This Review is part of a thematic series on Mechanisms of Vascular Calcification, which includes the following articles:

- Pathophysiology of Vascular Calcification in Chronic Kidney Disease
- Angiogenesis and Pericytes in Initiation of Ectopic Calcification
- Lineage Diversity of Vascular Stem Cells: Bone, Cartilage, Marrow
- Osteopontin Promoter Regulation and Phosphate Transport Molecules in Vascular Calcification
- Regulation of Vascular Calcification by Osteoclast Regulatory Factors RANKL and Osteoprotegerin
- Role of Bone Morphogenetic Proteins in Vascular Calcification

Linda Demer, Guest Editor

Pathophysiology of Vascular Calcification in Chronic Kidney Disease

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Abstract—Patients with chronic kidney disease (CKD) on dialysis have 2- to 5-fold more coronary artery calcification than age-matched individuals with angiographically proven coronary artery disease. In addition to increased traditional risk factors, CKD patients also have a number of nontraditional cardiovascular risk factors that may play a prominent role in the pathogenesis of arterial calcification, including duration of dialysis and disorders of mineral metabolism. In histological specimens from the inferior epigastric artery of dialysis patients, we have found expression of the osteoblast differentiation factor core binding factor $\alpha$-1 (Cbfa1) and several bone-associated proteins (osteopontin, bone sialoprotein, alkaline phosphatase, type I collagen) in both the intima and medial layers when calcification was present. In cultured vascular smooth muscle cells, the addition of pooled serum from dialysis patients (versus normal healthy controls) accelerated mineralization and increased expression of Cbfa1, osteopontin, and alkaline phosphatase to a similar magnitude as does $\beta$-glycerophosphate alone. However, a lack of inhibitors of calcification may also be important. Dialysis patients with low levels of serum fetuin-A, a circulating inhibitor of mineralization, have increased coronary artery calcification and fetuin-A can inhibit mineralization of vascular smooth muscle cells in vitro. These data support that elevated levels of phosphorus and/or other potential uremic toxins may play an important role by transforming vascular smooth muscle cells into osteoblast-like cells, which can produce a matrix of bone collagen and noncollagenous proteins. This nidus can then mineralize if the balance of pro-mineralizing factors outweighs inhibitory factors. (Circ Res. 2004;95:560-567.)

Key Words: vascular calcification ■ chronic kidney disease ■ dialysis ■ core binding factor $\alpha$-1

It is estimated that 1 in 9 individuals in the United States have some manifestation of chronic kidney disease (CKD), ranging from proteinuria with normal renal clearance/function to advanced renal failure requiring renal replacement therapy in the form of dialysis or transplantation, commonly called end-stage renal disease (ESRD). In 2002, 406,000 individuals were undergoing renal replacement therapy (dialysis or transplant) in the United States. The American Heart Association recently published a Scientific Statement that details the strong evidence supporting that individuals with CKD should be included in the highest-risk group for cardiovascular disease and therefore receive aggressive preventive measures to reduce the prevalence and severity of cardiovascular disease. However, whether CKD causes cardiovascular disease (CVD) or is a marker of cardiovascular disease...
remains controversial, although clearly CKD patients have significant CVD morbidity and mortality.

Cardiovascular mortality is the leading cause of death in patients treated by dialysis, with mortality 10 to 30 times higher than the general population despite stratification for sex, race, and presence of diabetes. Similarly, cardiovascular mortality is 2 to 5 times higher than the general population in patients with a functioning renal transplant. This is likely from (1) the extremely high prevalence of atherosclerosis, heart failure, and left ventricular failure in hemodialysis patients, observed in 40% to 74% of incident dialysis patients and (2) a high case mortality rate after an acute myocardial infarct or of heart failure. The high prevalence of cardiovascular disease in ESRD patients is also from the high prevalence of Framingham risk factors. The patient population beginning dialysis has changed over the last 20 years. Information collected by the United States Renal Data System (USRDS) demonstrates that in 1980, 13.1% of new patients to dialysis had diabetes as their cause of ESRD. In 2002, 43% to 64% of individuals (range because of differences in race/ethnicity) have diabetes as their cause of ESRD, and 59% of all patients beginning dialysis have diabetes as a primary or secondary diagnosis. Hypertension is the second leading cause (28%) of ESRD, and is found in the majority of individuals at the start of dialysis. The population is also older: The median age of patients on dialysis is now 54.5 years. Thus, dialysis patients have increased risk factors for CVD compared with the general population. However, cross-sectional studies have demonstrated that the Framingham risk equation is insufficient to capture the extent of cardiovascular disease in CKD subjects, implying the presence of additional risk factors. More recently, the role of excessive arterial calcification in dialysis patients compared with the general population and the presence of extensive medial calcification have been cited as possible reasons for the increased cardiovascular mortality in CKD. The Table lists nontraditional risk factors associated with cardiovascular disease in dialysis patients, and arterial calcification in dialysis patients.

