***ATHEROSCLEROSIS***

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*ENDOTHELIAL CELLS*

* ECs comprise the single cell-thick, continuous lining of the entire cardiovascular system, collectively called the *endothelium.* Endothelial structural and functional integrity is fundamental to the maintenance of vessel wall homeostasis and normal circulatory function.

Smooth muscle cells

* SMCs are predominant cellular element of the vascular media. SMCs are responsible for vasoconstriction and dilation in response to normal or pharmacologic stimuli of arteries and arterioles.
* They also synthesize collagen, elastin, and proteoglycans; and elaborate growth factors and cytokines. They migrate to the intima and proliferate following vascular injury. Thus, SMCs are important elements of both normal vascular repair and pathologic processes such as atherosclerosis.
* *Vascular injury ( endothelial injury/dysfunction) stimulates SMC growth.* Reconstitution of the damaged vascular wall is a physiologic healing response that includes the formation of a *neointima*, in which SMCs (1) migrate from the media to the intima, (2) multiply as intimal SMCs, and (3) synthesize and deposit ECM
* During the healing response, SMCs undergo changes that resemble dedifferentiation. In the intima they lose the capacity to contract and gain the capacity to divide. Intimal SMCs may return to a nonproliferative state when either the overlying endothelial layer is re-established following acute injury or the chronic stimulation ceases.

 *Arteriosclerosis*

 *Arteriosclerosis* (literally, "hardening of the arteries") is a generic term for thickening and loss of elasticity of arterial walls. Three patterns of arteriosclerosis are recognized; they vary in pathophysiology and clinical and pathological consequences.

*1)Atherosclerosis*, the most frequent and important pattern.

*2)Mönckeberg medial calcific sclerosis* is characterized by calcific deposits in muscular arteries in persons older than age 50. They do not encroach on the vessel lumen.

*3)Arteriolosclerosis* affects small arteries and arterioles. There are two anatomic variants, hyaline and hyperplastic, both associated with thickening of vessel walls with luminal narrowing that may cause ischemic injury. Most often associated with hypertension and diabetes mellitus.

**Atherosclerosis**

* Atherosclerosis is characterized by intimal lesions called *atheromas*, or *atheromatous or fibrofatty plaques*, which protrude into and obstruct vascular lumens and weaken the underlying media. They may lead to serious complications

Atherosclerosis: Morphology

* *Fatty streaks* are the earliest lesion of atherosclerosis. They are composed of lipid-filled foam cells. They are not significantly raised and thus do not cause any disturbance in blood flow. Fatty streaks begin as multiple yellow, flat spots less than 1 mm in diameter that coalesce into elongated streaks, 1 cm long or longer. They contain T lymphocytes and extracellular lipid in smaller amounts than in plaques.
* **The key processes in atherosclerosis are intimal thickening and lipid accumulation. An atheroma or atheromatous plaque consists of a raised focal lesion initiating within the intima, having a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters), covered by a firm, white fibrous cap**.
* The atheromatous plaques appear white to whitish yellow and impinge on the lumen of the artery. They vary in size from approximately 0.3 to 1.5 cm in diameter but sometimes coalesce to form larger masses. Atherosclerotic lesions usually involve only a partial circumference of the arterial wall ("eccentric" lesions) and are patchy and variable along the vessel length.
* The most heavily involved vessels are the abdominal aorta then coronary arteries, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis.

 **Atherosclerotic plaques have three principal components:**

* **(1) cells, including SMCs, macrophages, and other leukocytes**
* **(2) ECM, including collagen, elastic fibers, and proteoglycans**
* **(3) intracellular and extracellular lipid . These components occur in varying proportions.**
* Typically, the superficial fibrous cap is composed of SMCs and relatively dense ECM. Beneath and to the side of the cap (the "shoulder") is a cellular area consisting of macrophages, SMCs, and T lymphocytes.
* Deep to the fibrous cap is a necrotic core, containing a disorganized mass of lipid (primarily cholesterol and cholesterol esters), cholesterol clefts, debris from dead cells, foam cells, fibrin, variably organized thrombus, and other plasma proteins.
* Foam cells are large, lipid-laden cells that derive predominantly from blood monocytes (tissue macrophages), but SMCs can also imbibe lipid to become foam cells.
* Around the periphery of the lesions, there is usually evidence of neovascularization (proliferating small blood vessels). Typical atheromas contain relatively abundant lipid.
* Atheromas often undergo **calcification**.

