INTRODUCTION
A significant number and variety of disorders cause extraskeletal deposition of calcium and phosphate (Table 1). In some, mineral is precipitated as amorphous calcium phosphate or as crystals of hydroxyapatite; in others, osseous tissue is formed. The pathogenesis of ectopic mineralization is generally attributed to one of three mechanisms (Table 1). First, a supranormal “calcium-phosphate solubility product” in extracellular fluid can cause metastatic calcification. Second, mineral may be deposited as dystrophic calcification into metabolically impaired or dead tissue despite normal serum levels of calcium and phosphate. Third, ectopic ossification (or true bone formation) occurs in a few disorders for which the pathogenesis is becoming increasingly understood.

Discussed briefly in this introduction are these three mechanisms for extraskeletal calcification or ossification. Subsequently, there follows a description of disorders that illustrate each pathogenesis.

MECHANISMS FOR EXTRASKELLETAL CALCIFICATION AND OSSIFICATION

Calcium and inorganic phosphate are normally present in serum or extracellular fluid at concentrations that form a “meta-stable” solution. That is, their levels are too low for spontaneous precipitation but sufficiently great to cause hydroxyapatite [Ca_{10}(PO_4)_6(OH)_2] formation once crystal nucleation has begun.(11) In health, the presence of a variety of inhibitors of mineralization, such as inorganic pyrophosphate, helps to prevent ectopic calcification.(22)

The pathogenesis of metastatic and dystrophic calcification at the cell level is partially understood. Both processes typically involve mineral accumulation within matrix vesicles and sometimes within mitochondria.(22) Conversely, the mechanisms which initiate ectopic ossification are less clear, but studies of progressive osseous heteroplasia (POH) identified deactivating mutations in \( \text{GNAS} \) (which also causes pseudohypparathyroidism type Ia).(33) Calcification and ossification within the vasculature is now being investigated intensely.(44) Metastatic calcification can occur from significant hypercalcemia or hyperphosphatemia (especially both) of any etiology (Table 1). In fact, therapy with phosphate supplements during mild hypercalcemia or treatment with vitamin D or calcium during mild hyperphosphatemia may trigger this problem. Mineral deposition can also occur ectopically from hyperphosphatemia despite concomitant hypocalcemia.(55)

Direct precipitation of mineral occurs when the calcium-phosphate solubility product in extracellular fluid is exceeded. A value of 75 (mg/dl \times mg/dl) is commonly taken as the limit that, if surpassed, causes mineral precipitation. However, the critical value for renal calcification is not precisely defined and may vary with age.(55) In adults, some consider 70 to be the maximal safe level for the kidney. Possibly, children tolerate a somewhat higher value because they have greater serum phosphate concentrations compared with adults. However, this is not well established.(55)

The material that comprises metastatic calcification may be amorphous calcium phosphate initially, but hydroxyapatite is deposited soon after.(22) The anatomic pattern of deposition varies somewhat between hypercalcemia and hyperphosphatemia, but occurs irrespective of the specific underlying condition or mechanism for the disturbed mineral homeostasis. Additionally, there is a predilection for certain tissues.

Hypercalcemia is typically associated with mineral deposits in the kidneys, lungs, and fundus of the stomach. In these “acid-secreting” organs, a local alkaline milieu may account for the calcium deposition. In addition, the media of large arteries, elastic tissue of the endocardium (especially the left atrium), conjunctiva, and periarticular soft tissues are often affected. However, why these sites are predisposed is not well understood. In the kidney, hypercalciuria may cause calcium phosphate casts to form within the tubule lumen, or calculi to develop in the calyces or pelvis. Furthermore, calcium phosphate may precipitate in peritubular tissues. In the lung, calcification affects the alveolar walls and the pulmonary venous system. Well-established causes of metastatic calcification mediated by hypercalcemia include the milk-alkali syndrome, hypervitaminosis D, sarcoidosis, and hyperparathyroidism (Table 1).

| TABLE 1. DISORDERS ASSOCIATED WITH EXTRASKELLETAL CALCIFICATION OR OSSIFICATION |
|-----------------|-----------------|-----------------|-----------------|
| A. Metastatic calcification |
| I. Hypercalcemia |
| a. Milk-alkali syndrome |
| b. Sarcoidosis |
| c. Hyperparathyroidism |
| d. Hyperphosphatemia |
| e. Renal failure |
| II. Hyperphosphatemia |
| a. Tumoral calcinosis |
| b. Hypoparathyroidism |
| c. Pseudohypoparathyroidism |
| d. Cell lysis after chemotherapy for leukemia |
| e. Renal failure |
| B. Dystrophic calcification |
| I. Calcinosus (universalis or circumscripta) |
| a. Childhood dermatomyositis |
| b. Scleroderma |
| c. Systemic lupus erythematosus |
| II. Post-traumatic |
| C. Ectopic ossification |
| I. Myositis ossificans (post-traumatic) |
| a. Burns |
| b. Surgery (joint replacement) |
| c. Neurologic injury |
| II. Fibrodysplasia (myositis) ossificans progressiva (FOP) |
| III. Progressive osseous heteroplasia (POH) |
| IV. Osteoma cutis |

The author has reported no conflicts of interest.
Hyperphosphatemia of sufficient severity to cause metastatic calcification occurs in idiopathic hypoparathyroidism or pseudohypoparathyroidism and with the massive cell lysis (release of cellular phosphate) that can follow chemotherapy for leukemia (Table 1). Renal insufficiency is commonly associated with metastatic calcification—the mechanism may involve hyperphosphatemia, hypercalcemia, or both. Of interest (but unexplained), ectopic calcification is more common in pseudohypoparathyroidism (type I) than in idiopathic hypoparathyroidism despite comparable elevations in serum phosphate levels. Furthermore, the location of ectopic calcification in pseudohypoparathyroidism and hypoparathyroidism (e.g., cerebral basal ganglion) is different from observations in hypercalcemia. With hyperphosphatemia, calcification of periarticular subcutaneous tissues is characteristic and may be related to tissue trauma from the movement of joints.

Dystrophic calcification occurs despite a normal serum calcium–phosphate solubility product. Injured tissue of any kind is predisposed to this type of extraskeletal calcification. Apparently, tissues can release material that has nucleating properties. One classic example is the caseous lesion of tuberculosis. However, what local factor predisposes to the precipitation of calcium salts is unknown. Indeed, several mechanisms seem likely. It is clear that mineral precipitation into injured tissue is even more striking and more severe when either the calcium or phosphate level in extracellular fluid is increased. The deposited mineral, as for metastatic calcification, may involve a relatively localized area with small deposits of calcium phosphate in the skin and subcutaneous tissues, especially over the extensor aspects of the joints and the fingertips (calcinosis circumscripta); or, it may be widespread and not only in the skin and subcutaneous tissues, but deeper in periarticular regions as well as areas of trauma (calcinosis universalis). The lesions of calcinosis are small or medium-sized hard nodules that can cause muscle atrophy and contractures. Other etiologies for calcinosis include metastases or trauma that produce necrotic tissue.

Ectopic ossification is associated with two principal etiologies. It occurs sporadically with the fasciitis that follows neurological injury, surgery, burns or trauma, when it is called myositis ossificans. It also occurs as the major feature of a separate, heritable entity—fibro dysplasia (myositis) ossificans progressiva—where the pathogenesis is becoming understood. Some ascribe the ectopic bone formation in this latter, genetic disorder to be a muscle abnormality (myositis ossificans progressiva), whereas others favor a connective tissue defect (fibro dysplasia ossificans progressiva). In all of these conditions, osseous tissue is formed. The bone is lamellar, is actively remodeled by osteoblasts and osteoclasts, has haversian systems, and sometimes contains marrow. Apparently, the injured or diseased tissue has the necessary inductive signals and precursor cells to form cartilage and bone. Described in the following chapters are tumoral calcinosis, dermatomyositis, fibro dysplasia ossificans progressiva (FOP), and vascular diseases, which represent the principal examples of each type of ectopic mineralization.

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Chapter 77. Tumoral Calcinosis

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INTRODUCTION

Tumoral calcinosis, first described in 1899, is a heritable disorder that features periarticular metastatic calcification. Hyperphosphatemia is a pathogenetic factor in many patients. Mineral deposition manifests as soft tissue masses around the major joints. Typically, the hips and shoulders are affected, although additional joints can be involved. Visceral calcification does not occur, but segments of vasculature may contain deposits. The differential diagnosis includes periarticular metastatic calcification from hypercalcemia associated with renal failure, milk-alkali syndrome, sarcoidosis, and vitamin D intoxication.

CLINICAL PRESENTATION

Most patients in North America with this disorder have black ancestry. About one third of cases are familial. Autosomal recessive inheritance is usually described, although autosomal dominant transmission has also been reported. There is no gender preference.

