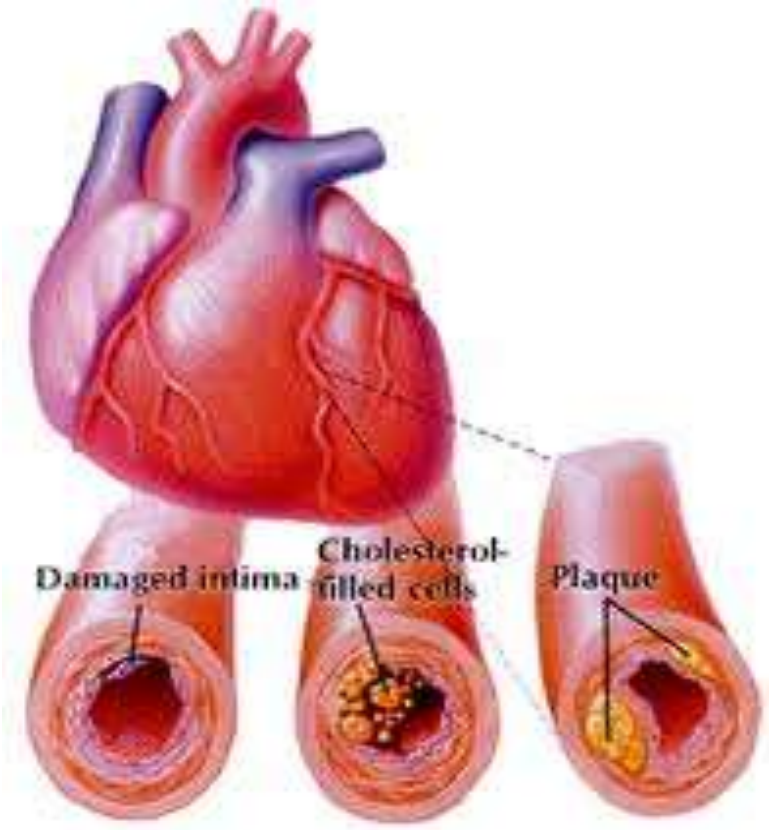
Atherosclerosis- A Brief Review



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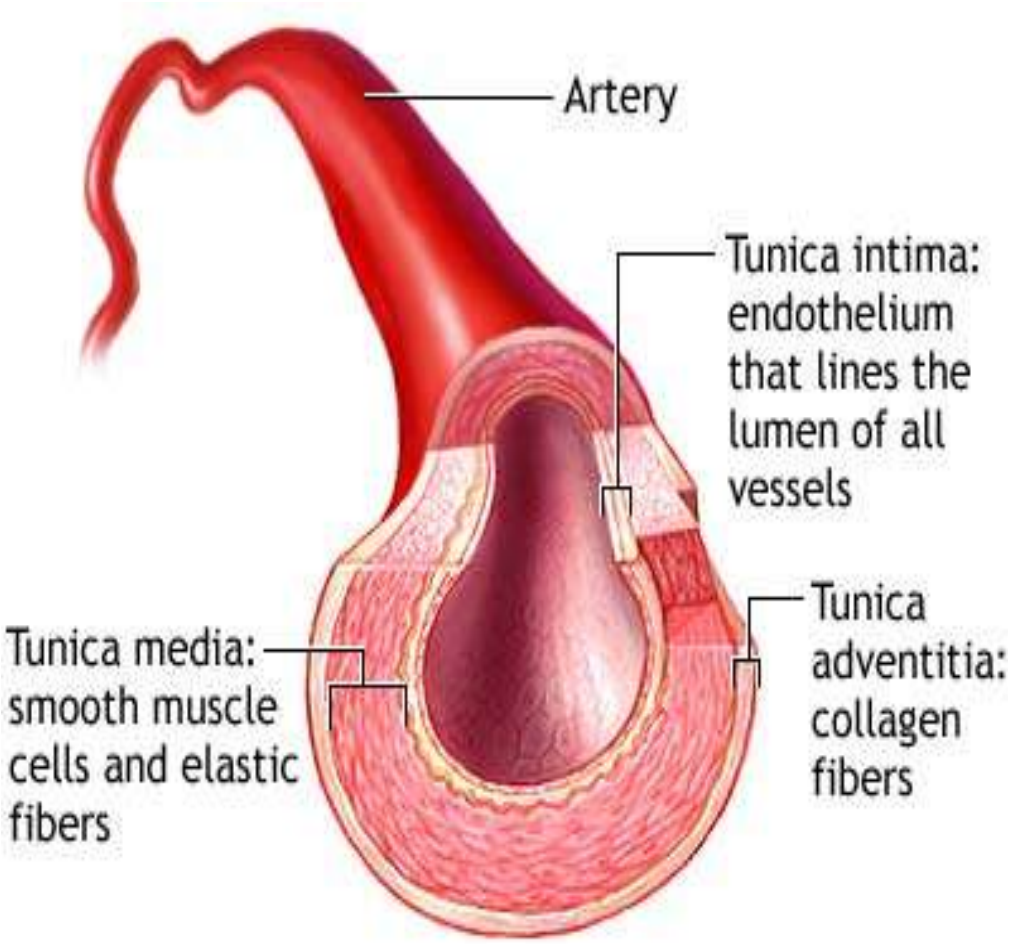
Normal Blood Vessel Wall

- Vessel walls are organized into three concentric layers: **intima, media, and adventitia**
- These are present to some extent in all vessels but are **most apparent in larger arteries and veins.**



