As with hyperlipidemia, hypertension (systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg) contributes to the risk of CAD-related complications. Hypertension, probably through sheer stress, causes vessel injury that supports the development of atherosclerotic plaque. Increasing severity of hypertension is associated with greater risk of CAD. Control of hypertension is associated with a reduced risk of CAD.

Diabetes mellitus is a prominent risk factor for CAD, and the disease is becoming epidemic. Diabetes mellitus typically is associated with other risk factors, such as elevated triglycerides, reduced HDL, and hypertension, which accounts for the enhanced risk of CAD-related problems in diabetic patients. It is not clear that control of hyperglycemia in diabetic patients translates into a reduced risk of CAD, but the presence of diabetes mellitus drives the need to ensure good treatment of other modifiable risk factors.

Cigarette smoking has long been known as a significant risk factor for both CAD and lung cancer. Cigarette smoking is associated with increased platelet reactivity and increased risk of thrombosis, as well as lipid abnormalities. This addictive habit is modifiable, and smoking cessation can lead to a decrease in CAD event rates by 50% in the first 2 years of cessation.

Similar to diabetes mellitus, obesity (body mass index >30 kg/m^2) is associated with risk factors such as hypertension, hyperlipidemia, and glucose intolerance. Although multiple risk factors are frequently present in obese people, obesity itself carries some independent risk for CAD. The location and type of adipose tissue appear to influence CAD risk, with abdominal obesity posing a greater risk for CAD in men and women.

Numerous clinical studies have shown the benefit of regular aerobic exercise in decreasing the risk for CAD-related problems, both in the people without known CAD and in those with the disease. Sedentary lifestyles carry an increased risk that is modifiable through exercise.

Another common attribute of life, alcohol consumption, can influence the risk of CAD in both directions. One to two ounces of alcohol per day may reduce the risk for CAD-related events, but more than 2 ounces of alcohol per day is associated with an increased risk of events. Lower levels of alcohol consumption can increase HDL levels, although it is not clear that this is the mechanism of benefit. In contrast, excessive alcohol consumption is associated with hypertension, a definite risk for CAD, although other effects of high-dose alcohol may also be at play.

Additional factors that may have some role in adding CAD risk include lipoprotein(a) and homocysteine. Lipoprotein(a) is structurally similar to plasminogen and may interfere with the activity of plasmin, thus contributing to a prothrombotic state. Hyperhomocysteinemia has been associated with increased vascular risks, including coronary, cerebral, and peripheral vascular disease. It is not clear that a causal link exists, and the use of folic acid supplementation to lower homocysteine levels has not been shown to reduce the risk of MI or stroke.

C-reactive protein (CRP) is a marker of systemic inflammation, and it indicates an increased risk for coronary plaque rupture. High-sensitivity assays for CRP (hsCRP) have measured elevated levels that correlate with risk for MI, stroke, peripheral vascular disease, and sudden cardiac death. Another marker for the presence of CAD is coronary calcification. The process of atherosclerosis is often associated with deposition of calcium within the plaque. Coronary artery calcification can be detected by fluoroscopy during cardiac catheterization as well by computed tomography (CT) scanning using either multidetector computed tomography (MDCT) or electron beam computed tomography (EBCT). CT technology allows for a quantitative measure of coronary calcium deposits that correlates with the probability of having significant obstructive lesions. The value of routine use of either hsCRP or CT for coronary calcification remains unclear, but patients in whom coronary calcification is identified should be approached with aggressive risk-factor modification.

PATHOLOGY

The process of atherosclerosis is known to begin at a young age. Autopsies of teenagers frequently demonstrate the presence of atherosclerotic changes in coronary arteries. Atherosclerosis is a process linked to the subintimal accumulation of small lipoprotein particles that are rich in LDL. Subintimal deposits of LDL are oxidized, setting off a cascade of events that culminate in not only the development of atherosclerotic plaque but also vascular inflammation. Vascular inflammation drives progression of atherosclerosis as well as the potential rupture of plaque leading to vessel occlusion. The process of lipoprotein uptake by the vessel wall is enhanced by vascular endothelial injury, which may be triggered by hypercholesterolemia, the toxic effects of cigarette smoking, sheer stresses associated with hypertension, or vascular effects of diabetes mellitus.

Oxidized LDL aggregates trigger the expression of endothelial cell surface adhesion molecules, including vascular adhesion molecule-1, intracellular adhesion molecule-1, and selectins, which results in the binding of circulating macrophages to the endothelium. In response to cytokines and chemokines released by endothelial and smooth muscle cells, macrophages migrate into the subintimal region, where they ingest oxidized LDL aggregates. These LDL-laden macrophages are also called foam cells (based on the microscopic appearance), and the accumulation of foam cells represents the development of atherosclerosis.

Foam cells break down, releasing pro-inflammatory substances that promote ongoing accumulation of both macrophages and T lymphocytes. This process potentiates the development of atherosclerotic plaque. Growth factors are also released that promote smooth muscle cell and fibroblast proliferation. The net result is the development of a fibrous cap, which covers a lipid-rich core.

Important contributors to the pathologic evolution of atherosclerotic plaque include impaired endothelial synthesis of nitric oxide and prostacyclin, both of which play major roles in vascular homeostasis. The loss of these vasodilators leads to abnormal regulation of vascular tone and also plays a role in evolving a local prothrombotic state. Platelets adhere to areas of vascular injury and are not only prothrombotic but also release growth factors that help drive the aforementioned proliferation of smooth muscle cells and fibroblasts. A key structural constituent of the fibrous cap is collagen, and its synthesis by fibroblasts is inhibited by cytokines elaborated by accumulating T lymphocytes. Foam cell degradation also releases matrix metalloproteinases that break down collagen, leading to weakening of the fibrous core