Published in final edited form as:
Kidney Int. 2010 December ; 78(12): 1232–1239. doi:10.1038/ki.2010.334.

Recent progress in the treatment of vascular calcification

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Abstract

Vascular calcification is common in patients with advanced chronic kidney disease and is associated with poorer outcomes. Although the pathophysiology is not completely understood, it is clear that it is a multifactorial process involving altered mineral metabolism, as well as changes in systemic and local factors that can promote or inhibit vascular calcification, and all of these are potential therapeutic targets. Current therapy is closely linked to strategies for preventing disordered bone and mineral metabolism in advanced kidney disease and involves lowering the circulating levels of both phosphate and calcium. The efficacy of compounds that specifically target calcification, such as bisphosphonates and thiosulfate, has been shown in animals but only in small numbers of humans, and safety remains an issue. Additional therapies, such as pyrophosphate, vitamin K, and lowering of pH, are supported by animal studies, but are yet to be investigated clinically. As the mineral composition of vascular calcifications is the same as in bone, potential effects on bone must be addressed with any therapy for vascular calcification.

Keywords

bone; chronic kidney disease; vascular calcification; vascular disease

OVERVIEW

Vascular calcification in renal failure

Vascular calcification is restricted to arteries and occurs in two locations, the intima and the media. Although the endpoint of both is hydroxyapatite formation, the pathophysiology and clinical significance are different.[1] (The term hydroxyapatite will be used here, even though *in vivo* it is primarily carbonate apatite with partial substitutions of other ions, such as Mg^{2+} and F^{-}.) Intimal (actually neointimal) calcification is part of the atherosclerotic process and can occur in any person with atherosclerosis whether or not they have kidney disease. It occurs in areas devoid of smooth muscle cells and is associated with lipid, macrophages, and mast cells.[2] Medial calcification occurs in elastin fibers around smooth muscle cells in the absence of atherosclerosis or inflammation[1,2] and is seen primarily in chronic renal failure or diabetes. The prevalence of medial calcification clearly increases with age,[3,4] but whether this is a specific effect of age or is related to underlying diseases is unclear. The pattern of vascular involvement differs as well. Neointimal calcification is limited to the large and medium-sized conduit arteries in which atherosclerosis occurs,[5] whereas medial calcification occurs in arteries of any size, including small arteries in which atherosclerosis does not occur.[6–8] A recent autopsy study of chronic kidney disease (CKD) patients with

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DISCLOSURE
All the authors declared no competing interests.

known coronary artery disease revealed that most of the calcification was atherosclerotic with very little medial calcification,[9] whereas a study of mammograms (presented in abstract form) showed that breast arterial calcification (which is exclusively medial) was present in close to 70% of women with end-stage renal disease (ESRD).[10] Involvement can extend to arterioles, which is observed in calcific uremic arteriolopathy (CUA), a particularly virulent form of medial calcification previously known as calciphylaxis. Although there is debate about whether the CUA has a pathophysiology distinct from medial calcification in larger vessels, it will be considered as a form of medial calcification for the purposes of this review.

Renal failure increases the extent of calcification in atherosclerotic plaques,[11] but the effect on medial calcification is probably greater as it rarely occurs in individuals without renal insufficiency under the age of 60 years. The histological prevalence of medial calcification in radial arteries was 45-fold greater in patients with CKD compared with those without CKD,[7] and the preliminary report of breast arterial calcification showed a four-fold higher prevalence in women with ESRD compared with age-matched women without renal disease.[10] Coronary artery calcification scores are almost three-fold greater in ESRD patients than in the age and sex-matched general population.[12] Because the ESRD patients probably have some medial calcification as well, the increase in intimal calcification is probably less. In unselected autopsy cases, the prevalence of calcified coronary plaques was 52% in 27 patients with renal insufficiency compared with 37% in 30 subjects without CKD.[13]

