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Regulatory Mechanisms in Atherosclerotic Calcification

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Abstract

In the past decade, the prevalence, significance, and regulatory mechanisms of vascular calcification have gained increasing recognition. Over a century ago, pathologists recognized atherosclerotic calcification as a form of extraskeletal ossification. Recent studies are identifying the mechanisms of this remarkable process as a recapitulation of embryonic endochondral ossification through phenotypic plasticity of vascular cells that function as adult mesenchymal stem cells. These embryonic developmental programs, involving bone morphogenetic proteins and potent osteochondrogenic transcription factors, are triggered and modulated by a variety of inflammatory, metabolic, and genetic disorders particularly hyperlipidemia, chronic kidney disease, diabetes, hyperparathyroidism, and osteoporosis. They are also triggered by loss of powerful inhibitors, such as fetuin-A, matrix GLA protein, and pyrophosphate, which ordinarily restrict biomineralization to skeletal bone. Teleologically, soft tissue calcification probably serves to create a wall of bone to sequester noxious foci such as chronic infections, parasites, and foreign bodies. This review focuses on atherosclerotic calcification, with reference to other forms of cardiovascular calcification, such as medial and valvular calcification, each of which warrants its own review. The capacity of the asculature to produce mineral in culture and to produce de novo, vascularized, trabecular bone and cartilage tissue, even in patients with osteoporosis, should intrigue investigators in tissue engineering and regenerative biology.

Introduction

More than a century ago, investigators recognized vascular calcification as a form of extraskeletal ossification.[1, 2] This concept was forgotten in the past century, when cholesterol dominated the field. Vascular calcium deposits became regarded as passive, inevitable, unregulated, and degenerative consequences of aging. In the past decade, the prevalence, significance, and regulatory mechanisms of vascular calcification have gained recognition among clinicians.[3]

A recent meta-analysis of 30 prospective cohort studies demonstrated the consistent finding that presence of calcification poses an increased risk for cardiovascular and all-cause mortality.4 By far, the most extensive vascular calcification occurs in patients with renal disease (CKD),5 followed by those with type II diabetes.6 Nearly all cardiovascular disease (CVD) patients have some degree of calcification,7 and in asymptomatic adults, prevalence of coronary calcification corresponds roughly with age: among 60-year-olds, approximately 60% have calcific vasculopathy. 3› 4

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Etiology

Vascular calcification is the culmination of several distinct pathological processes, many of which overlap, such as in chronic kidney disease (CKD), which Towler aptly named the "perfect storm" for vascular calcification.[8] These processes largely follow developmental programs that recapitulate embryonic ossification, with modulation by inflammatory or metabolic phenomena (Figure 1). Both activators and inhibitors participate, and many of them interact. The developmental programs play out in vascular cells exhibiting lineage plasticity and inflammatory responses to chronic oxidative stress.

Given the potential adverse consequences of uncontrolled biomineralization, calcium-phosphate metabolism is tightly regulated and mineralization ordinarily limited to skeletal bone by circulating and local inhibitors. Early investigators believed that the process of vascular calcification was a passive process possible only when inhibitors were absent or deficient. The current view is that it is an active process that occurs despite the presence of inhibitors and, once underway, recapitulates regulated osteogenesis.

Recapitulation of osteogenesis

One of the first, and most compelling, clues that vascular calcification recapitulates osteogenesis was the presence of bone-like tissue in atherosclerotic arteries and valves.[2, 9] In 10–20% of atherosclerotic human vessels and valves, [9] architecturally-complete, trabecular bone emerges from amorphous mineralized matrix. All stages of endochondral ossification are found in a careful survey of such lesions,[10] even fully-formed marrow cavities with hematopoietic cells, vascular sinusoids, marrow adipocytes, and marrow stromal cells.[1, 10, 11] Spontaneous bone formation inside the wall of adult arteries is difficult to explain,

Vascular calcium deposits resemble bone from the macroscale to the nanoscale levels. Macroscopically, cortical bone osteons resemble a parallel array of calcified vessels, each containing concentric layers of mesenchymal cells surrounding the subendothelial basement membrane of a central vessel. The mineral deposits contain "osteoid" (bone matrix), which consists primarily of collagen I, but also has non-collagenous bone matrix proteins, including osteopontin, bone sialoprotein, osteocalcin, fetuin, and matrix GLA protein. Cellular components include osteoblasts, osteoclasts, chondroblasts, chondroclasts, osteocytes, lymphocytes, and vascular cells. Figure 2

Analysis of the mineral in vascular lesions and cell cultures by energy dispersive x-ray analysis consistently yields a calcium-phosphate molar ratio of approximately 1.6, matching that of hydroxyapatite (bone) mineral.[12, 13] The non-mineral components of the deposits include cells, proteins, proteoglycans,14 and lipids.15 Solid-state nuclear magnetic resonance spectroscopy reveals molecular surface features matching those of bone.[14].