The author has reported no conflicts of interest.
Tumoral calcinosis often presents in childhood, but characteristic masses have been discovered in infancy and in old age. Hyperphosphatemic patients are usually black, have a positive family history, manifest the disease before 20 years of age, and have multiple lesions. The soft tissue calcifications are typically painless and grow at variable rates. After 1 or 2 years, the masses may be the size of an orange or grapefruit and weigh 1 kg or more. Often they are hard, lobulated, and firmly attached to deep fascia. Occasionally, the swellings infiltrate into muscles and tendons. The major clinical complications are related to the tumors that occur around joints and the sequelae in skin, marrow, teeth, and blood vessels. Because the deposits are extracapsular, joint range of motion is not impaired unless the tumors are particularly large. There can, however, be compression of adjacent neural structures. The lesions can also ulcerate the skin and form a sinus tract that drains a chalky fluid; this complication may lead to infection. Other potential secondary problems include anemia, low-grade fever, regional lymphadenopathy, splenomegaly, and amyloidosis. Some patients have characteristics of pseudoxanthoma elasticum (i.e., skin and vascular calcifications and angiod streaks in the retina). A dental abnormality, featuring short bulbous tooth roots and calcific deposits that often obliterate pulp chambers, is a hallmark. Recurrent episodes of bone inflammation have been characterized. This is a lifelong disorder.

**RADIOGRAPHIC EXAMINATION**

The tumors typically appear as large aggregations of irregular, densely calcified lobules that are confined to soft tissues (Fig. 1). Radiolucent fibrous septae account for the lobular appearance. Occasionally, fluid layers are seen within the masses. The joints per se are unaffected. Bone texture and density are also unremarkable.

A “diaphysitis” has been recognized using radiographs, CT, or MRI in some cases of tumoral calcinosis. New bone formation occurs along the endosteal surface of the diaphysis, perhaps from calcific myelitis. This finding may be confused with osteomyelitis or a neoplasm. When only calcific myelitis is present, CT and MRI are excellent tools for diagnosis. Bone scanning, however, is the best method to detect and localize the calcified masses.

Periarticular masses that are radiologically indistinguishable from those of tumoral calcinosis occur in chronic renal failure when mineral homeostasis is poorly controlled.

**LABORATORY FINDINGS**

Serum calcium levels and alkaline phosphatase activity are usually normal. Hyperphosphatemia and increased serum calcitriol levels occur in some patients. The TmP/GFR (phosphate transport maximum/glomerular filtration rate) may be supranormal, but renal function is otherwise unremarkable. Patients are in positive calcium/phosphate balance. Urinary studies reflect both the ongoing calcium and phosphate retention, and some patients are frankly hypocalcemic.

The chalky fluid in lesions is predominantly hydroxyapatite.

**HISTOPATHOLOGY**

The masses of tumoral calcinosis are essentially foreign body granuloma reactions that form multicellular, cystic structures. The early lesion may involve hemorrhage and histiocytic nodules embedded in a dense collagenous stroma. The cysts have tough connective tissue capsules, and their fibrous walls contain numerous foreign body giant cells. Mature lesions are filled with calcific deposits that occur around joints and the sequelae in skin, marrow, teeth, and blood vessels. Because the deposits are extracapsular, joint range of motion is not impaired unless the tumors are particularly large. There can, however, be compression of adjacent neural structures. The lesions can also ulcerate the skin and form a sinus tract that drains a chalky fluid; this complication may lead to infection. Other potential secondary problems include anemia, low-grade fever, regional lymphadenopathy, splenomegaly, and amyloidosis. Some patients have characteristics of pseudoxanthoma elasticum (i.e., skin and vascular calcifications and angiod streaks in the retina). A dental abnormality, featuring short bulbous tooth roots and calcific deposits that often obliterate pulp chambers, is a hallmark. Recurrent episodes of bone inflammation have been characterized. This is a lifelong disorder.

**TREATMENT**

Surgical removal of subcutaneous calcified masses may be helpful if they are painful, interfere with function, or are cosmetically unacceptable. When tumor excision is complete, recurrence seems unlikely.

Radiation therapy and cortisone treatment have not been effective. Although it might seem that large masses of apatite crystals would be refractory to dissolution, success with aluminum hydroxide therapy (together with dietary phosphate and calcium deprivation) has been reported. Furthermore, reduction of phosphate levels in extracellular fluid could help
to prevent reformation of mineral deposits.\(^{(2)}\) Preliminary studies indicate that calcitomin therapy may also be efficacious by enhancing phosphaturia.\(^{(23)}\) Acetazolamide, together with aluminum hydroxide, seemed to be helpful for one patient.\(^{(24)}\)

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**Chapter 78. Dermatomyositis in Children**

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**INTRODUCTION**

Dermatomyositis is a multisystem connective tissue disorder caused by small vessel vasculitis.\(^{(1,2)}\) Acute and chronic, non-suppurative inflammation involves especially the skin and striated muscles. Dystrophic calcification can follow episodes of inflammation and can be severely debilitating.\(^{(1,3)}\)

**CLINICAL PRESENTATION**

There are more female than male patients and two peak ages of incidence: childhood (5–15 years) and adulthood (50–60 years). When the disorder manifests before age 16 years, it is called juvenile or childhood dermatomyositis.\(^{(1,2)}\) The adult form is associated with malignancy.\(^{(3)}\)

In juvenile dermatomyositis, the patient’s sex and the age-of-onset of symptoms seem unrelated to the severity of any calcinosis, although increased time to diagnosis and treatment worsen this complication.\(^{(4)}\) Calcification is generally noted 1–3 years after the disease onset and occurred in 25–50% of patients before intensive therapeutic regimens became available for dermatomyositis. Calcification may predate the myopathy.\(^{(5)}\) Mineral deposits develop over 1–3 years. In calcinosis universalis (see below), calcification occurs throughout the subcutaneous tissues, but primarily in periarticular regions or in areas that are subject to trauma (Fig. 1). In calcinosis circumscripta, the deposits are more localized and typically occur around joints. The ectopic mineralization can cause pain, ulcerate the skin, limit mobility, result in contractures, and predispose to abscess formation. Although the dystrophic calcification then typically remains stable, rarely some spontaneous resolution is reported.\(^{(1,2)}\) Dystrophic calcification is rare in adults with dermatomyositis.\(^{(3)}\)

**LABORATORY FINDINGS**

Although hypercalcemia with hypercalcuria and hyperphosphaturia may occur in juvenile dermatomyositis, parameters of mineral homeostasis are usually normal.\(^{(5)}\) Elevated levels of γ-carboxyglutamic acid have been found in the urine of af-

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fected children—especially if there is calcinosis.(8) Hydroxyapatite comprises the nucleus of the calcinosis deposits, but other factors (including cytokines and macrophages) are also present.(9)

**RADIOGRAPHIC FINDINGS**

In juvenile dermatomyositis, four types of dystrophic calcification occur:(10)

1. Superficial masses (small circumscribed nodules or plaques) within the skin
2. Deep, discrete, subcutaneous, nodular masses (Fig. 1) near joints that can impair movement (calcinosis circumscripta)
3. Deep, linear, sheet-like deposits within intramuscular fascial planes (calcinosis universalis)
4. Lucy reticular subcutaneous deposits that encase the torso to form a generalized “exoskeleton”

Children with severe disease refractory to medical therapy seem especially prone to developing exoskeleton-like calcifications. In turn, the exoskeleton is associated with severe calcinosis and poor physical function. Skeletal scintigraphy can be useful.(11) MRI is also helpful for diagnosis by showing muscle edema.(12)

**ETIOLOGY AND PATHOGENESIS**

Juvenile dermatomyositis seems to be a form of complement-mediated microangiopathy.(13) HLA-DQA1*051 may be a predisposing factor.(14) The precise cause of the dystrophic calcification is unknown. However, immune deficiencies may predispose the patient to this complication.(15) Calcinosis seems to occur in the majority of long-term survivors and may reflect a scarring process. This hypothesis is supported by the observation that mineral deposition appears primarily in the muscles that were most severely affected during the disease’s acute phase. Electron microscopy shows that the calcification consists of hydroxyapatite crystals,(16) but other important factors and cells seem to be significant constituents.(9) μCT and X-ray diffraction reveal hydroxyapatite with varied microstructures.(17)

A variety of mechanisms considered for the dystrophic calcification include release of alkaline phosphatase or free fatty acids from diseased muscle that, in turn, directly precipitate calcium or first bind acid mucopolysaccharides. Increased urinary levels of γ-carboxylated peptides suggest that calcium-binding proteins may be responsible for the mineral deposition.

**TREATMENT**

High-dose prednisone therapy soon after the onset of symptoms seems to be important for minimizing the risk of calcinosis and for ensuring good, functional recovery.(1,2,18,19) If the response is incomplete, consideration is given to additional immunosuppressive agents, including methotrexate and cyclosporine.(20) In a small clinical trial, warfarin treatment to decrease γ-carboxylation was not associated with changes in calcium or phosphorus excretion or in a reduction of calcinosis.(21) Phosphate-binding antacid therapy may reverse the mineral deposition.(22) Remarkable resolution of calcinosis can occur with probenecid therapy to improve renal handling of phosphate.(23) Positive responses to alendronate(24) and increasingly positive responses to diltiazem treatment are reported.(25) Troublesome calcium deposits can be removed surgically.