Coronary artery calcification is very common in dialysis patients. Depending on the age of the patient population examined, 54% to 100% (mean 83%) of dialysis patients in case series have some degree of coronary artery calcification, with scores markedly above the general population (see recent review). Coronary artery calcification is also present in adolescents and young adults with CKD. Once coronary artery calcification is present in dialysis patients, it is rapidly progressive in nearly all studies, with minimal or no progression after renal transplantation. Unfortunately, there is a paucity of direct comparative data to the general population. Using electron beam CT scan (EBCT), Braun and colleagues documented a 2- to 5-fold increase in coronary artery calcification in dialysis patients compared with age-matched non-CKD patients with angiographically proven coronary artery disease. Pathologically, a comparative study of coronary atherosclerotic lesions in autopsy specimens from 27 ESRD patients and 27 age/gender-matched controls revealed that the plaque area and volume were not different in the two groups, however the plaque was more calcified in the ESRD population. Intimal thickness was not different between the two groups, whereas medial thickness was greater in the ESRD patients. Thus, these data do not support “accelerated” atherosclerosis in ESRD patients but simply more calcification of existing atherosclerosis. There was no medial calcification observed in this study, but it should be emphasized that segments examined were selected based on severe obstructive lesions. Thus, by noninvasive techniques and pathological analysis, there appears to be similar volume of atherosclerotic disease, but excessive calcification. It remains to be determined if some of that excessive calcification observed by EBCT is located in the medial layer.

Another explanation for the increased cardiovascular mortality in ESRD patients is the presence of large vessel disease, which increases myocardial oxygen demand, subendocardial ischemia, and vascular afterload, with a propensity to develop LVH. Studies have demonstrated increased pulse wave velocity, increased pulse pressure, and decreased distensibility in the elastic arteries of the aorta, carotid, and femoral arteries, and increased pulse pressure and pulse wave velocity is associated with increased mortality in ESRD patients. Guerin et al demonstrated that the magnitude of increased pulse wave velocity and pulse pressure was proportional to the magnitude of calcification detected by ultrasound. Histologically, Ibels et al in 1979 evaluated the renal arteries of individuals undergoing renal transplant compared with 25 age-matched controls from autopsy.
or donors, and found that dialysis patients had increased intimal thickness (97% versus 38%), concentric intimal thickness (67% versus 4%), intimal calcification (67% versus 17%), reduplication of the internal elastic lamina (83% versus 38%), and medial calcification (58% versus 17%). Similarly, calcification of the internal iliac arteries in one or more locations was greater in the uremic patients compared with controls (57% versus 7%), as was concentric intimal thickening. Ejerblad noted similar observations in radial arteries: intimal and medial thickening was greater in dialysis patients compared with controls, and calcification was found in the media in 6 of 15 subjects and the intima in 2 of 15 subjects, but in no controls. Thus, there appears to be both intimal/atherosclerotic calcification and medial calcification in the elastic arteries of dialysis patients. The importance of these pathological findings was recently confirmed. London and colleagues examined femoral arteries by plain radiographs, and found that the all-cause and cardiovascular specific mortality was greatest in individuals with intimal calcification, followed by medial calcification, followed by no calcification. Those patients with intimal calcification were more likely to be older, have traditional cardiovascular risk factors, and a history of CVD, whereas those patients with medial calcification were younger and had more severe derangements of mineral metabolism.

