Atherosclerosis

- hardening of the arteries due to the deposition of atheromas
- heart disease is the leading cause of death
- caused by the deposition of cholesteryl esters on the walls of arteries
- atherosclerosis is correlated with high LDL and low HDL

Hyperlipidemia

- How does atherosclerosis start?
  - Complex process of damage to the inner layer of the artery (endothelium)
    - Elevated levels of lipids in the blood
    - High blood pressure
    - Tobacco smoke
What is Hypercholesterolemia

Is a high level of cholesterol in the blood that can cause plaque to form and build up leading to blockages in the arteries (arteriosclerosis) increasing the risk for heart attack, stroke, circulation problems, and death.

Normal Arterial Wall

- Tunica adventitia
- Tunica media
- Tunica intima
- Endothelium
- Subendothelial connective tissue
- Internal elastic membrane
- Smooth muscle cell
- Elastic/collagen fibres
- External elastic membrane
How it affects your body

- High Cholesterol Causes Arteriosclerosis
  The arteriosclerosis, involves several steps.
- (1) The innermost lining of the arteries (the endothelium) is damaged or becomes dysfunctional and cholesterol particles deposit into the damaged wall.
- (2) The cholesterol becomes incorporated into a mixture called plaque, which is composed of cholesterol, other fatty substances, fibrous tissue, and calcium.
- (3) As more cholesterol and other substances incorporate, the plaque grows, narrowing the artery.

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- (4) Plaque build-up can grow large enough to impede blood flow through the artery (called a "blockage").
- When the arteries supplying the heart with blood are blocked, chest pain (angina) may occur.
- When arteries in the legs are blocked, leg pain or cramping may occur; when arteries supplying the brain with blood are blocked, stroke may occur.
- If the plaque ruptures, a blood clot may develop on top of it. If the blood clot completely blocks blood flow through a coronary artery, it may result in a heart attack (myocardial infarction);
Pathogenesis of Atherosclerotic Plaques

- Endothelial damage
- Protective response results in production of cellular adhesion molecules
- Monocytes and T lymphocytes attached to 'sticky' surface of endothelial cells
- Migrate through arterial wall to subendothelial space
- Macrophages take up oxidised LDL cholesterol
- Lipid-rich foam cells
- Fatty streak and plaque

Photograph of an arterial plaque
Development of Atherosclerotic Plaques

Factors promoting elevated blood lipids

- age
  - men >45 years of age; women > 55 years of age
- family history of CAD
- smoking
- hypertension >140/90 mm Hg
- low HDL cholesterol
- obesity >30% overweight
- diabetes mellitus
- inactivity/ lack of exercise
Treatment for Hypercholesterolemia

- There are many different ways to treat high cholesterol like Nonpharmacological Therapy, Diet, Weight loss, Exercise, & Pharmacological (Drug) therapy
- Standard nonpharmacological therapy mostly consists of adjusting to eating and exercise habits.
- Lowers the LDL cholesterol level by about 30 mg/dL.
- Diet minimizes extra cholesterol and fat intake, especially saturated fat.
- Weight Loss, even if losing 5-10lbs. of weight can double the reduction in LDL levels achieved through a diet.

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- Statins lower LDL cholesterol levels by 20%-40%. If someone takes maximum doses, they lower LDL levels by 40%-50%.
- They get a benefit of increasing the amount of HDL ("good") cholesterol level in the body by about 5%-10%.
Dyslipidemia & Exercise

- Generally, dyslipidemia does not alter the exercise response
- Regular participation in physical activity can manifest beneficial changes
  - Lowering TG concentrations
  - Increase HDL concentrations
  - Increase in enzyme activity in lipoprotein metabolism (LPL, HL)
- Exercise can (in)directly improve profiles

Relationship of Serum Cholesterol to Mortality
(Seven Countries Study)

(Adapted from Verschuren et al.)
Symptoms of Hypercholesterolemia

- High cholesterol rarely causes symptoms. It is usually detected during a regular blood test that measures cholesterol levels.
- Being diagnosed with conditions that may be caused in part by high cholesterol (such as arteriosclerosis, coronary artery block, and stroke) may be the first clue that a person has high cholesterol.
- For example:
  - The first symptom of coronary artery disease (CAD) is often chest pain (angina). Chest pain may occur during activities that increase the heart rate.

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- However, many people have CAD for several years without symptoms.
- Unless the person has a transient ischemic attack (TIA).
- Some people with lipid disorders or familial hypercholesterolemia may have other distinct symptoms such as deposits of excess cholesterol that collect in the skin or eye tissue.
- These cholesterol deposits can also cause nodules in tendons in the hands or feet or rarely yellow streaks in the hands.
HDL: A Major Risk Factor for CHD

- A low plasma HDL is an important risk factor for CHD in the general population
- A high level of HDL may confer cardioprotection
- Reverse cholesterol transport by HDL may be the principle cardioprotective mechanism

*On average, a 10% decrease in CHD risk occurs for each increase of 4 mg/dL in the HDL level.*

HDL in Clinical Practice

- Routinely measured in all adult patients
- HDL-C <35 mg/dL is a major risk factor
- Nonpharmacologic therapy (exercise, weight loss, smoking cessation)
- Pharmacologic therapy

*Consider drug therapy that lowers LDL-C and also increases HDL-C levels.*


The Role of

Small, Dense LDL as a CHD Risk Factor
Evidence from in vitro studies suggests that large, buoyant LDL particles are more resistant to oxidative stress and small, dense LDL particles more susceptible to oxidation.

Role of LDL in atherosclerosis

- LDLs penetrate vascular wall, deposit in the intima and with time are damaged by oxidation.
- Oxidised LDLs attract the attention of macrophages which ingest the LDL.
- Macrophages become overloaded with lipid and become “foam” cells which die and release pools of lipid in the vessel wall (plaques).
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- A complex processes mediated by cytokines and growth factors causes smooth muscle cells to form a collagenous cap over the lipid (mature atherosclerotic plaque).
- Cap grows and can constrict the vessel (causing angina for example).

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- Macrophages can degrade the cap while T cells can inhibit collagen synthesis – the cap can rupture to expose collagen and lipids
- This leads to aggregation of platelets and blood clot formation.
- If the coronary artery is blocked by a clot – heart attack.
- Blocking of arteries in the brain causes stroke.
- Antioxidants (vitamin E and C) may protect LDL from oxidation and so protect against heart attack and stroke.
Clinical Manifestations of Atherosclerosis

- **Coronary heart disease**
  - Angina pectoris, myocardial infarction, sudden cardiac death
- **Cerebrovascular disease**
  - Transient ischaemic attacks, stroke
- **Peripheral vascular disease**
  - Intermittent claudication, gangrene
The End