Cardiovascular disease, studies at the cellular and molecular level

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Bioscience in the 21st Century
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Content

• Introduction – The number 1 killer in America
  – Some statistics
  – Recommendations
• The disease process
  – Damage
  – Current treatments
• Control of vascular tone
• Control of endothelial damage
Risk Factors

• High blood pressure (above 120/80 mm Hg)
• Serum cholesterol [aim for below 100 mg/dL LDL cholesterol and above 50 mg/dL HDL, or aim for total cholesterol below 200 mg/dL]
• Body Mass Index (BMI) [above 30]
• Smoking
• Drinking
• Diabetes
Metabolic Syndrome

- **Central obesity** (excessive fat tissue in and around the abdomen)
- **Atherogenic dyslipidemia** (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
- **Insulin resistance or glucose intolerance** (the body can’t properly use insulin or blood sugar)
- **Prothrombotic state** (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- **Raised blood pressure** (130/85 mmHg or higher)
- **Proinflammatory state**
Chart 2-1 Trends in the age-adjusted prevalence of health conditions
US adults ages 20 to 74


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Age-adjusted death rates for CHD, stroke, lung and breast cancer for white and black females (United States: 2005).

Source: NCHS and NHLBI.
Chart 3-6. Ten year risk for CHD by risk factors

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<th>B</th>
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<th>D</th>
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<td>Yes</td>
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<td>Cigarettes</td>
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<td>No</td>
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Direct Costs (Billions of dollars) of the 10 Leading Diagnostic Groups (United States: 2009). Source: NHLBI.
Recommendations

• Limit your saturated fat intake (trans fat too)
• Consume less than 200 (300) mg/day cholesterol
• Eat fish regularly
• Limit your salt intake (less than 2300 mg/day)
• Consume vegetables and whole grains
• Diet options for lowering cholesterol
  • Plant sterols and/or soluble fiber
• Eat only enough calories to maintain weight (or reach a healthy weight)
• At least 30 min of moderate physical activity/day
• Diet
• Portion size
• Physical Activity
• Genes

• Fat as an endocrine tissue
  – Makes leptin – lowered desire to eat, more use of stored fat
  – Makes inflammatory signaling molecules
  – Decreases synthesis of signals that in turn cause a decrease in blood pressure
    – with the result being increased blood pressure

Ob/ob mouse from “Nutritional Science”
Progression of Vascular Disease

MedlinePlus Medical Encyclopedia
Atherosclerosis

- Leads to narrowing/blocking of arteries
  - Blocked flow to the heart
    - Myocardial Infarction *(heart attack)*
  - Blocked flow to the brain
    - Ischemic Stroke

Bypass
Cut-section of artery

- Tear in artery wall
- Macrophage cell
- Cholesterol deposits
- Red blood cell
- Macrophage foam cell
- Fat deposits

MedlinePlus Medical Encyclopedia
Atherosclerosis is Geometrically Focal

Smooth Flow Region

“Non-Sticky” ECs

Intact Endothelium

Disturbed Flow Region

“Sticky” ECs

Inflamed vasculature

“Inflamed” Endothelium

Flow, along with other factors, contributes to risk.

Meron Mengistu
Vessel Anatomy
Contraction of blood vessels

- Angiotensin is a major contraction signal that increases blood pressure transiently.

**Diuretics, Ace inhibitors, β-blockers, Calcium channel blockers**
Relaxation of blood vessels

• NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP

Nitroglycerin
• But cGMP is typically rapidly degraded by proteins called PDEs

\[ \text{cGMP} \rightarrow \text{GMP} \]

• PDE3 is primarily in cardiac muscle
• PDE6 is primarily in the retinas
• PDE5 is primarily in vascular smooth muscle
Sildenafil citrate

• Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
• Therefore in vascular smooth muscle cells cGMP remains elevated longer.

• Viagra is a trade name for sildenafil citrate
Cell proliferation and wound repair

• Lack of contact, damaging chemicals, etc.
• Growth factors, Angiotensin
• Immune system