Cellular plasticity and vascular stem cells

Ectopic bone in the artery wall is dramatic evidence of mesenchymal cell plasticity. The notion that smooth muscle cells undergo "de-differentiation into a synthetic phenotype" and "phenotypic modulation" already has gained acceptance,[16] and these terms may be viewed as euphemisms for "transdifferentiation." Indeed, conventional distinctions among many cell lineages are becoming less clear as investigators report that: endothelial cells differentiate to smooth muscle cells;[17] adult mesoangioblasts to myocytes and cardiomyocytes;[18] adipocytes to vascular cells;[19] osteoclasts to dendritic cells;[20] dendritic cells to osteoclasts;[21] smooth muscle cells to osteoblasts;[22, 23] and microvascular pericytes to osteoblasts, myocytes and adipocytes.[24, 25] The doctrines of lineage commitment and terminal differentiation are giving way to the view of mesenchymal cell plasticity.

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Mature vascular cells, such as SMCs and valvular interstitial cells, may transdifferentiate[22] or dedifferentiate-redifferentiate into osteochondrogenic cells. As with other cells, vascular cell differentiation responds to microenvironmental[26] and mechanical cues. As evidence of the mechanical influence, mineral deposits co-localize with sites of mechanical stress on valves.[27] Furthermore, substrates of greater stiffness, such as fibronectin, induce osteochondrogenic differentiation, whereas distensible substrates, such as laminin, promote smooth muscle and/or adipogenic differentiation. [28] Since cross-linking increases matrix stiffness, this may account for the vascular calcification induced by the matrix cross-linker, transglutaminase-2.[29] Positive feedback may occur when calcium deposition increases plaque stiffness, which would induces osteochondrogenic differentiation of adjoining cells.

Adult mesenchymal stem cells residing in the artery wall have a lineage repertoire similar to that of marrow stromal cells.18, 23, [25] Located primarily in the subendothelial (perivascular) basement membrane,[19] they appear to form an anatomic continuum30 ranging from the microvascular pericytes to the macrovascular intimal cells, once known as “atherophils” and “intimacytes.” Even the adventitial layer has subendothelial pericytes in its microvessels, the vasa vasorum.31, 32

Paradox of vascular calcification and osteoporosis

Interestingly, aortic calcification is often greater in patients with osteoporosis, independently of age.[33, 34] Public health programs currently promote calcium supplements to prevent osteoporosis, giving the impression that dietary calcium is the limiting factor for bone growth. However, the fact that the vascular tissues of osteoporotic patients can produce mature, well-mineralized bone tissue raises questions about the need for dietary supplements and emphasizes the role of local, tissue-specific factors, such as inflammation, in osteoporosis.

If the relationship is independent of age, possible explanations for the correlation include: 1) vascular calcification causes osteoporosis, 2) osteoporosis causes vascular calcification, or 3) the two processes share a common etiology. A potential shared etiology is oxidant stress from hyperlipidemia. Though most widely recognized in the vessel wall, hyperlipidemia leads to deposition and nonenzymatic oxidation of lipoprotein particles in tissue. The pro-inflammatory lipid oxidation products initiate atherogenesis. They also accumulate in other tissues, including bone.[35, 36]

This concept has to the “lipid hypothesis of osteoporosis.”[37] High fat-fed mice develop skeletal bone loss,[38] which is accelerated in hyperlipidemia.[39] Lipid oxidation products have direct effects on both bone-forming and bone-resorbing cells. They directly inhibit differentiation of osteoblasts[37] while directly inducing differentiation of osteoclasts.[40] They also regulate osteoclastogenic cytokines produced by osteoblasts[41] and T lymphocytes.[42] Recent studies have shown that patients with hyperlipidemia may not achieve efficacy with intermittent PTH treatment for osteoporosis because the oxidized lipids blunt the bone anabolic effects of PTH.[43, 44]

