Atherosclerosis

Objectives:

(1) Understand the pathogenesis and clinical consequences of atherosclerosis.

(2) Be able to discuss pathology and complications of ischemic heart diseases with special emphasis on myocardial infarction.

(3) Know how lifestyle modifications can reduce the risk of ischemic heart diseases.

Editing file

Black: original content.
Red: Important.
Light Purple:From Robbin's.
Blue:only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

Reviewed by Rezan AlRabah & Ibrahim AlBakri

MED438 KING SAUD UNIVERSITY

Pathology Teamwork 438

Normal 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 /arterioles**

-all smooth muscle cells
-blood pressure controlled here

Capillaries

-Has same Diameter as RBC.

-Thin walls, slow flow (For gas exchange).

-Great for exchanging oxygen and nutrients.

Normal Blood Vessels

Veins

- Large diameter.

-Thin walls.

- Compressible, penetrable by tumor.

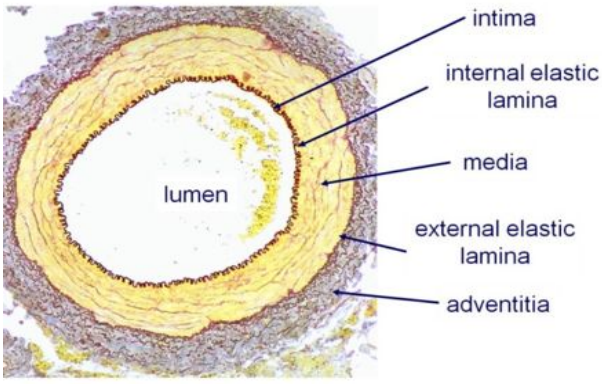
- Have valves.

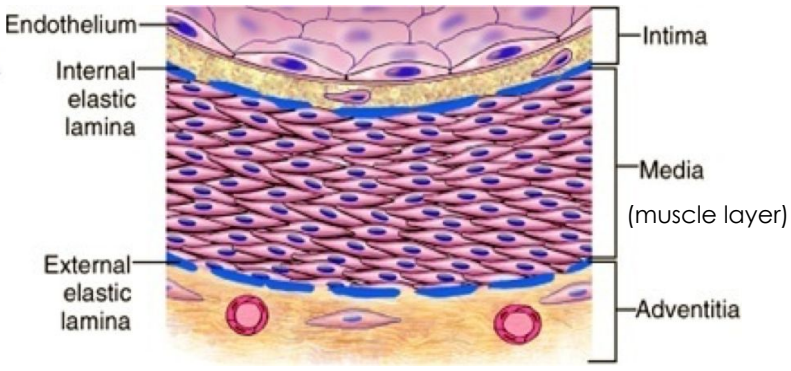
Lymphatics

-Drains excessive interstitial fluid.

-Passes through lymph nodes.

Histology of normal artery :





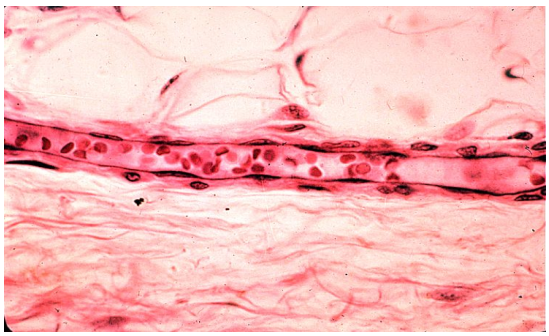
Normal blood vessels

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.

1. It is in direct contact with the blood/lymph and the cells circulating in it.

2. Its structural and functional integrity is fundamental to:
   - maintenance of vessel 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.

