ATHEROSCLEROSIS 🩸

Atherosclerosis is best understood as a chronic inflammatory vascular response to endothelial injury.

🔑 Unifying concept:
Although the initiating insults differ, the vascular response is stereotyped.

Endothelial Injury & Neointimal Formation

Initial Event

- Endothelial cell (EC) injury or dysfunction

This triggers a repair response similar to wound healing.

Vascular Response to Injury (Flowchart):

Endothelial injury → EC dysfunction or loss → Release of growth factors & cytokines → Smooth muscle cell (SMC) migration into intima → SMC proliferation → ECM synthesis → Neointima formation

🧠 *Analogy:*
SMCs behave like fibroblasts in wound healing 🧵

Source of Intimal SMCs

- Migration from:
  - Media
  - Circulating SMC precursor cells

Regulators of SMC Activity

Produced by:

- Platelets
- Endothelial cells
- Macrophages

- Activated coagulation proteins
- Complement system

These mediators regulate:

- SMC migration
- Proliferation
- ECM synthesis

Triggers of Endothelial Injury

This stereotyped response occurs with:

- Infection
- Chronic inflammation
- Immune injury
- Physical trauma
  (hypertension, balloon angioplasty)
- Toxic injury
  (oxidized lipids, cigarette smoke 🚬)

Progression with Persistent Injury

Persistent or recurrent endothelial damage → Progressive intimal thickening → Luminal narrowing → Stenosis of small- and medium-sized arteries

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Atheromatous Plaques (Atheromas) ⭐

Definition

Atherosclerosis is characterized by intimal lesions called atheromas that impinge on the vascular lumen.

Structure of an Atheromatous Plaque

Atheroma = Lipid core + Fibrous cap

Component	Composition
Lipid core	Cholesterol, cholesterol esters, necrotic debris

Fibrous cap	SMCs + collagen + ECM

🧠 *Descriptive term:*

Core is soft, friable, grumous 🟡

Plaque Effects (Flowchart):

Plaque enlargement → Mechanical luminal narrowing → Chronic ischemia

OR

Plaque rupture → Thrombus formation → Acute vascular occlusion → MI / stroke ⚠️

Plaque Rupture: The Major Danger

- More dangerous than slow luminal narrowing
- Leads to:
    - Sudden thrombosis

- Acute vessel occlusion

Effects on Vessel Wall Integrity

Medial Weakening

Two mechanisms compromise the media:

1. Reduced perfusion
    - Thick intima impairs nutrient diffusion
2. Inflammation-mediated ECM degradation

Aneurysm Formation (Flowchart):

Intimal thickening → Medial ischemia → Inflammatory ECM damage → Weakening of vessel wall → Aneurysm formation 🩸

Clinical Importance of Atherosclerosis

- Underlies:
  - Coronary artery disease
  - Cerebrovascular disease
  - Peripheral vascular disease
- Causes:
  - ~50% of all deaths in Western countries

Epidemiology of Atherosclerosis

Global Distribution

- Virtually ubiquitous in high-income countries
- Rapidly increasing in low-income countries due to:
  - Urbanization
  - Western dietary patterns 🍔

Regional Mortality Trends

- CAD death rates:
  - Africa, India, Southeast Asia → now exceed U.S.

- Eastern Europe →
  - 3–5× higher than U.S.
  - 7–12× higher than Japan

Relationship to Ischemic Heart Disease

- Epidemiologic data often reflect IHD mortality
- Myocardial infarction accounts for:
  - ~25% of all deaths in the United States 🫀

Risk Factors for Atherosclerosis ⭐

Identified through major studies, notably the Framingham Heart Study.

Categories

- Constitutional (non-modifiable)
- Acquired / behavioral (modifiable)

Risk Factor Interaction

Risk factors act in a multiplicative, not additive manner.

