ABSTRACT

Atherosclerosis is a variable disease that involves various pathologic, inflammatory, and mechanical processes. Atherosclerosis is particularly complex in the patient with diabetes. Atherosclerotic lesions are more severe and more numerous in persons with diabetes than in those who do not have this disease. Considerable evidence indicates defects in the coagulation and fibrinolytic systems of those with diabetes, with these abnormalities leading to hypercoagulability and increased thrombus formation. Other explanations for the increased vascular pathology in patients with diabetes include elevated triglyceride and glucose levels, advanced glycosylation end-products, and low levels of high-density lipoprotein cholesterol. Ligand-activated transcription factors known as peroxisome proliferator-activated receptors (PPARs) are of particular relevance in diabetic atherosclerosis as they may influence cardiovascular disease through their regulation of anti-inflammatory as well as proatherosclerotic gene targets. Among known PPAR gene targets are matrix metalloproteinases, chemokines, adhesion molecules, and tissue factor. (Advanced Studies in Medicine 2001;1(9):363-366)

THE INFLAMMATORY NATURE OF ATHEROSCLEROSIS

Atherosclerosis is an exceedingly complex disease that remains the subject of intense scientific investigation. New insights into the disease process resulting from years of extensive and diversified laboratory research have yielded valuable information that is germane to the understanding of current therapies and the development of future interventions. Such issues are particularly relevant to diabetic atherosclerosis.

Whereas atherosclerosis involves processes such as cholesterol deposition, plaque formation and potential rupture, and inflammation in all patients with the disease, these forces may be especially pervasive in patients with diabetes or the insulin resistance syndrome. Pro-inflammatory and pro-atherogenic effects are seen in the vasculature of patients with diabetes as well as those with the insulin resistance syndrome. Indeed, the extensive and diffuse nature of vascular pathology in persons with diabetes may stem from some of the systemic abnormalities that are present in the circulation of diabetic patients. Among these abnormalities, which literally bar the artery in pro-atherogenic substances, are elevated triglyceride and glucose levels, low levels of high-density lipoprotein (HDL) cholesterol, advanced glycosylation end-products (AGEs), and defective responses of the coagulation and fibrinolytic systems.

THE INFLAMMATORY NATURE OF ATHEROSCLEROSIS

The inflammatory nature of atherosclerosis is supported by findings from numerous pathologic and cel-
lular studies. The earliest stages of atherosclerosis involve the endothelium, a layer of cells that lines the vessel and serves as a critical endocrine organ. Atherogenic risk factors such as elevated cholesterol levels or cigarette smoking alter the endothelium, activ-

ating it and promoting the entry of inflammatory cells. Ultimately, a lipid core forms. Monocytes, macro-

phages, and T-lymphocytes are found encircled in the shoulder regions of these plaques. Smooth muscle cells (SMCs) express major histocompatibility complex (MHC) II antigens, evidence of their activation. These SMCs produce the collagen and extracellular matrix that forms the fibrous cap overlying the lipid core. SMCs also proliferate and migrate to these cells of injury. At this stage of the atherosclerotic process, the lesion is not visible on angiography; it is, however, lurking in the vessel wall.

The interactions of inflammatory cells with each other leads to the elaboration of enzymes such as matrix metalloproteinases (MMPs) that may destabilize the fibrous cap and result in its rupture. The lipid core is highly coagulable. A thrombus forms, which can occlude the vessel and lead to a myocardial infarction (MI). As confirmed by numerous pathology studies, most MIIs are preceded by plaque rupture, with an occlusive thrombus at the rupture site (the shoulder region) precipitating acute events.

In many cases, the thrombus does not completely occlude the vessel at the rupture site. A subacute occlusion forms and leads to unstable angina, which may in turn lead to increased lesion formation and additional growth of the fibrous cap.

The reasons for the increased vasculopathy associated with diabetes have not yet been fully elucidated. A fundamental imbalance may exist, with increased levels of plasminogen activator inhibitor (PAI)-1 and decreased levels of plasminogen activator. Overall, ath-

erosclerotic lesions in patients with diabetes may not be qualitatively different from lesions in nondiabetics; these patients simply have more lesions that develop earlier. The lesions may not result from different mechanisms or pathways; they are simply more aggres-

sive, more diffuse, and more severe as a result of dia-

betic abnormalities.

