Advances in Clinical Medicine

Pathogenesis of Atherosclerosis

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Cardiovascular disease is the leading cause of death in the United States. According to numbers compiled by the American Heart Association, nearly one of every two Americans dies of cardiovascular disease. For example, in 1987, 976,706 (46%) of the estimated 2,127,000 deaths recorded in the United States were attributable to diseases of the heart and blood vessels [1]. Most of these deaths can be attributed to atherosclerosis and its ensuing complications. The pathogenesis of atherosclerosis is not completely understood. Nevertheless, the purpose of this review is to provide an overview of how an atherosclerotic lesion might develop on the basis of our current understanding. This overview will focus on one hypothesis of atherosclerosis development, the modified response-to-injury hypothesis. Several additional hypotheses will be described briefly. These descriptions can serve as a framework on which researchers can build a more complete understanding of the processes involved in this complicated, multifactorial disease.

Modified Response-to-Injury Hypothesis

The original response-to-injury hypothesis, as proposed in 1976 [2], hypothesized that atherosclerotic lesions developed in response to factors released from platelets that had adhered to sites of hypercholesterolemia-induced endothelial denudation. Since then, the original hypothesis has undergone several revisions [3, 4], resulting in the scenario described below.

Initiation of Atherosclerosis: Endothelial Injury

The luminal surface of a normal artery is covered with a monolayer of endothelial cells attached to a subendothelial matrix [5] (Fig. 1). These endothelial cells serve several important physiologic functions that retard the development of atherosclerosis [6–10] (Table 1). For example, arterial endothelial cells are joined together tightly to form a semipermeable barrier that limits the efflux of large molecules, such as low-density lipoprotein, into the subendothelial spaces [4, 11]. These endothelial cells also provide the artery with a nonthrombogenic surface; platelet deposition is inhibited by the negative surface charge of the endothelium and by endothelial cell release of the platelet inhibitors prostacyclin (PGI_2) and endothelium-derived relaxing factor or nitric oxide (EDRF-NO). PGI_2 and EDRF-NO, released by the endothelium, also relax smooth muscle cells in the media and thereby increase the diameter of the lumen. Endothelial cells also secrete factors that inhibit smooth muscle cell migration and proliferation; these factors include heparan sulfate and EDRF-NO. Finally, endothelial cells provide the artery with a luminal surface to which monocytes and lymphocytes cannot adhere.

In contrast to normal endothelial cells, injured endothelial cells are dysfunctional (Table 1). Injured endothelial cells appear morphologically different from normal endothelial cells; unlike normal cells, they are typically not aligned in the direction of blood flow, and they have fewer intercellular attachments, resulting in increased permeability [12]. Injured endothelial cells also are more thrombogenic than are normal endothelial cells because of their diminished production of PGI_2 and EDRF-NO [13]. Injured endothelial cells promote vascular smooth muscle

Received July 7, 1994; accepted after revision October 7, 1994.

This is another in the continuing series of nonradiology articles concerning recent developments in the clinical and basic sciences. It is designed to help radiologists keep abreast of advances in medicine to ensure that their understanding of disease stays current.

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AJR 1995;164:553–558 0361–803X/95/1643–553