Normal Blood Vessel Wall

Blood vessel walls

1. The three tunics:

a) Tunica intima

(1) Endothelium

(2) Subendothelial layer

b) Tunica media

(1) Smooth muscle

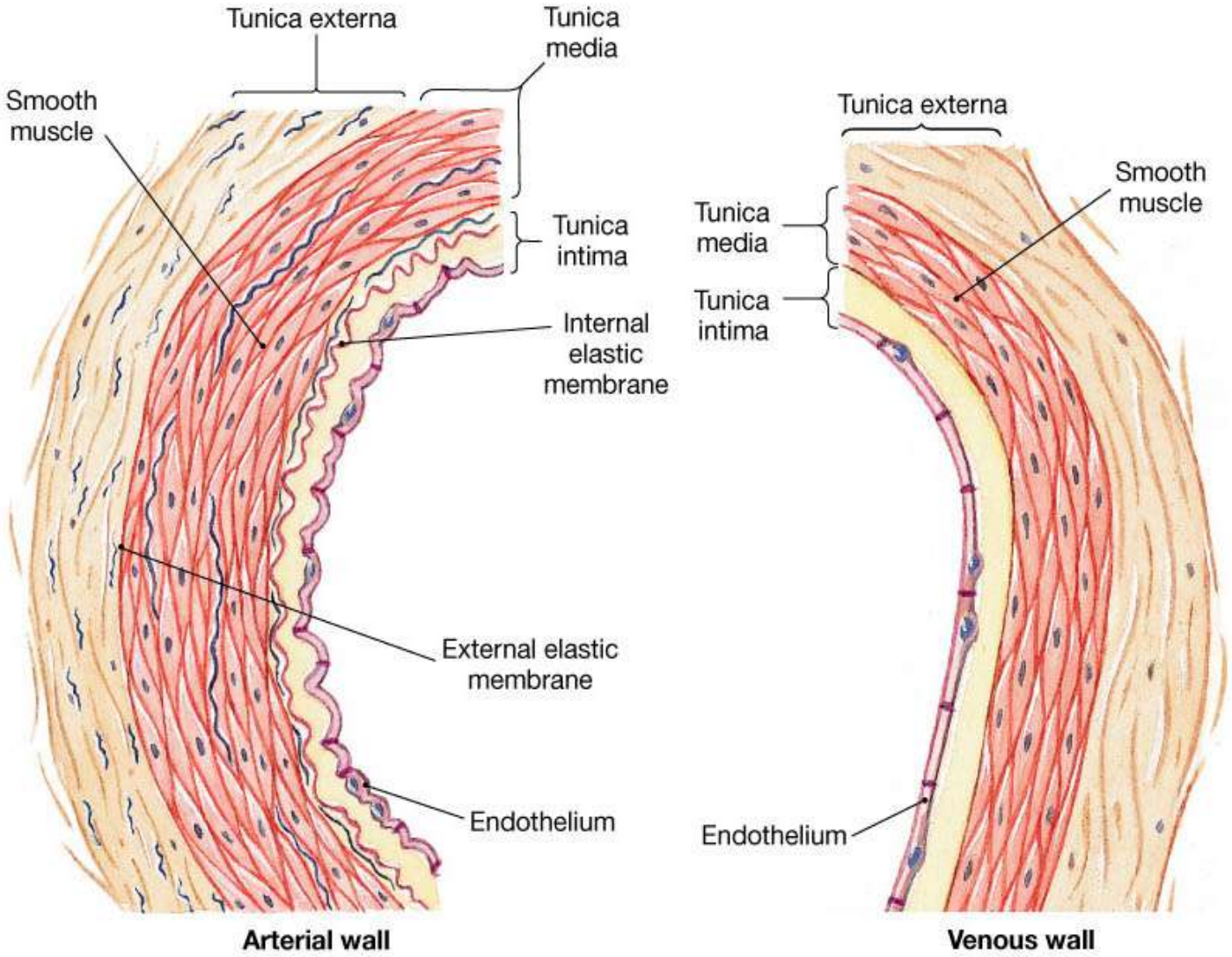
(2) Elastin

c) Tunica adventitia (externa)

(1) CT(Connective tissue) surrounding TM(Tunica Media)

