Definition of atherosclerosis; Etiology, Pathomorphology, pathogenesis and clinical manifestations of atherosclerosis

What is atherosclerosis?

Arteriosclerosis literally means “hardening of the arteries”; it is a generic term for arterial wall thickening and loss of elasticity. There are three general patterns, with different clinical and pathologic consequences:

- *Arteriolosclerosis* affects small arteries and arterioles, and may cause downstream ischemic injury. It is discussed in relation to hypertension.
- *Mönckeberg medial sclerosis* is characterized by calcification of the walls of muscular arteries. Usually not clinically significant.
- Atherosclerosis, from Greek root words for “gruel” and “hardening,” is the most frequent and clinically important pattern.

Atherosclerosis underlies the pathogenesis of coronary, cerebral and peripheral vascular disease, and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder.

Epidemiology

Epidemiology is the study of both the distribution of disease (who has it, where, and when), as well as its causes (etiology).

Epidemiologic data related to atherosclerosis mortality typically reflect deaths caused by ischemic heart disease.

Etiology

The likelihood of atherosclerosis is determined by the combination of **acquired** (e.g., cholesterol levels, smoking, hypertension) and **inherited** (LDL receptor gene mutations) risk factors.

These cause initimal lesions called atheromas (also called atheromatous or atherosclerotic plaques) that protrude into vessel lumens.

Besides mechanically obstructing blood flow, atherosclerotic plaques can rupture leading to catastrophic obstructive vascular thrombosis.

Atherosclerotic plaque can also increase the diffusion distance from the lumen to the media, leading to ischemic injury and weakening of the vessel wall, changes that may result in aneurysm formation.

Pathogenesis of atherosclerosis

The contemporary view of atherogenesis integrates the risk factors previously discussed and is called the “response to injury” hypothesis. This model views atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury.

Lesion progression occurs through interaction of modified lipoproteins, macrophages, and T lymphocytes with endothelial cells and smooth muscle cells of the arterial wall.
According to this schema, atherosclerosis progresses in the following sequence:

Pathogenesis of atherosclerosis

1. Endothelial injury and dysfunction, increased vascular permeability, leukocyte adhesion.
2. Accumulation of lipoproteins (LDL) in the vessel wall.
3. Monocyte adhesion to the endothelium, followed by migration into the intima and transformation into foam cells.
4. Smooth muscle cell activation

Pathogenesis of atherosclerosis

5. Smooth muscle cell proliferation, extracellular matrix production, and recruitment of T cells.
6. Lipid accumulation both extracellularly and within cells(macrophages and smooth muscle cell)

Endothelial injury

Endothelial cell injury is the cornerstone of the response to injury hypothesis.

It results in intimal thickening; in the presence of high-lipid diets, typical atheromas ensue.

Early atherosclerotic lesions begin at sites of intact, but dysfunctional, endothelium. These dysfunctional endothelial cells exhibit increased permeability, enhanced leukocyte adhesion.

Suspected triggers of early atheromatous lesions include hypertension, hyperlipidemia, toxins from cigarette smoke, homocysteine, and even infectious agents.

The two most important causes of endothelial dysfunction are hemodynamic disturbances and hypercholesterolemia.

Hemodynamic Disturbances

- The importance of hemodynamic turbulence in atherogenesis is illustrated by the observation that plaques tend to occur at ostia of exiting vessels, branch points, and along the posterior wall of the abdominal aorta, where there are disturbed flow patterns.

What is the problem with lipids?

- The dominant lipids in atheromatous plaques are cholesterol and cholesterol esters.
- Genetic defects in lipoprotein uptake and metabolism (homozygous familial hypercholesterolemia) that cause hyperlipoproteinemia are associated with accelerated atherosclerosis.
- Lowering serum cholesterol by diet or drugs slows the rate of progression of atherosclerosis, causes regression of some plaques, and reduces the risk of cardiovascular events.*

**There's a great lack of knowledge today on what dietary guidelines are best for long-term health. We simply don't know. Do your research.*

Chronic hyperlipidemia can directly impair endothelial cell function by increasing local oxygen free radical production.
With chronic hyperlipidemia, lipoproteins accumulate within the intima, where they are hypothesized to generate two pathogenic derivatives, **oxidized LDL and cholesterol crystals.**
LDL is oxidized through the action of oxygen free radicals.
LDL is ingested by macrophages through the **scavenger receptor,** resulting in **foam cell** formation.
Oxidized LDL stimulates the local release of growth factors, cytokines, and chemokines, increasing monocyte recruitment, and also is cytotoxic to endothelial cells and smooth muscle cells.

Inflammation

Inflammation contributes to the initiation, progression, and complications of atherosclerotic lesions.

Normal vessels do not bind inflammatory cells!

Early in atherogenesis, however, dysfunctional endothelial cells express adhesion molecules that promote leukocyte adhesion; vascular cell adhesion molecule-1 (VCAM-1), in particular, binds monocytes and T cells.