Risk Multiplication (Flowchart):

One risk factor → Baseline risk

Two risk factors → ~4× MI risk

Three risk factors (hyperlipidemia + hypertension + smoking) → ~7× MI risk 📈

High-Yield Example

- Hyperlipidemia alone → moderate risk
- Hyperlipidemia + HTN + smoking → explosive risk escalation 🚨

EXAM PEARLS 📝

- Atherosclerosis = response to endothelial injury
- SMCs are central players in plaque formation
- Plaque rupture > luminal narrowing in acute events
- Media weakening predisposes to aneurysm
- Risk factors are multiplicative
- MI ≈ ¼ of all U.S. deaths

PATHOGENESIS OF ATHEROSCLEROSIS 🩺

Definition

Atherosclerosis is a chronic inflammatory disease of medium- and large-sized arteries, best understood as a vascular response to endothelial injury, resulting in lipid-rich plaques (atheromas) within the intima that can cause ischemia, thrombosis, and aneurysm formation.

Response-to-Injury Hypothesis

Central Concept

Atherosclerosis is a chronic inflammatory disease of the arterial wall, initiated and driven by endothelial injury and dysfunction.

📌 Key phrase for exams:

> *"Atherosclerosis represents a chronic inflammatory response of the arterial wall to endothelial injury."*

Overview: Cellular & Molecular Interactions 🔬

Lesion progression involves complex interactions between:

- Modified lipoproteins (especially oxidized LDL)
- Monocyte-derived macrophages
- T lymphocytes
- Endothelial cells (ECs)
- Smooth muscle cells (SMCs)

These interactions collectively lead to atheromatous plaque formation.

Sequential Pathogenic Events

Endothelial Injury / Dysfunction
(hemodynamic stress, hyperlipidemia, smoking, diabetes)
→ ↑ vascular permeability → ↑ adhesion molecules (VCAM-1, ICAM-1) → ↓ nitric oxide → ↑ thrombogenicity

⬇️

LDL Entry into Intima → LDL oxidation (oxLDL) → cholesterol crystal formation

⬇️

Monocyte Adhesion & Migration → Monocytes enter intima → Differentiate into macrophages → Uptake oxLDL (via scavenger receptors) → Foam cell formation

⬇️

Fatty Streak Formation → Accumulation of foam cells → Early visible lesion

⬇️

Platelet Adhesion to Dysfunctional Endothelium → Release of growth factors (PDGF, TGF-β)

⬇️

Cytokine & Growth Factor Release
(from macrophages, platelets, endothelial cells, T-cells) → Pro-inflammatory state → Stimulates SMC activation

⬇️

Smooth Muscle Cell (SMC) Migration → From media → intima → Also from circulating SMC precursors

⬇️

SMC Proliferation & ECM Production → Collagen / Elastin / Proteoglycans → Formation of neointima

⬇️

Lipid Accumulation (Advanced Lesion) → Intracellular lipid (foam cells) → Extracellular lipid pools → Necrotic lipid

core formation

⬇️

Fibrous Cap Formation → SMCs + collagen cover lipid core→ Plaque covered by endothelium

⬇️

🏁 Mature Atheromatous Plaque

(lipid-rich necrotic core + fibrous cap)

Key Mediators Involved 🔬

Produced by:

- Platelets
- Endothelial cells
- Macrophages
- Activated coagulation & complement proteins

Major actions:

- SMC migration

- SMC proliferation
- ECM synthesis
- Sustained inflammation

Triggers of Endothelial Injury ⚠️

This response occurs with any form of vascular damage, including:

- Infection
- Chronic inflammation
- Immune-mediated injury
- Physical trauma
    - Balloon angioplasty
    - Hypertension
- Toxic exposure
    - Oxidized lipids
    - Cigarette smoke

👉 Persistent injury → progressive intimal thickening → vascular stenosis

Atheromatous Plaque (Atheroma): Structure 🧱

Gross & Microscopic Components

Component	Description
Fibrous cap	SMCs + collagen + ECM
Lipid core	Cholesterol, cholesterol esters
Necrotic debris	Dead foam cells
Inflammatory cells	Macrophages, T cells

