The “metabolic syndrome,” also known as the insulin resistance syndrome or syndrome X, provides an effective framework for investigating the increased cardiovascular risk factors and adverse events related to atherosclerosis. Metabolic syndrome includes obesity, hypertension, dyslipidemia, and impaired glucose tolerance. An increasing body of evidence in both human and mouse studies now suggests that insulin resistance plays a key role in the metabolic syndrome and contributes to the pathogenesis of type 2 diabetes. In type 2 diabetes, macrovascular and microvascular diseases are the most common causes of morbidity and mortality. According to epidemiological studies, patients with type 2 diabetes are 2 to 4 times more likely to develop macrovascular diseases than nondiabetics. With this background, prevention measures should be implemented to control the development of atherosclerosis. Such measures would benefit not only patients having atherosclerosis but also high-risk groups in the diabetic population. To prevent progression of atherosclerosis, it is of great importance to provide treatments targeting risk factors, such as obesity, hyperglycemia, dyslipidemia, and hypertension.

Various approaches have been taken to deal with these risk factors. Chronic hyperglycemia is a hallmark of diabetes. According to the United Kingdom Prospective Diabetes Study (UKPDS), there was a 16% decrease in myocardial infarction (MI) incidence in patients with tight glycemic control, a decrease which approached statistical significance. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed the mortality to be significantly decreased in diabetic patients whose glycemic control improved after MI. Dyslipidemia, characterized by increased low-density lipoprotein (LDL) cholesterol and triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol levels, is another risk factor and is alleviated by agents such as statins. In the Heart Protection Study, diabetic patients treated with simvastatin had a 33% reduction in coronary or vascular events. With the goal of secondary prevention in diabetic patients with known coronary artery disease, the Scandinavian Simvastatin Survival Study showed reductions in rates of major cardiac events, mortality, and myocardial infarction. As for hypertension, the Hypertension in Diabetes Study embedded in UKPDS demonstrated that strict blood pressure control led to a decrease in diabetes-related mortality and in stroke incidence.

In addition to control of risk factors, direct effects on vessels have been highlighted as new therapeutic options. These include the use of statins, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II Type I receptor (AT1-R) antagonists. For example, statins stabilize atherosclerotic plaque, thus improving endothelial dysfunction, decreasing thrombus formation, and controlling inflammatory responses. ACE inhibitors have the effect of maintaining endothelial function whereas AT1-R antagonists improve endothelial function in patients with hypertension and hypercholesterolemia.

Endothelial function is regarded as a critical factor in the progression of atherosclerosis; endothelial dysfunction is involved not only in microangiopathy but also macroangiopathy in diabetes. The molecular mechanism underlying diabetic vascular diseases is complex. First, endothelial cells, when damaged by free radicals and oxidized LDL, produce adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which are already at high levels before diabetic angiopathy manifests. These molecules recruit macrophages and monocytes to the surfaces of injured endothelial cells, and leukocytes and lipoproteins then infiltrate the arterial wall to form foam cells. This is the initial step in forming a plaque. These cells secrete various proinflammatory and growth factors and stimulate migration and proliferation of smooth muscle cells from the media through the intimal endothelial layer. Smooth muscle cells produce large amounts of collagen, elastin, and proteoglycans, which form part of the atherosclerotic plaque, and secrete various cytokines including platelet-derived growth factor (PDGF) and heparin-binding EGF growth factor (HB-EGF). This leads to the migration of smooth muscle cells and their proliferation in response to growth factors such as VEGF and transforming growth factor (TGF)-β, further accelerating the formation of atherosclerosis, thereby forming an autocrine/paracrine network.

PDGF is important for angiopathy as well as embryonic development of the kidneys, brain, lungs, and cardiovascular system. Clinical studies have revealed that aberrant expression of PDGF and its receptors is often associated with a variety of disorders including fibroproliferative diseases, neoplasma, and atherosclerosis in, for example, catheter-injured arteries and postpercutaneous transluminal coronary angioplasty coronary arteries.
Imatinib is a tyrosine kinase inhibitor and blocks the activity of the PDGF receptor (PDGFR) and the BCR/ABL oncogene. With its minimal side effects, imatinib is widely used for patients with chronic myeloid leukemia (CML) and other cancers. More recently, imatinib has attracted attention for its effects exerted on vessels via inhibition of abnormal PDGFR activation.

The article by Lassila et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology provides significant insights into antiatherogenic therapy and also has direct relevance to the use of imatinib for atherosclerosis in the context of diabetes. In their study, they used streptozotocin-induced diabetic apolipoprotein knockout (apoE-KO) mice, with and without imatinib treatment, on normal chow. Nondiabetic apoE-KO mice served as controls.

Diabetic apoE-KO mice showed blunted body weight gain and increased HbA1c, total cholesterol, and triglyceride levels compared with the control mice, but these parameters were not affected by imatinib treatment. Systolic blood pressure was similar in all three groups during the study. Compared with control mice, total and specific plaque areas (aortic arch, thoracic aorta, and abdominal aorta) were increased in association with increased PDGF-B expression and increased PDGFR-β phosphorylation in diabetic apoE-KO mice. Imatinib treatment reduced the total plaque area in the entire aorta in association with reduced PDGF-B expression and reduced PDGFR-β phosphorylation in the diabetic apoE-KO mice. Similarly, imatinib treatment reduced plaque areas in the thoracic and abdominal regions, while having no effect on the lesion area in the arch. Imatinib treatment significantly reduced plaque areas in the lower portions of these vessels, as did ACE inhibitors, but did not reduce that in the aortic arch. This is probably because ACE inhibitors lower blood pressure thus improving hemodynamic conditions, whereas imatinib does not. Hemodynamic effects may play an important role in the development of atherosclerosis in the aortic arch, whereas cytokine signaling may be more important in the thoracic and abdominal aorta than blood flow and shear stress. Imatinib treatment also decreased the expression levels of proinflammatory cytokines and inhibited cell proliferation in the plaque.

The authors demonstrated that PDGF signaling plays an important role in the development of atherosclerosis and that the PDGFR antagonist imatinib inhibits atherosclerotic progression in the context of diabetes. Recent studies suggest that overactivation of PDGF signaling may be involved in atherogenesis with hyperlipidemia, and that antibodies against PDGF inhibit this atherogenic process. These findings suggest the importance of PDGF and regulation of its signal transduction via PDGFRs in the development of atherosclerotic lesions in the setting of hyperlipidemia and diabetes.

Although imatinib has been used primarily for cancers such as CML, it is now a potential drug targeting atherosclerosis. Importantly, imatinib treatment improved atherosclerosis without significantly affecting blood pressure, plasma lipids, or glycemic control.

As the molecular mechanism of atherosclerosis is clarified, targeted molecular therapy may emerge as a new therapeutic option. Imatinib may herald a new era in the treatment of atherosclerosis.

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Protective Role of Imatinib in Atherosclerosis
Takashi Kadowaki and Naoto Kubota

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