In summary, at the present time the data supports that there is excessive atherosclerosis in ESRD patients, but this may represent the high prevalence of underlying risk factors in this population. However, compared with the general population, atherosclerotic lesions are more likely to be heavily calcified. In addition, there is increased stiffening of larger elastic arteries, with increased calcification. Another form of vascular calcification also occurs nearly exclusively in CKD patients: calciphylaxis or calcific uremic arteriolopathy. This is a disorder of medial calcification of the small arterioles of the skin, resulting in skin necrosis. Unfortunately, although there is increased recognition of the importance of controlling serum phosphorus in the therapeutic approach to this devastating disease, therapy remains suboptimal (see review). Thus, there is increased vascular calcification in renal failure of all arteries, representing a continuum of clinical manifestations depending on the location of the affected arteries.

**Pathogenesis of Vascular Calcification in CKD**

The pathogenesis of vascular calcification in CKD is not well understood and, similar to the general population, is almost certainly multifatorial. In CKD patients, several studies have found associations of both traditional and uremic-specific risk factors with calcification. However, these associations do not prove cause-effect and prospective studies in humans or, at minimum, experimental data are needed to confirm the role of these factors. These nontraditional risk factors are listed in the Table, and duration of dialysis and disorders of mineral metabolism have the most data to support a causative role in the vascular calcification of CKD.

In humans with CKD, there appears to be a relationship between disorders of mineral metabolism (abnormal levels of serum calcium and phosphorus), abnormal bone (renal osteodystrophy), and vascular calcification. Most patients with progressive CKD develop elevated parathyroid hormone (PTH) and phosphorus. Phosphate binders are given to decrease the gastrointestinal absorption of phosphorus, and vitamin D is given to suppress PTH secretion. Early on, patients are usually hypocalcemic, but then can develop hypercalcemia when given calcium or vitamin D. Rats with chronic kidney disease induced experimentally, or naturally occurring, develop medial calcification, but not atherogenic/intimal calcification. In these models, the animals also develop secondary hyperparathyroid bone disease and altered mineral homeostasis. Treatment of CKD rats with the non-calcium containing phosphate binder sevelamer reduces aortic vascular calcification compared with treatment with calcium containing phosphate binders, supporting an important role for excess calcium intake in the pathogenesis of vascular calcification in CKD. In addition, rats with experimentally induced CKD treated by the less-calcemic vitamin D analog 22-oxa-1,25-dihydroxyvitamin D3 (OCT), compared with calcitriol, also show reduced aorta medial vascular calcification, again supporting a role for altered mineral metabolism and renal osteodystrophy in the pathogenesis of medial vascular calcification. In mouse models of CKD, there is also abnormal bone. Inducing CKD in apo-E knockout mice appears to accelerate or increase the atheromatous volume in the aorta although no changes in calcification were noted. However, inducing CKD in the LDL-receptor knockout mice fed a high cholesterol diet led to increased calcification of both the intima and media of the aorta, and could be ameliorated by bone morphogenic protein-7 infusion, possibly by improving renal bone disease and thus mineral balance. Thus, experimental data supports a relationship with disorders of mineral metabolism and vascular calcification in CKD.

These data are also supported by the only interventional trial aimed at preventing progression of vascular calcification in dialysis patients, the Treat to Goal Study. In this study, dialysis patients were randomized to receive calcium containing phosphate binders, or the non-calcium-containing phosphate binder sevelamer, with tight control of phosphorus and PTH. The results showed that despite identical serum phosphorus and calcium x phosphorus products, patients in the calcium binder arm had progression of both coronary artery and aorta calcification by EBCT, whereas those treated with sevelamer did not. These results support that sevelamer can prevent the progression of calcification, but the mechanism remains unclear. Patients treated with sevelamer had less hypercalcemia, oversuppressed parathyroid hormone, lower C-reactive protein levels, and reduced total and LDL cholesterol. In patients on dialysis, there is decreased urinary calcium excretion because of renal impairment, and usually abnormal bone remodeling. As a result, calcium that is absorbed from the gastrointestinal tract cannot be excreted, and may not be taken up by the bone leading to excess extraskeletal deposition of the increased calcium burden or load. Thus the results may be from reduced calcium load, more “normal” bone remodeling, or reduced inflammation and lipids. Clearly, more data are needed.
Is Vascular Calcification in CKD a Purely Passive or an Active, Cell-Mediated Process?
Animal knockout models have demonstrated that selective deletion of many genes, including matrix gla protein, osteoprotegerin, and others (see review), induces vascular calcification. Important work in the 1990s demonstrated the presence of bone proteins in areas of calcification in pathological specimens from both coronary arteries and peripheral arteries. Furthermore, it was demonstrated that vascular smooth muscle cells isolated from human or bovine arteries were capable of mineralizing in vitro in a similar manner to osteoblasts. These data clearly demonstrate that both intimal and medial calcification is regulated processes that parallel osteogenesis in several respects. Furthermore, using this in vitro vascular smooth muscle cell model, several of the nontraditional risk factors associated with cardiovascular disease and/or vascular calcification in CKD patients have been found to increase mineralization including elevated phosphorus, parathyroid hormone and parathyroid hormone-related peptide, calcitriol, uremic serum, advanced glycation end-products, alterations of lipoproteins, and homocysteine. These data led to questioning of the existing dogma that extraskeletal calcification in CKD patients was only from passive precipitation from supersaturation of mineral in blood. To determine whether vascular calcification was an active cell-mediated process in CKD, as opposed to a purely passive process, we have performed a series of ex vivo experiments, examining pathological specimens obtained from dialysis patients.

