Inflammation, Atherosclerosis, and Coronary Artery Disease

*Introduction*

Atherosclerosis, the main cause of coronary artery disease (CAD), is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes.

• **Atherosclerosis is characterized by the accumulation of cholesterol** deposits in macrophages in large- and medium-sized arteries. This deposition leads to a proliferation of certain cell types within the arterial wall that gradually impinge on the vessel lumen and impede blood flow. This process may be quite insidious lasting for decades until an atherosclerotic lesion, through physical forces from blood flow, becomes disrupted and deep arterial wall components are exposed to flowing blood, leading to thrombosis.
• **Epidemiology**
Cardiovascular diseases are expected to be the main cause of death globally within the next 15 years owing to a rapidly increasing prevalence in developing countries and eastern Europe and the rising incidence of obesity and diabetes in the Western world. Cardiovascular diseases cause *38 percent of all deaths in North America* and are the most common cause of death in European men under 65 years of age and the second most common cause in women. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.

• **Risk factors**
1. **AGE.** Although it is not subject to modification, age is among the most important risk factors for predicting incident cardiovascular disease. This concept is best illustrated if one considers that the average risk of developing cardiovascular disease for a 30-year-old male is 3% but rises some sevenfold to 21% for a comparable individual aged 60 yr.

2. **GENDER.** Numerous observational studies have indicated that males exhibit excess risk for cardiovascular disease compared with age-matched women. There has been considerable speculation that estrogens offer a “protective” effect to women, as cardiovascular disease accelerates in women after menopause. However, this speculation has been difficult to substantiate, as the treatment with estrogen has not reduced the incidence of cardiovascular disease of postmenopausal women.
3. OBESITY. There is now a growing appreciation that obesity is a condition that increases the incident risk of cardiovascular disease. The exact mechanism(s) to explain this phenomenon, however, are controversial. A number of other risk factors for cardiovascular disease, such as hypertension, low HDL cholesterol, and diabetes mellitus, often coexist with obesity. **This relation between obesity and cardiovascular disease has become of considerable concern as the prevalence of obesity in the developed world is increasing at an alarming rate.**

4. SMOKE. Recently, the reports estimates that smoking increases atherosclerotic disease by 50% and **doubles the incidence of coronary artery disease.** There is now considerable confidence that smoking is causally related to coronary artery disease, as smoking cessation is quite effective in lowering the future risk of the disease. **In fact, the risk of heart attack in ex-smokers approaches that of nonsmokers in only 2 years.**

5. HYPERTENSION. Hypertension is defined as a systolic blood pressure in excess of 140 mmHg or a diastolic blood pressure above 90 mmHg. The current estimates indicate that the elderly are particularly predisposed to hypertension, with up to 75% of people over 75 years of age qualifying for this diagnosis. **There appears to be an approximately linear relation between blood pressure elevation and the increased incidence of atherosclerotic vascular disease.**

6. DIABETES MELLITUS. Approximately 17 million people in the United States are diabetic. In patients with diabetes, **the risk of coronary atherosclerosis is 4 fold greater than in nondiabetics** despite controlling for other risk factors. A number of other known risk factors for coronary disease, such as hypertension and abnormal lipids, are also more common in diabetics than the general population, but no more than 25% of the risk excess can be attributed to these known risk factors. **Thus diabetes represents a major contributing factor to atherosclerosis.**
7) **SERUM CHOLESTEROL.** The association between LDL cholesterol and atherosclerosis has been established based, in part, on an experiment of nature. **Familial hypercholesterolemia** is an autosomal dominant disorder that affects 1 in 500 persons from the general population. Heterozygotes for this disease manifest a fourfold elevation in plasma LDL cholesterol that is due to a functional impairment of the LDL receptor, resulting in a defect in LDL clearance. Homozygotes for this disorder demonstrate a fivefold elevation in plasma cholesterol that produces precocious atherosclerosis. In heterozygotes, 85% of individuals have experienced a myocardial infarction by the age of 60, and this age is reduced to 15 yr in homozygous. In contrast, the relation between **HDL cholesterol** and atherosclerosis is an inverse one. The causal nature of this association is also supported by an experiment of nature, Tangier disease (682). This autosomal codominant condition is characterized by the essential absence of HDL cholesterol levels due to a defect in the ATP binding cassette transporter-1 that impairs cholesterol efflux from cells. Thus considerable evidence supports the inverse relation between coronary artery disease and serum levels of HDL cholesterol.
Figure 1, panel A and B
Atherosclerotic lesion in a human artery
Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood.
Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in (the asterisk/circle indicates cholesterol crystals).
(Courtesy of Dr. Erling Falk, University of Aarhus, Aarhus, Denmark.)
The structure of the atherosclerotic lesion

- Atherosclerotic lesions (atheromata or atheroma) are asymmetric focal thickenings of the innermost layer of the artery, the intima (Fig. 1). The atheroma is preceded by a fatty streak, an accumulation of lipid-laden macrophages beneath the endothelium. Fatty streaks are prevalent in young people, never cause symptoms, and may progress to atheromata or eventually disappear.

- Plaques contain a central lipid core that is most often hypocellular and may even include crystals of cholesterol that have formed from necrotic foam cells. In this late stage of lesion development, residual foam cells may be difficult to see but have often left the core with an abundant quantity of tissue factor, an important activator of the clotting cascade. This lipid core is separated from the arterial lumen by a fibrous cap and proliferative tissue that consists of extracellular matrix, smooth muscle cells and inflammatory cells.

- Vascular endothelial cells cover the atheroma.