COMPLICATIONS of ATHEROSCLEROSIS

 The **advanced lesion** of atherosclerosis is at risk for the following pathological changes that have clinical significance:

1) Focal **rupture, ulceration**, or **erosion** of the luminal surface of atheromatous plaques may result in exposure of highly thrombogenic substances that induce thrombus formation or discharge of debris into the bloodstream, producing microemboli composed of lesion contents **(cholesterol emboli or atheroemboli)**.

**2) Hemorrhage** into a plaque, especially in the coronary arteries, may be initiated by rupture of either the overlying fibrous cap or the thin-walled capillaries that vascularize the plaque. A contained hematoma may expand the plaque or induce plaque rupture.

3)Superimposed **thrombosis**, the most feared complication, usually occurs on disrupted lesions (those with rupture, ulceration, erosion, or hemorrhage) and may partially or completely occlude the lumen. Thrombi may heal and become incorporated into and thereby enlarge the intimal plaque. The thrombus may embolise.

**4)Aneurysmal dilation** may result from ATH-induced atrophy of the underlying media, with loss of elastic tissue, causing weakness and potential rupture

5) Calcifications.

Risk Factors for Atherosclerosis

**A)Major**

*Nonmodifiable*

* Increasing age
* Male gender
* Family history
* Genetic abnormalities

*PotentiallyControllable*

* Hyperlipidemia
* Hypertension
* Cigarette smoking
* Diabetes
* Risk Factors for Atherosclerosis

**B) Lesser, Uncertain, or Nonquantitated**

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

**Types of lipoproteins**

* Low-density lipoproteins (LDLs):

When too much LDL (bad) cholesterol circulates in the blood, it promotes atheroma formation in the arteries.LDLs contribute to heart disease because they carry large amounts of cholesterol

* Very-low-density lipoproteins (VLDLs):

is also considered to be a type of bad cholesterol because it helps cholesterol build up on the walls of arteries

* Chylomicrons

also promote atherosclerosis.

* High-density lipoproteins (HDLs):

is known as “good” cholesterol, because high levels of HDL seem to protect against heart attack. Low levels of HDL (less than 40 mg/dL) also increase the risk of heart disease. HDLs help to reverse the effects of high cholesterol by collecting cholesterol from other lipoproteins and transporting it to places where it can be utilized by the cells

PATHOGENESIS of ATHEROSCLEROSIS: *response to injury hypothesis*

* This concept, called *the* *response to injury hypothesis, considers atherosclerosis to be a chronic inflammatory response of the arterial wall initiated by injury to the endothelium. Moreover, lesion progression is sustained by interaction between modified lipoproteins, monocyte-derived macrophages, T lymphocytes, and the normal cellular constituents of the arterial wall*.

 Central to this thesis are the following:

* Accumulation of *lipoproteins*, mainly LDL, with its high cholesterol content, in the vessel wall
* *Chronic endothelial injury*, usually subtle, yielding increased permeability, leukocyte adhesion, and thrombotic potential.
* Adhesion of *blood monocytes* (and other leukocytes) to the endothelium, followed by their migration into the intima and their transformation into *macrophages* and *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 elaboration of extracellular matrix, leading to the accumulation of collagen and proteoglycans
* *Enhanced accumulation of lipids* both within cells (macrophages and SMCs) and extracellularly.

*PREVENTION of ATHEROSCLEROSIS*

* *primary prevention* programs, aimed at either delaying atheroma formation or causing regression of established lesions in persons who have never suffered a serious complication of atherosclerotic coronary artery disease
* *secondary prevention* programs, intended to prevent recurrence of events such as myocardial infarction in patients with symptomatic disease.
* based on risk factor modification: abstention from or cessation of cigarette smoking, control of hypertension, weight reduction and increased exercise, moderation of alcohol consumption, and, most importantly, lowering total and LDL blood cholesterol levels while increasing HDL.