🧠 *Robbins keyword:* "grumous" lipid core

Clinical Consequences of Atherosclerosis 🚨

1. Luminal Narrowing → progressive ischemia → stable angina, claudication

2. Plaque Rupture (Most Dangerous) → exposure of thrombogenic material → acute thrombosis → sudden vessel occlusion → MI / stroke

3. Medial Weakening → impaired diffusion from lumen → ischemia of media → ECM degradation → aneurysm formation

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Risk Factors for Atherosclerosis

Major Risk Factors

Non-Modifiable (Constitutional)	Modifiable
Genetics	Hyperlipidemia
Family history	Hypertension
Increasing age	Cigarette smoking

Male sex	Diabetes mellitus
	Inflammation

⚠️ Risk factors are multiplicative, not additive

→ 3 major factors (HTN + smoking + hyperlipidemia)

→ 7-fold increase in MI risk

Constitutional (Non-Modifiable) Risk Factors

1. Genetics 🧬

- Strongest independent risk factor
- Familial hypercholesterolemia (Mendelian)
- Most risk due to multifactorial inheritance
    - HTN
    - Diabetes

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2. Age ⏳

- Clinically silent until middle age
- MI incidence:
    - 5-fold increase between 40–60 years
- Death rates rise with each decade

🧠 New Robbins Concept: CHIP

- Clonal hematopoiesis of indeterminate potential
- Mutated monocytes/macrophages
- Promotes inflammation → atherogenesis

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3. Gender 🚺

- Premenopausal women relatively protected
- Risk increases after menopause
- Estrogen:
    - Previously thought protective
    - HRT does NOT reduce risk
    - May increase CV risk if started after age 65

Modifiable Major Risk Factors

1. Hyperlipidemia 🧈

Key Lipoproteins

Lipoprotein	Role
LDL	Delivers cholesterol → tissues (bad)
HDL	Removes cholesterol → liver (good)

📌 Hypercholesterolemia alone can cause atherosclerosis

Dietary & Lifestyle Effects

- ↑ Cholesterol:
  - Saturated fats
  - Animal fats
  - Egg yolks
- ↓ Cholesterol:

    - Polyunsaturated fats
    - Omega-3 fatty acids 🐟
- Harmful:
    - Trans fats (hydrogenated oils)
- ↑ HDL:
    - Exercise
    - Moderate alcohol
- ↓ HDL:
    - Smoking
    - Obesity

Statins 💊

- Inhibit HMG-CoA reductase
- ↓ hepatic cholesterol synthesis
- ↓ LDL
- ↓ cardiovascular events

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2. Hypertension 🔥

- ↑ endothelial injury
- ↑ risk of IHD by ~60%
- Causes:
    - Left ventricular hypertrophy
    - ↑ myocardial oxygen demand

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3. Cigarette Smoking 🚬

- Doubles IHD mortality
- Particularly increases risk in women
- Smoking cessation → risk reduction

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4. Diabetes Mellitus 🍬

- ↑ serum cholesterol
- MI risk 2× higher
- ↑ risk of:
    - Stroke
    - Peripheral vascular disease

- 100-fold ↑ gangrene risk

Additional Risk Factors

1. Inflammation 🔥

- Present at all stages of plaque development
- C-reactive protein (CRP):
  - Acute phase reactant
  - Independent predictor of CV risk
- IL-1 β inhibition:
  - ↓ CRP, IL-6
  - ↓ non-fatal MI risk

📌 Marker vs cause? → Still unclear

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2. Homocystinuria

- Homocysteine >100 μ mol/L
- Early-onset vascular disease

- Vitamin supplementation ❌ does not reduce CV events

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3. Metabolic Syndrome ⚖️

Central obesity → insulin resistance → dyslipidemia → hypertension → hypercoagulable + inflammatory state → Endothelial dysfunction & thrombosis

