ARTERIOSCLEROSIS

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Normal blood vessels
A = artery
V = vein
Artery (A) versus vein (V)
ARTERIOSCLEROSIS

• *Arteriosclerosis* = "hardening of the arteries"

• arterial wall thickening and loss of elasticity.

• Three patterns are recognized, with different clinical and pathologic consequences:
1-Arteriolosclerosis

- affects small arteries and arterioles
- associated with hypertension and/or diabetes mellitus
2- Mönckeberg medial calcific sclerosis

- calcific deposits in muscular arteries
- typically in persons > age 50
- radiographically visible (x-rays, etc…)
- palpable vessels
- do **not** encroach on vessel lumen and are usually not clinically significant
2-Mönckeberg medial calcific sclerosis
3-Atherosclerosis

- Greek word="gruel" ,"hardening,"

- most frequent and clinically important pattern of arteriosclerosis

- characterized by intimal lesions = *atheromas* (a.k.a. *atherosclerotic plaques*)

- atheromatous plaque = raised lesion with a core of lipid (cholesterol and cholesterol esters) covered by a firm, white fibrous cap
Pathogenesis

• not fully understood
• ? inflammatory process in endothelial cells of vessel wall associated with retained low-density lipoprotein (LDL) particles → ? a cause, an effect, or both, of underlying inflammatory process
• initiation of inflammatory process $\rightarrow$ LDL particles and their content are susceptible to oxidation by free radicals $\rightarrow$ endothelial activation
The major components of a well-developed intimal atheromatous plaque

- **Fibrous Cap**: Smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization
- **Necrotic Center**: Cell debris, cholesterol crystals, foam cells, calcium
- **Media**
Atheromatous plaque
Formation of atheromatous plaque

1. Chronic endothelial “injury”:
   - Hyperlipidemia
   - Hypertension
   - Smoking
   - Homocysteine
   - Hemodynamic factors
   - Toxins
   - Viruses
   - Immune reactions

2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion, monocyte adhesion and emigration)

3. Macrophage activation, smooth muscle recruitment
Formation of atheromatous plaque

1. Fatty streak
2. Macrophages and smooth muscle cells engulf lipid
3. Lymphocyte
4. Fibrofatty atheroma
5. Smooth muscle proliferation, collagen and other ECM deposition, extracellular lipid

Lymphocyte
Collagen
Lipid debris
**Initial lesion**
- Histologically "normal"
- Macrophage infiltration
- Isolated foam cells

**Fatty streak**
- Mainly intracellular lipid accumulation

**Intermediate lesion**
- Intracellular lipid accumulation
- Small extracellular lipid pools

**Atheroma**
- Intracellular lipid accumulation
- Core of extracellular lipid

**Fibroatheroma**
- Single or multiple lipid cores
- Fibrotic/calcific layers

**Complicated lesion**
- Surface defect
- Hematoma-hemorrhage
- Thrombosis

**Sequences in Progression of Atherosclerosis**

<table>
<thead>
<tr>
<th>EARLIEST ONSET</th>
<th>MAIN GROWTH MECHANISM</th>
<th>CLINICAL COLLEGERATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>From first decade</td>
<td>Growth mainly by lipid addition</td>
<td>Clinically silent</td>
</tr>
<tr>
<td>From third decade</td>
<td></td>
<td></td>
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<tr>
<td>From fourth decade</td>
<td>Increased smooth muscle and collagen increase</td>
<td>Clinically silent or overt</td>
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</tbody>
</table>

**Endothelial Dysfunction**
Atherosclerosis: progression

Clinical Phase
Usually middle age to elderly

- Mural thrombosis
- Embolization
- Wall weakening
  - Aneurysm and rupture

- Plaque rupture
- Plaque erosion
- Plaque hemorrhage
- Mural thrombosis
- Embolization
  - Occlusion by thrombus

- Progressive plaque growth
  - Critical stenosis
Vulnerable vs stable plaque

Thick fat core
Thin fibrous cap
More inflammation

Thin fat core
Thick fibrous cap
Less inflammation
## Risk Factors for Atherosclerosis

<table>
<thead>
<tr>
<th>Major Risks</th>
<th>Lesser, Uncertain, or Non-quantitated Risks</th>
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</thead>
<tbody>
<tr>
<td><strong>Non-modifiable (non-controllable)</strong></td>
<td></td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Increasing age</td>
<td>Physical inactivity</td>
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<tr>
<td>Male gender</td>
<td>Stress (&quot;type A personality&quot;)</td>
</tr>
<tr>
<td>Family history</td>
<td>Postmenopausal estrogen deficiency</td>
</tr>
<tr>
<td>Genetic abnormalities</td>
<td>High carbohydrate intake</td>
</tr>
<tr>
<td></td>
<td>Lipoprotein(a)</td>
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<tr>
<td><strong>Potentially modifiable (Controllable)</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Hardened (trans)unsaturated fat intake</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Chlamydia pneumoniae infection</td>
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<tr>
<td>Cigarette smoking</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>C-reactive protein (inflammation)</td>
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# Major Risk Factors for Atherosclerosis

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<th>Nonmodifiable (Constitutional)</th>
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<td>Genetic abnormalities</td>
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<tr>
<td>Family history</td>
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<td>Male gender</td>
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<table>
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<td>Inflammation</td>
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</table>
• Epidemiology ….

• *Multiple risk factors have a multiplicative effect:* 2 risk factors increase the risk 4X.

• E.g. if 3 risk factors are present (e.g., hyperlipidemia, hypertension, and smoking), the rate of myocardial infarction is increased 7X.
1-age

- ages 40 to 60, incidence of MI in men increases 5 x
- Death rates from IHD rise with each decade

2-Gender

- Premenopausal* → protected against atherosclerosis compared with age-matched men.
- After menopause→ incidence of atherosclerosis-related diseases increases

* unless they are otherwise predisposed by diabetes, hyperlipidemia, or severe hypertension.
3-Genetics

• familial predisposition is *multifactorial*.
• Either:
  1- *familial clustering* of other risk factors
    - e.g. HTN or DM
  or:
  2- *well-defined genetic derangements in lipoprotein metabolism*
    - e.g. *familial hypercholesterolemia*
Additional Risk Factors for atherosclerosis

- 20% of cardiovascular events occur in the absence of identifiable risk factors:
  - Hyperhomocystinemia
  - *Metabolic syndrome*
  - Lipoprotein a levels
  - Factors Affecting Hemostasis (*Elevated levels of procoagulants; Clonal hematopoiesis*)
  - Others:
    - lack of exercise
    - competitive, stressful lifestyle (*"type A" personality*)
    - obesity
    - High carbohydrate intake