Smooth muscle cells

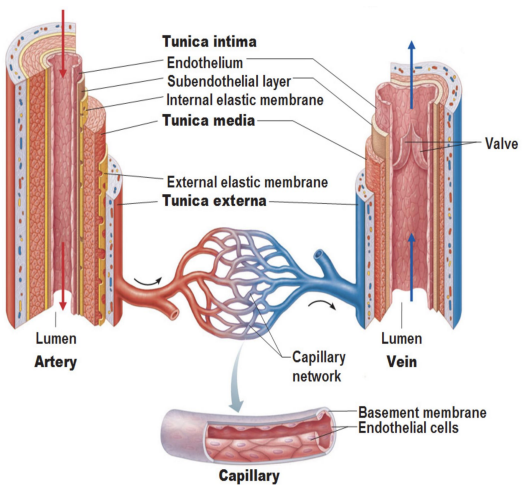
- responsible for vasoconstriction and vasodilation
- present in the media of blood vessels

Any vascular injury or dysfunction will stimulate SMCs, which will lead to:

1. Migrate from the media to the intima

2. In the intima the SMCs:
   1-lose their capacity to contract
   2- gain the capacity to divide
   So they proliferate as intimal SMCs

3. synthesize collagen, elastin, proteoglycans etc. and deposit extracellular matrix.



Atherosclerosis

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

- **Atherosclerosis** (Treatment: Angioplasty)
- **Fibromuscular intimal hyperplasia** (non-atherosclerotic, occurs in muscular arteries larger than arterioles)
- **Mönckeberg medial calcific sclerosis** (presence of calcific deposits in muscular arteries, mainly occurs in old age)
- **Arteriolosclerosis** (affects small arteries and arterioles. The two variants hyaline and hyperplastic. related to Hypertension)

Definition

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.[1]

The most commonly affected vessels are:

abdominal aorta → coronary and popliteal → internal carotid arteries (supplies the brain) → vessels of the Circle of Willis[2]

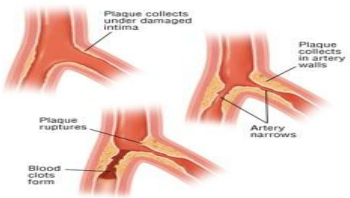
Occlusion of:

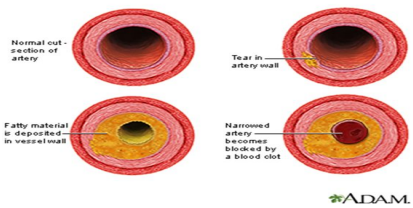
Coronary arteries may lead to angina and MI.

Internal carotid and middle cerebral may lead to stroke and cerebral atrophy.

Superior mesenteric may lead to infraction of the small intestines.

Popliteal artery may lead to peripheral ischemia which may lead to gangrene and claudication (cramping pain in the leg induced by exercise).



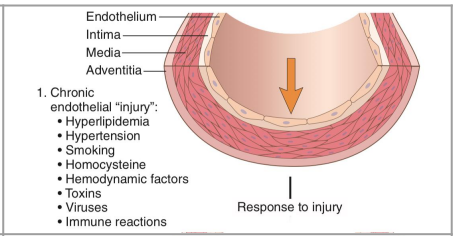
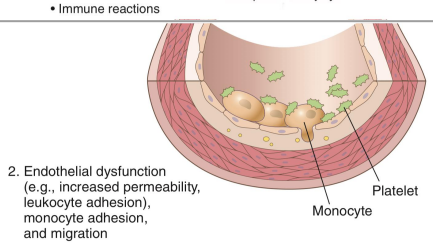
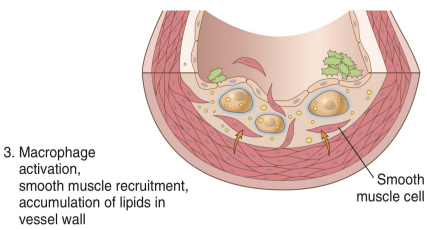
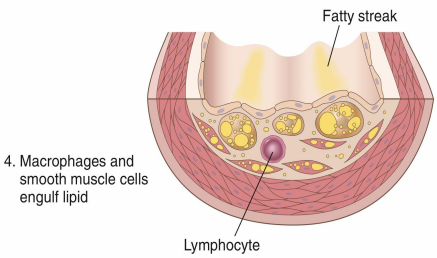
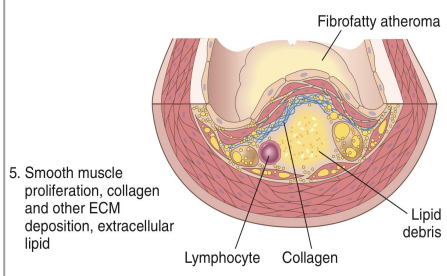