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4. Lipoprotein(a) 🧪

- LDL-like particle
- Promotes:
  - Endothelial dysfunction
  - Thrombosis
  - Impaired fibrinolysis
- Independent CV risk factor

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5. Clonal Hematopoiesis

- Somatic mutations in HSCs
- Normal blood counts
- ↑ cardiovascular mortality
- Altered innate immune cell function

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6. Other Factors

- Sedentary lifestyle
- Chronic stress
- "Type A" personality

Exam Pearl 💎

~20% of cardiovascular events occur WITHOUT identifiable risk factors

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Endothelial Injury: The Cornerstone 🧱

Why Endothelium Is Central

- Early atherosclerotic lesions arise at sites of intact but dysfunctional endothelium
- There is no need for complete endothelial denudation

📌 Important exam line:

> *"Early atherosclerotic lesions begin at sites of intact but dysfunctional endothelium."*

What Is Endothelial Dysfunction? ⚠️

Endothelial dysfunction = failure of normal endothelial protective functions

Normal EC Functions

- Maintain vascular tone (via NO, prostacyclin)
- Regulate hemostasis
- Act as a selective permeability barrier
- Control inflammation

Dysfunctional ECs Show

- ↑ permeability to lipoproteins
- ↑ leukocyte adhesion
- ↑ thrombosis
- ↓ nitric oxide production

➡️ All of these promote atherogenesis

Major Triggers of Endothelial Dysfunction 🚨

Most Important Causes

1. Hemodynamic disturbances
2. Hypercholesterolemia

Other Contributing Factors

- Hypertension
- Cigarette smoke toxins
- Inflammatory cytokines (e.g., TNF-α)

📌 Cytokines induce pro-atherogenic EC gene expression

Hemodynamic Disturbances in Atherogenesis 🌊

Key Observation

Atherosclerotic plaques form at sites of turbulent blood flow, not randomly.

Common Locations

- Ostia of branching vessels
- Arterial bifurcations
- Posterior wall of abdominal aorta

Flow Pattern vs Endothelial Behavior

Laminar (Non-turbulent) Flow → induction of *atheroprotective genes* → anti-inflammatory → anti-thrombotic → ↓ atherosclerosis

⬇️⬆️

Turbulent Flow → endothelial dysfunction → ↑ permeability → ↑ leukocyte adhesion → ↑ plaque formation

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Atheroprotective Genes 🛡️

- Expressed under laminar flow
- Promote:
  - Anti-inflammatory state
  - Anti-coagulant properties
  - Vascular homeostasis

📌 This explains the non-random distribution of plaques

Exam Pearls 💎

- Endothelial injury is necessary and sufficient to initiate atherosclerosis
- Dysfunction ≠ denudation
- Oxidized LDL is more atherogenic than native LDL

- Turbulent flow = atheroprone sites
- Laminar flow = atheroprotective gene expression

Lipids and Atherosclerosis ❤️‍🩹

Common Lipoprotein Abnormalities

In the general population and myocardial infarction survivors, dyslipoproteinemias often include:

- ↑ LDL cholesterol – "bad cholesterol" that promotes plaque formation 🧱
- ↓ HDL cholesterol – "good cholesterol" that removes excess cholesterol 🛡️
- ↑ Lipoprotein(a) – genetically determined, increases atherosclerosis risk

Causes of Dyslipoproteinemia:

- Genetic: Mutations in apoproteins or lipoprotein receptors
- Acquired: Disorders affecting lipid metabolism

- Nephrotic syndrome
- Alcoholism
- Hypothyroidism
- Diabetes mellitus

Mechanism: Lipids travel in the blood bound to apoproteins → form lipoprotein complexes. Defects in apoproteins or receptors → accumulation → vascular injury.