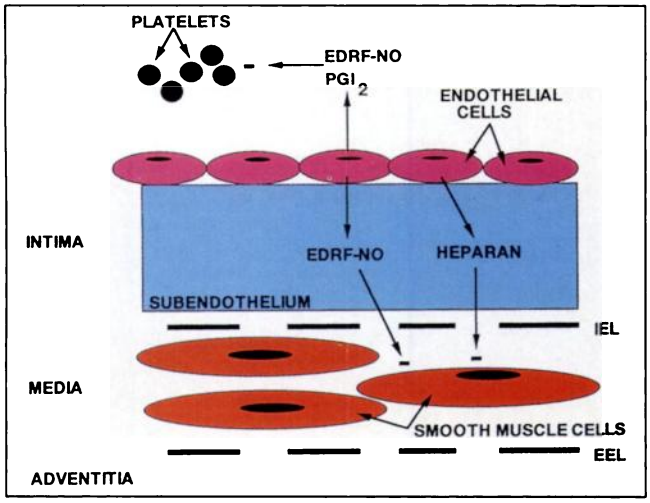

Fig. 1.—Diagram of normal muscular artery. Intima is composed of endothelial cells and subendothelial matrix. Media is demarcated by internal elastic lamina (IEL) and external elastic lamina (EEL) and consists of vascular smooth muscle cells tethered together by an extracellular matrix of elastin and collagen. Components of adventitia are not shown. Endothelium of normal artery secretes several physiologically important factors, including inhibitors of platelet adhesion and aggregation—prostacyclin (PGI_2) and endothelium-derived relaxing factor or nitric oxide (EDRF-NO)—and inhibitors of smooth muscle cell migration and proliferation—heparan sulfate and EDRF-NO.

cell migration and proliferation by releasing less EDRF-NO and by secreting platelet-derived growth factor (PDGF) and endothelin-1 [14]. Finally, injured endothelial cells promote the recruitment of macrophages by secreting monocyte chemoattractant protein-1, MCP-1, and by expressing cell surface receptors, or selectins, to which monocytes can bind [4, 6, 15].

The probability of developi.ng atherosclerosis is highly correlated with several risk factors, including age, sex, hypertension, hypercholesterolemia, diabetes, obesity, smoking, physical inactivity, and stress [16, 17]. Although it is unclear exactly how these risk factors promote atherosclerosis, endothelial cell injury most likely is involved [6, 7, 9]. In particular, considerable evidence indicates that these risk factors initiate the atherosclerotic process by blunting the release of EDRF-NO by the endothelium [9]. For example, clinical studies have demonstrated that endothelial cell release of EDRF-NO is diminished with aging [18], smoking [19], hypercholesterolemia [20], essential hypertension [21], and diabetes [22]. Furthermore, animal studies have revealed diminished endothelial cell production of EDRF-NO in hypercholesterolemic animals before any morphologic changes take place in the artery [23], suggesting that this change may be a causative factor in atherosclerosis. This suggestion is supported further by experimental animal studies showing that the inhibition of nitric oxide synthase, the enzyme responsible for EDRF-NO synthesis, increased the severity of atherosclerosis [24], whereas an increase in EDRF-NO synthesis achieved through supplementation of the diet with L-arginine, the substrate for EDRF-NO production, diminished the severity of atherosclerosis [25].

Fatty Streak Formation

Fatty streaks are the earliest visible atherosclerotic lesions and generally are found first in the vicinity of arterial branch points, where irregular hemodynamic shear stresses induce endothelial cell injury [26]. Fatty streaks are relatively flat intimal lesions, consisting of macrophages and smooth muscle cells that contain droplets of lipids that give these cells a foamy appearance [4, 12, 27, 28] (Fig. 2). The endothelial cells that cover fatty streaks often are morphologically abnormal, suggesting that the cells are dysfunctional. Precursors of these lesions, microscopic type I, or initial, lesions, can be found in children as early as age 1 [28]. However, not all initial lesions develop into fatty streaks, nor do all fatty streaks develop into more advanced fibrotic lesions. In addition, experimental studies suggest that fatty streaks can regress [29, 30].