Coagulation and Fibrinolytic Defects

One pathway that may be particularly dysregulated in diabetes involves coagulation and fibrinolysis. Many patients with diabetes have increased platelet activity and aggregation, increased platelet factor IV, increased beta thromboglobulin, and increased fi-

brinogen. These combine with the changes in PAI-1 and plasminogen activator cited earlier, with a net result of hypercoagulability and increased thrombus formation.

Many studies have demonstrated altered coagula-

tion and fibrinolysis in patients with diabetes. In one study, lesions recovered from diabetic patients by atherectomy were examined for various prothrombotic and antifibrinolytic factors. The lesions were found to have increased levels of platelet aggregation in addi-

tion to increased levels of platelet factor IV, beta-

thromboglobulin, and fibrinogen. The lesions were also found to have lower levels of the fibrinolytic plas-

minogen activator and higher levels of the antifib-

rino lytic PAI-1.

Proatherogenic Proteins

Both pathologic and mechanical forces play roles in the development of atherosclerosis, as reflected by plaque rupture and its antecedents, inflammation, coagulation abnormalities, shear stress, and turbu-

lence at branch points of blood flow. A variety of proteins and lipoproteins have been implicated in these and other pro-atherogenic processes. These include low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, chemokines, adhesion mole-

ules, and AGEs.

AGEs have received a great deal of attention late in terms of their role in diabetic atherosclerosis. AGEs, by a product of hyperglycemia, are capable of inducing inflammation, promoting cytokine release, and increasing monocyte chemotaxis. The responses occur in part through receptor AGE (RAGE)-medi-

ated responses.

The identification of proteins that have crucial roles in atherosclerosis has also prompted inquiries into their transcriptional regulation. In the case of proteins thought to be protective, the question is how might expression be induced. In the case of pro-atherogenic proteins, therapeutic approaches might include efforts to repress expression. In this regard, ligand-activated transcription factors known as peroxisome proliferator-activated receptors (PPARs) are of particular relevance in diabetic atherosclerosis.

PPAR Ligands and Activators

Although the PPAR system may seem daunting, physicians in clinical practice routinely use nuclear receptor ligands. For example, fibric acids, which are used to treat dyslipidemia in diabetic and nondiabetic patients, are ligands for nuclear receptor PPAR-alpha, as are certain fatty acids. PPAR-alpha activation may be a mechanism through which fatty acids, such as omega-3, or fibrates exert the beneficial effects report-

ed in clinical trials.

Future Prospects

The study of PPARs, and especially PPARs in the vasculature, has been a rapidly evolving field. This progress will continue to be driven, in part, by new data from clinical trials with PPAR agonists. Furthermore, new PPAR agonists are in develop-

ment, which may also offer additional insights into biol-

ogy and opportunities for treatment of diabetes and its complications, such as atherosclerosis.

Two other PPAR forms, gamma and delta, have been identified. Less is known about PPAR-delta, but PPAR-gamma is known to be a major regulator of adipogenesis, lipid metabolism, and glucose homeostasis. Like all nuclear receptors, it has a ligand-binding domain and a DNA-binding domain. PPAR-gamma is the mechanism through which the thiazolidinedione insulin sensitizers (eg, rosiglitazone and pioglitaza-

zone) exert their actions.

Recent research suggests that both PPAR-alpha and PPAR-gamma may influence cardiovascular disease, indirectly or directly, through their regulation of anti-inflammatory as well as proatherosclerotic gene targets.

PPAR-gamma–regulated target genes in relevant atherosclerosis.

Vascular Cell Adhesion Molecule-1 (VCAM-1) in endothe-

lial cells can be inhibited by PPAR-alpha ago-

nists, suggesting that VCAM-1 is a target gene. Tissue factor expression is a key player in thrombus and plaque formation through its procoagulant activity. Tissue factor is highly enriched in the lipid core produced by mono-

cytes. Recent reports suggest that tissue factor is a PPAR-

gamma regulated target gene. —PTH

REFERENCE

1. Sobel BE, Woolcock-JM, Schneider D, et al. Increased plasminogen activator inhibitor type 1 in coro-

nary artery atherectomy specimens from type 2 diabetic compared with nondiabetic patients: a potential factor pre-

**Additional Sources**


