PATHOPHYSIOLOGY AND PHARMACOTHERAPY OF Atherosclerosis

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ABSTRACT

Many recent studies have suggested that low-density lipoprotein (LDL) oxidation, endothelial dysfunction, and inflammation are involved in the pathogenesis of atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effect or molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes. This review highlights the role of inflammation in the pathogenesis of atherosclerotic CAD. It will recount the evidence that atherosclerosis, the main cause of CAD, is an inflammatory disease in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the arterial tree. These facts force us to revisit cardiovascular disease and consider new strategies for prediction, prevention, and treatment.

Key Words: low-density lipoprotein, of atherosclerotic, treatment.

INTRODUCTION

Atherosclerosis is the major cause of coronary heart disease (CHD) in humans. Many recent studies have indicated that oxidative modification of low-density lipoprotein (LDL), endothelial dysfunction, and inflammation are involved in the pathogenesis of atherosclerosis. Functionally disturbed endothelial cells express MCP-1, cell adhesion molecules (CAMs), and selectins to recruit the circulating monocytes. Uptake of oxLDL by the macrophage scavenger receptors (MSRs) of monocyte-derived macrophages leads to the formation of foam cells, fatty streaks, and fibrous plaques.

Many potential targets have been identified for therapeutic intervention. Among them, plasma cholesterol-lowering, particularly LDL-cholesterol (LDL-C), remains a major goal of anti-atherosclerotic treatment. However, clinical studies have not been able to demonstrate...
that antioxidant vitamins, such as vitamin E and C, reduce cardiovascular disease. Lipophilic antioxidants which co-migrate with circulating LDL particles, may protect LDL from oxidative modification in the intimal area. Hydrophilic antioxidants also reduce atherosclerosis in animal models\cite{5}.

FACTORS THAT INDUCE AND PROMOTE INFLAMMATION OR ATEROGENESIS

Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis. The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive, this process will result in an advanced, complicated lesion\cite{4}.

Continued inflammation results in increased numbers of macrophages and lymphocytes, which both emigrate from the blood and multiply within the lesion. Activation of these cells leads to the release of hydrolytic enzymes, cytokines, chemokines, and growth factors, which can induce further damage and eventually lead to focal necrosis\cite{4}.

Hypercholesterolemia And Modified Lipids And Lipoproteins

LDL, which may be modified by oxidation, glycation (in diabetes), aggregation, association with proteoglycans, or incorporation into immune complexes, is a major cause of injury to the endothelium and underlying smooth muscle. When LDL particles become trapped in an artery, they can undergo progressive oxidation and be internalized by macrophages by means of the scavenger receptors on the surfaces of these cells he internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, resulting in the formation of foam cells\cite{4}.

Homocysteine

High plasma homocysteine concentrations were initially thought to be associated with advanced atherosclerosis on the basis of autopsy findings in patients with homozygous defects in enzymes necessary for homocysteine metabolism, such as cystathionine betasynthase or ethyl eneteta hydro folate reductase. In patients with such defects, severe atherosclerosis develops in childhood, and many have their first myocardial infarction by the
age of 20 years. Homocysteine is toxic to endothelium and is prothrombotic, and it increases collagen production and decreases the availability of nitric oxide.[4]

**Hypertension**
Concentrations of angiotensin II, the principal product of the renin–angiotensin system, are often elevated in patients with hypertension; angiotensin II is a potent vasoconstrictor. In addition to causing hypertension, it can contribute to atherogenesis by stimulating the growth of smooth muscle.[4]

**Infection**
Several reports have shown a correlation between the incidence of atherosclerosis and the presence of at least two types of infectious microorganisms, herpesviruses and *C. pneumoniae*. Both organisms have been identified in atheromatous lesions in coronary arteries and in other organs obtained at autopsy. It is nevertheless possible that infection, combined with other factors, may be responsible for the genesis of the lesions of atherosclerosis in some patients.[4]

**PATHOPHYSIOLOGY**
Atherosclerosis is the main cause of coronary artery disease. The process begins as disruption of endothelial function due to the accumulation of lipoprotein droplets in the intima of the coronary vessels. Water insoluble lipids are carried in the bloodstream attached to water soluble apolipoproteins (lipoproteins). High concentrations of low density lipoprotein (LDL) can permeate an already disrupted or dysfunctional endothelium where it undergoes oxidation and, in diabetics, glycation. Modified LDL attracts leukocytes into the intima and can be scavenged by macrophages leading to the formation of foam cells.[3]

These cells replicate giving rise to one of the earliest pathological lesions; the fatty streak. The fatty streak is the earliest visualized lesion of atherosclerosis. Smooth muscle cells are then recruited and migrate to the site of the foamy cells. Smooth muscle cells proliferate and manufacture extracellular matrix. A large volume of the plaque is occupied by extracellular matrix (collagen and proteoglycan) secreted by the smooth muscle cells. The fatty streak is now transformed into the fibrous plaque. At this point the lesion begins to encroach on the lumen of the vessel. Small blood vessels form in these plaques (angiogenesis) and these plaques can subsequently calcify. Inflammation plays an important role in promoting smooth muscle cell migration and proliferation. The final lesion, the advanced complicated lesion,
consists of a fibrous cap overlying a lipid rich core which also contains necrotic material, this core is highly thrombogenic\textsuperscript{[3]}.