**PROGNOSIS**

The clinical course of dermatomyositis in children is variable. Some have long-term relapsing or persistent disease, whereas others recover. When recovery is incomplete, there may be severe residual weakness, joint contractures, and calcinosis. The calcinosis may be the principal cause of long-term disability.(1–6,23)

**REFERENCES**

Chapter 79. Vascular Calcification

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INTRODUCTION

The details of tissue calcium homeostasis in the skeleton are beginning to emerge. Interactions between a functional triumvirate of endothelial, mesenchymal, and hematopoietic cell lineages control bone formation and bone resorption—entrained to morphogenetic, metabolic, inflammatory, and mechanical demands placed on the skeleton. However, with advancing age, vascular inflammation, hypertension, and certain dysmetabolic states (diabetes, dyslipidemia, uremia, hyperphosphatemia), calcium accumulates to a substantial extent in another venue—the arterial macrovasculature.1,2 Mechanistic studies of vascular calcification and vascular calcium metabolism significantly lag behind those of skeletal mineral physiology. Recent data show that “osteogenic” and “chondrogenic” mechanisms resembling those of craniofacial or endochondral bone formation control vascular mineral deposition.1,2 As in bone, cells of endothelial, mesenchymal, and hematopoietic cell lineages control vascular mineral metabolism, entrained to morphogenetic, metabolic, inflammatory, and mechanical demands experienced by any particular vascular segment. This chapter provides a very brief overview of vascular calcification, organized into histoanatomic categories that highlight known or probable differences in pathobiology, and thus may potentially guide future development of effective pharmacotherapeutic approaches.

ATHEROSCLEROTIC CALCIFICATION

The most common form of vascular calcification is atherosclerotic calcification (Table 1), in which hydroxyapatite mineral forms inside intimal plaque in association with lipid deposits and monocyte–macrophage infiltration. Until recently, atherosclerotic vascular calcification was considered an uncommon, passive, degenerative, inevitable process of aging. However, with advancing age, vascular inflammation, hypertension, and certain dysmetabolic states (diabetes, dyslipidemia, uremia, hyperphosphatemia), calcium accumulates to a substantial extent in another venue—the arterial macrovasculature.1,2 Mechanistic studies of vascular calcification and vascular calcium metabolism significantly lag behind those of skeletal mineral physiology. Recent data show that “osteogenic” and “chondrogenic” mechanisms resembling those of craniofacial or endochondral bone formation control vascular mineral deposition.1,2 As in bone, cells of endothelial, mesenchymal, and hematopoietic cell lineages control vascular mineral metabolism, entrained to morphogenetic, metabolic, inflammatory, and mechanical demands experienced by any particular vascular segment. This chapter provides a very brief overview of vascular calcification, organized into histoanatomic categories that highlight known or probable differences in pathobiology, and thus may potentially guide future development of effective pharmacotherapeutic approaches.

atherosclerotic calcification


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Atherosclerotic intimal calcification (type Vb atherosclerotic plaque)
Medial artery calcification of diabetes and chronic kidney disease
Elastocalcific medial artery calcification (Marfan’s syndrome, pseudoxanthoma elasticum)
Cardiac valve calcification (native and bioprosthetic)
Calcific uremic arteriolopathy (‘cutaneous calciphylaxis’)
Cardiac annulus calcification
Post-infarct myocardial calcification
Pericardial calcification
Soft tissue calciphylaxis including vessels (acute hyperphosphatemia and renal failure)
Calcifying primary cardiac tumors
Portal vein calcification
Pelvic vein pleboliths

TABLE 1. Histoanatomic Types of Vascular Calcification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Atherosclerotic intimal calcification</td>
<td>Calcium deposits in the artery wall are generally composed of hydroxyapatite mineral, and it is little known that calcium deposits in the artery wall are generally composed of hydroxyapatite mineral, it is little known that ~15% of calcified plaques contain fully formed lamellar bone. As Virchow noted in 1863, some cases of vascular calcification are not mere calcification, but “ossification with real plates of bone.” Usually, the bone tissue is positive for osteoclast markers. Usually, the bone tissue is associated with and appears to arise from calcified matrix. The mature bone tissue does not usually appear until vascular invasion of the deposit. It is remarkable to note that, in its mature stage, atherosclerotic calcification actually contains vessels within bone structures that are, themselves, within a vessel. Thus, angiogenesis and biology of the vasa vasorum play important roles in the formation of advanced atherosclerotic calcification.</td>
</tr>
<tr>
<td>Medial artery calcification</td>
<td>Calcium deposition with inflammation, fibrosis, compromise of the internal elastic lamina, apoptic body formation, and calcium deposition herald formation of the type Vb calcified atherosclerotic plaque. Atherosclerosis deforms the lumen and potentially provides a focus for thrombosis and acute occlusion. In medial artery calcification, calcium deposition is concentric, compromising vascular compliance without lumen deformation. Low-grade adventitial inflammation, elastinolysis, and vascular smooth muscle cell matrix vesicle formation drive concentric disease processes. Of note, vascular calcification is only one component of the pathobiology that contributes to reduced vascular compliance. Myofibroblast proliferation, vascular monocyte–macrophage infiltration, and microvessel formation (angiogenesis) are key components of osteogenic vascular calcification responses in macrovascular settings. CaPO4, apatitic calcium phosphate deposition.</td>
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<td>Elastocalcific medial artery calcification</td>
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<tr>
<td>Calcific uremic arteriolopathy (‘cutaneous calciphylaxis’)</td>
<td>Calcium deposition with inflammation, fibrosis, compromise of the internal elastic lamina, apoptic body formation, and calcium deposition herald formation of the type Vb calcified atherosclerotic plaque. Atherosclerosis deforms the lumen and potentially provides a focus for thrombosis and acute occlusion. In medial artery calcification, calcium deposition is concentric, compromising vascular compliance without lumen deformation. Low-grade adventitial inflammation, elastinolysis, and vascular smooth muscle cell matrix vesicle formation drive concentric disease processes. Of note, vascular calcification is only one component of the pathobiology that contributes to reduced vascular compliance. Myofibroblast proliferation, vascular monocyte–macrophage infiltration, and microvessel formation (angiogenesis) are key components of osteogenic vascular calcification responses in macrovascular settings. CaPO4, apatitic calcium phosphate deposition.</td>
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<td>Calcium deposition with inflammation, fibrosis, compromise of the internal elastic lamina, apoptic body formation, and calcium deposition herald formation of the type Vb calcified atherosclerotic plaque. Atherosclerosis deforms the lumen and potentially provides a focus for thrombosis and acute occlusion. In medial artery calcification, calcium deposition is concentric, compromising vascular compliance without lumen deformation. Low-grade adventitial inflammation, elastinolysis, and vascular smooth muscle cell matrix vesicle formation drive concentric disease processes. Of note, vascular calcification is only one component of the pathobiology that contributes to reduced vascular compliance. Myofibroblast proliferation, vascular monocyte–macrophage infiltration, and microvessel formation (angiogenesis) are key components of osteogenic vascular calcification responses in macrovascular settings. CaPO4, apatitic calcium phosphate deposition.</td>
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</table>

FIG. 1. Arterial calcification. In arterial cross-section, three layers—intima, media, and adventitia—are present from the lumen outward. In atherosclerosis, eccentric, subintimal atheroma formation, cholesterol deposition with inflammation, fibrosis, compromise of the internal elastic lamina, apoptic body formation, and calcium deposition herald formation of the type Vb calcified atherosclerotic plaque. Atherosclerosis deforms the lumen and potentially provides a focus for thrombosis and acute occlusion. In medial artery calcification, calcium deposition is concentric, compromising vascular compliance without lumen deformation. Low-grade adventitial inflammation, elastinolysis, and vascular smooth muscle cell matrix vesicle formation drive concentric disease processes. Of note, vascular calcification is only one component of the pathobiology that contributes to reduced vascular compliance. Myofibroblast proliferation, vascular monocyte–macrophage infiltration, and microvessel formation (angiogenesis) are key components of osteogenic vascular calcification responses in macrovascular settings. CaPO4, apatitic calcium phosphate deposition. © 2006 American Society for Bone and Mineral Research
calcific arterial lesions also contain osteogenic regulatory and transcription factors such as BMP2, Mxs2, Runx2, Osterix, and Wnts. Current evidence indicates that, in vascular cells, BMP2 signaling initiates ectopic osteoblastic differentiation.

In addition to bone, atherosclerotic lesions may contain cartilage tissue, amorphous calcification, marrow-like tissue, and adipose tissue. The origin of all these tissues is not clear, but the possibilities are intriguing. One consideration is that there are resident mesenchymal stem cells in the artery wall. The smooth muscle cells of the tunica media contain heterogeneous subpopulations. Some, including aortic myofibroblasts, bovine aortic calcifying vascular cells (CVCs), and microvascular pericytes, are now known to have multilineage potential in vitro, generating osteogenic, chondrogenic, leiomyogenic, marrow stromal, and adipogenic lineages under regulation of BMP2 and Wnt signaling. It is also possible that the multipotential cells in the artery wall arise from the adventitial layer. Adventitial cells, in turn, may originate in the bone as marrow stromal cells and immigrate to the atherosclerotic plaque through the circulation entering through the adventitial vasa vasorum. Recent evidence that atherosclerotic plaques derive in part from progenitor cells in the adventitia and circulation. However, the relative contributions of regional vascular mesenchymal progenitors versus circulating marrow-derived mesenchymal progenitors has yet to be determined.