[1] Ultimately, as it grows it will come to a point where there is no space for the blood to flow, that means that whatever is supplied there will undergo ischemia (this is the mechanism of myocardial infarction or heart attack) or necrosis either coagulative or liquefactive depending on the location. two factors weaken the media: ischemia & changes in the ECM

[2] is a circulatory anastomosis that supplies blood to the brain. It's composed of branches of anterior, middle and posterior arteries.

pathogenesis of atherosclerosis

Helpful video

1	The first step of AS starts with a chronic injury caused by LDLs, smoking, high blood pressure or other causes.	
2	The damaged endothelium (endothelial dysfunction)[1] becomes more permeable, also monocytes will adhere and migrate to the tunica Intima.	
3	The increased permeability allows lipoproteins (mainly LDL with its high cholesterol content) accumulate in the walls, Monocytes will become macrophages and SMCs will migrate to tunica Intima.	
4	SMCs[6] and Macrophages engulf lipids then differentiate into foam cells. accumulation of lipid within macrophages [2], respond by releasing cytokines (TNF, IL-1[3] and IFN-γ[4]), growth factors [5] and chemokines that increases the inflammation. This growing inflammatory area "lesion" is called a fatty streak.	
5	Platelets bind to the damaged endothelium of the fatty streak, releasing PDGF[5], which encourages intimal SMCs[6] to proliferate. It also secretes ECMs[7] forming a fibrous cap. Finally, the fatty streak causes calcium to accumulate in the SMCs, which harden the vessels. Extracellular lipid deposition.	

[1] two causes of endothelial dysfunction are hemodynamic disturbances (induction of endothelial genes, ex: atheroprotective gene) and hypercholesterolemia.
[2] LDL is oxidized through the action of oxygen free radicals generated locally by macrophages or ECs and cholesterol crystals formation
[3] cholesterol crystals can activate innate immune cells to produce IL-1 and other pro-inflammatory mediators.
[4] activated T cells in the growing intimal lesions elaborate inflammatory cytokines (IFN-γ)
[5] ex: platelet-derived growth factor, fibroblast growth factor and TGF-a
[6] Smooth muscle cells in the tunica intima
[7] Extracellular matrix, such as collagen, proteoglycans, and elastin fibrous cells

Atherosclerosis (cont.)

Morphology

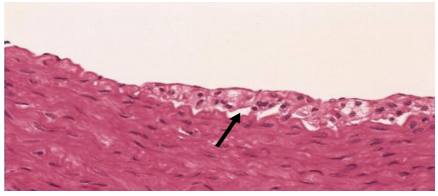
Fatty streaks

- The earliest lesions of atherosclerosis are a collection of lipid and lipid laden foam cells in the intima.
- begin as multiple yellow, flat spots less than 1mm in diameter that coalesce into elongated streaks, 1 cm long or longer.
- contain T lymphocytes, extracellular lipid in smaller amounts and rarer lipid laden foam cells than in plaques.
- It is the precursor lesion of atheromas.

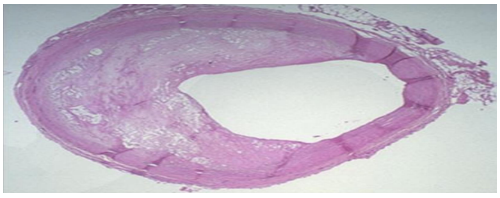
They do not cause any disturbance in blood flow.

Atheroma (Atheromatous plaque)

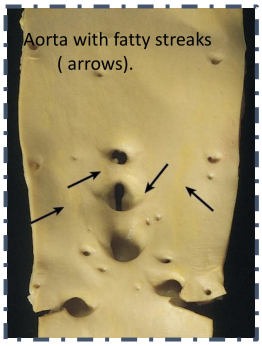
- The key process is intimal(inner) thickening and lipid accumulation.
- Impinges (protrudes) into the lumen of the artery.
- Vary in size.
- Usually involve only a partial circumference of the arterial wall ("eccentric" lesions) and are patchy and variable along the vessel length.