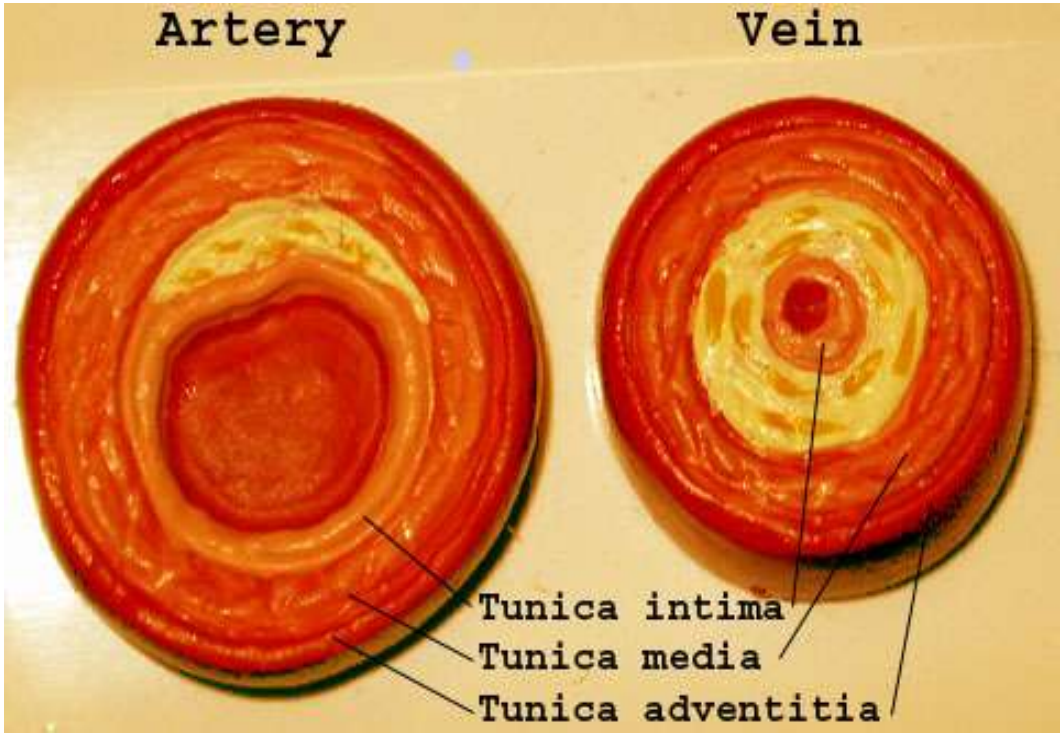
(2) Arterioles in larger vessels

Normal Blood Vessel Wall



Normal Blood Vessel Wall

- Arterial walls are thicker than corresponding veins at the same level of branching to accommodate pulsatile flow and higher blood pressure.



Classes of Arteries

Arteries

a) **Elastic arteries** – large arteries near heart

b) **Muscular (distributing) arteries** – thick tunica media

c) **Arterioles-** Diameter regulated by vasoconstriction/dilation

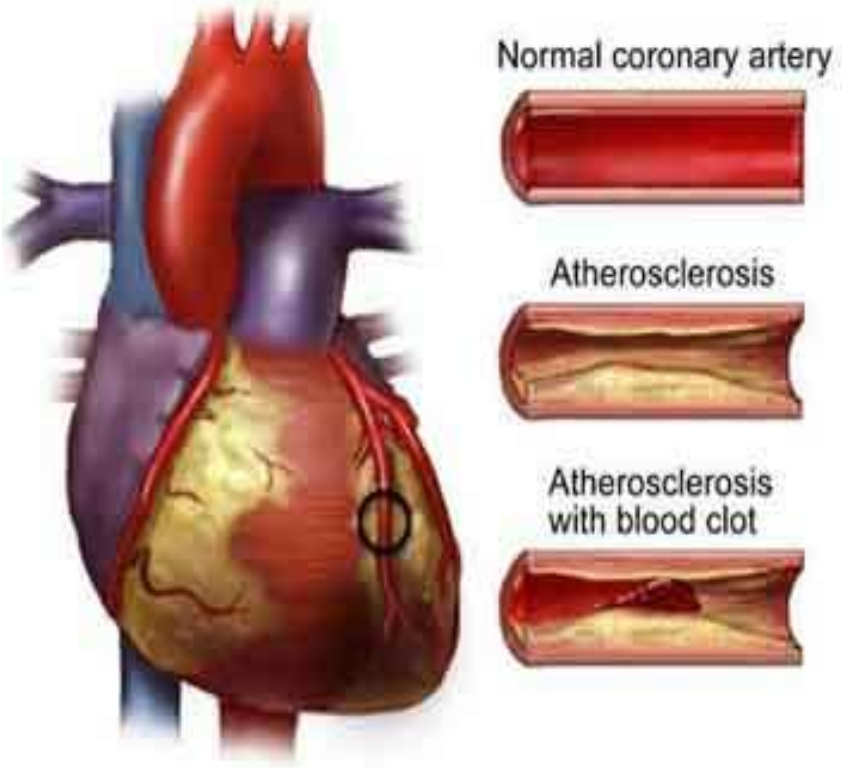
Atherosclerosis affects mainly elastic and muscular arteries and hypertension affects small muscular arteries and arterioles.

Atherosclerosis

- Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by –
- endothelial dysfunction,
- vascular inflammation, and
- the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall.

Atherosclerosis

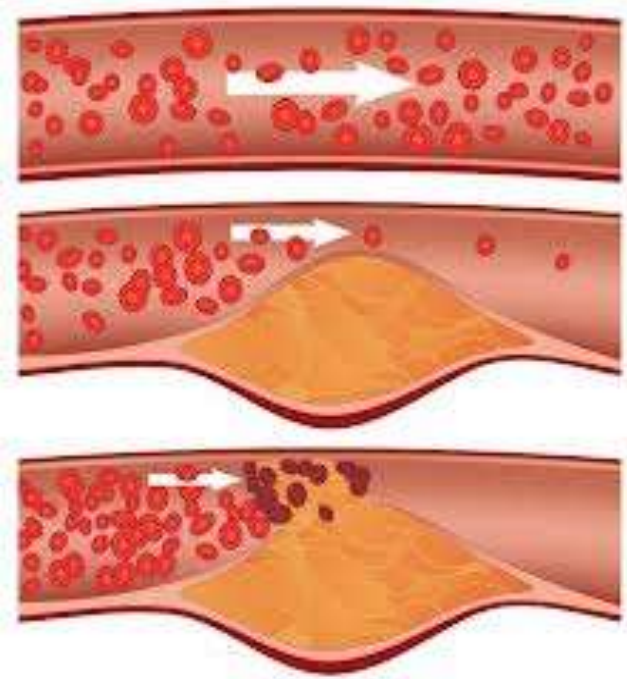
It is characterized by intimal lesions called atheromas (also called Atheromatous or atherosclerotic plaques), that protrude into vascular lumina.