In calcific uremic arteriolopathy (CUA, calciphylaxis), medial calcification was accompanied by the expression of osteopontin, bone sialoprotein, and osteonectin. In arteries in the same skin biopsy section that were not calcified, no osteopontin or other bone proteins were observed. Electron microscopy of CUA specimens revealed the presence of matrix vesicles identical to those observed in human bone. We then prospectively evaluated inferior epigastric arteries obtained from ESRD patients at the time of renal transplantation. The degree of vascular calcification by both spiral CT of the arterial specimen, and histological stains for calcification were proportional to the expression of the bone matrix proteins osteopontin, bone sialoprotein, alkaline phosphatase, and type I collagen. Furthermore, the presence of positive immunostaining for these bone proteins was found more frequently than was overt calcification, which suggests that the deposition of these proteins precedes calcification. In addition, we have demonstrated the presence of a multinucleated, tartrate resistant acid-phosphatase positive, osteoclast-like cell in an area of medial calcification of an inferior epigastric artery supporting that not only bone formation, but perhaps bone resorption, can occur in calcified arteries. These results confirm a cell-mediated, osteogenic process in vascular calcification in CKD patients.

Vascular smooth muscle cells and osteoblasts derive from a similar mesenchymal precursor cell. Core binding factor α-1 (Cbfa1) is thought to be the switch that turns this mesenchymal cell into an osteoblast, as mice deficient in Cbfa1 fail to mineralize bone. Jono et al first demonstrated that vascular smooth muscle cells mineralize in the presence of β-glycerophosphate, a phosphate donor, with upregulation of Cbfa1. To determine the importance of Cbfa1 in the vascular calcification of CKD, we examined samples of the inferior epigastric artery obtained from patients undergoing renal transplantation. Cbfa1 was expressed by in situ hybridization, immunostaining, and RT-PCR in both the media and intima in calcified arteries from renal transplant patients, but only minimal expression was observed in non-calcified vessels. This supports our hypothesis that Cbfa1 is a key regulator factor in the vascular calcification observed in dialysis patients. In addition, we also found expression of the Cbfa1 downstream proteins osteopontin and type I collagen in areas with Cbfa1 expression in both intimal and medial calcification in arteries from CKD patients. These findings suggest that the expression of Cbfa1 may lead to dedifferentiation of VSMC into osteoblast-like cells. Tyson et al also recently demonstrated expression of Cbfa1, alkaline phosphatase, bone sialoprotein, and osteocalcin by RT-PCR in calcified, but not noncalcified arteries, with atherosclerotic disease from non-CKD patients. However, at the present time we do not yet know if Cbfa1 expression is a prerequisite for, or a marker of, dedifferentiation. The findings of Cbfa1 in both CKD associated intimal and medial calcification and non-CKD atherosclerotic disease suggest that calcification may occur by similar processes in several forms of vascular calcification.

