MECHANISMS OF Atherosclerosis

Hossein Mehrani
Professor of Clinical Biochemistry
DEFINITION

Atherosclerosis: atherosclerosis, is a Greek words atheros (meaning “gruel” or “paste”) and sclerosis (meaning “hardness”), is a type of arteriosclerosis in which arteries are narrowed by fatty deposit.

Arteriosclerosis: is a hardening of the artery walls, resulting in thickening and calcification.

Atherosclerosis is a multifactorial disease process and is the principal cause of myocardial infarction, stroke, and peripheral vascular disease, accounting for almost 40% of all mortality in the western Society.
ATHEROSCLEROSIS

The image shows a comparison between a normal human artery and an artery narrowed by an atherosclerotic plaque. The normal artery has an intact endothelium and smooth muscle layers, whereas the diseased artery has a damaged endothelium, smooth muscle cells, macrophages transformed into foam cells, lipids, calcium, and cellular debris, leading to narrowing of the artery.

Key components:
- Endothelial cell
- Intima
- SMCs (Smooth Muscle Cells)
- Media
- Adventitia
- Mast cell
- Fibroblast

The diagram illustrates the process of atherosclerosis, a condition characterized by the build-up of fatty deposits on the inner lining of the artery walls, which can lead to heart disease if severe.
Coronary Atherosclerosis Causes MI
Intracerebral Atherosclerosis Causes Cerebral Infarction
Pathogenesis of Coronary Heart Diseases

Adventitia — Media — Intima — Lumen — Asymptomatic atherosclerotic plaque

Stable fixed atherosclerotic plaque — Stable angina

Plaque disruption and platelet aggregation — Unstable plaque — Unstable angina

Thrombus — Non-ST-segment elevation MI — ST-segment elevation MI

Acute coronary syndromes
1- CAD Risk Factors
2- Oxidative Stress
3- Endothelial Dysfunction

Endothelial Cells and Vascular Smooth Muscle

Endothelial Dysfunction

Apoptosis
Leukocyte adhesion
Lipid deposition
Vasoconstriction
VSMC growth
Thrombosis

Hypertension
Diabetes
Smoking
LDL
Homocysteine
Estrogen deficiency

Oxidative Stress
Endothelial Dysfunction

Hypertension
Diabetes
Smoking
LDL
Homocysteine
Estrogen deficiency

O$_2$
H$_2$O$_2$
Coronary Arteries Diseases Risk Factors

- **Non modifiable risk factors:**
  - Increasing age
  - Gender
  - Family history of premature heart disease
  - Genetics Defects

- **Modifiable risk factors:**
  - High LDL cholesterol
  - Low HDL cholesterol
  - High blood pressure
  - Diabetes
  - Obesity (especially abdominal obesity)
  - Physical inactivity
  - Cigarette smoking
  - Diet high in saturated fat, trans fat, cholesterol, low in fruits, vegetables and whole grains
Genetic Defects of Lipid Metabolism

• 1-Monogenic:
  - Familial Hypercholesterolemia
    - (homozygous or heterozygous)
    - defect: inactive LDL receptor
  - Familial Hypertriglyceridemia
    - defect: inactive lipoprotein lipase
  - Familial Combined Hyperlipidemia
    - defect: unknown

• 2- Polygenic/Multifactorial:
  - Hypercholesterolemia,
  - Hypertriglyceridemia
SMOKING

- Twice the risk of stroke and heart attack
- Lowers HDL
- Produces free radicals
- Promotes ↑fibrinogen
- Increase plasminogen activator inhibitor
Surface Monolayer
- Phospholipids (25%)
- Free Cholesterol (15%)
- Protein (22%)

Hydrophobic Core
- Triglyceride (5%)
- Cholesteryl Esters (35%)
### Most Important Reactive Oxygen and Nitrogen Species

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>$O_2 + e^- \rightarrow O_2^-$</td>
<td>Superoxide formation (various sources, see text)</td>
</tr>
<tr>
<td>$2 O_2^- + 2 H^+ \rightarrow H_2O_2 + O_2$</td>
<td>Hydrogen peroxide formation, catalyzed by SODs</td>
</tr>
<tr>
<td>$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$</td>
<td>Fenton reaction</td>
</tr>
<tr>
<td>$O_2^- + H_2O_2 \rightarrow \cdot OH + OH^- + O_2$</td>
<td>Haber-Weiss reaction (iron-catalyzed)</td>
</tr>
<tr>
<td>L-arginine $\rightarrow$ NO$^- +$ L-citrulline</td>
<td>NO$^-$ formation (catalyzed by NOS)</td>
</tr>
<tr>
<td>NO$^- + O_2^- \rightarrow$ ONOO$^-$</td>
<td>Peroxynitrite formation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>•NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>•NO$_2$</td>
<td>Nitrogen dioxide</td>
</tr>
<tr>
<td>ONOO$^-$</td>
<td>Peroxynitrite</td>
</tr>
<tr>
<td>O$_2^-$</td>
<td>Superoxide</td>
</tr>
<tr>
<td>•OH</td>
<td>Hydroxyl radical</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>ROO$^-$</td>
<td>Peroxy radical</td>
</tr>
<tr>
<td>HOCI</td>
<td>Hypochlorous acid</td>
</tr>
</tbody>
</table>