TABLE 1: Functions of Vascular Endothelium in Normal and Injured States

Function	Normal Endothelium	Injured Endothelium
Permeability	Tight endothelial cell junctions prevent passage of large molecules into subendothelium.	Loss of tight junctions increases penetration of large molecules, e.g., low-density lipoprotein, into subendothelial space.
Thrombogenicity	Platelets are repelled by negative surface charge of endothelial cells. Platelet aggregation is inhibited by endothelial secretion of PGI_2 and EDRF-NO. Thrombolysis is promoted by secretion of tPA.	Function is converted from antithrombotic to prothrombotic. PGI_2, EDRF-NO, and tPA secretions are diminished. Plasminogen activator inhibitor and tissue factor secretions are increased.
Vasomotor tone	Vasodilation is promoted by secretion of PGI_2 and EDRF-NO.	Vasoconstriction is promoted by diminished secretion of PGI_2 and EDRF-NO and by increased secretion of endothelin-1.
Vascular smooth muscle migration and proliferation	Smooth muscle cell migration and proliferation are inhibited by secretion of heparan sulfate and EDRF-NO.	Smooth muscle proliferation is promoted by diminished secretion of EDRF-NO and increased secretion of platelet-derived growth factor and endothelin-1.
Inflammation	Inflammatory cells fail to adhere to normal endothelium.	Leukocytes are recruited to sites of injury by expression on cell surface of proteins (endothelium-leukocyte adhesion molecule and intercellular adhesion molecule). T lymphocytes are recruited by endothelial cells expressing major histocompatibility complex class II proteins.

Note.—PGI_2 = prostacyclin, EDRF-NO = endothelium-derived relaxing factor or nitric oxide, tPA = tissue plasminogen activator.

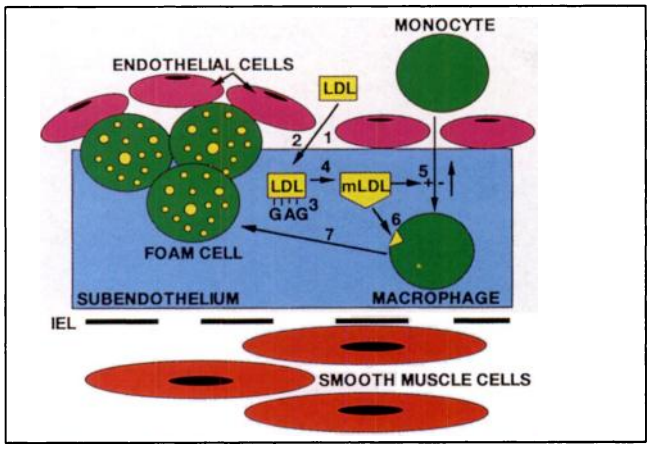

Fig. 2.—Diagram of fatty streak and processes that contribute to its formation. Fatty streak is composed of foam cells of monocyte/macrophage origin beneath dysfunctional endothelium. Appearance of macrophage-derived foam cells is culmination of series of steps beginning with injury-induced increase in endothelial cell permeability (1). Low-density lipoprotein (LDL) penetrates permeable endothelium into subendothelium (2), where it binds to glycosaminoglycans (GAG) (3) and can undergo modification to form modified LDL (mLDL) (4). Macrophages, recruited to the area by presence of mLDL (5), take up mLDL via scavenger receptors (6), resulting in formation of foam cells (7). IEL = internal elastic lamina.

Fatty streaks typically develop at sites at which endothelial injury has increased endothelial cell permeability enough to allow low-density lipoprotein and other large molecules to penetrate the subendothelium [4, 31] (Fig. 2). Once beneath the endothelium, low-density lipoprotein, which has a high affinity for glycosaminoglycans, becomes trapped. This trapping increases the duration of low-density lipoprotein retention in the subendothelium and thereby increases the probability that the low-density lipoprotein will undergo a series of chemical changes that result in the formation of modified low-density lipoprotein [11, 32]. As this modification most likely involves oxidation by oxygen free radicals or by lipoxygenases of endothelial cell or macrophage origin, considerable interest has focused on antioxidants (probucol, vitamin E, vitamin C, β-carotene, and red wine) as inhibitors of atherosclerosis [11, 32–34].