To further understand the mechanism by which uremia and/or hyperphosphatemia induces vascular calcification, we incubated bovine vascular smooth muscle cells (BVSMCs) in the presence of β-glycerophosphate for 48 hours. Our data confirmed previous results by Jono and Giachelli (see review) that β-glycerophosphate induced osteopontin expression, mineralization, and alkaline phosphatase activity in a dose-dependent manner. Phosphonoformic acid (foscarnet), a competitive inhibitor of Na/Pi cotransporter, completely inhibited the induction of osteopontin expression and alkaline phosphatase activity, suggesting that Na/Pi cotransport is necessary for phosphorus-induced osteopontin expression in BVSMCs. Furthermore, inhibition of alkaline phosphatase activity by levamisole, an inhibitor of alkaline phosphatase, also abolished β-glycerophosphate-induced osteopontin expression in BVSMCs. Thus, β-glycerophosphate-induced osteopontin expression in BVSMCs is indeed dependent on Na/Pi cotransport and alkaline phosphatase activity. These findings support the clinical data that phosphorus is a risk factor for vascular calcification in CKD patients. Interestingly, a study in non-CKD patients also found a relationship between increasing serum phosphorus levels and obstructive atherosclerotic coronary artery disease by angiography.

We then asked the question, “Is it only phosphorus, or are there other uremic factors involved in vascular calcification?” To determine whether the retention of toxins in CKD (uremia) contributes to vascular calcification, we collected pooled serum from patients undergoing hemodialysis for at least two years (to eliminate residual renal function) and compared with age-matched healthy controls. As expected, compared with control serum, the pooled uremic serum had elevated levels of phosphorus, parathyroid hormone, total and bone
alkaline phosphatase, and C-reactive protein. BVSMCs were incubated in the presence of uremic or control serum plus β-glycerophosphate. BVSMCs incubated in uremic serum also upregulated the osteoblast transcription factor Cbfa1, osteopontin expression, and alkaline phosphatase activity compared with cells incubated in control serum.63 Additional studies demonstrated that uremic serum increased and accelerated calcification in BVSMCs in vitro, compared with control serum.64 The inorganic phosphorus concentration was measured in media plus β-glycerophosphate before addition to BVSMCs, and remeasured after 48 hours of incubation (Figure 1). The results confirmed that β-glycerophosphate was converted by cells to inorganic phosphorus in DMEM in the presence of both control human serum and uremic serum. In addition, when diluted to 10% sera, the final phosphorus concentration in uremic sera was not different from that in the control serum cultures. Furthermore, addition of inorganic phosphorus failed to augment the Cbfa1 and osteopontin expression in BVSMCs induced by uremic serum alone (Figure 1).72 Furthermore, the effects of uremic serum on Cbfa1 expression were only partially inhibited by blocking (Na/Pi) cotransporter, whereas the same inhibitor completely prevented the effect of β-glycerophosphate in cultures with healthy control human serum.72 These results demonstrate that other uremic factor(s), in addition to hyperphosphatemia, likely participate in the development of vascular calcification. What these factor(s) are is not yet known, although further work has demonstrated that protein kinase A, but not protein kinase C is involved in uremic serum effects.76

In search of potential factors in uremic serum that upregulate Cbfa1, we have recently demonstrated that bone morphogenic protein-2 (BMP-2) concentration in pooled uremic serum is two times higher than in normal human serum.77 In addition, BMP-2 production by BVSMCs progressively increases during calcification with uremic serum, compared with control healthy human serum, indicating uremic serum further increases BMP-2 production from cultured BVSMCs.77 BMP-2 is a potent osteoinductive factor in mesenchymal stem cells and marrow stromal cells,78 and the expression of BMP-2 has been detected in human calcified arteries79 and in calcifying vascular smooth muscle cells.80 Thus, our data suggests that vascular calcification is accelerated by uremic toxins present in serum from dialysis patients, possibly by upregulating Cbfa1, leading to accelerated transformation of VSMCs into osteoblast-like cells. This process is only partially mediated by hyperphosphatemia and additional factors such as BMP-2 may accelerate this dedifferentiation.

**Inhibitors of Vascular Calcification**

Vascular calcification, although very prevalent in dialysis patients, is not uniform. Depending on the series, an average of 17% of dialysis patients have no vascular calcification, and continue to not have calcification on followup.30 Whereas younger age is partially responsible for the protection against calcification, the data also supports the presence of naturally occurring inhibitors of calcification. Matrix gla protein, as discussed in another article in this series, is a locally produced inhibitor. We measured serum levels of MGP in dialysis patients, and found no significant correlation between serum MGP levels and coronary artery or aorta calcification score by spiral CT in a cohort of dialysis patients,31 despite findings of correlation in non-CKD patients.32 However, we then examined sections from the inferior epigastric artery of dialysis patients and demonstrated that MGP expression correlated with the presence of calcification by Von Kossa staining.30 The increased MGP expressed locally during vascular calcification may limit the extent of calcification because MGP can bind to BMP-2, a prominalization factor.81