**In Vitro Models of Vascular Calcification.** A variety of cells harvested from the artery wall, with the exception of endothelial cells, produce hydroxyapatite mineral in vitro. Unschooled medial smooth muscle cells, in the same manner as osteoblastic cells, mineralize the film of extracellular matrix overlying cellular monolayers in the presence of exogenous phosphate donors. Occasionally, these cultures will produce a 3D cellular aggregate containing mineral. Such mineralized aggregates are produced in cultures of bovine microvascular pericytes, human aortic smooth muscle cells, and bovine aortic smooth muscle cells. The spatial frequency of nodules is increased several-fold in about one third of single-cell derived subcultures of bovine aortic smooth muscle cells (SMCs) termed CVCs. The nodules range widely in size—from about 100 to 1500 mm in diameter—and contain irregularly shaped hydroxyapatite mineral deposits within their core. The regular spacing of the nodules seems to be mediated by a reaction–diffusion process involving the morphogens BMP2 and one of its inhibitors, matrix GLA protein (MGP). Bovine pericytes, retinal microvascular smooth muscle cells, require several weeks to produce calcified nodules; bovine cloned CVCs and human SMCs require about 10–14 days. The rate is affected by exogenous ascorbic acid, presumably caused by the changes in extracellular type I collagen production.

**In Vivo Models of Atherosclerotic Calcification.** Mice deficient in apolipoprotein E develop spontaneous vascular calcification, primarily in the form of cartilaginous metaplasia. Interestingly, these mice also have increased BMD, presumably related to deficiencies in vitamin K delivery. Most severely affected are the great vessels of the heart, especially the brachiocephalic (innominate) artery. Mice deficient in the low-density lipoprotein receptor (LDLR) develop hyperlipidemia and vascular calcification when exposed to a high-fat diabetogenic diet. Mice expressing the human LPA gene develop calcified aortic lesions. Certain strains of mice are more predisposed to develop spontaneous vascular calcification through endochondral calcific metaplasia. Atherosclerotic calcification can be induced by vitamin D and calcium supplements in hyperlipidemic rabbits. Vitamin D also enhances warfarin-induced vascular calcification in rats, but without atherosclerosis (see medial artery calcification below).

**Role of Hyperlipidemia and Inflammatory Lipids in Atherosclerotic Vascular Calcification.** Atherosclerosis and atherosclerotic vascular calcification associate epidemiologically with hyperlipidemia (Table 2). In young adults with homozygous familial hypercholesterolemia, atherosclerotic coronary calcification is essentially universal, and its severity correlates with the severity and duration of the hypercholesterolemia as measured in cholesterol-years. In coronary artery disease patients, progression of coronary calcification correlates with the severity of hyperlipidemia. Conversely, when patients successfully lower their cholesterol levels with lipid-lowering agents, the rate of progression of coronary calcification is reduced. This epidemiological evidence together with the close physical relationship between vascular calcification and atherosclerotic lesions strongly suggest that the two are mechanistically related. Lipid may directly contribute to hydroxyapatite mineral proliferation. At the ultrastructural level, hydroxyapatite mineral crystals from atherosclerotic lesions are physically associated with microcrystals of cholesterol. Boskey and Posner showed that phospholipids form complexes with calcium and phosphate in mineral initiation, and the phospholipids in matrix vesicles may be crucial in nodule formation. One of the earliest sites of calcification in atherosclerosis is in the elastin layer, where dietary lipids incorporate into the molecular structure. While it is generally assumed that the calcium deposits follow from inflammatory effects of the cholesterol deposits, some data suggest that calcium hydroxyapatite crystals trigger the inflammatory reaction in atherosclerosis rather than vice versa; such responses have the tremendous potential to fuel rapid vascular disease progression through procalcific “feedforward” mechanisms. In vitro, interleukin-6 (IL-6), TNF-α, 25-hydroxycholesterol, TGF-β, fibronectin and collagen I, and inflammatory lipoproteins/phospholipids induce osteoblastic differentiation in vascular smooth muscle cells. In vivo, mice with hyperlipidemia develop both atherosclerosis and vascular calcification. Apoptosis occurs in atherosclerotic plaques, producing apoptotic bodies that nucleate mineral deposition through mechanisms similar to those used by the geometrically smaller matrix vesicle.

### Clinical Issues in Atherosclerotic Calcification

**Clinical Significance.** The correlation between the degree of calcification and atherosclerosis is strong enough that the “calcium score” is a reliable clinical marker for coronary artery disease, predicting cardiovascular events independently and more accurately than some conventional risk factors. As
might be expected, the degree of calcification correlates quantitatively with the volume of atherosclerotic plaque burden. Clinical consequences of vascular calcification primarily stem from perturbed endothelial antithrombotic function and mechanical rigidity of the aortic arch and cardiac valves. Normally highly resilient and rich in elastin, these structures develop high flow impedance once calcified, resulting in hypertension, left ventricular hypertrophy, heart failure, aortic stenosis, coronary ischemia, complications of cardiovascular surgery and procedures, as well as possible acute coronary syndrome and myocardial infarction. Aortic recoil is required for maintaining diastolic aortic pressure, which, in turn, is required for coronary perfusion. Calcified aortas lack recoil, resulting in attenuated diastolic perfusion, high pulse pressure, and coronary insufficiency. It remains controversial whether calcified plaques convey mechanical stability or instability to atherosclerotic lesions. Although most plaques that rupture are calcified, and numerous calcium deposits increase the risk of rupture, ~80% of significantly narrowed plaques are calcified. Real-time imaging during human angioplasty and engineering considerations suggest that solid mechanical failure stresses are concentrated at the edges of calcium deposits.

Inhibition of Atherosclerotic Calcification. If lipids promote vascular calcification, an obvious approach to inhibition would be lipid-lowering agents. Patients who successfully lower their cholesterol levels significantly reduce progression of their coronary calcification.(24) Atherogenic effects of oxidized lipids are also blocked by high-density lipoprotein (HDL) and in vitro vascular calcification. In an entirely different mechanism, osteopontin seems to inhibit mineralization both at the physico-chemical level of stearic inhibition of crystal growth, as well as at the level of cellular genetic regulation.(34) An in vivo model for regression of ectopic calcification has been developed using an allograft of glutaraldehyde-fixed cardiac valvular tissue implanted subcutaneously in mice. Using this model, Steitz et al.(35) showed that osteopontin blocks ectopic calcification; in addition, osteopontin promotes calcium cress by inducing invading monocyte/macrophage/carbonic anhydrase II, thus acidifying the extracellular matrix and enhancing calcium mobilization. Given that atherosclerotic lesions are already rich in osteostat progenitors in the form of diapedetic monocytes, it is conceivable that existing atherosclerotic calcification could be reversed by local induction of osteostat resorption—essentially by eliciting osteoporosis in the artery wall. Indeed, osteostat-like cells have been identified histopathologically in calcified atherosclerotic lesions.(19) These multinucleated cells stain positively for tartrate resistant acid phosphatase and cathepsin K, but it remains to be established whether they are bona fide osteostats. The net effects of augmenting “vascular osteostat” activity on vascular health and integrity is as yet unknown.

CARDIAC VALVE CALCIFICATION

Cardiac valve leaflets are remarkably thin and pliable, yet strong and inelastic, consisting of two layers of interstitial cell myofibroblasts surrounded on either side by endothelial mono-layers.(36) Valvular sclerosis (fibrosis) is a common occurrence during hypertension, inflammation, diabetes, dyslipidemia, and advanced age, and can occur in the absence of narrowing of the valvular opening. Once the scarring becomes sufficiently advanced to narrow the orifice (i.e., stenotic), it is usually calcified. Hence, a common disorder is calcific cardiac valve stenosis. Stenosis is most clinically apparent in calcific aortic sclerosis because the aortic valve is in a high pressure system, supplies coronary and systemic circulation, and hence can rapidly threaten hemodynamic stability when severe. Calcification is primarily on the aortic face of the valve, the layer known as the fibrosa. The two other layers, the spongiosa and ventricularis, which face the ventricle, are generally spared.(36) The primary cell type, known as the valvular interstitial cell, is intermediate between fibroblasts and vascular smooth muscle cells. Valve interstitial cell myofibroblasts resemble the aortic adventitial myofibroblasts that contribute to medial artery calcification.(11,21)