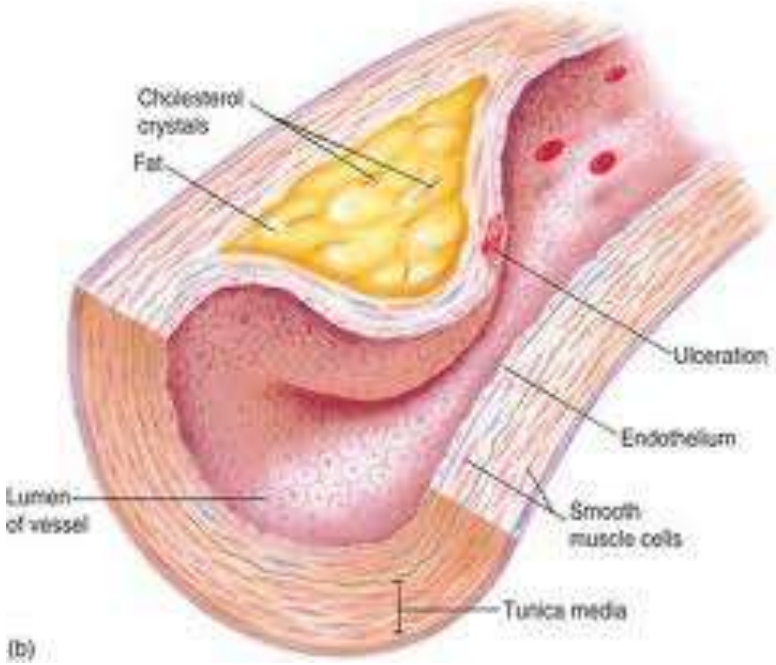


Atheromatous plaque

- An Atheromatous plaque consists of a raised lesion with a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a firm, white fibrous cap.
- Besides obstructing blood flow, atherosclerotic plaques weaken the underlying media and can themselves rupture, causing acute thrombosis.

Atheromatous plaque



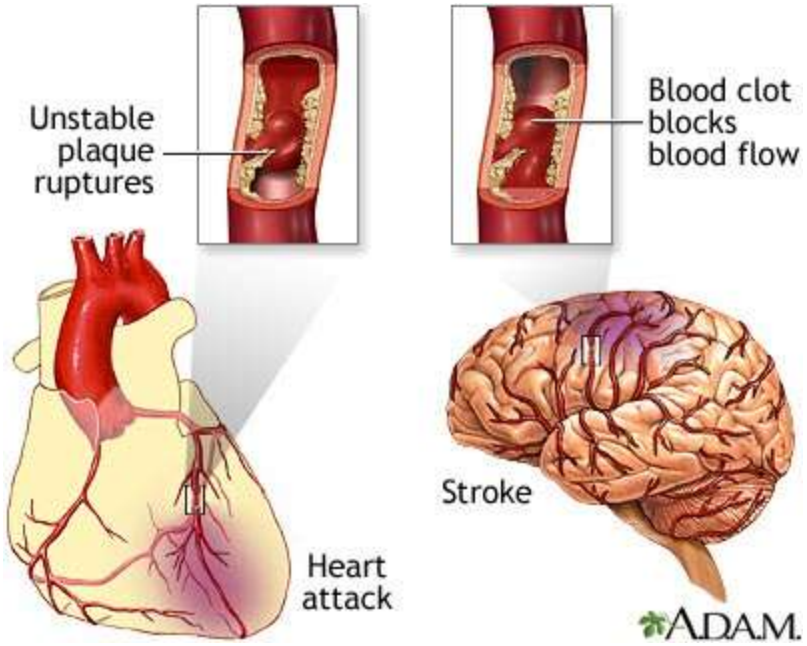


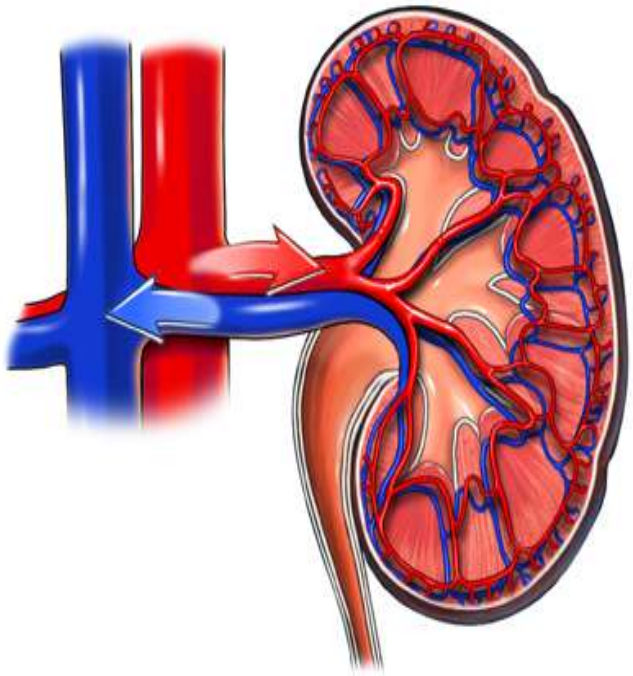
Atherosclerosis or Arteriosclerosis is a slow and progressive building up of plaque, fatty substances, cholesterol, cellular waste products, calcium and fibrin in the inner lining of

Atherosclerosis

- Atherosclerosis primarily affects elastic arteries (e.g., aorta, carotid, and iliac arteries)
- Large and medium-sized muscular arteries (e.g., coronary and popliteal arteries).
- In small arteries, atheromas can gradually occlude lumina, compromising blood flow to distal organs and cause ischemic injury.

Atherosclerosis





- Atherosclerosis also takes a toll through other consequences of acutely or chronically diminished arterial perfusion, *such as mesenteric occlusion, sudden cardiac death, chronic IHD, and ischemic encephalopathy.*

Risk Factors for Atherosclerosis

Major risk factors (Non Modifiable)-

- ❑ Increasing Age
- ❑ Male gender
- ❑ Family history
- ❑ Genetic abnormalities

Risk Factors for Atherosclerosis

Lesser, Uncertain, or Nonquantitated Risks-

- ❑Obesity
- ❑Physical Inactivity
- ❑Postmenopausal estrogen deficiency
- ❑High carbohydrate intake
- ❑Lipoprotein(a)
- ❑Hardened (trans)unsaturated fat intake
- ❑*Chlamydia pneumoniae* infection

Risk Factors for Atherosclerosis

Potentially Controllable-

- ❑ Hyperlipidemia
- ❑ Hypertension
- ❑ Cigarette smoking
- ❑ Diabetes
- ❑ C-reactive protein

Age as a risk factor

- Age is a dominant influence.
- Although the accumulation of atherosclerotic plaque is typically a progressive process, it does not usually become clinically manifest until lesions reach a critical threshold and begin to precipitate organ injury in middle age or later.
- Thus, between ages 40 and 60, the incidence of myocardial infarction in men increases fivefold
- Death rates from IHD rise with each decade even into advanced age.