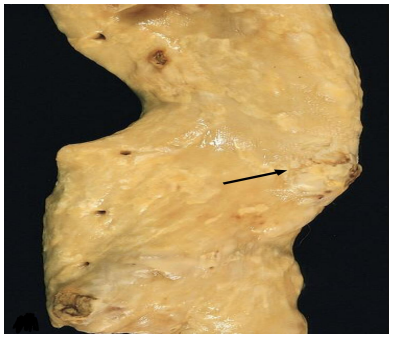


Photomicrograph of fatty streak in an experimental hypercholesterolemic rabbit, demonstrating intimal macrophage-derived foam cells (arrow).

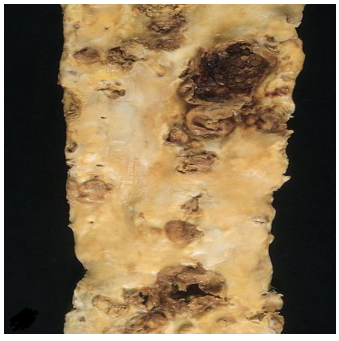


Overall architecture demonstrating an eccentric lesion with a fibrous cap and a central lipid core with typical cholesterol clefts. The lumen is moderately narrowed.

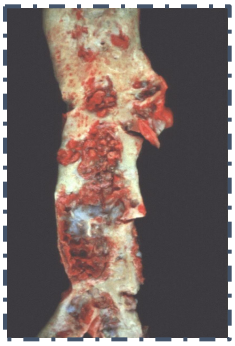




Mild atherosclerosis in Aorta composed of fibrous plaques, one of which is denoted by the arrow.



Severe disease with diffuse and complicated lesions.



Atherosclerosis (cont.)

Microscopic morphology

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.

three principal components of atherosclerotic plaques

Cells

- SMCs
- macrophages
- lymphocytes
- foam cell.*

Extracellular matrix

- collagen
- elastic fibers
- proteoglycans.

Lipid

- Typical atheromas contain relatively abundant lipid both intracellular and extracellular lipid

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

superficial fibrous cap

is composed of SMCs and extracellular matrix. With some macrophages and T lymphocytes.

VS

Deep to the fibrous cap

is a necrotic core, containing lipid deposits (primarily cholesterol and cholesterol esters), cholesterol clefts, debris from dead cells, foam cells, and fibrin.

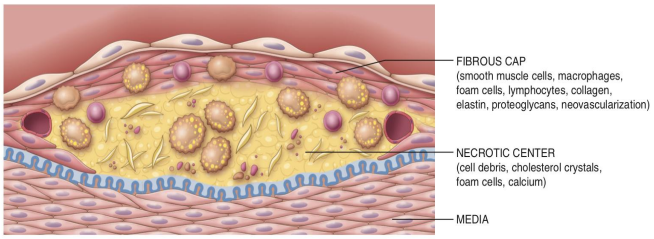


Fig. 10.7 The basic structure of an atheromatous plaque.

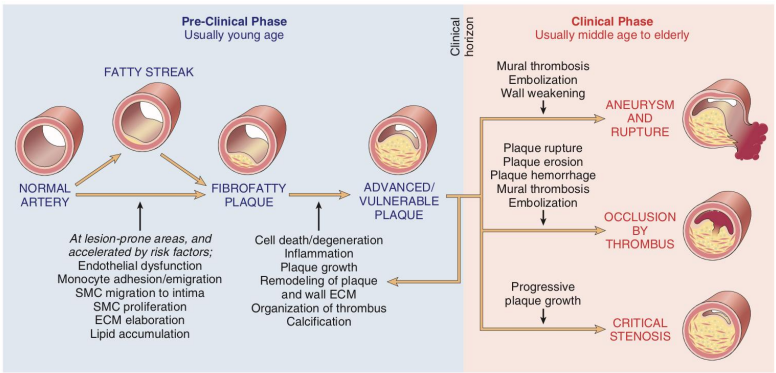


Fig. 10.15 Summary of the natural history, morphologic features, main pathogenic events, and clinical complications of atherosclerosis.

major clinical consequences of atherosclerosis:

- Myocardial infarction (heart attack)
- Cerebral infarction (stroke)
- aortic aneurysm
- peripheral vascular disease (gangrene of extremities)

-Pre clinical phase of atherosclerosis has no symptoms. Pre clinical turns to clinical (either by:70% obstruction of the lumen or Occurrence of a complication).**Clinical phase is the symptomatic phase.**

Atherosclerosis (cont.)

