Lipid Lowering and Enhancement of Fibrinolysis With Niacin
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Several controlled trials in patients with atherosclerotic heart disease have demonstrated that a 30% to 40% reduction in low-density lipoprotein (LDL) cholesterol levels is associated not only with a moderate reduction of angiographic progression but, importantly, also with an impressive reduction of ischemic clinical events, suggesting that intensive lipid lowering may stabilize existing lesions. Atherosclerotic plaque rupture occurs primarily at the site of unstable, lipid-rich areas where infiltrated macrophages facilitate matrix degradation, activate the extrinsic pathway of blood coagulation through tissue factor expression, and inhibit fibrinolysis via increased plasminogen activator inhibitor type 1 (PAI-1) synthesis.

LDL cholesterol levels are, however, only weak predictors of the progression of atherosclerotic disease. Their inherent susceptibility to oxidative modification may constitute a more important pathogenic mechanism. Oxidized LDL may facilitate atherogenesis by enhancing monocyte/macrophage adhesion and foam cell generation; inducing smooth muscle cell migration, proliferation, and foam cell generation; enhancing platelet adhesion and aggregation; initiating thrombosis; and impairing vasodilation (reviewed in Reference 7). Patients with hypertension, obesity, hypertriglyceridemia, depressed high-density lipoprotein (HDL) cholesterol levels and insulin resistance, for example, have increased levels of small, dense LDL particles with a pronounced predisposition to oxidative modification, whereas elevated levels of oxidatively modified LDL have also been demonstrated in the plasma of patients with acute myocardial infarction.

Deficient fibrinolytic capacity, eg, due to increased PAI-1 levels or reduced levels of tissue-type plasminogen activator (TPA), predisposes patients to thrombotic events. Ischemic heart disease, angina pectoris, and recurrent myocardial infarction are indeed associated with increased levels of PAI-1. Oxidized LDL may reduce the fibrinolytic capacity of endothelium by stimulating the synthesis of PAI-1 and by inhibiting the synthesis of TPA.

Defective fibrinolysis may also play a role in the early stages of the atherosclerotic process (reviewed in Reference 10). Elevated levels of both PAI-1 and (alpha)2-antiplasmin and decreased levels of TPA have been detected in both the intima and the media of atherosclerotic arterial
Treatment with niacin not only induces a significant reduction of LDL cholesterol and triglyceride levels and an increase of HDL cholesterol but also converts easily oxidized small, dense LDL particles to larger, buoyant, oxidation-resistant particles.\textsuperscript{8} Thus, both modulation of the lipoprotein profile and inhibition of the oxidation of LDL may contribute to the decreased mortality of patients with ischemic heart disease in secondary prevention trials.\textsuperscript{14} Niacin also reduces the level of lipoprotein (a) that may be atherogenic via inhibition of fibrinolysis in the arterial wall.\textsuperscript{14}

In this issue of Circulation, Brown et al\textsuperscript{15} demonstrate that niacin not only decreased the constitutive synthesis of PAI-1 by Hep G2 cells but also attenuated the induction of PAI-1 synthesis by transforming growth factor-\(\beta\)1. It was concluded that niacin may potentiate fibrinolysis, thereby reducing the induction of atherothrombosis by clot-associated mitogens. The modulation of PAI-1 synthesis appears to be unrelated to triggers such as (1) oxidized LDL that may be produced by activated endothelium and/or activated platelets, (2) interleukin-1 that may be produced by infiltrating leukocytes, or (3) platelet-derived growth factor that may be produced by activated platelets and/or infiltrated macrophages. Provided this phenomenon also occurs in vascular smooth muscle and/or endothelial cells, it might constitute an alternative pathway for pharmacological interference with atherogenesis.

References:


5. Buring JE, O’Connor GT, Goldhaber SZ, Rosner B, Herbert PN, Blum