Pathobiology of Cardiac Valve Calcification

Native Cardiac Valve Calcification. For years, cardiac valvar stenosis had been attributed solely to mechanical “wear and tear.” Indeed, the endothelium on the two faces are heterogeneous, both in development and in adult valves, which have reduced expression of calcification inhibitors on the high-pressure, aortic face of the leaflets.(37) However, recent evidence converges to support the concept that most aortic calcific valvular stenosis is atherosclerotic. Many of the same molecular and cellular processes driving atherosclerotic calcification have now been shown to enhance valvular calcification. Atherosclerotic and coronary risk factors also convey risk for calcific aortic stenosis. As with atherosclerotic calcification, most of these factors can be categorized as inflammatory or oxidative stressors. In early lesions, increases in subendothelial thicknesses on the aortic face, with myofibroblast intracellular lipid accumulation, expansion of the valve intimal valve fibrous, diffuse stippled calcium deposition, and monocyte-macrophage infiltration histologically evident.(36) Of note, whether valvular calcification arises in response to atherosclerotic stimuli or the hemodynamic stresses such as those experienced with bicuspid aortic valves, inflammatory T-cell infiltrates are observed during the later stages of disease progression. As in atherosclerotic calcification, mature lamellar or endochondral bone tissue is found in ~15% of stenotic cardiac valves.(6) Calcified aortic valves express many of the same osteogenic processes as atherosclerotic calcification, including osteopontin at the mRNA and protein level, BMP2, RANKL, tenasin C, osteocalcin, and alkaline phosphatase activity.(2)

Bioprosthetic Cardiac Valve Calcification. Cardiac valves can be replaced by mechanical or biological tissue protheses. The biological prostheses are usually fashioned from devitalized, glutaraldehyde treated, allograft or xenograft (porcine, bovine) valve or pericardium. Glutaraldehyde treatment is believed to reduce immunogenicity. Bioprosthetic valves have the advantage of not requiring long-term anticoagulation; however, the greatest concern in these valves is ultimate mechanical failure because of mineralization. The observations that cell-free bioprosthetic valves and vascular matrix can mineralize in vitro with inorganic phosphate supplementation(38) has generated some confusion about whether vascular calcification is “cell-regulated.” A clarifying point is that even normal physiological calcification occurs outside of cells, as in cartilage calcification that occurs after apoptotic death of hypertrophic chondrocytes. Interestingly, the valve fixation procedure does not usually remove lipids; however, when lipids are removed experimentally, ex vivo mineralization is reduced.(39) Thus, the cellular regulation occurs at the level of removing PPI-like mineralization inhibitors and generating matrix:lipid complexes that nucleate mineral deposition. As such, valve calcification occurs through cell-regulated mechanisms similar to those directing skeletal mineralization. Of note, vascular and valvular cells require no more, and possibly less, exogenous...
organic phosphate than skeletal-derived osteoblastic primary cells or cell lines; some vascular cells require no supplemental organic phosphate to mineralize in vitro.\(^{(2)}\)

Models of Valve Calcification. Myofibroblastic valve interstitial cells can be harvested from human, canine, lapine, or ovine aortic valves obtained at surgery.\(^{(23)}\) Rajamannan et al.\(^{(49)}\) developed a rabbit model for studying calcific valvuloplasty elicited by diet-induced hyperlipidemia. As with mural vascular cells, these valvular cells incorporate calcium and deposit hydroxyapatite mineral in their matrix. Osteogenic calcification is enhanced by oxysterols, RANKL, and canonical Wnt signaling.\(^{(41)}\) However, it is as yet unclear whether these models fully recapitulate the pathobiology and pharmacology of established human cardiac valve calcification.

Clinical Issues in Cardiac Valve Calcification

Clinical Significance of Calcific Valvular Stenosis and Bioprosthetic Valve Calcification. Calcific aortic stenosis is the most frequent cardiac valve disorder in developed countries and the primary valve disorder in the elderly. It confers high morbidity and mortality.\(^{(42)}\) Valvular calcification can be diagnosed by ultrasonic imaging (echocardiography), but the narrowing of the orifice is ideally assessed by Doppler techniques. Recent evidence suggests that valve calcification can be reliably quantified by EBCT. While bioprosthetic valves do not require long-term anticoagulation, the life span of these implants is generally limited to about 10 years because of calcification that results in stenosis and insufficiency.

Inhibition of Cardiac Valve Calcification. Several strategies have been evaluated in preclinical and clinical models to inhibit cardiac valve calcification. Osteopontin, known to be inhibitory in vascular calcification, is also inhibitory in the in vivo model of valvular calcification developed by Steitz et al.\(^{(35)}\) and co-localizes with mineralization in valves. Another inhibitor validated in vivo is pulsatile teriparatide, a PTH/PTH-related peptide (PTHrP) receptor agonist and bone anabolic agent that concomitantly inhibited cardiac valve calcification in LDL receptor null mice.\(^{(45)}\) Etidronate, used to inhibit heterotopic bone formation after hip surgery, seems to inhibit progression of aortic calcification in patients with end-stage renal disease (ESRD).\(^{(44)}\) Some evidence suggests that lipid lowering may reduce valvular calcification. In the hyperlipidemic rabbit model, treatment to lower serum lipids levels reduced the severity of calcification\(^{(40)}\) through effects on the LDL receptor related protein, LRPS, and canonical Wnt signaling.\(^{(41)}\) Aortic valve calcification progresses more rapidly in subjects with high LDL levels.\(^{(23)}\) However, strategies aggressively focused on LDL-cholesterol reduction with statin therapy seem insufficient to prevent vascular calcification progression once the disease has been initiated.\(^{(63)}\)

MEDIAL ARTERY CALCIFICATION (MONCKEBERG’S MEDIAL CALCIFIC SCLEROSIS)

Medial artery calcification is a highly characteristic feature of diabetes and ESRD.\(^{(1)}\) Although diabetes is the leading cause of ESRD, diabetes is also an independent risk factor for vascular calcification\(^{(46)}\); indeed, even in the presence of chronic renal insufficiency, the extent of medial artery calcification increases with worsening glycemic control.\(^{(47)}\) Uremic and renal insufficiency, the extent of medial artery calcification is enhanced by oxysterols, RANKL, and canonical Wnt signaling.\(^{(41)}\) However, it is as yet unclear whether these models fully recapitulate the pathobiology and pharmacology of established human cardiac valve calcification.

Pathobiology of Medial Artery Calcification

Medial Artery Calcification of Diabetes and Uremia. Medial artery calcification is characterized by the deposition of apatitic calcium phosphate in the tunica media of large vessels—with the notable absence of neointima formation. Medial artery calcium deposition is nucleated by lipopidaemic matrix vesicles that arise from a minimum of two sources: (1) the apoptotic bodies of dying vascular smooth muscle cells (VSMCs) reminiscent of hypertrophic chondrocyte mineralization and (2) the regulated extrusion of mineralizing matrix vesicles from viable VSMCs.\(^{(50)}\) The latter process closely resembles the mineralization of membranous bone formation during craniofacial skeletogenesis. Importantly, Reynolds et al.\(^{(48)}\) have convincingly shown that matrix vesicles can promote or inhibit calcium deposition, dependent on whether serum-derived inhibitors such as fetuin are recruited into MGP-containing complexes. Serum fetuin is taken up by VSMCs and packaged into matrix vesicles that serve to inhibit calcium deposition. Besides inhibiting matrix vesicle nucleation, fetuin promotes VSMC “phagocytosis” of pro-osteogenic matrix vesicles; this highlights the complexity of VSMC-regulated vesicle metabolism that controls the initiation and propagation of vascular calcification. Importantly, production of pro-osteogenic matrix vesicles entails the upregulation of bone alkaline phosphatase (ALP), a key osteoblast ectoenzyme that promotes deposition of calcified extracellular matrix. ALP (a.k.a. tissue nonspecific alkaline phosphatase) is of particular importance. Inorganic pyrophosphate (PiPi) is a cell-generated organic anion that inhibits mineralization—and is a physiologically relevant substrate for ALP hydrolysis. Johnson and Terkeltaub\(^{(49)}\) have elegantly shown that loss of extracellular PiPi derived from (1) the extracellular enzyme NPP1 (ectonucleotide pyrophosphatase/phosphodiesterase I) or (2) the cellular PiPi exporter ANK pre-aspires to massive arterial calcification in murine models. Intriguingly, extracellular pyrophosphate is required to stabilize the myogenic phenotype of VSMCs; VSMCs incapable of generating a PiPi-replete extracellular milieu undergo phenotypic drift and begin to express molecular markers of the chondrogenic lineage. Importantly, chondrogenic “trans-differentiation” and tissue mineralization are inhibited by treatment with nanomolar concentrations of PiPi.\(^{(49)}\) Of note, in the setting of ESRD, circulating PiPi levels are reduced.\(^{(60)}\) Thus, along with the prevalent glucose intolerance, hyperphosphatemia, and fetuin deficiency, reduction in PiPi synergistically promotes the profound calcific vasculopathy that afflicts patients with ESRD.\(^{(41)}\) Strategies that seek to restore serum PiPi “tone” using non-hydrolyzable bisphosphonate PiPi analogs may in fact inhibit progression of vascular calcification.\(^{(44)}\)