Clinical significance

Treatment of vascular calcification in renal failure rests on the assumption that it is harmful and that a reduction will be beneficial. The morbidity of atherosclerosis is related to vascular occlusion, but it is unclear whether this is exacerbated by plaque calcification. Medial calcification does not narrow vessels, but is assumed to stiffen them,[14] predisposing to heart failure. This is supported by the fact that heart failure is the cause of death in children with infantile arterial calcification, a disorder of severe medial calcification.[15] Lack of arterial distensibility may also transmit greater pulse pressures to the distal arterial bed, leading to arteriolosclerosis with resulting vascular insufficiency and tissue damage.[14] Of course, without a specific treatment, these hypotheses cannot be confirmed. Despite this, a large body of indirect data indicates poorer outcomes in patients with vascular calcification, and recent clinical trials suggest a benefit with treatment. A number of studies have shown that arterial calcification[14,16] and progression of calcification[17] correlate with cardiovascular events or death, and with hemodynamic parameters, such as pulse wave velocity. A study of new hemodialysis patients found a decrease in mortality associated with the reduced progression of coronary artery calcification (CAC) in patients treated with sevelamer compared with calcium-containing phosphate binders, suggesting a beneficial effect of treating vascular calcification.[18] Another study of prevalent dialysis patients treated with sevelamer found improved mortality that was not significant in the entire cohort, but was significant in predetermined subgroups.[19] This mortality effect is unlikely to be explained by the reduction in low-density lipoprotein cholesterol that occurs with sevelamer since cholesterol-lowering therapy does not alter mortality in ESRD patients.[20,21] An additional, clinically important effect of vascular calcification in renal failure is the unsuitability of arteries for vascular surgery, including creation of arteriovenous fistulae and renal transplantation. Lastly, CUA is a severe, life-threatening condition. Despite the lack of definitive data, it is hard to envision that vascular calcification is not detrimental.

Measurement of vascular calcification

The evaluation of therapies for vascular calcification is problematic because of the lack of good methods to quantify it. The sensitivity of the various imaging modalities that have been used is unknown and the precision can be poor. Computed tomography of the aorta or coronary arteries is commonly used and is the only modality that can yield truly quantitative results, but different scoring systems can yield different results. In addition, the progression of vascular calcification is quite variable and has a very skewed distribution so that large numbers of patients are required and statistical analyses are not straightforward. Lastly, none of the methods can reliably distinguish between atherosclerotic and medial calcification and, therefore, measure the combined changes in two different pathophysiological processes. Calcification of coronary arteries, the site most commonly studied, is mostly atherosclerotic in ESRD patients,[9] and any changes detected could be due to progression or regression of atherosclerosis rather than to changes in calcification.

Therapeutic strategies

Vascular calcification and its treatment are linked to the management of the disordered bone and mineral metabolism that accompanies CKD. However, there are a number of potential therapies that directly target the calcification process. In addition to efficacy and overall safety, two important issues affect potential therapies for vascular calcification. First, is the treatment only preventative or can it reverse calcification? Second, can vascular calcification be treated without adversely affecting calcification in normal sites, such as bone and teeth? Although reversal of calcification is a desirable therapeutic goal, hydroxyapatite is extremely insoluble and stable under physiological conditions. Vascular calcifications also contain whitlockite, which is equally insoluble, and amorphous calcium phosphate, which may be more soluble.[22] However, medial vascular calcification, in rats treated with calcitriol or warfarin, does regress when calcitriol is withheld[23] or vitamin K is supplemented,[24] indicating that there are endogenous mechanisms for the dissolution of ectopic hydroxyapatite. Whether this occurs in more longstanding calcification is unknown, but has been reported in humans,[25] suggesting that prevention of calcification may eventually lead to reversal. Unwanted effects on bone is an extremely important therapeutic issue as mineralized vessels and bone are both composed of hydroxyapatite and the mechanisms of formation may be similar. Therefore, an understanding of differences between vascular calcification and bone formation is essential for targeting therapy specifically to vessels, and effects on bone must be addressed with any therapy for vascular calcification.