**Diagram:**

- $O_2^-$
- HOCI
- H$_2$O
- O$_2$ + OH$^-$
- Cl$^-$
- H$_2$O$_2$ + H$^+$

**Reaction:**

$O_2 + \cdot OH \rightarrow HOCI \rightarrow H_2O + H^+$
F2-isoprostanes in HDL₂ and HDL₃ were 4- to 6-fold higher than in LDL; HDL₃ contained 50% more F2-isoprostanes than HDL₂. Importantly, the amount of arachidonic acid was significantly higher in LDL than in HDL. These observations indicate that HDL is the major carrier of both early and late products of lipid oxidation.
Contributing Factors for Generation of ROS
Hypercholesterolemia, Hyperglycemia, Hypertension
Shear Stress, Proinflammatory Cytokines
Smoking, Stress

NAD(P)H oxidase
Xanthine oxidase
Uncoupled eNOS
Cyclooxygenase
Lipooxygenase
Mitochondrial electron transport chain
Cytochrome P450s

1e⁻

O₂⁻ + O₂⁺

SOD

H₂O₂

Oxidative stress
Intracellular signaling pathway
Atherogenic Responses
Endothelial Dysfunction

Vasodilation
Thrombolysis
Platelet disaggregation
Antiproliferation
Antiinflammation
Antioxidant

Vasoconstriction
Thrombosis
Adhesion molecules
Growth factors
Inflammation
Oxidant activity

Lumen

Receptor-dependent EDNO agonist

Shear stress

↑ [Ca^{2+}]

O_{2} + L-arginine → eNOS → NO + L-citrulline

Ca^{2+}, FAD, NADPH, TH_{4}

Platelet inhibition

↑ cGMP

Inhibition of monocyte adhesion

Smooth muscle cell relaxation and growth inhibition

Guanylyl cyclase
GTP → cGMP
Stepwise Formation of Atherosclerosis

1. Accumulation of lipids (fatty streak)
2. Surrounded by proliferating smooth muscle
3. LDL enters the endothelium
4. LDL becomes oxidized by several types of cells
5. The oxidized LDL attracts macrophages, forming foam cells
6. Proliferating smooth muscle, lipids, and connective tissue become incorporated into the maturing Plaque
7. Formation of a fibrous cap, having areas of cell necrosis and calcification
8. Narrowing of the arterial’s lumen diameter
Lesion Initiation

Minimally Modified LDL induces expression of cell adhesion molecules
Smooth muscle cells migrate into the Intima, proliferate and secrete extracellular matrix proteins that form a fibrous plaque.
Macrophage death as a factor that limits lesion cellularity

Apoptotic Inducers:
- TNFα
- Fas Ligand
- Growth factor withdrawal
- Oxidized LDL
- Oxidized Phospholipids
- Oxysterol (7-ketocholesterol)
Fibrous Cap is weakened, tissue factors are released, recruitment of platelets and formation thrombosis
CRP promotes complement Activation
Decrease eNOS Expression
Enhances the release of ET-1, VCAM-1, ICAM
MCP-1, migration of SMCs facilitate LDL uptake by macrophage
Relative Risk Factors for Future Outcomes

- Lipoprotein(a)
- Homocysteine
- IL-6
- TC
- LDLC
- ICAM-1
- SAA
- Apo B
- TC: HDLC
- hs-CRP
- hs-CRP + TC: HDLC

Relative Risk of Future Cardiovascular Events
Myeloperoxidase Early Indicator of Acute Coronary Syndrome and Predictor of Future Cardiovascular Events
## Lipid Lowering Agents

<table>
<thead>
<tr>
<th>Subclass</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
<th>Side effects/problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid resins (cholestyramine, colestipol)</td>
<td>↓</td>
<td></td>
<td>↑</td>
<td>Tastes bad and causes GI discomfort</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Safety unknown for long term use; Most expensive</td>
</tr>
<tr>
<td>(lovastatin, atorvastatin, pravastatin, simvastatin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL secretion inhibitor (Niacin)</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Evokes flushing; itchiness and GI discomfort</td>
</tr>
<tr>
<td>Lipoprotein lipase stimulants</td>
<td>↓</td>
<td></td>
<td></td>
<td>More effective in reducing TG than cholesterol; long-term effect not known</td>
</tr>
<tr>
<td>(Fibrates: clofibrate, gemfibrozil, fenofibrate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probuclol</td>
<td></td>
<td></td>
<td></td>
<td>HDL decrease, not effective in single drug therapy; no long term clinical data</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Hepatocytes**
  - Ac-CoA → HMG-CoA → Cholesterol → Bile acids
  - Niacin
  - Resins
  - HMG-CoA reductase inhibitors

- **Blood**
  - LDL, HDL, IDL, VLDL, Apoproteins
  - Lipoprotein lipase
  - Lipid oxidation

- **Endothelial Cells**
  - Gemfibrozil

- **GUT**
  - Resorption process