The modification of low-density lipoprotein is important for at least three reasons [4, 6, 12]. First, modified low-density lipoprotein is a chemoattractant that, in conjunction with other chemoattractant molecules, such as monocyte chemoattractant protein secreted by injured endothelial cells, recruits circulating monocytes to the subendothelium, where they become macrophages (Fig. 2). Monocyte recruitment is directed further by adhesion molecules—endothelium-leukocyte adhesion molecule and vascular cell adhesion molecule—which are expressed on the luminal surface of injured endothelial cells. Second, modified low-density lipoprotein may inhibit the egress of macrophages from the lesion. Third, and most important, modification of low-density lipoprotein enables cells to take up large amounts of lipid. In contrast to low-density lipoprotein uptake, which is mediated by low-density lipoprotein receptors, which are under negative feedback control, modified low-density lipoprotein uptake is mediated by scavenger receptors, which are not subject to negative feedback regulation [32, 35]. As this modified low-density lipoprotein uptake is not saturable, large amounts of modified low-density lipoprotein can be incorporated into macrophages and smooth muscle cells, resulting in the formation of foam cells, so named because the lipid droplets found in the cytoplasm of these cells give them a foamy appearance.

Fibrotic Lesion Formation

The next stage in the development of an atherosclerotic lesion is the conversion of the fatty streak into a fibrotic lesion. Fibrotic lesions are characterized by a fibrotic cap composed of smooth muscle cells recruited from both the subendothelium and the media [4, 27, 28, 36] (Fig. 3). The smooth muscle cells of the fibrotic cap are embedded in connective tissue and characteristically contain little lipid (Fig. 4).

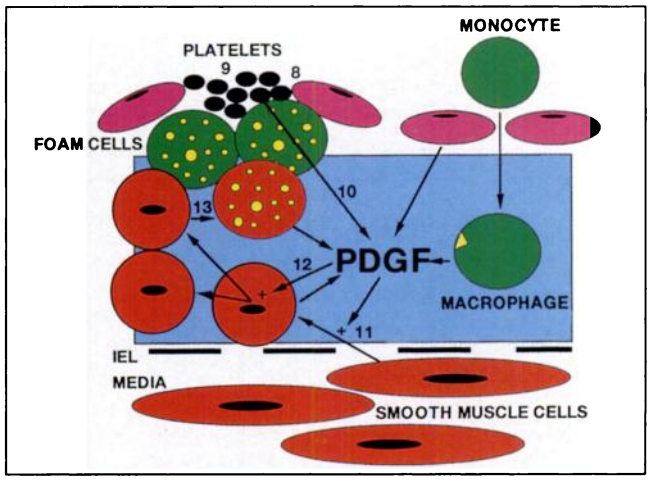

Fig. 3.—Diagram of smooth muscle cell recruitment to atherosclerotic lesion. Smooth muscle cells are recruited to atherosclerotic lesion from subendothelium and media. At sites of focal endothelial cell denudation (8), platelets adhere (9) and release platelet-derived growth factor (PDGF) (10). Chemoattractant properties of PDGF stimulate smooth muscle cells to migrate from media to intima (11), where mitogenic properties of PDGF stimulate smooth muscle cell proliferation (12). Some smooth muscle cells may take up lipid to form foam cells (13). IEL = internal elastic lamina.