THERAPIES RELATED TO DISORDERED BONE AND MINERAL METABOLISM

Secondary hyperparathyroidism (sHPT) is a universal consequence of renal failure and is central in the clinical approach to disordered bone and mineral metabolism. However, it is unlikely that parathyroid hormone (PTH) itself causes vascular calcification. Serum levels do not correlate positively with vascular calcification in patients[12,16,26] and PTH does not induce calcification in vascular smooth muscle cells (VSMCs)[27] or intact aortas in culture.[28] Although exogenous PTH produces vascular calcification in parathyroidectomized rats, this is most likely due an increase in circulating calcium levels.[29] Management of sHPT focuses on minimizing hyperphosphatemia and hypocalcemia without producing hypercalcemia and overly suppressing PTH. This is accomplished with oral phosphate binders, active vitamin D compounds, calcimimetics, and adjusting the calcium concentration in the dialysate, all of which could potentially affect vascular calcification. Consequently, a significant amount of research has been directed at optimizing these therapies to minimize vascular calcification.

Phosphate binders

Phosphate concentrations above physiological serum levels have been shown to promote vascular calcification in experimental models *in vivo* and *in vitro*. Supraphysiological concentrations of phosphate are necessary to induce calcification in vessels *in vitro*[28,30–32] and the extent of calcification varies directly with the phosphate concentration.[28] Similarly, vascular calcification in uremic rats or mice requires a high phosphorus diet with substantial hyperphosphatemia.[33,34] Although a higher serum phosphorus level has been observed in patients with CKD and ESRD who have vascular calcification,[12,16,35–37] a significant correlation has not been found in many studies.[17,26,38,39] Furthermore, atherosclerotic calcification in the general population and medial vascular calcification in diabetics clearly occurs in the absence of hyperphosphatemia.

The effect of reduced phosphate intake on vascular calcification is confounded by the concomitant calcium load from calcium-containing phosphate binders. Studies in VSMC and cultured aortas have shown dramatic increases in calcification with incremental calcium concentrations in culture medium.[28,40] In cultured rat aortas, calcification was proportional to the calcium concentration when the [Ca] × [PO_4] product was kept constant, and no calcification was observed in vessels exposed to high phosphate concentrations when the calcium concentration was kept low.[28] This effect of calcium is likely to be physicochemical, not only as a constituent of apatite but also in the initiation (nucleation) through binding to elastin[41] and through formation of nascent crystals in matrix vesicles.[42] It is not surprising that calcium intake has correlated with vascular calcification in several studies in ESRD patients.[12,16,26]

Several prospective studies have shown a markedly reduced rate of CAC in ESRD patients treated with sevelamer (a calcium-free phosphate binder) compared with patients treated with calcium carbonate or calcium acetate. In the treat-to-goal study of dialysis patients with existing CAC, the increase in calcification was 0 and 6% at 26 and 52 weeks with sevelamer compared with 14 and 25% increases with calcium carbonate or acetate.[43] Aortic calcification was also significantly reduced. Doses were titrated to the serum phosphorus level, which did not differ between the two groups at the end of the study. However, the serum calcium concentration was significantly lower in the sevelamer group. Similar results were obtained in a subsequent study of patients enrolled at the initiation of dialysis.[44] A recent study suggests that this beneficial effect extends to predialysis patients, with yearly increases in CAC of 48, 39, and 9% for patients on low phosphorus diet alone, with calcium carbonate or with sevelamer, respectively.[45] In all of these studies, sevelamer (but not calcium-containing binders) produced a significant decrease in the serum calcium concentration and this is presumably the explanation for the lower rates of vascular calcification. PTH levels and vitamin D usage were greater in the sevelamer-treated patients, but these would not be expected to contribute to a reduction in calcification. Although sevelamer also lowers low-density lipoprotein levels, a reduction in atherosclerosis is an unlikely explanation for the reduction in vascular calcification, as low-density lipoprotein-reduction therapy has not been successful at reducing coronary artery disease in ESRD.[20,21]

Two studies have shown no benefit of sevelamer over calcium-based phosphate binders.[46,47] A high dialysate calcium concentration was used in many patients in one study and two-thirds of the sevelamer-treated patients received calcitriol compared with one-third of the patients treated with calcium acetate.[46] It is not surprising that it is the only study not to show a decrease in the serum calcium level with sevelamer. The other study compared sevelamer with calcium acetate and atorvastatin (as control for the low-density lipoprotein reduction with sevelamer), but there was a very high drop-out rate in both treatment groups.[47] A very small study presented in abstract form suggests that lanthanum carbonate can also prevent CAC,[48] but this will require confirmation in a larger study. Magnesium

carbonate may be another safe and effective calcium-free phosphate binder[49] and it could have additional beneficial effects as magnesium inhibits hydroxyapatite formation at physiological concentrations.[50]