Gender

- Premenopausal women are relatively protected against atherosclerosis and its consequences compared with age-matched men
- Myocardial infarction and other complications of atherosclerosis are uncommon in premenopausal women unless otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension.
- After menopause, the incidence of atherosclerosis-related diseases increases and with greater age exceeds that of men.

Genetics

- The familial predisposition to atherosclerosis and IHD is multifactorial.
- In some instances it relates to familial clustering of other risk factors, such as hypertension or diabetes
- In others it involves well-defined genetic derangements in lipoprotein metabolism, such as familial hypercholesterolemia that result in excessively high blood lipid levels.

Hyperlipidemia

- *Hyperlipidemia*-more specifically, *hypercholesterolemia*-is a major risk factor for atherosclerosis;
- Even in the absence of other risk factors, hypercholesterolemia is sufficient to stimulate lesion development.
- The major component of serum cholesterol associated with increased risk is low-density lipoprotein (LDL) cholesterol ("bad cholesterol")

Hyperlipidemia

- LDL cholesterol has an essential physiologic role delivering cholesterol to peripheral tissues.
- In contrast, high-density lipoprotein (HDL, "good cholesterol") mobilizes cholesterol from developing and existing atheromas and transports it to the liver for excretion in the bile.
- Consequently, higher levels of HDL correlate with reduced risk.

Factors affecting plasma lipid levels

- High dietary intake of cholesterol and saturated fats (present in egg yolks, animal fats, and butter, for example) raises plasma cholesterol levels.
- Diets low in cholesterol and/or with higher ratios of polyunsaturated fats lower plasma cholesterol levels.
- Omega-3 fatty acids (abundant in fish oils) are beneficial, whereas (*trans*)unsaturated fats produced by artificial hydrogenation of polyunsaturated oils (used in baked goods and margarine) adversely affect cholesterol profiles.

Factors affecting plasma lipid levels

- Exercise and moderate consumption of ethanol both raise HDL levels, whereas obesity and smoking lower it.
- *Statins* are a class of drugs that lower circulating cholesterol levels by inhibiting hydroxy methylglutaryl coenzyme A reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis.

Hypertension

- On its own, hypertension can increase the risk of IHD by approximately 60% in comparison with normotensive populations
- Left untreated, roughly half of hypertensive patients will die of IHD or congestive heart failure, and another third will die of stroke.

Cigarette Smoking

- *Cigarette smoking* is a well-established risk factor in men
- An increase in the number of women who smoke probably accounts for the increasing incidence and severity of atherosclerosis in women.
- Prolonged (years) smoking of one pack of cigarettes or more daily increases the death rate from IHD by 200%.
- Smoking cessation reduces that risk substantially.

Diabetes Mellitus

- *Diabetes mellitus* induces hypercholesterolemia as well as a markedly increased predisposition to atherosclerosis.
- Other factors being equal, the incidence of myocardial infarction is twice as high in diabetic as in Nondiabetic individuals.
- There is also an increased risk of strokes and a 100-fold increased risk of atherosclerosis-induced gangrene of the lower extremities.

Additional Risk Factors

- Despite the identification of hypertension, diabetes, smoking, and hyperlipidemia as major risk factors, as many as 20% of all cardiovascular events occur in the absence of any of these.
- other "nontraditional" factors contribute to risk.

Lipoprotein a or *Lp(a)*

- Lipoprotein a or *Lp(a),* is an altered form of LDL that contains the apolipoprotein B-100 portion of LDL linked to apolipoprotein A;
- Increased Lp(a) levels are associated with a higher risk of coronary and cerebro vascular disease, independent of total cholesterol or LDL levels.

Additional Risk Factors

- Stressful lifestyle ("type A" personality);
- Obesity - Due to
  - Hypertension
  - Diabetes
  - Hypertriglyceridemia and
  - Decreased HDL.

Pathogenesis of Atherosclerosis

- The contemporary view of atherogenesis is expressed by the **response-to-injury hypothesis**.
- This model views atherosclerosis as a chronic inflammatory response of the arterial wall to endothelial injury.
- Lesion progression occurs through interactions of modified lipoproteins, monocyte-derived macrophages, T lymphocytes, and the normal cellular constituents of the arterial wall.

Pathogenesis of Atherosclerosis

1) Endothelial Injury

- Initial triggering event in the development of Atherosclerotic lesions
- Causes ascribed to endothelial injury in include **mechanical trauma, hemodynamic forces, immunological and chemical mechanisms, metabolic agents like chronic hyperlipidemia, homocystine, circulating toxins from systemic infections, viruses, and tobacco products**.

