • **Eccentric lesions, patchy, and variable AS plaques along the vessel length.**
Major risk factors (Minor risk factors page 9)	**Non modifiable** **age ↑** **Male gender** **Family history** **Genetic abnormalities**	**Modifiable** **Hyperlipidemia** **Hypertension** **Cigarette Smoking** **Diabetes** **Inflammation**
Pathogenesis	**Chronic endothelial injury → endothelial dysfunction (↑ permeability + leukocyte adhesion) → smooth muscle emigration from media to intima → macrophages & SMC engulf lipid → smooth muscle proliferation, collagen & other ECM deposition, extracellular lipid**	
Complications	• **Calcification: renal artery stenosis, angina, peripheral vascular disease** • **Rupture: MI, thrombotic stroke.** • **Hemorrhage** • **Embolic stroke** • **Aneurysm of abdominal aorta (AAA)** • **Weakening of the blood vessel wall with aneurysmal dilation**	

Summary

ATHEROSCLEROSIS | Risk factors and complications of atherosclerosis



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