Risk Factors of atherosclerosis [3]

non-modifiable **major** factors

- aging[1]
- male gender[2]
- family history
- Genetic abnormality

modifiable **major** risk factors

- hyperlipidemia ↑ LDL ↑ Modifications
- hypertension: Vascular permeability
- cigarette smoking
- Diabetes

minor risk factors

- obesity and physical inactivity
- Hardened (trans)unsaturated fat intake
- stress (type A personality)
- postmenopausal estrogen deficiency
- High carbohydrate intake
- alcohol
- Lipoprotein Lp(a)
- Chlamydia pneumoniae

IMPORTANCE OF TYPES OF LIPOPROTEINS IN HYPERLIPIDEMIA

↑ **high blood levels** of these promote **atherosclerosis** and **heart disease**

- low density lipoproteins (LDL) "bad cholesterol"
- Very-low-density lipoproteins (VLDLs)
- Chylomicrons
- increased levels of lipoprotein(a)

High density lipoproteins (HDLs) "good cholesterol":

- **high levels** prevent heart attack
- **low levels** increase the risks of heart disease

- it also reverse effects of high cholesterol. It removes the calcium deposits, which are made by LDLs. we can also reverse it by omega-3 fatty acid & exercise and statins (inhibit HMG-CoA)
- mobilizes cholesterol from developing & existing vascular plaques and transports it to the liver for biliary excretion

[1] Because women's estrogen levels decrease after menopause .
[2] Because women have higher estrogen levels which protect against atherosclerosis .
[3] Additional risk factors: pro-Inflammatory state (determination of C-reactive protein "CRP"), Hyperhomocysteinemia (inborn errors causes elevated circulating homocysteine), systemic hypercoagulabgramle, Elevated levels of procoagulants and Clonal hematopoiesis.

Atherosclerosis (cont.)

Complications of Atherosclerosis

Plaque rupture/ ulceration/ erosion of the AS plaques induce thrombus formation OR the AS plaque may discharge debris into the bloodstream, producing microemboli composed of plaque lipid (cholesterol emboli or atheroemboli).

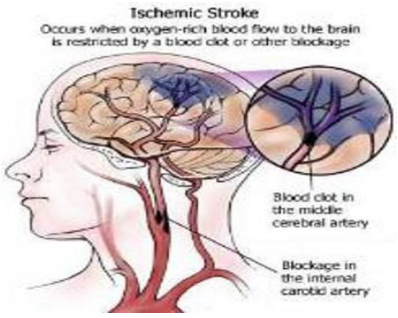
Hemorrhage into a plaque due to rupture of the overlying fibrous cap or the capillaries in the plaque. The hematoma may expand the plaque or induce plaque rupture.

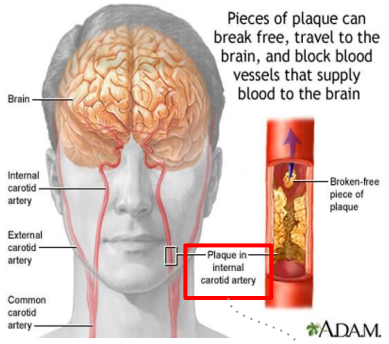
Superimposed thrombosis, which usually occurs on top of ruptured or ulcerated plaques. It is the most feared complication. The thrombus can lead to partial or complete occlusion of the lumen. The thrombus can also embolize.

Weakening of the blood vessel wall with aneurysmal dilation. Atheroma can induce atrophy of the underlying media, causing weakness, aneurysm and potential rupture.

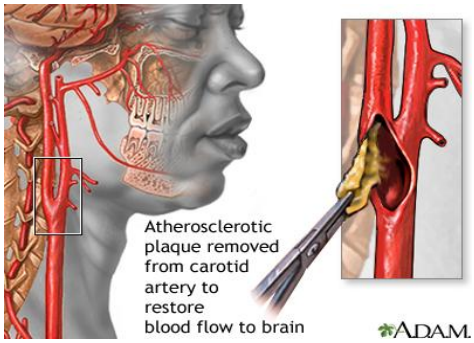
Calcifications: Atheromas often undergo calcification.