Molecular Mechanisms, Vascular Stem Cells, and Relationships to Bone Formation. The molecular mechanisms that regulate vascular calcification in diabetes are beginning to be understood. High-fat diets that induce obesity, insulin-resistant diabetes, and dyslipidemia promote vascular calcification in male LDLR-deficient mice.\(^{(17)}\) In this physiologically relevant model of type II diabetes, the high fat Western diet—a stimulus for obesity and vascular matrix vesicle formation\(^{(61)}\)—activates an aortic adventitial BMP2-Msx2 signaling cascade. Cell cul-
ture studies have shown that Msx2 enhances osteogenic differ-
entiation (ALP induction, calcification) of aortic myofibro-
blasts through Osterix-dependent signals. Analysis of condi-
tioned media from Msx2-expressing 10T1/2 mesenchym-
al cells revealed the elaboration of a pro-osteogenic signal characteris-
tic of a canonical Wnt ligand.(10) Canonical Wnts signal through the heteromeric LDLR-related protein receptors LRP5 and LRP6 to activate osteogenic gene expression through nuclear β-catenin–dependent transcription. Similarly, Msx2-expressing cells express a factor that enhances nuclear accumulation of β-catenin and upregulates activity of β-catenin–dependent transcription driven by a T-cell transcription-
factor/lymphoid enhancer binding factor (TCF/LEF) opti-
mal promoter (TOP)-reporter construct.(10) Pro-osteogenic ac-
tivities of Msx2 were reversed by treatment with Dkk1, an inhibitory ligand for LRP5 and LRP6 signaling. Similar results were observed in vivo in studies of cytomegalovirus immediate early promoter (CMV)-Msx2 transgenic mice,(10) a model previ-
ously validated in studies of Msx2-dependent ectopic calvarial bone formation. Aortic Wnt3a and Wnt7a were upregulated by Msx2 transgene, with concurrent suppression of aortic
Dkk1. Immunohistochemistry showed Msx2 accumulation in the aortic adventitia but induction of ALP in the tunica media. Calcium deposition coincides with ALP expression. Thus, a working model has emerged in which a paracrine BMP2-
Msx2-Wnt signaling cascade, initiated by the adventitial ox-
idative stressors of type 2 diabetes, controls the osteogenic differentia-
tion and mineralization of vascular progenitors through non-endochondral processes.(10) The vector of mural microvascular flow is concentric, with the vasa vaso-
rum coursing from the tunica adventitia to the tunica media. The cen-
tric medial calcification of diabetes arises in part from the anatomic relationship between (1) the Msx2 expressing cells of the periaortic adventitia that elaborate a Wnt-laden osteogenic milieu(10) and (2) CVCs of Demer in the tunica media that undergo osteogenic differentiation in response to signals or cells conveyed through the vasa vaso-
rum.(11) The precise ori-
gins of the Msx2-expressing cells and CVCs are not known; how-
ever, a Scl1+ stem cell population has recently been shown to reside within the aortic adventitia.(12) Whether these cells arise from circulating progenitors(12) or aortic mesoangioblast-like cells is also unclear.

In uremia, a “perfect storm” of calcific vasculopathy occurs.
Approximately 5% of Americans have impaired renal function, and three million patients have the chronic kidney disease (CKD). In this common clinical setting, phosphate ret-
ention, secondary hyperparathyroidism, and the accumula-
tion of PTH fragments that perturb normal calcium phosphate homeostasis drive tremendous vascular calcium loads.(53) The phosphate retention of CKD presents opportunity for intervention(64), but confounds simple interpretation of disease pathophysiology and progression. Hyperphosphatemia stimu-
lates vascular matrix accumulation of proximal calcific VMSC matrix vesicles.(19) Consistent with this, Giachelli et al.(53) have pro-
vided evidence that inhibition of the cellular phosphate trans-
porter, Pit-1, inhibits VMSC calcification and subsequent osteo-/chondrogenic differentiation. Moreover, Vyavahare et al.(59) showed that paracrine vascular PTH, limits VMSC calcification, consistent with results obtained with pulsatile PTH(1–34) administration in vivo(43); thus, the widespread use of calcitriol to limit secondary and tertiary hyperparathyroidism may exert unintended deleterious consequences on vascular calcification load(54) through suppression of vascular PTH, a proteolytic fragment of PTH, PTH(7–84), that accumulates in ESRD and functions to induce resistance to PTH binds the PTH1R and does not elicit signaling cascades; instead it down-
regulates cell surface expression by enhancing dynamin-
dependent internalization.(58) Thus, if PTH1R signaling plays
important roles in promoting skeletal mineral accumulation while simultaneously limiting vascular calcium accumulation, the accumulation of such antagonistic PTH fragments may contribute to the calcific vasculopathy of CKD.

Elastocalcinotic Vascular Calcification: A Distinct Form of Medial Artery Calcification. Recently, it has become apparent that vascular calcification associated with primary alterations in elastin metabolism may in fact represent a unique entry point in a feedforward cycle of medial artery calcification.(59) Large muscular arteries contain elastin as a major extracellular matrix constituent. Aberrant elastin organization and metabolism is characterized by aortic root dilatation, aneurysm formation, and medial calcification and degeneration. This is perhaps most evident in Marfan’s syndrome, where deficiencies in fibrillin 1 (1) cause homeostatic failure in the microfibrillar array of the tunica adventitia to withstand physiological hemodynamic stress; and (2) result in disruption of the tunica media elastin network, smooth muscle cell phenotypic modulation, metallo-
proteinase induction, and calcification as secondary events.(59) Elastocalcinotic calcification—unlike medial artery calcification of diabetes—is not initially associated with matrix vesicle formation; instead, calcium phosphate deposition occurs in associa-
tion with degenerating elastin fibrils of the tunica media. As such, it is a form of medial artery calcification. While molec-
ular mechanisms are not understood, it is apparent that elasti-
nolytic matrix remodeling processes degrading vascular tro-
poelastin and elastin enhance vascular matrix calcium deposition. During the progression of any form of medial calcification, perturbations in elastin metabolism likely contrib-
ute to vascular calcium load. Interestingly, elastin glycoxida-
tion products such as pentosidine accumulate in ESRD, in-
crease vessel stiffness, and enhance matrix calcium binding.(60) However, matrix vesicles are clearly evident in medial calcifi-
cation of ESRD, and as such progresses through mechanisms overlapping those of diabetic medial artery calcification.(30,48)

Elastin-nucleated calcification also occurs in the setting of pseudoexanthema elasticum (PXE), arising from mutations in the ABCG6 gene that causes fragmentation of elastic lamina.(61) Mechanisms are again unknown. Electron microscopy con-
firms deposition of calcium along thickened elastin fibers in the absence of matrix vesicle formation. A murine model of ABCG6 deficiency has been recently reported.(62) Detailed study of this model should provide further insights into the pathobiology of elastocalcinotic medial artery calcification.

In Vivo Models of Medial Artery Calcification. Several mod-
els of medial artery calcification have been developed. The best appreciated models are those associated with vitamin D excess with warfarin + menadione or hypervitaminosis D plus nico-
tine administration.(62,63) These treatments result in an elastocalcinotic medial artery calcification but may also suppress vascular calcification, a paracrine inhibitor of vascular osteogenic differentia-
tion.(57) Other models include genetic osteoprote-
gerin (OPG) deficiency and high-fat diet administration to nephrectomized LDLR+/mice(64) or C57Bl/6 mice possess-
ing the CMV-Msx2 transgene.(10) With OPG deficiency, inti-
mal and medial artery calcification arises.(65) Potentially related to unopposed actions of RANKL on vascular myofibro-
blasts.(66) Pro-osteogenic Wnt signaling cascades are activated by aortic Msx2 gene expression, with calcification triggered by high-fat diabetic diet (vide supra).(10) Induction of chronic renal insufficiency, with attendant phosphate retention, pro-
foundly accelerates calcium deposition in LDLR-/- mice.(66) Side-
by-side comparisons have yet to be performed with these models to clarify mechanistic similarities and differences.
Clinical Issues in Medial Artery Calcification

Clinical Significance of Medial Artery Calcification. Epidemiological studies have clearly shown that medial artery calcification increases the risk of cardiovascular mortality and morbidity in patients with diabetes(67) and uremia.(53) The excess risk for lower extremity amputation and cardiovascular mortality may arise from a type of vascular “diastolic” dysfunction that arises with reduced vascular compliance of elastic arteries. During systole, potential energy is stored within large elastic arteries such as the aorta. Kinetic energy is subsequently released during the relaxation phase of the cardiac cycle, providing diastolic perfusion of the myocardium and sustained perfusion of distal vascular beds.(68) With vessel stiffening, elevated pulse pressure and highly pulsatile flow kinetics interact with elevated systolic blood pressure and increased myocardial oxygen consumption to increase workload and decrease distal tissue perfusion.(68) Compromised elastic artery compliance is likely a major contributor to the increased risk for lower extremity amputation of patients with type 2 diabetes.(67)

Inhibition or Regression of Medial Artery Calcification. Very few studies have explored whether medial artery calcification is preventable or reversible. Price et al.(63) have shown that vitamin D plus warfarin-induced vascular calcification in the rat is inhibited by treatment with OPG. Giachelli et al.(55) have provided evidence that inhibition of the phosphate transporter, Pit-1, inhibits smooth muscle cell calcification and osteo/chondrogenic differentiation. The phosphate binding resin sevelamer inhibits the endochondral vascular calcification of apoE null mice.(69) Moreover, aggressive lipid-lowering therapy with statins suppresses cardiovascular calcification and associated canonical Wnt signaling in dyslipidemic rabbits.(41) However, in human studies, only sevelamer has been unambiguously shown to decrease progression of vascular calcification.(54) A very recent study showed that administration of the endothelin receptor antagonist darusentan induced regression of elastocalcinotic medial calcification in rodents by upregulation of carbonic anhydrase; whether this exciting new strategy is effective in other preclinical models of vascular calcification has yet to be determined.

