



MERCK

HOME | ABOUT MERCK | PRODUCTS | NEWSROOM | INVESTOR INFORMATION | CAREERS | RESEARCH | LICENSING | THE F

This Publication Is Searchable

SEARCH

Atherosclerosis

A form of arteriosclerosis characterized by patchy subintimal thickening (atheromas) of medium and large arteries, which can reduce or obstruct blood flow.

The prevalence of clinical manifestations of atherosclerosis in general increases in postmenopausal women and begins to approach that in age-matched men.

The Merck Manual of Diagnosis and Therapy

Section 16 Cardiovascular Disorders

Chapter 201 Arteriosclerosis

Topics

[General]

Atherosclerosis

Nonatheromatous Arteriosclerosis

Pathology and Pathogenesis

Atherosclerotic plaque consists of accumulated intracellular and extracellular lipids, smooth muscle cells, connective tissue, and glycosaminoglycans. The earliest detectable lesion of atherosclerosis is the fatty streak (consisting of lipid-laden foam cells, which are macrophages that have migrated as monocytes from the circulation into the subendothelial layer of the intima), which later evolves into the fibrous plaque (consisting of intimal smooth muscle cells surrounded by connective tissue and intracellular and extracellular lipids).

Atherosclerotic vessels have reduced systolic expansion and abnormally rapid wave propagation. Arteriosclerotic arteries of hypertensive persons also have reduced elasticity, which is further reduced when atherosclerosis develops.

Two main hypotheses have been proposed to explain the pathogenesis of atherosclerosis: the lipid hypothesis and the chronic endothelial injury hypothesis. They are probably interrelated.

The lipid hypothesis postulates that an elevation in plasma LDL levels results in penetration of LDL into the arterial wall, leading to lipid accumulation in smooth muscle cells and in macrophages (foam cells). LDL also augments smooth muscle cell hyperplasia and migration into the subintimal and intimal region in response to growth factors. LDL is modified or oxidized in this environment and is rendered more atherogenic. Small dense LDL cholesterol particles are also more susceptible to modification and oxidation. The modified or oxidized LDL is chemotactic to monocytes, promoting their migration into the intima, their early appearance in the fatty streak, and their transformation and retention in the subintimal compartment as macrophages. Scavenger receptors on the surface of macrophages facilitate the entry of oxidized LDL into these cells, transferring them into lipid-laden macrophages and foam cells. Oxidized LDL is also cytotoxic to endothelial cell and may be responsible for their dysfunction or loss from the more advanced lesion.

An atherosclerosis model has been studied in monkeys fed a cholesterol-rich diet. Within 1 to 2 wk of inducing hypercholesterolemia, monocytes become attached to the surface of the arterial endothelium through the induction of specific receptors, migrate into the subendothelium, and accumulate lipid (hence, foam cells). Proliferating smooth muscle cells also accumulate lipid. As the fatty streak and fibrous plaque enlarge and bulge into the lumen, the subendothelium becomes exposed to the blood at sites of endothelial retraction or tear, and platelet aggregates and mural thrombi form. Release of growth factors from the aggregated platelets may increase smooth muscle proliferation in the intima. Alternatively, organization and incorporation of the thrombus into the atherosclerotic plaque may contribute to its growth.

The chronic endothelial injury hypothesis postulates that endothelial injury by various mechanisms produces loss of endothelium, adhesion of platelets to subendothelium, aggregation of platelets, chemotaxis of monocytes and T-cell lymphocytes, and release of platelet-derived and monocyte-derived growth factors that induce migration of smooth muscle cells from the media into the intima, where they replicate, synthesize connective tissue and proteoglycans, and form a fibrous plaque. Other cells (eg, macrophages, endothelial cells, arterial smooth muscle cells) also produce growth factors that can contribute to smooth muscle hyperplasia and extracellular matrix production.

These two hypotheses are closely linked and not mutually exclusive. Modified LDL is cytotoxic to cultured endothelial cells and may induce endothelial injury, attract monocytes and macrophages, and stimulate smooth muscle growth. Modified LDL also inhibits macrophage mobility, so that once macrophages transform into foam cells in the subendothelial space they may become trapped. In addition, regenerating endothelial cells (after injury) are functionally impaired and increase the uptake of LDL from plasma.