Mechanisms of initiation

While intracellular osteogenic phenomena are becoming clear, the extracellular crystal initiation mechanism(s) remains less clear. In general, biomineralization is restricted to tissues that express both collagen I and alkaline phosphatase; engineered co-expression of these proteins suffices to induce ectopic calcification.[45] Type I collagen, but not ALP, is present in normal artery wall. Both type I collagen and ALP colocalize with mineral deposits in calcific atherosclerosis46 and are produced in vascular cells in vitro.47, 48

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In mature osteoid, mineral is associated with fibrillar collagen I. In earlier stages, crystallization may originate within extracellular membrane vesicles, such as matrix vesicles or apoptotic bodies, which offer a microenvironment high in calcium and phosphate and carry membrane-bound ALP.[49] By electron microscopy, such crystalline matrix vesicles, are often found in close proximity to apoptotic cells,[50] within atherosclerotic plaques and, when isolated, retain the ability to concentrate calcium and phosphate and initiate new crystal formation.[51, 52] Matrix vesicles may be specialized forms of general-purpose, membrane vesicles used for intercellular communication[53] while apoptotic bodies may represent a pathophysiological surrogate.[54]

Elastic lamellae are degraded in atherosclerotic plaque, and their degradation products may contribute to crystal initiation.[55, 56]

Pyrophosphate, a water softener and a cause of pseudogout, potently inhibits calcium phosphate crystal formation. Although ALP produces Pi, its main role in calcification is the breakdown of PPi. Extracellular PPi is produced in the extracellular space from nucleotide triphosphates, such as ATP, by enzymes such as nucleotide pyrophosphatase (NPP)1. PPi produced inside cells is exported via the transmembrane protein, Ank. Deficiency of either NPP1 or Ank in mice results in vascular and joint calcification with spontaneous chondrogenic metaplasia.[57]

Human genetic disorders

A lethal congenital disorder that causes myocardial infarction in infants, previously known as idiopathic infantile arterial calcinosis, is now recognized as homozygous NPP1 deficiency and has been renamed infantile arterial calcification.[58] Patients with another hereditary human disorder, fibrodysplasia ossificans progressiva (FOP), develop ectopic bone at sites of muscle and soft tissue injury, gradually causing petrification of its victims.[59] The ectopic bone formation is mediated by cells of vascular origin,60 that derive from a Tie2-positive, but not SM-MHC positive lineage, suggesting an endothelial or more primitive progenitor stem cell origin. Patients with homozygous familial hypercholesterolemia have premature severe calcific aortopathy and valvulopathy, suggesting a role for hyperlipidemia in both.61

Categories of vascular calcification

Vascular calcification can be distinguished by location as intimal (atherosclerotic), medial, or valvular, each having somewhat distinct mechanisms.

Calcific atherosclerosis occurs in the same distribution as atherosclerosis. Small (5–10 μm) hydroxyapatite mineral crystals arise in early lesions in the 3rd decade of life.[62] It was previously believed that calcification occurred only in the most advanced, end-stage plaque in the elderly. Yet, it is now used as a marker for early atherosclerosis.[63]

Calcific valvular stenosis, a lethal disorder formerly attributed to wear-and-tear injury, is now seen as an atherosclerotic process that shares risk factors and etiological factors with calcific atherosclerosis. Chondroosseous metaplasia is a common feature.[64] Oxidant stress,[65] lipids[66, 67] and Wnt/beta-catenin/LRP5 pathway[68, 69] have been implicated.

Medial calcification occurs primarily in association with chronic kidney disease and diabetes, independently of atherosclerosis, and it resembles embryonic *membranous* (vs. endochondral) ossification. In microvessels, medial calcification is known as calcific uremic arteriolopathy, previously calciphylaxis.

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Both medial calcification and calcific valvular stenosis have been reviewed extensively elsewhere. [5, 6, 64, 70, 71] The present review focuses primarily on atherosclerotic calcification and its mechanisms.