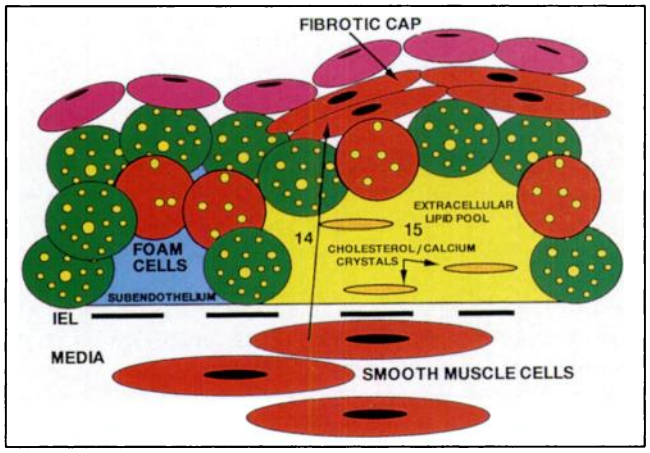

Fig. 4.—Diagram of fibrotic atherosclerotic lesion and processes that contribute to its formation. Fibrotic lesion is distinguished from fatty streak by presence of fibrotic cap of smooth muscle cells that have migrated to surface of lesion (14). Fibrotic lesion may have pools of extracellular material containing crystals of cholesterol and calcium (15). IEL = internal elastic lamina.

Other cells in the fibrotic cap include dysfunctional endothelial cells on the luminal surface of the fibrotic cap, macrophages, and T lymphocytes. Beneath the fibrotic cap, the fibrotic lesion consists of foam cells of macrophage and smooth muscle origin. In more advanced fibrotic lesions, the deeper layers of the plaque become necrotic, presumably because of the buildup of toxic lipids, the release of free radicals, and/or ischemia attributable to the increased diffusion distance between the tissue and the blood [4, 27] (Fig. 4). Calcium hydroxyapatite deposits usually are found in these deeper layers of the plaque, attributable either to the crystallization of calcium on preexisting cholesterol crystals or to the osteogenic activity of cells within the lesions [37].

One of the initial events responsible for the conversion of the fatty streak to a fibrotic lesion is the focal loss of endothelial cells covering the fatty streak [4, 12] (Fig. 3). This cell loss may result from shear stresses placed on the dysfunctional cells, from deformation of the arterial wall, or from toxins (free radicals or products of lipid oxidation) released by underlying foam cells. At the site of cell loss, platelets adhere to the underlying foam cells and subendothelial matrix and release a number of factors that promote lesion development. Heparinase, one of these platelet-derived factors, is an enzyme that degrades heparan sulfate, a polysaccharide in the extracellular matrix of the arterial wall that inhibits smooth muscle cell migration and proliferation [38] (Fig. 1). The combination of reduced heparan levels and diminished release of PGI_2 and EDRF-NO secondary to endothelial cell loss or injury may permit smooth muscle cells in the arterial media to convert from a contractile to a noncontractile, synthetic cell type [39]. Once the smooth muscle cells have undergone this change in phenotype, they are able to release enzymes that degrade the surrounding extracellular matrix, enabling them to migrate to the intima, where they can proliferate [4, 10]. Smooth muscle cell migration to the intima is under the direction of PDGF, a chemoattractant released from adherent platelets and from activated endothelial cells, macrophages, and smooth muscle cells. PDGF, in conjunction with other mitogens, including insulin growth factor and basic fibroblast growth factor, also stimulates some of these smooth muscle cells to undergo mitosis [4, 12].

Advanced Lesion Formation

The final stage in the development of an atherosclerotic lesion is the conversion of the fibrotic lesion into an advanced lesion, a lesion in which a thrombus has formed subsequent to either plaque ulceration or intraplaque hemorrhage [4, 27, 40, 41] (Fig. 5). Factors responsible for plaque fracture include turbulence or mechanical shear stresses, intraplaque hemorrhage attributable to rupture of the vasa vasorum, increased circumferential wall stress on the fibrotic cap attributable to the presence of the underlying lipid pool, and the release of matrix-degrading enzymes by macrophages present in the lesion [41–45].

