Regarding "A novel molecular mechanism to account for the action of simvastatin against limb ischemia"

In the article by Koksoy and colleagues,[1] the authors describe that simvastatin markedly suppresses the functional activity of neutrophils, which is underscored by reduced myeloperoxidase activity compared with a placebo. I would like to add to the discussion of Koksoy and coworkers[1] by introducing a major route through which simvastatin could suppress the activity of neutrophils.

The recent focus on ischemia-reperfusion injury has been on interaction between neutrophils and endothelial cells. The injury attributed to plugging of the microvasculature by neutrophils may initiate the cascade of injury by releasing free radicals, enzymes, and cytokines, and physically injuring the endothelium and obstructing the capillaries, thus, impairing oxygen supply to the tissue. Also, transendothelial migration of neutrophils, with release of reactive oxygen species and cytokines, causes further damage to the injured tissue.[2,3] However, a key component in the pathogenesis of reperfusion syndrome is the upregulation of surface adhesion molecules on the vascular endothelium and their subsequent interaction with the activated neutrophils.[4] The most important adhesion protein identified on neutrophils is the integrin lymphocyte function-associated antigen-1 (LFA-1; CD11a/CD18), which is the ligand for intercellular adhesion molecule-1 (ICAM-1) expressed on the endothelium. The LFA-1/ICAM-1 interaction is crucial for the ingress of neutrophils into the inflammatory sites.[5,6] Simvastatin downregulates the expression of ICAM-1 and LFA-1, and through binding to LFA-1, it interferes with ICAM-1–LFA-1 interaction.[7,8] This important mechanism should be borne in mind as the major mechanism for simvastatin-induced inhibition of neutrophil activity.

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Reply

Dr Namazi's comments offer additional insight to our study. Ischemia reperfusion injury provokes complex pathophysiologic network involving distinct cell populations and humoral mediators. As pointed by the Dr Namazi, the most crucial step is activation of the interaction between neutrophils and endothelial cells. In our study, our primary purpose was to clarify the effects of simvastatin pretreatment on the limb ischemia reperfusion injury in an experimental diabetes model. Several techniques were used to assess tissue injury including tissue myeloperoxidase (MPO) enzymatic activity as a measure of neutrophil infiltration. Statin pretreatment reduced the MPO activity compared with the untreated groups. Unfortunately, we did not attempt to further define the mechanisms for simvastatin induced inhibition of neutrophil activity. We agree with Dr Namazi who suggested that a key component in the pathogenesis of reperfusion injury is upregulated interaction between neutrophils and endothelial cells especially LFA-1/ICAM-1 pathway.[1,2] It has been shown that statins ameliorate tissue injury by concomitantly reducing expression of LFA-1 and/or ICAM-1 in several ischemia reperfusion models including the retina,[3] brain,[4] and the bowel.[5] Neutrophil adhesion to the endothelium indicates a major component of ischemia/reperfusion pathophysiology and may be a target for therapeutic intervention.

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Regarding "Vascular abnormalities in patients with neurofibromatosis syndrome type I: Clinical spectrum, management, and results"

We read the article by Oderich et al[1] and would like to add one more case that we recently had who underwent a successful operation.

The patient is a 38-year old woman with neurofibromatosis type I who has a history of bilateral renal and abdominal aortic angioplasty, at the age of 10 and 2 years ago, for severe hypertension measuring 240/120.

The patient presented for vascular consultation on November 6, 2006, with recurrent hypertension and ischemic symptoms of the lower extremities. Preoperative evaluation revealed suprarenal stricture extending to the juxtarenal and infrarenal aorta with bilateral renal artery stenoses. Rheumatology evaluation was essen-