Review

This Review is part of a thematic series on Pathobiology of Calcific Vasculopathy and Valvulopathy, which includes the following articles:

Thematic Series on the Pathobiology of Vascular Calcification: An Introduction

Molecular Imaging Insights into Early Inflammatory Stages of Arterial and Aortic Valve Calcification
Calcific Aortic Valve Stenosis: Methods, Models, and Mechanisms
Fetuin Regulation of Calcified Matrix Metabolism
Matricrine Cues and Substrate Compliance in the Pathobiology of Calcific Valvular Disease
Oxylipids and RANKL Signaling in Macrovascular Calcification
Osteogenic BMP-Wnt Signaling in Valvular and Vascular Sclerosis
Calcium-Phosphate Homeostasis in the Arterial Calcification of CKD
Molecular Genetics of Calcific Vasculopathy

Dwight A. Towler, Guest Editor

Thematic Series on the Pathobiology of Vascular Calcification
An Introduction

Dwight A. Towler, Linda L. Demer

Abstract: Vascular calcification increasingly afflicts our aging, dysmetabolic population. Once considered only a passive process of dead and dying cells, data from multiple laboratories worldwide have converged to demonstrate that vascular calcification is a highly regulated form of biomineralization. The goal of this thematic review series is to highlight what is known concerning the biological “players” and “game rules” with respect to vascular mineral metabolism. Armed with this understanding, it is hoped that novel therapeutic strategies can be crafted to prevent and treat vascular calcium accrual, to the benefit of our patients afflicted with arteriosclerotic valvular and vascular diseases. (Circ Res. 2011;108:1378-1380.)

Key Words: arteriosclerosis ■ atherosclerosis ■ vascular calcification ■ calcific aortic stenosis ■ review

In a recent meta-analysis from New Zealand, Bolland and colleagues reported that dietary calcium supplementation is associated with a significant increase in risk for myocardial infarction. Although the mechanism of this association is unknown, the finding calls attention to the process of artery wall calcification. For decades, calcific modification of the cardiovascular system was considered an uncommon condition limited to the most advanced atherosclerosis in the elderly; however, its prevalence actually corresponds roughly with age, with coronary calcification occurring in ~20% of young adults, ~60% of those in middle age, and ~90% of the elderly. Moreover, coronary calcification is now widely used as the preferred marker for the earliest “subclinical” phase of atherosclerosis. Additionally, implementation of tibial artery calcification scoring portends lower-extremity amputation risk, outperforming traditional methods of...
evaluation such as ankle-brachial indices. Clearly, the burgeoning unmet clinical needs in cardiovascular medicine will require a better understanding of the molecular mechanisms that control the initiation and progression of vascular mineralization.

Consistent with this need, our understanding of how arterial tissues undergo this mineralizing transformation has grown rapidly, as reflected in the surge of publications identified by a search of PubMed for the key phrase “vascular calcification.” There was only 1 such publication in 1994; 6 in 1995; about 12 per year from 1996 to 1999; 15 in 2000; about 75 per year from 2001 to 2004; and about 150 per year from 2005 to 2009. The number shot to 280 in 2010, and in the first 19 days of January 2011, there were as many publications using this term as there were in all of 1995 and 1996 combined.

Calcium deposits in the artery wall often contain fully formed bone tissue (ie, true ossification), including trabeculae, osteoblasts, osteoclasts, woven bone, and even marrow. However, even in the absence of overt vascular ossification, the molecular “fingerprints” of active osteochondrogenic gene regulatory programs are present in virtually all types of vascular calcification. At the molecular level, the regulatory factors that drive cardiovascular mineralization overlap with those driving embryonic osteogenesis and postnatale skeletal repair. Key factors include potent morphogens that activate osteogenic bone morphogenetic protein and Wnt (wingless-type MMTV integration site family member) signaling cascades. The investigators who have elucidated these mechanisms—Kristina Bostrom, Nalini Rajamannan, and Dwight Towler—will review these underlying osteogenic mechanisms.

Calcific vasculopathy was not limited only to modern humans and our 21st century lifestyle. Aortic wall calcification was detected by computed tomographic scan of a natural mummy found in ice floes of the Alps; the remains were estimated to be from 5300 years ago. In the present series, Robert Terkeltaub and Frank Rutsch (colleagues who identified the gene defect responsible for the previously mysterious disorder, generalized arterial calcification of infancy) will review the molecular genetics that predispose or protect humankind from vascular calcification.

The most severe calcific vasculopathy occurs in patients with chronic kidney disease, particularly those requiring dialysis, in whom the metabolic milieu generates a “perfect storm” in vascular calcification. This has been linked to abnormalities of phosphate metabolism, discovered by Cecilia Giachelli, as well as calcium dysregulation and apoptotic death of vascular cells, elucidated by Catherine Shanahan. These 2 investigators will collaborate on a review of these topics and their interrelations.

Vascular calcium deposits are perhaps most rapidly fatal when they accrue on the leaflets of the aortic valve. Calcific aortic stenosis has unique consequences and mechanisms that involve valvular interstitial cells and leaflet stiffening. Experts Jordan Miller, Don Heistad, and Robert Weiss will review this disease process.

Paradoxically, atherosclerotic calcification and osteoporosis are associated even after adjustment for age. This has been attributed to reciprocal effects of oxidatively modified atherogenic lipids, and resulting inflammation, on osteogenesis and osteoclastogenesis in both arteries and skeletal bone. Linda Demer and Yin Tintut will review these issues, as well as the potential for cellular resorption and remodeling of calcific vasculopathy.

In biomineralization, mechanical interactions between cells and their matrices dramatically influence progression or regression. Matrix stiffness clearly impacts the cellular fates adopted by multipotent mesenchymal progenitors. Craig Simmons will review the role of substrate compliance and matricrine cues on the osteogenic programming of vascular cells.

The normal calcium-phosphate product in serum and interstitial fluids is close to, and often in excess of, the threshold for spontaneous crystallization. Analogous to the lipoprotein particles that ferry otherwise insoluble lipids, fetuin-containing calciprotein particles possessing fetuin regulate solubility and deposition of calcium salts. How petrifaction is held off by hepatic ally–produced serum proteins such as fetuin A will be addressed by Willi Jahnen-Dechent and Markus Ketteler, who discovered and pioneered the clinical relevance of fetuin biology to soft tissue mineralization.

The process of vascular mineralization may be visualized in vivo with new molecular imaging techniques that implement near-infrared fluorescence imaging. Matrix metabolism and calcification can be coregistered with specific inflammatory cell infiltrates and osteogenic gene programs. Elena Aikawa will review these novel approaches.

An emerging concept from this growing field is that treatments for osteoporosis and atherosclerosis—calcium supplements, calcitropic hormones, statins, angiotensin signaling modifiers, β-blockers, and osteoporosis pharmacotherapies—should be expected to interact. Indeed, in a very recent analysis from MESA, the Multietnic Study of Atherosclerosis, aminobisphosphonate treatment for osteoporosis was associated with decreased prevalence of vascular calcification in older individuals but increased cardiovascular calcification in younger patients. The goal of this thematic review series is to highlight what is known concerning the biological “players” and “game rules” with respect to vascular mineral metabolism. Armed with this understanding, in the future it is hoped that findings such as those of Bolland et al1 and Elmariah and colleagues10 may be anticipated and considered as therapeutic strategies are crafted, to the benefit of human health and healthcare.

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Disclosures
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 References


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