The atherosclerotic plaque may grow slowly and over several decades may produce a severe stenosis or may progress to total arterial occlusion. With time, the plaque becomes calcified. Some plaques are stable, but others, especially those rich in lipids and inflammatory cells (eg, macrophages) and covered by a thin fibrous cap, may undergo spontaneous fissure or rupture, exposing the plaque contents to flowing blood.

These plaques are deemed to be unstable or vulnerable and are more closely associated to the onset of an acute ischemic event. The ruptured plaque stimulates thrombosis; the thrombi may embolize, rapidly occlude the lumen to precipitate a heart attack or an acute ischemic syndrome, or gradually become incorporated into the plaque, contributing to its stepwise growth.

Risk Factors

Major nonreversible risk factors for atherosclerosis include age, male sex, and family history of premature atherosclerosis. Major reversible risk factors are discussed below. Evidence also strongly suggests that physical inactivity is associated with an increased risk of CAD. Although personality type has been proposed as a risk factor, its role is controversial.

Abnormal serum lipid levels: Elevated levels of low density lipoprotein (LDL) and reduced levels of high density lipoprotein (HDL) predispose to atherosclerosis. The association of total serum cholesterol and LDL cholesterol levels with the risk of CAD is direct and continuous. HDL levels are inversely correlated with CAD risk. The main cause

of reduced HDL are cigarette smoking, obesity, and physical inactivity. Low HDL is also associated with the use of androgenic and related steroids (including anabolic steroids), β -blockers, hypertriglyceridemia, and genetic factors.

Cholesterol level and CAD prevalence are influenced by genetic and environmental factors (including diet). Persons with low serum cholesterol levels who move from a country with low CAD prevalence to a country with a high CAD prevalence and who tend to alter their eating habits accordingly develop higher serum cholesterol levels and an increased risk of CAD.

Hypertension: High diastolic or systolic BP is a risk factor for stroke, MI, and cardiac and renal failure. The risk associated with hypertension is lower in societies with low average cholesterol levels.

Cigarette smoking: Smoking increases the risk of peripheral artery disease, CAD, cerebrovascular disease, and graft occlusion after reconstructive arterial surgery. Smoking is particularly hazardous in persons at increased cardiovascular risk. There is a dose relationship between the risk of CAD and the number of cigarettes smoked daily. Passive smoking may also increase the risk of CAD. Men and women are both susceptible, but the risk for women may be greater. Nicotine and other tobacco-derived chemicals are toxic to vascular endothelium.

Cigarette smoking increases LDL and decreases HDL levels, raises blood carbon monoxide (and could thereby produce endothelial hypoxia), and promotes vasoconstriction of arteries already narrowed by atherosclerosis. It also increases platelet reactivity, which may favor platelet thrombus formation, and increases plasma fibrinogen concentration and Hct, resulting in increased blood viscosity.

Diabetes mellitus: Both insulin-dependent and non-insulin-dependent diabetes mellitus are associated with earlier and more extensive development of atherosclerosis as part of widespread metabolic derangement that includes dyslipidemia and glycosylation of connective tissue. Hyperinsulinemia damages vascular endothelium. Diabetes is a particularly strong risk factor in women and significantly negates the protective effect of female hormones.

Obesity: Some studies have found that obesity, particularly truncal obesity in men, is an independent risk factor for CAD. Hypertriglyceridemia is commonly associated with obesity, diabetes mellitus, and insulin resistance and appears to be an important independent risk factor in persons with lower LDL or HDL levels and in the nonelderly. Not all triglyceride elevations are likely to be atherogenic. Smaller, denser very low density lipoprotein particles may carry greater risk.

Physical inactivity: Several studies have associated a sedentary lifestyle with increased CAD risk, and others have shown that regular exercise may be protective.

Hyperhomocysteinemia: Elevated blood homocysteine due to a genetically determined decrease in its metabolism may cause vascular endothelial injury, which predisposes the vessels to atherosclerosis (see also Ch. 201 and **Hyperhomocysteinemia** in Ch. 132).

Chlamydia pneumoniae infection: *Chlamydia pneumoniae* infection or viral infection

may play a role in endothelial damage and chronic vascular inflammation that may lead to atherosclerosis.

Symptoms and Signs

Atherosclerosis is characteristically silent until critical stenosis, thrombosis, aneurysm, or embolus supervenes. Initially, symptoms and signs reflect an inability of blood flow to the affected tissue to increase with demand (eg, angina on exertion, intermittent claudication). Symptoms and signs commonly develop gradually as the atheroma slowly encroaches on the vessel lumen. However, when a major artery is acutely occluded, the symptoms and signs may be dramatic. Specific ischemic disorders related to occlusion are described elsewhere in §16 and in Ch.174.

