PITAVASTATIN DECREASES SERUM LOX-1 LIGAND LEVELS AND MT1-MMP EXPRESSION IN CD14 POSITIVE MONONUCLEAR CELLS IN HYPERCHOLESTEROLEMIC PATIENTS

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Background: Lectin-like oxidized LDL receptor 1 (LOX-1) system activation is involved in atherogenesis, however, molecular mechanisms of this system during plaque vulnerability remain elusive. We have previously reported that pericellularly localized membrane-type 1 matrix metalloproteinase (MT1-MMP) which is a main activator of secreted latent type MMPs, plays an important role in plaque vulnerability.

Methods: The aim of this study was to investigate the changes in the LOX-1 system and MT1-MMP expression in patients with hypercholesterolemia after the treatment of either pitavastatin or eicosapentaenoic acid (EPA). A total of 51 hypercholesterolemic patients who had not received anti-dyslipidemic agents and had LDL-C levels of more than 140 mg/dL were divided into two groups: group P received pitavastatin 2 mg once daily (n = 27), group E received EPA 1800 mg daily (n = 24). LOX-1 ligand, a soluble form of LOX-1 (sLOX-1) and MT1-MMP expression were measured before and at 6 months after treatment. Serum levels of LOX-1 with apolipoprotein B-100 particle ligand and sLOX-1 were measured by ELISA, expression of MT1-MMP on circulating peripheral blood mononuclear cells were examined for the frequencies of CD14 positive cells expressing MT1-MMP antigen at the single cell level using flow cytometry.

Results: Low-density lipoprotein cholesterol (LDL-C) (162 ± 29 vs. 103 ± 29 mg/dL: p < 0.01), LOX-1 ligand (8.73 ± 3.30 vs. 5.51 ± 2.13 ng/mL: p < 0.01), and MT1-MMP expression (33.6 ± 3.1 vs. 30.3 ± 6.1%: p < 0.05) were significantly reduced in the group P, but there were no significant changes in high-density lipoprotein cholesterol (HDL-C) and sLOX-1. In the group E, there were no significant changes in LDL-C, LOX-1 ligand, MT1-MMP expression, HDL-C and sLOX-1, except the ratio of eicosapentaenoic acid to arachidonic acid (EPA/AA) (0.44 ± 0.21 vs. 1.19 ± 0.64 : p < 0.01).

Conclusions: Pitavastatin therapy has beneficial effects on a marker of oxidative stress and pericellular MT1-MMP activity in hypercholesterolemic patients compared with EPA. These findings suggest that pitavastatin is useful in decreasing the plaque vulnerability in hypercholesterolemic patients.