Hypercholesterolemia and Atherogenesis ⚠️

Evidence linking cholesterol to atherosclerosis:

1. Plaque composition: Cholesterol & cholesterol esters are dominant in plaques
2. Genetic evidence:
   - Homozygous familial hypercholesterolemia → defective LDL receptors → MI by ~20 years
   - Other genetic/acquired causes → premature atherosclerosis

3. Epidemiology: Framingham study → total cholesterol & LDL correlate with severity
4. Therapeutics: Lowering cholesterol (diet/drugs) → slows progression, may regress plaques, reduces cardiovascular events

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Mechanisms of Dyslipidemia-Induced Atherogenesis

Flowchart of Pathogenesis:

Chronic hyperlipidemia → ↑ LDL in intima → Oxidation by free radicals → Formation of oxidized LDL & cholesterol crystals → Taken up by macrophages → Foam cells → Release of growth factors, cytokines, chemokines → ↑ Monocyte recruitment → Endothelial & SMC injury → Atherosclerotic lesion formation

Additional Mechanisms:

- Endothelial dysfunction: ↑ Oxygen free radicals → ↓ NO → impaired vasodilation

- Inflammation:
  - Cholesterol crystals & fatty acids → activate inflammasome
  - → ↑ IL-1 → recruits leukocytes (macrophages, T cells)
  - Activated T cells → release IFN-γ → stimulate macrophages, ECs, SMCs
- SMC proliferation & ECM synthesis:
  - Early fatty streak → SMC proliferation + collagen deposition → mature atheroma
  - Growth factors: PDGF, FGF
  - Stabilizes plaque but inflammation → SMC apoptosis → unstable plaques

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Morphology of Atherosclerosis

A. Fatty Streaks 🟡

- Minute yellow, flat macules → coalesce into elongated lesions (>1 cm)

- Composed of lipid-laden foam cells
- Minimal raised lesions → no flow disturbance
- Appear in infants <1 yr; present in most children >10 yrs
- Coronary fatty streaks appear in adolescence → future plaque sites

B. Atherosclerotic Plaques 🟤

- Key features: Intimal thickening + lipid accumulation
- Appearance: White-yellow raised lesions (0.3–1.5 cm)
- Can coalesce → larger masses
- Red-brown color if thrombus on ulcerated plaque

Distribution & Severity:

- Eccentric (patchy) → only part of arterial wall affected
- Common sites (descending severity):
    - Infrarenal abdominal aorta > Coronary arteries > Popliteal > Internal carotid > Circle of Willis

- Upper extremities, mesenteric, renal arteries usually spared (except ostia)

C. Plaque Composition

Component	Description
Cells	SMCs, macrophages, T cells
ECM	Collagen, elastic fibers, proteoglycans
Lipids	Intracellular & extracellular cholesterol, foam cells

Plaque Structure (from lumen → deep):

- Fibrous cap: SMCs + dense collagen
- Shoulder: Macrophages, T cells, SMCs
- Necrotic core: Cholesterol, cholesterol esters, foam cells, fibrin, thrombus, plasma proteins
- Peripheral: Neovascularization
- Deep media: Attenuated, fibrosis due to SMC atrophy

Progression:

- Plaque enlarges via cell death, ECM remodeling, thrombus organization
- Necrotic core may undergo dystrophic calcification

Flowchart: Morphologic Progression of Atherosclerosis 🧬

Normal artery → Fatty streak (foam cells, minimal flow disturbance) → Intimal SMC proliferation & ECM deposition → Formation of mature atheroma (fibrous cap + necrotic core) → Plaque enlargement & remodeling → Plaque complications:

- Calcification
- Ulceration & thrombosis
- Rupture → acute cardiovascular events

💡 Key Exam Points:

- Oxidized LDL → central in foam cell formation
- Chronic inflammation → drives lesion progression
- Fatty streaks common in children → predictive but not always progressive
- Plaque structure: fibrous cap, necrotic core, shoulder, neovascularization
- Plaque instability → SMC apoptosis + matrix degradation

Consequences of Atherosclerosis ⚠️🫀

1. Overview

The clinical impact of atherosclerosis depends on:

- Vessel size (large vs. small)
- Plaque size & stability
- Degree of vessel wall disruption

Most commonly involved vessels:

- Large elastic arteries: aorta, carotid, iliac

- Medium/Large muscular arteries: coronary, renal, popliteal

Major clinical outcomes:

- Myocardial infarction (heart attack) ❤️
- Cerebral infarction (stroke) 🧠
- Aortic aneurysm 🫁
- Peripheral vascular disease (e.g., gangrene of extremities) 🦵

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2. Atherosclerotic Stenosis 🩸

Mechanism:

- Early stages → media remodeling preserves lumen
- Eventually, expanding atheroma impinges on blood flow → critical stenosis
- Coronary arteries: symptomatic at ~70% occlusion

Clinical Correlation:

- At rest → adequate perfusion

- With exertion → tissue demand > supply → ischemic symptoms (e.g., stable angina)

Other chronic hypoperfusion consequences:

- Bowel ischemia 🍽️
- Sudden cardiac death 💔
- Chronic ischemic heart disease (IHD)
- Ischemic encephalopathy 🧠
- Intermittent claudication (leg pain on walking) 🦵

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3. Acute Plaque Changes ⚡

Acute events often occur without prior symptoms.

Types of Plaque Changes:

1. Rupture, ulceration, or erosion
    - Exposes thrombogenic substances → thrombus formation 🩸
2. Intraplaque hemorrhage

- Rupture of fibrous cap or fragile neovessels → hematoma → rapid plaque expansion or rupture

3. Atheroembolism
    - Plaque debris released → microemboli → downstream ischemia

Key Point:

- Thrombosis can occur even on previously asymptomatic plaques
- Central in acute coronary syndromes

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4. Vulnerable Plaques 🧱

Plaques with high rupture risk share these features:

Feature	Explanation
Foam cells & extracellular lipid	Large lipid core weakens cap

Thin fibrous cap, few SMCs	Less structural integrity
Clusters of inflammatory cells	Increased collagen degradation → mechanical instability

Fibrous cap stability:

- Depends on collagen synthesis vs. degradation
- Inflammation → ↓ collagen synthesis, ↑ collagen breakdown → destabilization

Extrinsic Factors Affecting Plaque Rupture:

- Adrenergic stimulation (stress/emotions) → ↑ BP & vasoconstriction
- Circadian influence → peak MI incidence 6 AM–12 noon
- Statins → stabilize plaques by reducing inflammation + improving endothelial function

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5. Flowchart: Consequences of Atherosclerotic Plaque 🧬

Large/medium artery → Atherosclerotic plaque →

- Chronic stenosis → reduced perfusion → ischemia → stable angina, claudication, chronic organ ischemia
- Acute plaque change →

  - Rupture/ulceration/erosion → thrombosis → acute coronary syndrome (MI)

  - Intraplaque hemorrhage → rapid expansion → sudden ischemic events

  - Atheroembolism → distal microvascular occlusion → stroke, limb ischemia

Modifiers:

- Plaque factors: lipid content, fibrous cap thickness, inflammation
- Extrinsic factors: BP spikes, adrenergic surges, hemodynamic stress
- Therapy: Statins → plaque stabilization, endothelial improvement

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💡 High-Yield Exam Points

- Critical stenosis: ~70% luminal occlusion → ischemia on exertion
- Acute plaque change: main mechanism of acute coronary syndromes
- Vulnerable plaques: thin cap, lipid-rich, inflammatory cells
- Statins: reduce cholesterol AND stabilize plaques
- Circadian variation: peak MI incidence in morning due to adrenergic surge

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-> The End <-