Clinical significance

Controversy remains with respect to whether vascular calcification is a cause or consequence of cardiovascular disease. Most likely, it is both: a cause, in that atherosclerosis induces cellular osteogenic differentiation; and a consequence, in that vascular calcification stiffens the aorta and affects plaque stability. In the coronary arteries, calcified plaque independently predicts a 1.7-fold increase in mortality. In peripheral arteries, it independently predicts amputation and mortality.[72] When coronary calcification is extensive, the risk is 60-fold higher.[3]

Aortic stiffness is an important consequence of medial calcification, and calcification has the greatest effect on aortic rigidity.[73, 74] Aortic rigidity results in hypertension, left ventricular hypertrophy, ischemia, heart failure, amputation, and death.[6]

Plaque stability may be affected by calcium deposits because they introduce compliance mismatch at the interface of the rigid mineral with the more distensible artery wall tissue. Under mechanical stress, this interface has a greater risk for mechanical failure (plaque rupture). Such plaque rupture is believed to cause most myocardial infarction and stroke.[75] Based on finite element analysis, calcium deposits dramatically redistribute stress in plaque, reducing it in some regions at the cost of increasing it in others,76 with the net effect on risk of rupture depending on the anatomic orientation of the calcium deposits relative to the plaque and any necrotic core.77, 78

Regulatory factors

Factors that regulate vascular calcification are shown in Figure 3. Developmental, inflammatory and metabolic factors all impact on this process.

Developmental factors

Several developmental regulatory factors, and their respective inhibitors, govern osteogenesis in skeletal bone and in vascular calcification. The master transcription factors, Msx2, Runx2 (Cbfa1), Osterix, and Sox9, designate cells for osteoblast vs. chondrocyte lineages through induction of downstream matrix components such as collagen I, alkaline phosphatase, osteopontin, tissue factor, and osteocalcin. Osteopontin, a multifunctional protein involved in diverse processes including inhibition mineralization, is reviewed in detail by Giachelli and colleagues.[79]

Bone morphogenetic proteins—BMP2 and 4, potent osteogenic differentiation factors originally isolated from bovine bone, induce ectopic ossification in muscle tissue *in vivo* and mineralization in SMC *in vitro*. BMP-2 acts through Runx2,[80] which induces type I collagen and alkaline phosphatase. It is antagonized by noggin, chordin and matrix carboxyglutamic acid protein (MGP). [81] BMP4 is induced by RANKL in rat smooth muscle cells,82 and BMP7 inhibits calcification.83

MGP—MGP, the BMP inhibitor, associates with conventional cardiovascular risk factors (Framingham), but, surprisingly, not with coronary calcification.[84] It is highly expressed in calcified vs. normal human arteries.46 Its inhibitory role in vascular calcification was revealed with the unexpected phenotype of the MGP deficient mouse – complete ossification of the aortic wall and major branches by calcified cartilage.85 Later studies

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showed two mechanisms of MGP inhibition of calcification: direct binding of nascent crystals, and direct binding and inhibition of BMP-2.86 MGP is blocked, in turn, by heat shock protein-70,[87] and lack of vitamin K. Its function depends on vitamin K-dependent gamma-carboxylation of glutamate residues,[88] a process inhibited by warfarin. Accordingly, long-term warfarin therapy is associated with increased femoral artery calcification,[4] and its possible contribution to other vascular calcification is under investigation.

RANKL—RANKL, expressed by osteoblasts, is an essential regulator of osteoclast differentiation. Deficiency of osteoprotegerin (OPG), a decoy receptor for RANK, leads to medial calcifcation.[89, 90] Unexpectedly, RANKL levels increase with age and reliably predict cardiovascular events.91 The OPG/RANKL system may govern differentiation of osteoclast-like cells at sites of vascular calcification.[9, 92]

Inflammatory factors

Inflammation is closely associated with calcification. Macrophages, lymphocytes, and dendritic cells infiltrate plaque and release cytokines that regulate calcification.[20, 40] Perivascular adipose inflammation and systemic inflammation [93, 94] as well as systemic inflammation.[95] In elegant work by Towler and colleagues, the link between inflammatory and developmental mechanisms was identified as the pro-osteogenic Msx2-Wnt-β-catenin signaling mechanism.