Pathogenesis of Atherosclerosis

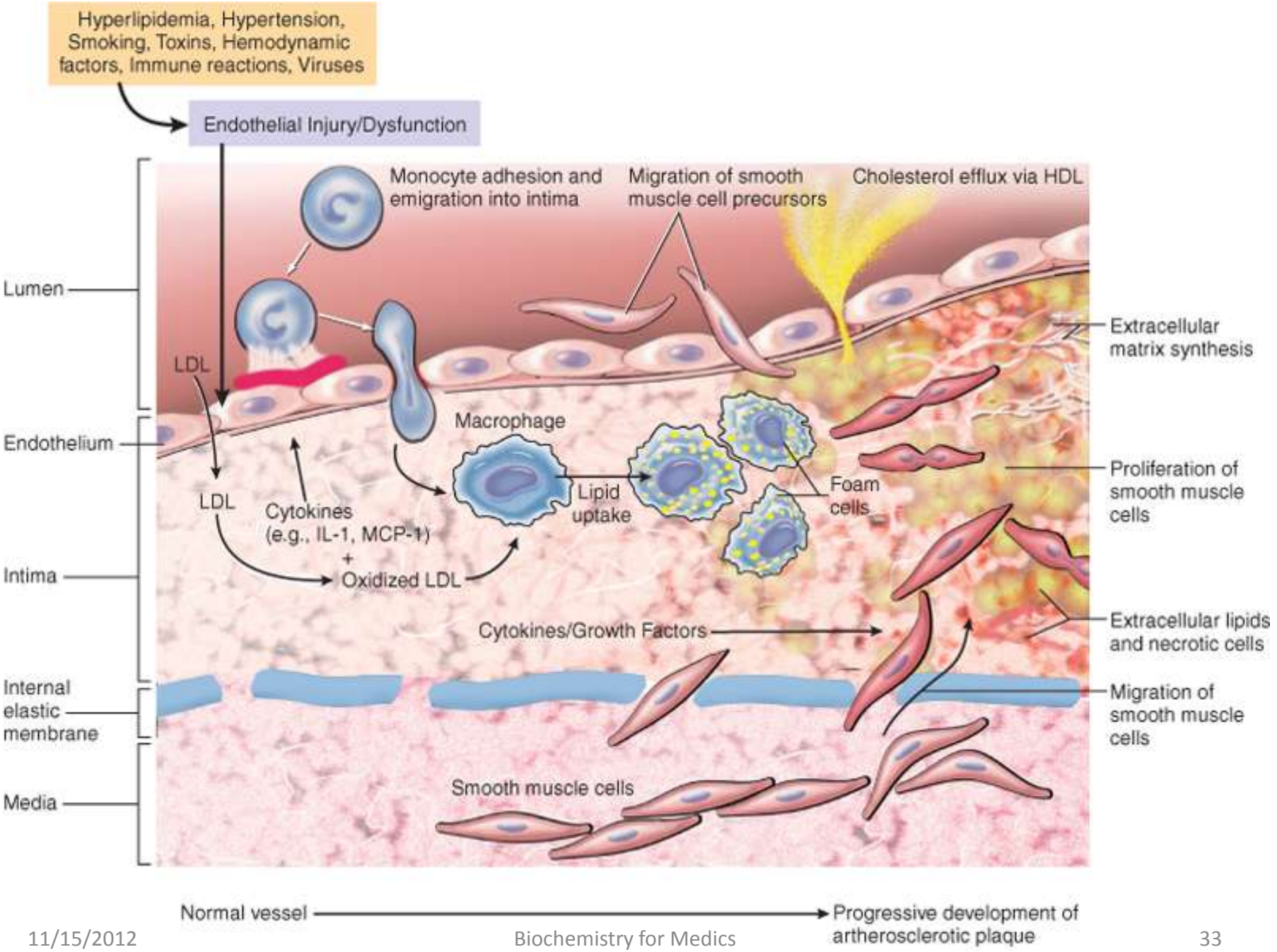
2. Intimal Smooth Muscle Cell Proliferation

- Endothelial injury causes adherence aggregation and platelet release reaction at the site of exposed sub endothelial connective tissue.
- Proliferation of intimal smooth muscle cells is stimulated by various mitogens released from platelets adherent at the site of endothelial injury.
- These mitogens include platelet derived growth factor (PDGF), fibroblast growth factor, TNF-ά.
- Proliferation is also facilitated by nitric oxide and endothelin released from endothelial cells.

Pathogenesis of Atherosclerosis

3) Role of Blood Monocytes

- Though blood monocytes do not possess receptors for normal LDL, LDL does appear in the monocyte cytoplasm to form foam cell.
- Plasma LDL on entry into the intima undergoes oxidation.
- Oxidized LDL formed in the intima is readily taken up by scavenger receptor on the monocyte to transform it to a lipid laden foam cell.


Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Migration of smooth muscle cell precursors
Cholesterol efflux via HDL
Lumen
Endothelium
Intima
Internal elastic membrane
Media
LDL
LDL
Macrophage
Lipid uptake
Foam cells
Cytokines (e.g., IL-1, MCP-1) + Oxidized LDL
Extracellular matrix synthesis
Proliferation of smooth muscle cells
Cytokines/Growth Factors
Extracellular lipids and necrotic cells
Migration of smooth muscle cells
Smooth muscle cells
Normal vessel
Progressive development of artherosclerotic plaque