Inflammation

- Monocytes differentiate into macrophages and engulf lipoproteins, including oxidized LDL and small cholesterol crystals. Activated macrophages also produce toxic oxygen species that drive LDL oxidation and stimulate smooth muscle cell proliferation.
- T lymphocytes recruited to the intima interact with the macrophages and also contribute to a state of chronic inflammation. Activated T cells in the growing intimal lesions elaborate inflammatory cytokines (e.g., IFN-γ), which stimulate macrophages, endothelial cells, and smooth muscle cells.
- As a consequence of the chronic inflammatory state, activated leukocytes stimulate smooth muscle cell proliferation and matrix synthesis.

Infection

There is circumstantial evidence linking infections to atherosclerosis.

Infections, however, are exceedingly common (as is atherosclerosis), making it difficult to draw conclusions about causality.

It also is important to recognize that atherosclerosis can be induced in germ-free mice.

Smooth Muscle Proliferation and Matrix Synthesis

- Intimal smooth muscle cell proliferation and ECM deposition lead to conversion of the earliest lesion, a **fatty streak,** into a mature atheroma.
- Intimal smooth muscle cells can originate from the media or from circulating precursors.
- The recruited smooth muscle cells synthesize ECM (most notably collagen), which **stabilizes** atherosclerotic plaques.
- However, activated inflammatory cells in atheromas also can cause intimal smooth muscle cell apoptosis and breakdown of matrix, leading to the development of **unstable** plaques.

Morphology

- **Fatty streaks** begin as minute yellow, flat macules that coalesce into elongated lesions.
- They are composed of lipid-filled foamy macrophages, they are only minimally raised and do not cause any flow disturbance.
- Fatty streaks can appear in the aortas of infants younger than 1 year of age and are present in virtually all children older than 10 years.

- **Atherosclerotic plaques** are patchy, usually involving only a portion of any given arterial wall.
- Local flow disturbances, such as turbulence at branch points, make certain parts of a vessel wall susceptible to plaque formation.

Atherosclerotic plaques have three principal components: (1) cells, including smooth muscle cells, macrophages, and T cells; (2) extracellular matrix, including collagen, elastic fibers, and proteoglycans; and (3) intracellular and extracellular lipid.

Morphology

- The proportion and configuration of each component varies from lesion to lesion.
- Most commonly plaques have a superficial fibrous cap composed of smooth muscle cells and relatively dense collagen.
- Deep to the fibrous cap is a necrotic core, containing lipid (primarily cholesterol and cholesterol esters), necrotic debris, lipid-laden macrophages and smooth muscle cells (foam cells), fibrin, variably organized thrombus, and other plasma proteins.
- The extracellular cholesterol frequently takes the forms of crystalline aggregates that are washed out during routine tissue processing, leaving behind empty “cholesterol clefts.” The periphery of the lesions shows neovascularization.
- Atheromas also often undergo calcification.

Clinical consequences

The principal pathophysiologic outcomes depend on the size of the affected vessel, the size and stability of the plaques, and the degree to which plaques disrupt the vessel wall:

- ACUTE Occlusion of smaller vessels can compromise tissue perfusion.
- ACUTE Plaque rupture can expose atherosclerotic debris, leading to acute (and frequently catastrophic) vascular thrombosis or (with shedding of debris) distal embolization.
- CHRONIC Destruction of the underlying vessel wall can lead to **aneurysm** formation, with secondary rupture and/or **thrombosis.**

Clinical consequences - Atherosclerotic Stenosis

If plaque is stable, critical stenosis is the tipping point at which chronic occlusion limits flow so severely that tissue demand exceeds supply.

In the coronary artery (and other) circulations, this typically occurs at 70% fixed occlusion.

At rest, patients have adequate cardiac perfusion.

But with even modest exertion demand exceeds supply, and chest pain develops because of **cardiac ischemia** (stable angina).

There is also bowel ischemia, sudden cardiac death, chronic ischemic heart disease, ischemic encephalopathy, and intermittent claudication (ischemic leg pain). *About these in the cardiovascular chapter.*

Clinical consequences

- The principal pathophysiologic outcomes depend on the size of the affected vessel, the size and stability of the plaques, and the degree to which plaques disrupt the vessel wall:
- Occlusion of smaller vessels can compromise tissue perfusion.
- Plaque rupture can expose atherosclerotic debris, leading to acute (and frequently catastrophic) vascular thrombosis or (with shedding of debris) distal embolization.
- Destruction of the underlying vessel wall can lead to aneurysm formation, with secondary rupture and/or thrombosis.

Clinical consequences - Acute Plaque Change

Plaque erosion or rupture typically triggers thrombosis, leading to partial or complete vascular obstruction and often tissue infarction.

Plaque changes fall into three general categories:

1. Rupture/fissuring, exposing highly thrombogenic plaque constituents

2. Erosion/ulceration, exposing the thrombogenic subendothelial basement membrane to blood

3. Hemorrhage into the atheroma, expanding its volume