TNF-a—TNFα induces the Msx2-Wnt-beta-catenin signaling pathway[96] as do oxidant stress[6] and hyperphosphatemia.[97] TNFα also promotes calcification in vitro by reducing anti-apoptotic Gas6[98] and by inducing ALP via PKA signaling.[48] TNFα may also act on ALP via NADPH-mediated ROS and induction of Msx2.[6, 99] In vivo, targeted TNFα overexpression in SMCs enhances Msx2-Wnt induced calcification in Ldlr−/− mice, and the clinically-used monoclonal antibody to TNFα, infliximab, inhibits Wnt activation and calcification in Ldlr−/− mice.[96]

Gas6/Axl—A prominent anti-apoptotic pathway in VSMCs is regulated by Axl tyrosine kinase and its ligand, Gas6, another GLA protein. Reduced expression of Axl and Gas6 correlates with progression of calcification *in vitro*,[100] whereas restoration prevents calcification.[101, 102] This pathway is a downstream effector for a number of key regulators of vascular calcification, including inorganic phosphate[103] and TNFa[98] as well as testosterone [104] and adiponectin.[98] The role of Gas6 and Axl in cardiovascular diseases may be complex, since they also mediate atherogenesis, platelet function and immune cell activation.

Fetuin-A—Fetuin-A, an abundant serum protein produced in the liver, binds and complexes calcium phosphate nanocrystals, forming calcioprotein particles (CPPs), preventing aggregation into insoluble mineral crystals, and preventing further growth. Fetuin-A also promotes cellular uptake and removal of the complexes.[105] Fetuin accumulates at sites of vascular calcification106 as well as in bone. Other bone-associated proteins also bind crystals particularly osteopontin.107 In vitro, fetuin taken up by VSMCs reduces the ability of their matrix vesicles to calcify.106, [108] Low fetuin-A levels are associated with increased vascular calcification and mortality in CKD patients.[109]

Crystals—Nanoscale hydroxyapatite crystals[13, 14] may have direct biological effects on cells through physicochemical interactions that trigger inflammation and apoptosis. [13] These effects are known pyrophosphate and urate crystals, but less so for hydroxyapatite.[110] A positive feedback loop may ensue when inflammation triggers mineralization and

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mineralization triggers inflammation. In osteoarthritis crystals induce MMPs and cell proliferation through Erk and calcium signaling.[111]

Metabolic factors

Excess lipids, phosphate and/or glucose, in chronic diseases, have both direct and indirect effects on vascular calcification. A central downstream mediator of these changes and their link with inflammatory and developmental processes described above may be oxidant stress.

Oxidant stress—Oxidant stress, alone, promotes vascular cell calcification,[112] It may account for the procalcific effects of inflammatory cytokines, oxidized lipids and certain oxysterols. The classical oxidant stressor, H_20_2, promotes osteochondrocytic differentiation of VSMC by upregulating Runx2.[47] Reactive oxygen species are increased at sites of calcification in human valves.[65, 113] Products of lipid oxidation, such as minimally-modified LDL and oxidized phospholipids, induce osteogenic[37, 114] and apoptosis-mediated calcification of vascular cells.[115] The osteogenic differentiation induced by TNF-alpha and H_20_2 is inhibited by insulin-like growth factor-1.[116]

Hyperphosphatemia—The important role of hyperphosphatemia in the medial calcification associated with chronic kidney disease has been reviewed in detail.[70, 97] Serum phosphate levels are regulated by FGF23, which is released from bone osteocytes and activates its coreceptor Klotho in the kidney, controlling phosphate elimination.

Vitamin D—High dose, dietary vitamin D reliably induces medial calcification; it is often used to generate animal models of vascular calcification.[117] As a fat-soluble vitamin, dietary vitamin D may be carried by chylomicrons and lipoprotein particles, which are deposited into the artery wall, where it may be converted to active form by 1-alpha-hydroxylase in VSMC and in monocyte-macrophages. This raises interesting questions about the potential for vitamin D to promote atherosclerotic calcification and cardiovascular risk. The role of vitamin D in vascular calcification has been reviewed recently.[118] Other metabolic factors that affect calcific vasculopathy include insulin and glucose as well as the adipose-derived factors, leptin and adiponectin, which promote and inhibit vascular calcification, respectively.[119–121]

Treatments

Currently, no therapy is available to reverse vascular calcification; several are available for underlying disorders such as atherosclerosis, CKD, diabetes mellitus, and osteoporosis. Interestingly, this disorder is now afforded such importance in CKD that new therapies are largely judged by their impact on vascular calcification.[122] Under investigation are HMG-CoA reductase inhibitors, sevelamer, bisphosphonates, the phosphorus binder, lanthanum carbonate, bisphosphonates, alkaline phosphatase inhibitors, calcimimetics, , and the RANK blocker, denosumab. Importantly, procalcific treatments used for skeletal osteoporosis may have adverse effects on vascular calcification.