Diagnosis

Atherosclerosis is suspected based on the risk factors and on its symptoms and signs, of which there may be few. Atheromatous obstruction is commonly confirmed by arteriography or Doppler ultrasonography. Diagnosis of specific manifestations (eg, CAD) is described elsewhere in *The Manual*.

Hyperlipidemia (see also Ch 1.5) commonly presents with symptoms and signs of premature obliterative atherosclerosis affecting the brain (cerebral transient ischemic attacks or stroke), heart (angina pectoris or MI), intestine, and lower extremities (intermittent claudication). Xanthomas (in the creases of hands and elbows and along tendon sheaths) and xanthelasmas are sometimes associated with hyperlipidemia, particularly of the familial type. Recurrent attacks of acute pancreatitis, with or without alcoholism, suggest hypertriglyceridemia. A family history of hyperlipidemia or onset of cardiovascular disease before age 60 is further reason to look for premature atherosclerosis

Prevention

The most effective way to prevent the cardiovascular and cerebrovascular complications of atherosclerosis and the associated arterial thrombosis is to prevent atherosclerosis itself.

Reversible risk factors for atherosclerosis are abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, hyperhomocysteinemia, and possibly *C. pneumoniae* infection. Increased understanding of these risk factors and their role in the etiology, pathogenesis, and course of atherosclerosis will lead to more focused intervention for preclinical or overt atherosclerotic disease and will thereby contribute to further declines in morbidity and mortality.

Abnormal serum lipid levels: At least 20 randomized trials show that lowering serum LDL cholesterol levels slows progression or induces regression of CAD and reduces coronary events. The benefits are greatest in patients at greater risk of CAD (ie, those with other risk factors, eg, hypertension, cigarette smoking) and in those with the most elevated cholesterol levels. Lowering serum LDL is also beneficial in those with preexisting CAD, even if their LDL levels are not elevated. Recent trials have shown a significant decrease in cardiovascular and total mortality when the statins are used to lower cholesterol. Statins also slow the progression of CAD (shown by angiography) in patients with arterial bypass grafts and elevated LDL cholesterol levels. Guidelines for screening and treatment of mild, moderate, and severe hypercholesterolemia are discussed in Ch. 15.

Hypertension: Treatment of patients with elevated BP reduces stroke and overall mortality, but the effect on coronary event reduction is less striking. Pooled analysis of all studies of BP lowering shows a risk reduction of 40% in stroke, 8% in MI, and 10% in cardiovascular mortality.

Cigarette smoking: Smoking cessation should be encouraged whenever possible. The risk in persons who quit, regardless of how long they smoked, is half of that in those who continue to smoke. Smoking cessation also decreases morbidity and mortality in patients with peripheral vascular disease and decreases mortality after coronary bypass surgery and in post-MI patients.

Diabetes mellitus: Although tight glycemic control reduces the risk of microvascular complications of diabetes, the effects on macrovascular disease and atherosclerosis are less clear. Hyperlipidemia and hypertension are more common in diabetics, and these risk factors together with hyperinsulinemia may contribute to the increased CAD risk.

Obesity: Weight loss raises HDL levels and should be encouraged when possible.

Physical inactivity: Several randomized trials have demonstrated that moderate exercise performed consistently reduces the clinical manifestations and mortality of CAD in high-risk patients. Regular exercise has also been reported to lower the incidence of MI and death, but it is uncertain whether the association is causal or merely indicates that healthier persons are more likely to exercise regularly. Regular exercise increases HDL levels and can lower BP.

Hyperhomocysteinemia: Hyperhomocysteinemia in the presence or absence of low plasma concentrations of vitamin B can be corrected by folate administration with or without vitamin B supplementation. However, it is unclear whether this treatment is beneficial.

***Chlamydia pneumoniae* infection:** Understanding of the role of infection and inflammation in atherosclerosis and its complications is improving. Trials are underway to assess whether antibiotic treatment will impact the infection's clinical manifestations.

Treatment

Treatment of established atherosclerosis is directed at its complications (eg, angina pectoris, MI, arrhythmias, heart failure, kidney failure, ischemic stroke, and peripheral arterial occlusion). These subjects are covered elsewhere in *The Manual*.