Subsequent to plaque fracture, thrombosis ensues and involves platelet adhesion and aggregation as well as activation of the coagulation cascade [41, 46] (Fig. 5). The coagulation cascade is initiated by the exposure of blood to collagen within the plaque and by tissue factor (tissue thromboplastin), produced by endothelial cells and macrophages within the fibrotic lesion. Tissue factor enables factor VII to activate factor

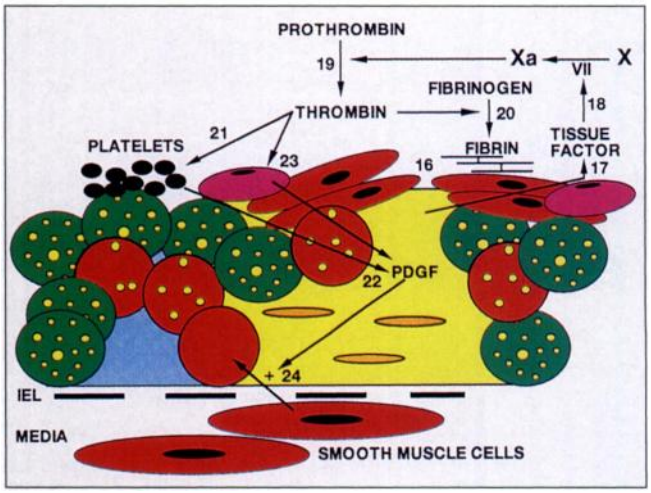

Fig. 5.—Diagram of advanced, complicated atherosclerotic lesion and processes that contribute to its formation. Complicated lesion is distinguished from fibrotic lesion by presence of fracture (16) that typically occurs in fibrotic cap overlying extracellular lipid pool. Subsequent to plaque fracture, release of tissue factor (17) stimulates extrinsic pathway of coagulation (18). Cascade involves generation of thrombin (19), which catalyzes fibrin formation (20), stimulates platelet aggregation (21) and platelet-derived growth factor (PDGF) release (22), and induces PDGF release from endothelial cells (23). PDGF promotes lesion development by recruiting additional smooth muscle cells to lesion (24). IEL = internal elastic lamina.

X, which then catalyzes the conversion of prothrombin to thrombin. Thrombin then catalyzes the conversion of fibrinogen to monomeric fibrin, which subsequently undergoes polymerization to stabilize the thrombus. Thrombin also stimulates cellular proliferation within the fractured lesion by promoting additional platelet deposition and PDGF release and by stimulating other cells in the lesion to synthesize and release PDGF [46]. Thrombosis may be potentiated further by lipoprotein (a), which inhibits thrombolysis by competitively inhibiting the conversion of plasminogen to plasmin [47].

Depending on the balance between thrombotic and thrombolytic processes, the thrombus may undergo one of several fates. The thrombus may undergo dissolution with no clinical sequelae, or it may be incorporated into the atherosclerotic lesion, resulting in lesion enlargement and clinical sequelae if the resultant stenosis is severe enough to limit blood flow through the artery. Plaque fracture also may result in clinical sequelae if the resultant thrombus becomes enlarged enough to occlude the artery or if it is sloughed off and travels as an embolus to a distal vessel [41, 44]. When large pieces of a thrombus are released, the thrombi typically occlude large muscular arteries. In contrast, when microscopic emboli, consisting of fibrin-platelet aggregates or cholesterol crystals, are released, they typically travel to smaller arteries and arterioles [48].

Alternative Hypotheses

In addition to the modified response-to-injury hypothesis outlined above, several alternative explanations for the genesis of atherosclerosis have been proposed. According to the monoclonal hypothesis, proposed in 1973 [49], the smooth muscle cells within an atherosclerotic lesion are derived from a stable transformed cell population. This hypothesis was tested by studying the expression of the enzyme glucose-6-phosphate

dehydrogenase in atherosclerotic lesions obtained from women, because the two X chromosomes in women code for different glucose-6-phosphate dehydrogenase isozymes and only one X chromosome is active within each cell. In support of this hypothesis, most of the lesions examined expressed only one isozyme, and different lesions expressed different isozymes.