Another potential inhibitor of vascular calcification is fetuin-A (AHSG or α2-HS glycoprotein) a circulating inhibitor. Fetuin-A is abundant in the plasma, and mainly produced by liver in adults.82 Fetuin-A inhibits the de novo formation and precipitation of the apatite precursor mineral, basic calcium phosphate, but does not dissolve it once the basic calcium phosphate is formed.83 Therefore, fetuin-A can prevent undesirable calcification in the circulation without inhibiting bone mineralization. In bone marrow stromal cells, fetuin-A binds to BMP-2 and transforming growth factor β, inhibiting mineralization, and suppressing the expression of bone matrix proteins.84,85 Fetuin-A knockout mice have extraskeletal calcification in the presence of hypercalcemia or when cross-bred on a mouse strain with a predisposition to calcification.19 Fetuin-A is inversely correlated with the acute phase response. A study by Ketteler et al18 has demonstrated that fetuin concentration in serum of dialysis patients was inversely related to C-reactive protein. Furthermore, low fetuin-A levels were associated with increased cardiovascular mortality. Serum from dialysis patients with calcific uremic arteriolopathy had impaired ex vivo capacity to inhibit hydroxyapatite precipitation, which could be normalized by the addition of purified fetuin-A.19 We have also recently demonstrated the presence of fetuin-A expression by immu-

![Figure 1. Effect of phosphorus on uremic serum-induced Cbfa1 expression. RT-PCR for Cbfa1 expression in bovine vascular smooth muscle cells incubated in the presence of pooled sera from control or uremic subjects, without or with the addition of 12 mmol/L β-glycerophosphate for 48 hours. Media (DMEM plus serum) concentration of phosphorus (Pi) was measured at the end of the incubation period and confirmed an increase in the Pi concentration in the presence of β-glycerophosphate (BGP). Results demonstrate that BVSMCs incubated with uremic serum had increased expression of Cbfa1 compared with control serum, despite similar final concentrations of phosphorus. Furthermore, the addition of β-glycerophosphate doubled the expression of Cbfa1 in BVSMCs incubated in control serum, but had no additive effect on BVSMC incubated in uremic serum. *P<0.05 compared with control. Reprinted from Moe et al72 with permission.](564_circresaha00564fig1_h.jpg)
nostaining of the inferior epigastric artery positively correlated with the presence of calcification. Furthermore, an in vitro study demonstrated that fetuin-A can inhibit both control and uremic serum-induced calcification in BVSMCs in a dose-dependent manner. Lastly, in a preliminary report, we have demonstrated serum levels of fetuin-A in individual dialysis patients were inversely correlated to coronary artery calcification by spiral CT scan. It should be clarified that serum fetuin-A levels are not uniformly low in dialysis patients. Thus, fetuin-A deficiency may only be a factor in some patients, or perhaps there is a relative deficiency of fetuin-A in most dialysis patients given the high serum concentration of calcium and phosphorus. The precise role of fetuin-A in most dialysis patients given the high serum phosphorus and calcium x phosphate product from abnormal bone, secondary hyperparathyroidism, or excessive calcium intake may accelerate the process. In contrast, serum fetuin-A and other inhibitors in the vascular calcification in CKD patients remains to be determined, but clearly, there are multiple mechanisms to regulate extraskeletal calcification. We are only beginning to understand this complex process.

Conclusion
Vascular calcification is common in patients with CKD as well as the general aging population, and is an active process (Figure 2). An initial step in the process of calcification of arteries may be dedifferentiation of VSMCs to osteoblast-like cells via upregulation of Cbfa1. In vitro studies suggest that elevated phosphorus as well as other yet unidentified uremic toxins, can induce differentiation. These osteoblast-like cells are capable of producing bone matrix proteins, which may subsequently regulate mineralization. Once mineralization is initiated, increased calcium x phosphorus product from abnormal bone, secondary hyperparathyroidism, or excessive calcium intake may accelerate the process. In contrast, serum fetuin-A and other inhibitors may be protective. Thus, similar to findings in bone, mineralization proceeds when the balance of promoting factors outweighs inhibitory proteins. Further understanding of the mechanism by which vascular calcification occurs should offer the potential hope of developing therapeutic strategies to arrest this process.

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