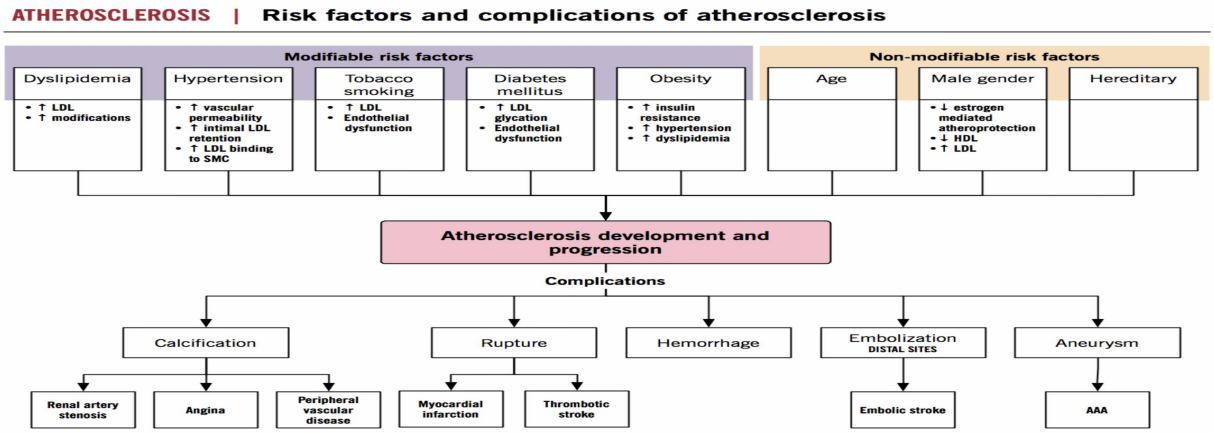
Atheroembolism: ruptured plaque can discharge debris into the blood, producing microemboli composed of plaque contents.





Leading to stroke



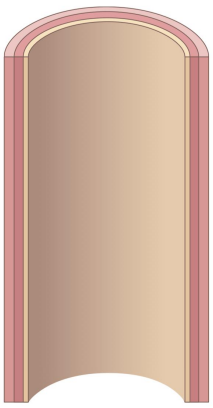
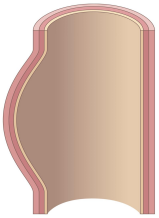
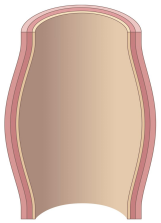
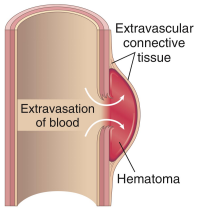
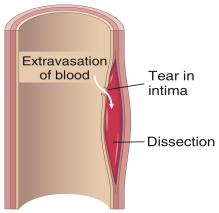


Extra information (Robbins)

Helpful video

➔ Aneurysms

Are congenital or acquired dilation of blood vessels or the heart that, involve the entire wall thickness.

Normal vessel	True aneurysm (saccular)	True aneurysm (fusiform)	False aneurysm	Dissection
				
	The wall bulges outward and may be attenuated but is otherwise intact	circumferential dilation of the vessel	The wall is ruptured, creating a collection of blood (hematoma) bounded externally by adherent extravascular tissues ex: ventricular rupture	Blood has entered the wall of the vessel and separated (dissected) the layers could cause stasis (thrombosis)

predisposing conditions for aneurysms:

- **Atherosclerosis**
  - aortic aneurysm
- **Hypertension + congenital**
- **infection**
  - mycotic aneurysm
- **septic emboli**
  - obliterative endarteritis

factors affecting aneurysms:

1. **abnormal CT synthesis**
   - mutations in TGF-β (defective elastin\collagen)
   - marfan syndrome (↓ fibrillin)
   - ehlers danlos syndrome (collagen III)
2. **excessive CT degradation**
   - ↑ MMP by macrophages
   - ↓ inhibitors
3. **loss of SMCs\synthesis**
   - ischemia
   - cystic medial degeneration

- Complications are related to rupture, thrombosis, and embolization.