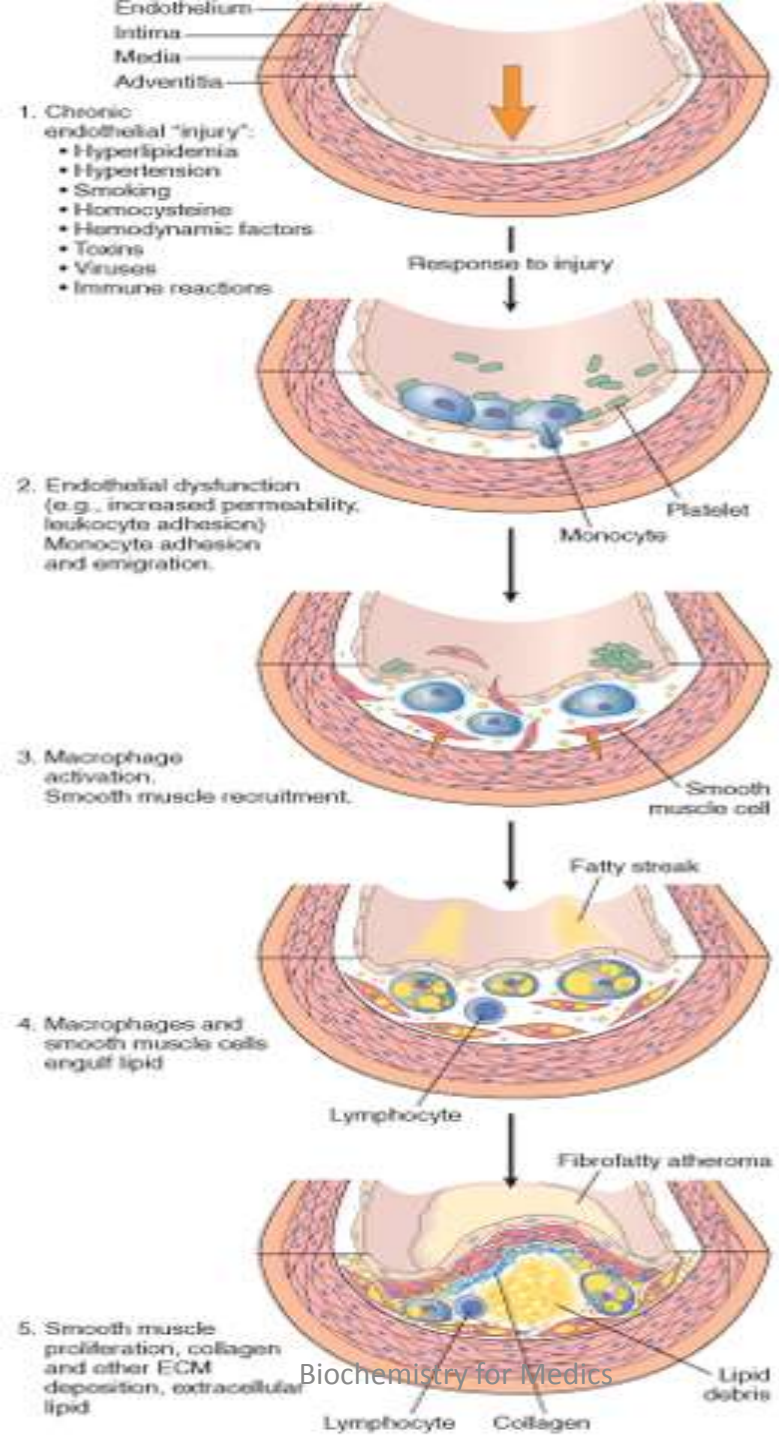
Pathogenesis of Atherosclerosis

- Oxidized LDL stimulates the release of growth factors, cytokines, and chemokines by endothelial cells (EC)and macrophages that increase monocyte recruitment into lesions.
- Oxidized LDL is cytotoxic to ECs and smooth muscle cells (SMCs)and can induce Endothelial dysfunction.

Pathogenesis of Atherosclerosis

4) Role of Hyperlipidemia

- Chronic hyperlipidemia in itself may initiate endothelial injury and dysfunction by causing increased permeability.
- Increased serum concentration of LDL and VLDL promote formation of foam cells, while high serum concentration of HDL has anti-atherogenic effect.


Endothelium
Intima
Media
Adventitia
1. Chronic endothelial "injury":
• Hyperlipidemia
• Hypertension
• Smoking
• Homocysteine
• Hemodynamic factors
• Toxins
• Viruses
• Immune reactions
Response to injury
2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion) Monocyte adhesion and emigration.
Platelet
Monocyte
3. Macrophage activation. Smooth muscle recruitment.
Smooth muscle cell
Fatty streak
4. Macrophages and smooth muscle cells engulf lipid
Lymphocyte
Fibrofatty atheroma
5. Smooth muscle proliferation, collagen and other ECM deposition, extracellular lipid
Lipid debris
Lymphocyte
Collagen

Progression of Atherosclerosis

- ***Fatty Streaks-*** Fatty streaks are composed of lipid-filled foam cells but are not significantly raised and thus do not cause any disturbance in blood flow
- Fatty streaks can appear in the aortas of infants younger than 1 year and are present in virtually all children older than 10 years, regardless of geography, race, sex, or environment.
- The relationship of fatty streaks to atherosclerotic plaques is uncertain; although they may evolve into precursors of plaques, not all fatty streaks are destined to become advanced atherosclerotic lesions.

Progression of Atherosclerosis

Atherosclerotic Plaque-The key processes in atherosclerosis are intimal thickening and lipid accumulation Atheromatous plaques (also called fibrous or fibro fatty plaques) impinge on the lumen of the artery and grossly appear white to yellow

Plaques vary from 0.3 to 1.5 cm in diameter but can coalesce to form larger masses.