CALCIFIC UREMIC ARTERIOLOPATHY (CUTANEOUS CALCIPHYLAXIS)

A particularly severe and mercifully uncommon form of vascular calcification is calcific uremic arteriolopathy (CUA), observed in the setting of ESRD. Unlike the highly common macrovascular medial artery and atherosclerotic calcification of ESRD, CUA affects much smaller arteries, most notably the arterioles of the dermis.(70) Clinically, it presents as a vasculitis, with livido reticularis followed by cord-like dermal thickening and subsequent “dry” cutaneous necrosis. The histopathology is medial arteriolar (100–600 micron diameter) calcification with concomitant (1) endovascular, fibroproliferative neointimal constriction; (2) frequent small vessel thrombosis; and (3) fat necrosis with panniculitis and acute inflammatory changes. Similar histopathology can occur in intestinal mesenteric arterioles, and contributes to poor clinical outcome.(70) The pathobiology of CUA is poorly understood. Antecedent hyperphosphatemia and elevated calcium-phosphate product is prevalent but insufficient to explain the disease process. However, treatment with warfarin before onset of CUA is observed in one half of the afflicted patients.(70) MGP is a highly important modulator of BMP signaling and inhibitor of osteo/chondrogenic vascular calcification. BMPs are powerful bone morphogens that promote osteogenic differentiation and ALP induction.

Zebboudj et al.(71) first showed that MGP forms an inhibitory complex with BMPs that precludes ALP induction; this bioactivity is dependent on modification of MGP by Gla residues. Moreover, as shown by Shanahan et al.,(48) MGP–fetuin complexes assembled by vascular smooth muscle cells form vesicles that can actually inhibit vascular calcium deposition. Of note, recent data suggest that undercarboxylated MGP is associated with the risk of calcific vascular disease in patients with normal renal function.(72) Thus, given the above data, we speculate that MGP–fetuin deficiencies associated with weight loss and warfarin treatment in patients with CUA contributes to pathogenesis. However, until a robust animal model of CUA is developed, these notions are again speculative; as previously noted,(70) the original calciphylaxis model of Selye that causes skin necrosis in experimental animals does not recapitulate the histopathology of CUA. Thus, the use of the term “cutaneous calciphylaxis” to connote CUA should probably be discontinued. Future studies will no doubt address whether patients with CUA are particularly deficient in the formation of these novel inhibitory MGP–fetuin vesicles.(48) Infusion of sodium thiosulfate has been used to treat severe calcific uremic arteriolopathy,(73) but no randomized control trial of thiosulfate therapy in any form of vascular calcification has been reported.

MYOCARDIAL, PERICARDIAL, AND ANNULAR CALCIFICATION

Calcium deposits also develop in human myocardial and pericardial tissue in a variety of conditions; these include myocardial infarction—especially with aneurysm formation, pericarditis, and myocarditis. Myocardial dystrophic calcification is visible by chest X-ray in ~ 5–10% of patients who have survived 5+ years after a left ventricular infarct.(74) In mice, spontaneous calcification of the myocardial tissue, known as dystrophic cardiac calcinosis, can be induced by a high-fat diet in certain strains. Using intercrosses of resistant C57Bl/6J and susceptible C3H/HeJ inbred mice, Ivandic et al.(75) identified a major predisposing quantitative trait locus, Dyscalc1, on proximal chromosome 7. Granulomatous diseases (tuberculosis, histoplasmosis, sarcoidosis) were historically the common causes of pericardial calcification; with the incidence of tuberculosis in decline, granulomatous pericardial calcification has also declined.(76) Uremia, systemic lupus, and postviral, post-irradiation, or post-hemopericardium pericardial inflammation are the more common settings in which pericardial calcification is seen today.(76) The stiffening of this tissue produces clinically significant hemodynamic abnormalities leading to restrictive heart failure. The valve annulus, a fibrous ring embedded in the myocardium surrounding each valve, often undergoes calcification through endochondral metaplasia. Cardiac annulus calcification is commonly observed after middle age in women (mitral) or in the setting of uremia and aortic valve calcification. Rarely, primary cardiac tumors such as rhabdomyomas, endothe liomas, and myxomas can also calcify.

VENOUS VASCULAR CALCIFICATION

Calcification does occur in the venous vasculature; indeed, calcified pelvic venous thromboli ths are commonly observed on plain film, but have little known clinical consequence. However, venous vasculature exposed to elevated transmural pressures may become subject to “arterialization” and thus clinically relevant macrovascular calcification in certain disease settings. Calcification of saphenous vein grafts used for coronary bypass certainly represents a visible and relevant example. However, orthotopic venous calcification has been uniformly reported in another common clinical setting—portal
hypertension. Verma et al.\textsuperscript{77} have recently identified that ~11% of patients with cirrhosis have portal and mesenteric venous calcification. The pathobiology and clinical consequences have yet to be evaluated, but a detailed understanding of how venous Wnt/LRP signaling and sphronic venous matrix remodeling responds to elevated transmural pressure promises to be fruitful.

SUMMARY

The above pathogenetic mechanisms—reduced tissue pyrophosphate, elevated serum phosphate levels, enhanced vascular inflammation and oxylipid formation with reduced serum fe- tuin, activated vascular BMP2-Msx2-Wnt signaling, and diminished vascular PTH/PTHrP receptor signaling—offer multiple potential therapeutic strategies. However, in humans, only sevelamer has been unambiguously shown to decrease progression of vascular calcification\textsuperscript{54}; clinical studies of bisphosphonates have been disappointing.\textsuperscript{43} There are a number of biological and epidemiologic links between the processes of osteoporosis and atherosclerosis, suggesting common pathophysiological mechanisms and, thus, potential therapeutic linkage.\textsuperscript{78} Given that bone has vascular channels, lipids deposits in subendothelial spaces of bone tissue and resultant oxidative stress may contribute to both disorders.\textsuperscript{79} Of note, maintaining bone anabolism is important to diminish the risk of vascular calcification in ESRD; excessive reductions in serum PTH in hemodialysis patients results in low-turnover osteoporosis and profound vascular calcification.\textsuperscript{100,101} Indeed, in murine models bone anabolic agents inhibit vascular calcium deposition.\textsuperscript{43,64} The pulsatile PTH responses elicited by calcium receptor antagonists in chronic renal insufficiency may thus help normalize both vascular and skeletal calcium homeostasis.\textsuperscript{56} However, the biological heterogeneity of vascular calcification demonstrates that carefully crafted, controlled and monitored translational research studies are desperately needed to address the tremendous unmet clinical need in this bone and mineral disease.

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51. Column 112:i229–i234.

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Chapter 80. Fibrodysplasia (Myositis) Ossificans Progressiva

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare heritable disorder of connective tissue disease characterized by (1) congenital malformations of the great toes and (2) recurrent episodes of painful soft-tissue swelling that lead to heterotopic ossification.\(^1,2\)

Post-traumatic myositis ossificans, a different disorder, also features heterotopic bone and cartilage formation within soft tissues. Heterotopic ossification may also follow hip replacement, spinal cord injury, and brain injury.

FOP was first described in 1692; >600 cases have been reported.\(^1,2\) This disorder is among the rarest of human afflictions, with an estimated incidence of one per two million live births.\(^1,2\) All races are affected.\(^3\) Autosomal dominant transmission with variable expressivity is established.\(^4,5\) However, reproductive fitness is low, and most cases are sporadic. Gonadal mosaicism has been described.\(^6\)

CLINICAL PRESENTATION

If the typical congenital skeletal malformations are recognized, FOP can be suspected at birth before soft tissue lesions occur.\(^1,2\) The characteristic feature is short great toes, caused by malformation (hallaux valgus) of the cartilaginous anlage of the first metatarsal and proximal phalanx (Fig. 1). In some cases, the thumbs also are strikingly short. Synostosis and hypoplasia of the phalanges is typical.\(^1,2\) FOP is usually diagnosed when soft tissue swellings and radiographic evidence of heterotopic ossification are first noted, although misdiagnosis is common.\(^1,2\)

The severity of FOP differs significantly among patients,\(^3,5\) although most become immobilized and confined to a wheelchair by the third decade of life.\(^1,2,6\) Typically, episodes of soft tissue swelling begin during the first decade of life (Fig. 1);\(^7\) although occasionally, the onset occurs as late as early adulthood.

