DIRECT EFFECTS OF EZETIMIBE ON EXPRESSION OF CD62P AND CD40L ON PLATELETS AND UPAR ON ENDOThELIAL CELLS IN AN IN VITRO MODEL

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Background: Lipid lowering therapy constitutes the basis of cardiovascular disease therapy. The purpose of this study was to investigate effects of ezetimibe, a selective inhibitor of intestinal cholesterol absorption, on platelets and endothelial cells under proinflammatory conditions in an in vitro endothelial cell model.

Methods: After a 24 hour incubation period with ezetimibe (1/50/100/1000 ng/ml), human umbilical vein endothelial cells (HUVEC) were stimulated for one hour with LPS, and were then incubated in direct contact with activated platelets. Following this incubation, the expression of CD40L and CD62P on platelets, and the expression of ICAM-1, VCAM-1, uPAR, and MT1-MMP on endothelial cells were measured by flow cytometry. Supernatants were analyzed by ELISA for soluble MCP-1, IL-6 and MMP-1.

Results: The increased expression of uPAR on endothelial cells by proinflammatory stimulation with LPS and by direct endothelial contact with activated platelets was significantly reduced through pre-incubation with 100 ng/ml and 1000 ng/ml ezetimibe (p<0.05). Platelets directly incubated with ezetimibe but without endothelial cell contact showed a significant reduction in CD62P and CD40L surface expression (p<0.05). However, ezetimibe had no significant effects on HUVEC expression of MT1-MMP, ICAM-1 and VCAM-1 and on CD40L expression on platelets in direct contact with endothelial cells. Levels of soluble IL-6 in supernatants were significantly lower after pre-incubation with different concentrations of ezetimibe.

Conclusions: Ezetimibe directly attenuates platelet activation and has significant endothelial cell mediated effects on selected markers of atherosclerosis in vitro.