Conclusions

Mineral deposits in atherosclerotic plaque result from several different pathways involving metabolic and/or inflammatory processes that trigger reversion to embryonic developmental programs for osteochondrogenesis. What evolutionary advantage might this confer? One possibility is that soft tissue calcification in general is an immune response of last resort. Certain chronic infections, such as mycobacteria, parasitic worms, abscesses, or foreign body infections, may be unabated by cellular and humoral immunity. By surrounding such infections with a wall of bone, the body may contain the noxious focus. Radiologists have

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described such calcified structures as “ostrich eggs.” The capacity of the artery wall to generate complete, vascularized, trabecular bone tissue, as well as cartilage and fat, should capture the attention investigators in tissue regenerative and tissue engineering medicine.

Key Points

- Calcific vasculopathy and valvulopathy encompass amorphous calcification and chondro-osseous metaplasia in atherosclerotic plaque, the medial layer of large arteries, and cardiac valves, with different, but overlapping mechanisms.
- The process is associated with, and possibly driven by, developmental, inflammatory, and/or metabolic abnormalities. A disturbance of one or any combination of activating and inhibiting factors may be responsible. The list of regulatory factors continues to grow, and the complex feedback regulatory mechanisms require nonlinear and systems engineering analysis.
- Vascular calcification associates with most conventional cardiovascular risk factors, and it is a significant, independent risk factor in itself.
- Clinical consequences of calcific disease include heart failure, valvular sclerosis and stenosis, ventricular hypertrophy, diastolic dysfunction, and hypertension. Plaque calcification introduces mechanical discontinuities and compliance mismatch.
- Targeting hyperlipidemia in CVD patients and hyperphosphatemia in CKD patients remain the current major approaches to preventing vascular calcification, but definitive studies remain in progress.

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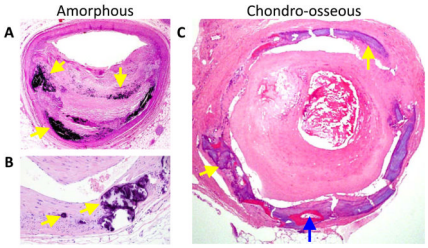

Figure 1.

Histological sections of human vascular calcification. Medial arterial calcification, osseous metaplasia, and cartilaginous metaplasia (mineral is stained balck by the von Kossa method and eosin counterstain; original magnification X 40; provided by M. Fishbein, Department of Pathlogy and Laboratory Medicine, University of California, Los Angeles, CA, USA.) (B) Higher-power view of a sequential section from (A) showing chondrocytes in a basophilic matrix (arrows). (C) The tunica media of a human artery (hematoxylin and eosin stain; the lumen contains a thrombus). The yellow arrows indicate amorphous mineral, and the blue arrow identifies a region of osseous tissue that includes a marrow space. (Original magnification X 100; provided by J. H. Qiao, Department of Pathology, California Hospital Medical Center, Los Angeles, CA, USA.)

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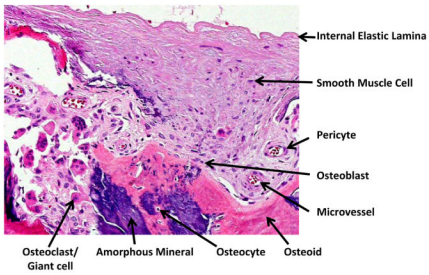

Figure 2.

Chondro-osseous calcific vasculopathy of the medial layer of an atherosclerotic human artery. Histological section (hematoxylin and eosin stain; original magnification X100; provided by Qiao, J.H., Mertens, R. B., Fishbein, M.C. & Geller S.A. Cartilagenous metaplasia in calcified diabetic peripheral vascular disease: morphologic evidence of endochondral ossification. Hum. Pathol. 34(4), 402–407© 2003, with permission from Elsevier).

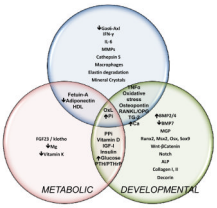

Figure 3.
Regulatory factors in vascular calcification. The Venn diagram illustrates overlap between the three categories of factors regulating vascular calcification. The importance of oxidized lipids (OxL) and hyperphosphatemia is reflected by their inclusion in each category.

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