Painful, tender, and rubbery soft tissue lesions appear spontaneously or may seem to be precipitated by minor trauma including intramuscular injections and influenza-like viral illnesses.\(^8,9\) Swellings develop rapidly during the course of several days. Typically, lesions affect the paraspinal muscles in the back or in the limb girdles and may persist for several months.\(^10\) Aponeuroses, fascia, tendons, ligaments, and connective tissue of voluntary muscles may be affected. Although some swellings may regress spontaneously, most mature through an endochondral pathway, engendering true heterotopic bone.\(^10\) The episodes of induration recur with unpredictable frequency. Some patients seem to have periods of quiescent disease. However, once ossification develops, it is permanent.

Gradually, bony masses immobilize joints and cause contractures and deformity, particularly in the neck and shoulders. Ossification around the hips, typically present by the third decade of life, often prevents ambulation.\(^6\) Involvement of the muscles of mastication (frequently the outcome of injection of local anesthetic or overstretching of the jaw during dental procedures) can severely limit movement of the mandible and ultimately impair nutrition.\(^11,12\) Ankylosis of the spine and rib cage further restricts mobility and may imperil cardiopulmonary function. (Fig. 1).\(^1,11,12,13\) Scoliosis is common and associated with heterotopic bone that asymmetrically connects the rib cage to the pelvis.\(^14\) Hypophosphatasia results from ossification of the paravertebral musculature. Restrictive lung disease and predisposition to pneumonia may follow. However, the vocal muscles, diaphragm, extracardiac muscles, heart, and smooth muscles are characteristically spared.\(^1\) Although secondary amenorrhea may develop, reproduction has occurred.\(^1,5\) Hearing impairment (beginning in late childhood or adolescence) manifests with increased frequency.\(^15\)

RADIOLOGIC FEATURES

Skeletal anomalies and soft tissue ossification are the characteristic radiologic features of FOP.\(^1,16\) The principal malformations involve the great toe, although other anomalies of digits in the feet and hands may occur. Exostoses are frequent.\(^10\) A remarkable feature of FOP is progressive fusion of cervical vertebrae that may be confused with Klippel-Feil syndrome.\(^1,17\) The familial necks may be broad yet short.
However, the remainder of the skeleton is generally unremarkable.\(^{(16)}\)

Ectopic ossification in FOP progresses in several regular patterns or gradients (involvement is generally proximal before distal, axial before appendicular, cranial before caudal, and dorsal before ventral).\(^{(15)}\) Paraspinal muscles are involved early in life, with subsequent spread to the shoulders and hips. The ankles, wrists, and jaw may be affected at later stages.\(^{(17)}\)

Radiographic and bone scan findings suggest normal modeling and remodeling of heterotopic bone.\(^{(18)}\) Fractures are not increased and respond similarly in either the heterotopic or normotopic skeleton.\(^{(19)}\)

Bone scans are abnormal before ossification can be shown by conventional radiographs.\(^{(18)}\) CT and MRI of early lesions have been described.\(^{(20)}\)

**LABORATORY FINDINGS**

Routine biochemical studies of mineral metabolism are usually normal, although alkaline phosphatase activity in serum may be increased, especially during disease “flare-ups,” (i.e., periods of active heterotopic bone formation).\(^{1,2,21}\) Urinary basic fibroblast growth factor (FGF) levels may be elevated during disease flare-ups and coincide with the preosseous angiogenic fibroproliferative lesions.\(^{(22)}\)

**HISTOPATHOLOGY**

The earliest stage of FOP lesion formation consists of an intense aggregation of B and T lymphocytes in the perivascular spaces of otherwise normal-appearing skeletal muscle.\(^{(23)}\) Subsequently, a nearly pure T cell occurs between edematous muscle fibers at the leading edge of an angiogenic fibroproliferative lesion, which is indistinguishable from aggressive juvenile fibromatosis.\(^{(23,24)}\) Immunostaining with a monoclonal antibody against bone morphogenetic protein (BMP)-2/4 is intense in FOP lesions, but not in aggressive fibromatosis.\(^{(24)}\)

Mast cell infiltration is seen at all stages of FOP flare-ups.\(^{(25)}\) Endochondral ossification is the major pathway for heterotopic bone formation.\(^{(10)}\) Mature osseous lesions have haversian systems and can contain hematopoietic tissue.

**ETIOLOGY AND PATHOGENESIS**

Similarities between FOP and the effects of *Drosophila* decapentaplegic gene (*BMP4* homolog) mutations have suggested involvement of the BMP signaling pathway in the pathogenesis of FOP.\(^{(26)}\) In fact, the BMP signaling pathway is highly dysregulated in FOP cells.\(^{(27–31)}\) FOP cells overexpress BMP4, and are unable to appropriately upregulate the expression of multiple BMP antagonists, including Noggin and Gremlin, in response to a BMP challenge.\(^{(27,29,30)}\) Additionally, FOP cells exhibit a defect in BMP receptor internalization and increased activation of downstream signaling, suggesting that altered BMP receptor trafficking underlies ectopic bone formation in this disease.\(^{(31)}\) Recently, BMP4 transgenic mice that develop an FOP-like phenotype have been described.\(^{(32)}\)

An initial genome-wide linkage analysis mapped FOP to 4q27-31; however, subsequent DNA sequence analysis of candidate genes in this and other regions did not identify any mutations.\(^{(33,34)}\) With the discovery of additional pedigrees, a more conservative genome-wide linkage analysis excluded the 4q27-31 region and identified linkage of FOP to 2q23-24, a locus that includes the activin A type I receptor gene, ACVR1, a receptor for bone morphogenetic protein.\(^{(35)}\) An identical heterozygous missense mutation (c.617G>A; R206H) in the glycine-serine (GS) activation domain of ACVR1 was identified in all affected individuals with classic features of either FOP.

**FIG. 1.** Fibrodysplasia (myositis) ossificans progressiva. Characteristic features of FOP are seen in early childhood. The presence of short malformed great toes at birth (A, arrows) heralds the later spontaneous appearance of the preosseous soft tissue lesions on the neck and back (B, arrowheads) and should provoke suspicion of FOP even before the transformation to heterotopic bone (arrows). An inspection of the toes (C) will confirm the diagnosis and may alleviate the need for a lesional biopsy (trauma) that could exacerbate the condition [from Kaplan FS and Smith RM 1997 Clinical vignette: Fibrodysplasia ossificans progressiva (FOP). J Bone Miner Res 12:855 with permission of the American Society for Bone and Mineral Research].

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sporadic or inherited FOP. Protein modeling predicts destabilization of the GS domain, consistent with constitutive activation of ACVR1 as the underlying cause of the ectopic chondrogenesis, osteogenesis, and joint fusions seen in FOP.

**TREATMENT**

There is no established medical treatment for FOP. The disorder’s rarity, variable severity, and fluctuating clinical course pose substantial uncertainties when evaluating experimental therapies. Binders of dietary calcium, radiotherapy, and warfarin are ineffective. Limited benefits have been reported using corticosteroids and disodium etidronate during flare-ups or using isotretinoin to prevent disease activation. However, these impressions reflect uncontrolled studies. Accordingly, medical intervention is currently supportive. Nevertheless, physical therapy to maintain joint mobility may be harmful by provoking or exacerbating lesions. Surgical release of joint contractures is unsuccessful and risks new trauma-induced heterotopic ossification. Removal of FOP lesions is often followed by significant recurrence. Osteotomy of ectopic bone to mobilize a joint is uniformly counterproductive because additional heterotopic ossification develops at the operative site. Spinal bracing is ineffective, and surgical intervention is associated with numerous complications. Dental therapy should preclude injection of local anesthetics and stretching of the jaw. In fact, newer dental techniques for focused administration of anesthetic are available. Guidelines for general anesthesia have been reported. Intramuscular injections should be avoided. Prevention of falls is crucial. Measures against recurrent pulmonary infections and onset of cardiopulmonary complications of restrictive lung disease are important. More focused efforts based on inhibition of BMP signaling may offer hope for the future.

**PROGNOSIS**

Despite widespread heterotopic ossification and severe disability, some patients live productive lives into the seventh decade. Most, however, die earlier from pulmonary complications including pneumonia, secondary to restricted ventilation from chest wall involvement.

**PROGRESSIVE OSSEOUS HETEROPLASIA**

Research on FOP led to the discovery of progressive osseous heteroplasia (POH), a distinct developmental disorder of heterotopic ossification. Like FOP, POH is an autosomal dominant genetic disorder of heterotopic ossification within soft connective tissues. However, unlike in FOP, heterotopic ossification in POH commonly occurs within the dermis and forms by an intramembraneous, rather than an endochondral pathway. Identification of two patients with POH-like features who also had Albright hereditary osteodystrophy suggested the possibility of a genetic link between the two conditions, which was confirmed in a third patient with pure POH. These discoveries led to the rapid identification of paternally inherited inactivating mutations of the GNAS gene as the genetic cause of POH. Reduced expression of G\(\alpha\)s, one of several proteins encoded by GNAS, can induce an osteoblast-like phenotype in human mesenchymal stem cells.

**REFERENCES**

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