★ **Abdominal Aortic Aneurysm (AAA)**

- Occurring as a consequence of atherosclerosis, from most commonly in the abdominal aorta and common iliac arteries.

★ **Thoracic Aortic Aneurysm**

- Associated with hypertension, bicuspid aortic valves and marfan syndrome. Less common, cause by mutations in TGF-β.

★ **Aortic Dissection**

- Occurs when blood splays apart the laminar planes of the media to form a blood filled channel within the aortic wall.

Summary

Atherosclerosis

Definition	is characterized by **atheromas (intimal thickening + lipid accumulation)**, which protrude into and obstruct vascular lumens and weakens the underlying media.	
Morphology	**Gross** - Early lesion → Fatty streaks - Eccentric lesions, patchy, and variable AS plaques along the vessel length.	**Microscopic** - Components of Atherosclerotic plaques: (1) Cells: SMCs, macrophages, lymphocytes and foam cell. (2) Extracellular matrix: including collagen, elastic fibers, and proteoglycans. (3) Lipid: intracellular and extracellular lipid . - Fibrous cap. - Central Necrotic core.
Risk factors	**Modifiable** Hyperlipidemia Hypertension Cigarette Smoking Diabetes Inflammation	**Non-modifiable (Constitutional)** ↑ age Male gender Family history Genetic abnormalities
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)	

Quiz

Answer key: Answers Explanation File

1) B 2) A 3) B 4) A 5) A 6)

1) An 80-year-old man with long-standing diabetes and systemic hypertension dies of congestive heart failure. The luminal surface of the abdominal aorta is shown in the image. Which of the following pathologic changes would you expect to see on microscopic examination?

A) Acute inflammation of the vessel wall.

B) Bacterial colonies in the vessel wall.

C) Cystic medial necrosis.

D) Obliterative endarteritis of the vasa vasorum.

E) Lipid deposition and smooth muscle cell hyperplasia.

2) An autopsy study reveals that evidence for atheroma formation can begin even in children. The gross appearances of the aortas 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.

E) Exudate.

3) A 48-year-old man with diabetes presents with a history of progressive pain in both legs for several years. The pain is severe after walking two blocks or climbing one flight of stairs. Blood pressure is 145/90 mm Hg. Laboratory studies show a serum cholesterol of 320 mg/dL. He neither smokes nor drinks. Bruits are evident upon auscultation of both femoral arteries. The pathogenesis of intermittent claudication in this patient is most closely associated with which of the following risk factors?

A) Hyperglycemia.

B) Hyperlipidemia.

C) Obesity.

D) Sedentary lifestyle.

E) Systemic hypertension.

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) Abdominal aorta.

B) Ascending aorta.

C) Circle of Willis.

D) Coronary artery.

E) Renal artery.

5) A 76-year-old woman presents with a 1-hour history of substernal chest pain. Shortly after admission the patient expires. At autopsy, extensive calcium deposits are noted in the coronary and other arteries affected by severe atherosclerosis. Which of the following terms best describes these autopsy findings?

A) Dystrophic calcification.

B) Hyperplastic calcification.

C) Hypertrophic calcification.

D) Metastatic calcification.

E) Physiologic calcification.

6) A pathologist performs an autopsy on a 75-year-old female, who dies after complaining of sudden severe pain in the abdomen that radiates to the back. The examination reveals a ruptured abdominal aortic aneurysm. Which of the following is the appropriate Pathologic diagnosis?

A) Diabetes mellitus.

B) Atherosclerosis.

C) High HDL cholesterol.

D) Female sex.

E) Low body mass index (BMI).

Team leaders

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- Mashal Abaalkhail

Team Members

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- Danah Alhalees
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- Leen Almazroa
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- Noura Alturki
- Reema Alserhani
- Rema Almutawa
- Taibah Alzaid
- Abdulaziz Alghamdi
- Alwaleed Alarabi
- Alwaleed Alsaleh
- Faisal Almuhid
- Jehad Alorainy
- Khalid Alkhani
- Mohammad Alhamoud
- Mohammad Aljumah
- Mohanad makkawi
- Muath Aljehani
- Nawaf AlBhijan
- Suhail Basuhail
- Abdulla Alhawamdeh
- Hani Alhudhaif
- Tariq Aloqail

THANK YOU