Vascular Calcification in Homozygote Familial Hypercholesterolemia

Joel D. Morrisett, Kasey C. Vickers

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Awan and coworkers describe the study of 25 homozygous familial hypercholesterolemic (FH) patients aged 5 to 54 years. Eighteen of the patients had aortic calcification scores >1000. The inference of this study is a strong linkage between homozygous FH and premature aortic calcification. Bazan et al have recently described the age dependence of aortic calcification (Agatston units): 12.6±12.3 for <50 years, 14.6±8.2 for 50 to 59 years; 276±120 for 60 to 69 years, 1382±366 for 70 to 79 years, and 3889±778 for 80 years. Hence most of the elevated calcification observed in the Awan cohort is not attributable to age and may be attributable to hypercholesterolemia. The apparent connection between premature aortic calcification and hypercholesterolemia begs for a mechanistic explanation. One explanation is that hypercholesterolemia may ultimately stimulate transdifferentiation of atherosclerosis-associated cells into osteoblast-like calcifying vascular cells, an irreversible process leading to arterial wall calcification. Hypercholesterolemia has been shown to accelerate vascular calcification through Vitamin D and its metabolites. 1,25-Dihydroxyvitamin D3, is a Vitamin D metabolite known to induce calcium uptake and in vitro osteogenesis in vascular smooth muscle cells. Additionally, hypercholesterolemia-induced oxidative stress may play a significant role in the generation of modified LDL and oxidized lipid products, which are also thought to induce differentiation of calcifying vascular cells resulting in vascular calcification.

A second explanation could be a hypercholesterolemia-induced increase in osteoprotegerin, a decoy protein that hijacks RANK ligand (RANKL), preventing binding to its cognate receptor on preosteoclasts, attenuating their development into mature osteoclasts, and reducing calcium desorption. Hence, possibly useful interventions in FH patients at risk for arterial calcification could be downregulation of the osteoblast-like differentiation pathways or upregulation of the osteoclast pathways. These interventions must be specific to arterial tissue lest they cause undesirable effects on bone.

Indeed, Yuan et al have shown that infusion of RANKL markedly stimulates serum osteocalcin and TRAP-5b and reduces femur cortical bone volume and trabecular volume fraction at the proximal tibia.

The burning question is whether neutralizing the hypercholesterolemia (eg, by diet, pheresis, drugs) will also reverse the arterial calcification. Stary’s study of rhesus monkeys showed that 3.5 years of drastic reduction of hypercholesterolemia resulted in loss or reduction of extracellular accumulation of lipid and cell remnants from advanced lesions, but virtually no change in calcium deposits in the arterial wall. Similarly, Zhao and colleagues using MRI showed that 10 years of intensive lipid lowering treatment in CAD patients produced a 16% lower lipid content in carotid plaques compared to that of matched CAD patients who had never been treated with lipid-lowering drugs; however, the proportion of calcification was 7% greater in the treated than untreated groups. Mohler et al have recently reported their study of statin therapy on aortic valve and coronary artery calcification using electron beam computed tomography. They observed no significant reduction in calcium accumulation in the aortic valve of the statin-treated compared to the untreated group. However, there was a significant decrease in the progression of coronary artery calcification in the treated group. Hence, whereas reverse cholesterol transport may play a significant role in depletion of lipid from atherosclerotic plaques, we have not yet discovered a corresponding mechanism for lesion demineralization. Identifying such a mechanism will be a significant advance in the treatment of vascular calcification.

Disclosures
None.

References

From the Departments of Medicine and Biochemistry, Baylor College of Medicine, Houston, Tex.
Correspondence to Joel Morrisett, Departments of Medicine and Biochemistry, Baylor College of Medicine, Brown-Fondren Bldg, A601, Houston, TX 77030. E-mail morrisett@bcm.tmc.edu

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