New perspectives on the formation and progression of lesions smooth muscle

To understand the factors that are important in the proliferative and migratory responses that lead to differences in the organization and enlargement of the lesions in different parts of the arterial tree, it may be helpful to understand the embryonic derivation of the smooth-muscle cells that make up the arteries in different regions. The smooth-muscle cells of coronary arteries appear to originate from a third precursor population in the intra cardiac mesenchyme. The existence of these different lineages suggests that smooth muscle in different parts of the arterial tree may respond differently to the stimuli that generate atherosclerotic lesions at each of these sites\textsuperscript{[4]}.

The role of the matrix

Smooth-muscle cells in the media of arteries, as well as in lesions, are surrounded by different types of connective tissue. In the media of arteries, the matrix consists largely of type I and III fibrillar collagen, whereas in the lesions of atherosclerosis it consists largely of proteo glycan, intermixed with loosely scattered collagen fibrils\textsuperscript{[4]}.

Therapeutic opportunities

The knowledge that atherosclerosis is an inflammatory disease offers new opportunities for the prevention and treatment of CAD. The immunosuppressive drugs cyclosporine and sirolimus block the activation of T cells and, at high levels, smooth-muscle proliferation. They inhibit intimal lesions and sirolimus-coated stents are currently used to prevent restenosis after angioplasty\textsuperscript{[1]}.

Anti inflammatory compounds include cyclooxygenase- 2 inhibitors and other inhibitors of eicosanoid synthesis. The situation is complex, however, since enzymes inhibited by such compounds are also involved in the production of prothrombotic eicosanoids by platelets and endothelial synthesis of antithrombotic eicosanoids.

The recent findings of an increased incidence of cardiovascular events in patients treated with the cyclooxygenase-2 inhibitor rofecoxib (Vioxx)\textsuperscript{98} demonstrate the complexity of eicosanoid biology and indicate the need for a cautious approach to the use of this type of anti-inflammatory compounds in patients with cardiovascular disease.
Lipid-lowering statins have anti-inflammatory properties. They are among the most important of the pleiotropic effects of statins (i.e., effects not directly dependent on reduced cholesterol.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Study type</th>
<th>Therapeutic intervention</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>CHAOS</td>
<td>2002 patients with angiographically proven coronary artery disease, follow up for 1.5 years (UK).</td>
<td>vitamin ( \delta ) 800 mg/d or 400 mg/d</td>
<td>Significant reduction in cardiovascular events and nonfatal myocardial infarction. No significant reduction in mortality rate from cardiovascular events.</td>
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<td>ASAP</td>
<td>520 smoking and non-smoking males and postmenopausal female patients, age 45–69 with hypercholesterolemia. The extent of atherosclerosis in the common carotid arteries was assessed ultrasonographically. Follow up 6 years.</td>
<td>a-tocopherol 91 mg/d and vitamin C 250 mg/d</td>
<td>Significant reduction in the slope of the mean intima-media thickness in the common carotid arteries.</td>
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<td>CARET</td>
<td>4060 males, 45–74 years old, asbestos workers, and 14,254 men and women, heavy smokers (&gt;20 pack-years) follow up for 5.5 years (US).</td>
<td>b-carotene 30 mg/d, +/- retinALE (vitamin ( \alpha )) 25,000 IU/d.</td>
<td>The trial was terminated early due to an increase in all-cause mortality in the supplement combination.</td>
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<td>HPS</td>
<td>20,536 high risk individuals, follow up 5 years</td>
<td>vitamin ( \delta ) 600 IU/d, vitamin C 250 mg/d, b-carotene 20 mg/d</td>
<td>The combined antioxidant strategy failed to reduce the risk and mortality rate for cardiovascular events during the followup.</td>
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<tr>
<td>HATS</td>
<td>160 patients with clinical coronary syndrome, follow up for 3 years.</td>
<td>simvastatin, niacin and/or combination of vitamin ( \delta )(800 IU/d), C (1 g/d), b-carotene (25 mg/d), selenium (100 mg/d)</td>
<td>The use of antioxidants did not reduce the relevant risk of new cardiovascular events.</td>
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<td>ATBC</td>
<td>27,271 male smokers, 50-69 years old, free personal history.</td>
<td>b-carotene 20 mg/d, vitamin ( \delta ) 50 mg/d</td>
<td>Vitamin ( \delta ): important reduction in fatal myocardial infarction. B-carotene: no significant effect on fatal myocardial infarction.</td>
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levels). These properties likely result from the ability of statins to inhibit the formation of mevalonic acid\(^1\).

Other important targets include endothelial nitric oxide production and fibrinolysis, both of which are enhanced by statins, and platelet activity, which is reduced. Inhibition of inflammation adds to lipid lowering as beneficial effects of statins on CAD, as recently demonstrated in two clinical trials of patients with atherosclerosis and CAD\(^1\).

Anti oxidants Feeding rabbits a high-cholesterol diet supplemented with antioxidants prevented the intimal thickening of aortas, even though their blood continued to have a cholesterol level 40 times higher than control rabbits, but their plasma oxysterol levels decreased significantly compared to the rabbits fed without antioxidants. The same results occurred in hyper lipidemic chickens fed vitamin E, where lipid peroxidation and coronary heart disease lesions significantly decreased while hyper lipidemia remained high\(^2\)

**Important trails involving anti oxidents administration**\(^6\)

**CONCLUSION**

In this study, extensive search for antioxidants, endothelium-protecting agents, macrophage scavenger receptor inhibitors have been carried out. If we can selectively modify the harmful components of inflammation in the arteries and leave the protective aspects intact, we may create new avenues for the diagnosis and management of disease in the 50 percent of patients with cardiovascular disease that do not have hypercholesterolemia.

**REFERENCES**