Components of Atherosclerotic plaque

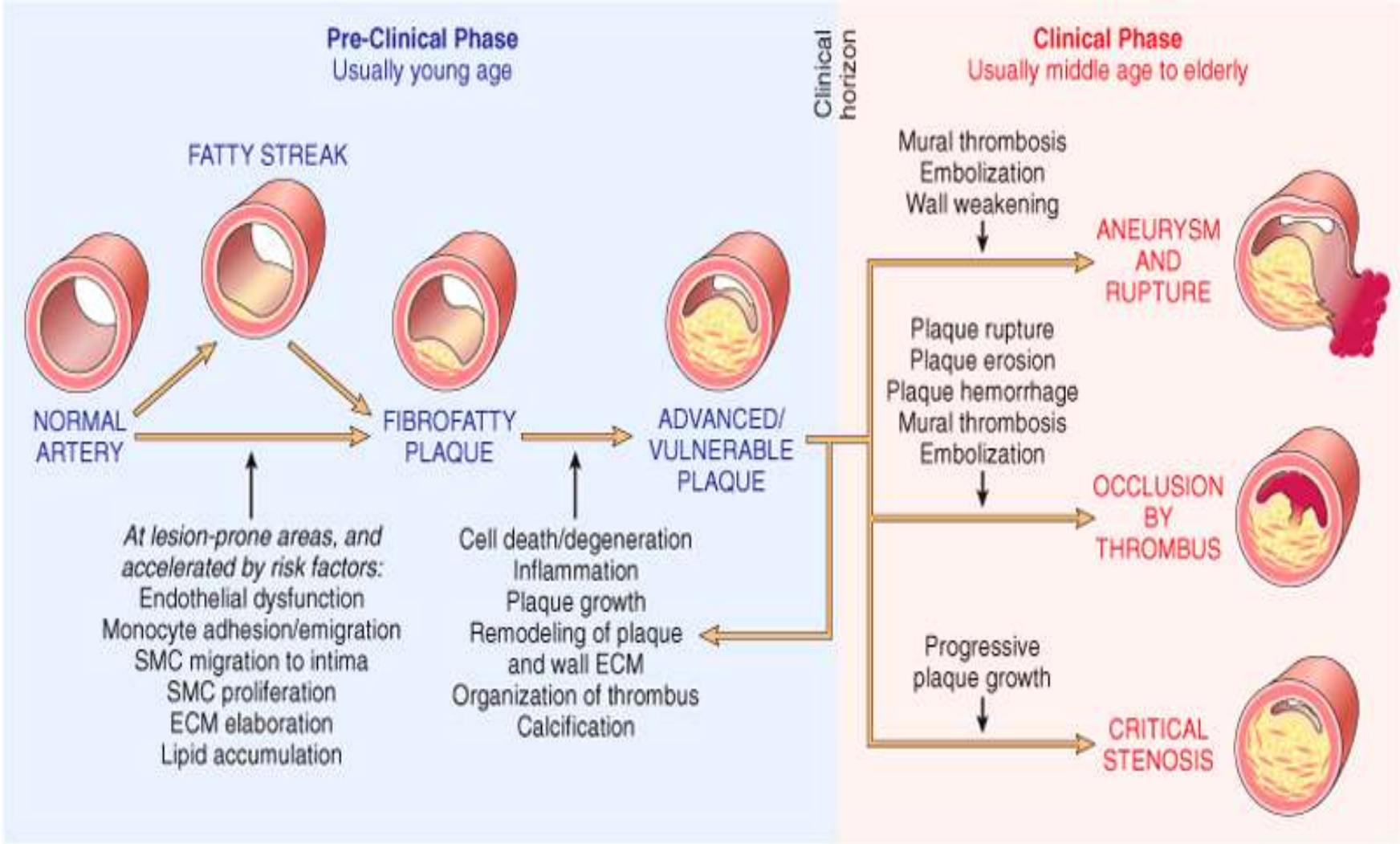
- **Atherosclerotic plaques have three principal components:**
- **Cells, including SMCs, macrophages, and T cells**
- **ECM, including collagen, elastic fibers, and proteoglycans and**
- **Intracellular and extracellular lipid**
- These components occur in varying proportions and configurations in different lesions.

Changes in Atherosclerotic Plaque

Atherosclerotic plaques are susceptible to the following pathologic changes with clinical significance:

- **Rupture, ulceration, or erosion**
- **Hemorrhage**
- **Atheroembolism**
- **Aneurysm formation**
- Atherosclerosis is a slowly evolving lesion usually requiring many decades to become significant.
- However, acute plaque changes (e.g., rupture, thrombosis, or hematoma formation) can rapidly precipitate clinical sequelae (the so-called "clinical horizon“)

Progression of Atherosclerosis



Atherosclerosis- Symptoms

- Symptomatic atherosclerotic disease most often involves the arteries supplying the **heart, brain, kidneys, and lower extremities.**
- **Myocardial infarction** (heart attack), **cerebral infarction** (stroke), **aortic aneurysms**, and **peripheral vascular disease** (gangrene of the legs) are the major consequences of atherosclerosis.

Prevention of Atherosclerotic Vascular Disease

Primary prevention aims at either delaying atheroma formation or encouraging regression of established lesions in persons who have not yet suffered a serious complication of atherosclerosis

Secondary prevention is intended to prevent recurrence of events such as myocardial infarction or stroke in symptomatic patients

Prevention of Atherosclerotic Vascular Disease

Primary prevention of atherosclerosis

- ❑ Cessation of cigarette smoking
- ❑ Control of hypertension
- ❑ Weight loss
- ❑ Exercise, and lowering total and LDL blood cholesterol levels while increasing HDL (e.g., by diet or through statins).
- ❑ Statin use may also modulate the inflammatory state of the vascular wall.
- ❑ Risk factor stratification and reduction should even begin in childhood.

Prevention of Atherosclerotic Vascular Disease

Secondary prevention involves use of –

- Aspirin (anti-platelet agent),
- Statins, and beta blockers (to limit cardiac demand),
- Surgical interventions (e.g., coronary artery bypass surgery, carotid endarterectomy).
- These can successfully reduce recurrent myocardial or cerebral events.

Summary

- Atherosclerosis is an intima-based lesion organized into a fibrous cap and an atheromatous (gruel-like) core and composed of SMCs, ECM, inflammatory cells, lipids, and necrotic debris.
- Atherogenesis is driven by an interplay of inflammation and injury to vessel wall cells.
- Atherosclerotic plaques accrue slowly over decades but may acutely cause symptoms due to rupture, thrombosis, hemorrhage, or embolization.
- Risk factor recognition and reduction can reduce the incidence and severity of atherosclerosis-related disease.