- Many of the immune cells exhibit signs of activation and produce inflammatory cytokines.
FIG. 2. *Response-to-injury hypothesis of atherosclerosis.* In this hypothesis atherosclerosis begins with endothelial injury or dysfunction (A) that is characterized by **enhanced endothelial permeability** and LDL deposition in the subendothelial space. This is followed by leukocyte adhesion and transmigration across the endothelium. In intermediate stages (B), atherosclerosis is characterized by foam cell formation and an inflammatory response including T-cell activation, the adherence and aggregation of platelets, and further entry of leukocytes into the arterial wall along with migration of smooth muscle cells into the intima. Finally, advanced atherosclerosis (C) is characterized by continued macrophage accumulation, fibrous cap formation, and necrosis in the core of the lesion.
The “response-to-injury” hypothesis

In the “response-to-injury” hypothesis, the initial step in atherogenesis is endothelial denudation. For example, injury enhances endothelial adhesiveness for leukocytes and platelets and alters the local vascular anticoagulant milieu to a procoagulant one. Recruited leukocytes and platelets then release cytokines, vasoactive agents, and growth factors that promote an inflammatory response that is characterized by migration of smooth muscle cells into the intima and their proliferation to form an intermediate lesion. Another component of the inflammatory response is the recruitment of macrophages into the arterial wall (Fig. 2. These macrophages take up deposited LDL lipid to form lipid-laden “foam cells,” the hallmark of early atherosclerosis. The process of lipid accumulation and foam cell formation perpetuates an inflammatory response that perpetuates macrophage and lymphocyte recruitment. More recently, it has become clear that endothelial desquamation is not common and that an intact endothelial cell layer covers developing atherosclerotic lesions. These facts, among others, promoted refinement of the initial hypothesis such that endothelial dysfunction is sufficient to initiate atherogenesis through increased endothelial permeability to atherogenic lipoproteins. In fact, the rate of LDL entry into the arterial wall is rather uniform, but the accumulation of atherogenic lipoproteins is concentrated in areas that are predisposed to future lesion development. Such lesion-prone sites tend rather to demonstrate an enhanced retention of atherogenic apolipoprotein B-containing lipoproteins. Such observations have prompted alternative hypotheses for the initiation of atherosclerosis (Fig. 3).
The response-to-retention hypothesis
This hypothesis submits that the lipoprotein retention is the inciting event for atherosclerosis. The retention of lipoproteins within the arterial wall, however, appears tightly linked to components of the extracellular matrix. **Apolipoprotein B-100, the single protein associated with LDL, is retained within the arterial wall in close association with arterial proteoglycans,** supporting an important role for proteoglycan binding in the retention of apolipoprotein B-containing lipoproteins in the early stages of atherosclerosis. Most importantly, aggregated LDL is avidly taken up by macrophages and smooth muscle cells and thus can support foam cell formation. Thus many features of atherosclerosis can be attributed to **enhanced retention of LDL within the arterial wall and its association with proteoglycans.**
The oxidative modification hypothesis

The oxidative modification hypothesis focuses on the concept that LDL in its native state is not atherogenic. **However, LDL modified chemically is readily internalized by macrophages through a so-called “scavenger receptor” pathway.** Exposure to vascular cells in medium that contains transition metals also results in modification of LDL such that it serves as a ligand for the scavenger receptor pathway. It is now clear that one mechanism whereby cells in vitro render LDL a substrate for the scavenger receptor pathway is via oxidation of LDL lipids and the resulting modification of apolipoprotein B-100. These observations form the basis for the oxidative modification hypothesis of atherosclerosis (Fig. 4), **in which LDL traverses the subendothelial space of lesion-prone arterial sites.** During this process, LDL lipids are subject to oxidation and, as a consequence, apolipoprotein B-100 lysine groups are modified so that the net negative charge of the lipoprotein particle increases. This modification of apolipoprotein B-100 renders LDL susceptible to macrophage uptake via a number of scavenger receptor pathways producing cholesterol ester-laden foam cells. It is this accumulation of foam cells that forms the nidus of a developing atherosclerotic lesion.
FIG. 4. **Oxidative modification hypothesis** of atherosclerosis. LDL becomes entrapped in the subendothelial space where it is subject to oxidative modification by resident vascular cells such as smooth muscle cells, endothelial cells, and macrophages. Oxidized LDL stimulates monocyte chemotaxis (A), prevents monocyte egress (B), and supports foam cell formation (C). Once formed, oxidized LDL also results in endothelial dysfunction and injury (D), and foam cells become necrotic due to the accumulation of oxidized LDL (E).
Fig. 2. Activating effect of LDL infiltration on inflammation in the artery.
In patients with hypercholesterolemia, excess LDL infiltrates the artery and is retained in the intima, particularly at sites of hemodynamic strain. Oxidative and enzymatic modifications make the lipids able to activate endothelial cells, which express leukocyte adhesion molecules. The modified LDL particles are taken up by scavenger receptors of macrophages, which evolve into foam cells.
Atherosclerotic lesion in an artery.

Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate T cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (e.g., interferon-γ and tumor necrosis factor) that reduce the stability of plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagen and other components of the tissue matrix. These cells may also produce prothrombotic and procoagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.

Note that the atheroma is covered by endothelial cells.
Effects of T-Cell Activation on Plaque Inflammation.
Antigens presented by macrophages and dendritic cells (antigen-presenting cells) trigger the activation of antigen-specific T cells in the artery.
Most of the activated T cells produce Th1 cytokines (e.g., interferon-γ), which activate macrophages and vascular cells, leading to inflammation.
Regulatory T cells modulate the process by secreting antiinflammatory cytokines (such as interleukin-10 and transforming growth factor β).