Although several factors, including carcinogens or mutations, could elicit smooth muscle cell transformation, considerable attention has focused on herpesvirus-mediated cell transformation. Herpesviruses have been implicated in the development of atherosclerosis on the basis of several observations: herpesvirus antigens and nucleic acids have been detected in human atherosclerotic lesions; chickens infected with a herpesvirus develop atherosclerotic lesions very similar to those observed in humans (Marek's disease); herpesviruses can infect human vascular smooth muscle and endothelial cells in vitro; cells infected with herpesvirus exhibit altered cellular cholesterol metabolism, including reduced cholesterol ester hydrolysis and the accumulation of free and esterified cholesterol; and endothelial cells infected with herpesvirus exhibit enhanced monocyte adhesion [50–52]. Most recently, it was demonstrated that herpesviruses can transform human smooth muscle cells by inducing the expression of a viral protein, IE84, that prevents human tumor suppressor protein p53 from inhibiting the cell cycle [53].

Atherosclerosis also may be viewed as an immune response, because immunohistochemical studies have demonstrated that approximately 25% of the cells within the fibrotic cap are T lymphocytes and that many of these T lymphocytes are activated [54]. These activated T lymphocytes can release a number of factors, including interleukin-1 and interferon-γ, that can promote or retard the development of atherosclerotic lesions. The identities of the antigens responsible for stimulating these immune responses are unclear, but modified low-density lipoprotein and viral antigens have been implicated.

Implications for Radiologists

Because atherosclerosis is a progressive disease that involves changes in both morphology and chemical composition, various imaging techniques have been used to characterize atherosclerotic lesions. For example, angiography is used to localize and grade arterial stenoses. Angiography also is useful in distinguishing between simple and complex atherosclerotic lesions, if the lesions are viewed at the appropriate angle [55]. However, the results of several recent animal and clinical studies indicate that the severity of atherosclerosis is underestimated when angiography is used [56–58]. These studies found that, as atherosclerosis develops, the diseased arteries undergo a compensatory enlargement and, as a result, a reduction in lumen diameter is not apparent angiographically until the area occupied by the plaque represents approximately 40% of the area encircled by the internal elastic lamina. Beyond this point, the rate of compensatory enlargement differs for different arteries [59]. Although the mechanisms responsible for this compensatory enlargement are unknown, one suggestion is that arterial enlargement is a homeostatic response of the artery in an attempt to maintain the endothelial shear stress constant [60].

A second technique used to image atherosclerotic lesions is sonography. Transcutaneous sonography can provide good images of both the lumen and the distal wall of noncalcified superficial arteries but is unable to show ulcerated plaques consistently [61]. Recent studies have shown that the intima-media thickness of the distal wall of the common carotid artery is correlated with the severity of atherosclerosis in the coronary arteries [62]. On the basis of this observation, the thickness of the distal wall of the carotid artery has been used to determine the effects of drug therapy on the progression or regression of atherosclerotic lesions [63]. Intravascular sonography can provide images of the arterial lumen, intima, and media and can be used to identify intimal flaps and areas of calcification, which tend to fracture during balloon angioplasty [64, 65]. Intravascular sonography also can be used to visualize RBC-rich thrombi but not platelet-rich thrombi [66].

One of the more promising techniques for the imaging of atherosclerotic lesions is MR imaging. MR imaging can provide not only angiographic images but also images of plaque [67–69]. In addition, chemical-shift MR imaging may be able to identify different types of plaque because the mobility of the lipids in the plaque changes as the disease progresses [29].

Summary

The purpose of this review has been to provide an overview of how an atherosclerotic lesion might develop. Obviously, the process of lesion development is gradual, involving multiple cell types and multiple cell secretions. The process differs depending on the individual, the location, and the risk factors involved. It is hoped that, by understanding the pathogenesis of atherosclerosis, radiologists can modify current imaging techniques or develop new techniques that will permit the diagnosis and treatment of atherosclerotic lesions before they become advanced lesions capable of producing clinical sequelae.

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