Active vitamin D compounds

These compounds, which are widely used to treat sHPT in ESRD and pre-ESRD, are well known to induce medial vascular calcification in uremic animals. Vascular calcification is barely observed in rats with subtotal (5/6) nephrectomy fed a high-phosphate diet unless calcitriol is administered,[51,52] and is greatly accelerated by calcitriol in the adenine-feeding model of renal failure in rats.[53] Recent studies in the latter model, presented in abstract form, showed that doses of calcitriol required to suppress sHPT increased vascular calcification.[54] Paricalcitol, an analog of calcitriol with a relatively lower calcemic effect, appears to produce much less vascular calcification.[51] The mechanism by which active vitamin D affects vascular calcification is unclear. Vascular smooth muscle has vitamin D receptors and induction of calcification and calcification-related genes has been observed in cultured smooth muscle cells exposed to calcitriol.[55] However, this does not occur when intact vessels are treated *in vitro* with calcitriol.[28] These genes are upregulated in aortas after prolonged treatment with calcitriol,[51] but not with acute treatment in a recent report in abstract form,[54] suggesting an indirect effect.

Data from a mouse model of atherosclerosis and uremia indicate a biphasic effect of calcitriol, whereby very low doses inhibit calcification and higher doses promote calcification.[56] This could explain the discrepancy between observational studies showing a survival benefit of calcitriol and analogs in ESRD, and studies showing promotion of vascular calcification in animals. The protective effect of the lower doses may be due to suppression of sHPT, but the authors have recently presented evidence in abstract form of effects on smooth muscle differentiation.[57] However, the mouse model is primarily one of atherosclerotic calcification and the findings may not apply to medial calcification. The effect of vitamin D on vascular calcification has not been studied in humans, but intake does not correlate with vascular calcification in cross-sectional studies.[12,17,58]

Other therapies for sHPT

Calcimimetics are the newest therapy for sHPT and reduce vascular calcification in uremic rats.[23,53,59] Again, data are lacking in humans, but a recently completed study presented only in abstract form showed a beneficial effect of cinacalcet on coronary artery and aortic calcification.[60] The former was significant by the volume scoring method, but not the Agatston scoring method, whereas the latter did not quite reach significance (Agatston scoring method). Lastly, parathyroidectomy prevents vascular calcification in uremic rats[59] and subtotal parathyroidectomy can arrest the progression of CAC in dialysis patients.[61] This latter finding was confirmed in a recent study presented in abstract form.[62] It is important to note that the parathyroidectomized patients had substantially lower serum calcium levels than the nonsurgical patients, whereas PTH and phosphate levels were unchanged and the intake of calcitriol and calcium was substantially higher. Although the number of patients is small, it is hard to ascribe the effect on vascular calcification to any factor besides calcium levels.

The role of calcium

A common thread that ties treatment of sHPT to vascular calcification may be the effect on circulating calcium concentrations. Although it has been proposed that the link between these therapies and vascular calcification may relate to induction of low-turnover bone disease and inability to buffer calcium loads, severe vascular calcification is also observed in the high-turnover bone disease associated with sHPT. Calcium can drive the initial steps in

hydroxyapatite formation[63] and small changes in calcium concentration have profound effects on calcification of aortas in culture.[28] Accordingly, calcium-free phosphate binders, calcimimetics, and parathyroidectomy, which decrease circulating calcium levels, arrest or prevent vascular calcification, whereas active vitamin D and calcium-containing phosphate binders, which increases calcium levels, promote calcification. This suggests that, in the presence of hyperphosphatemia, circulating calcium levels should be maintained at the low end of the normal range and perhaps even below the normal range.

POTENTIAL THERAPIES THAT DIRECTLY TARGET VASCULAR CALCIFICATION

Pyrophosphate and bisphosphonates

Pyrophosphate (PPi) is a potent inhibitor of calcium crystallization that circulates at concentrations sufficient to prevent hydroxyapatite formation *in vitro*,[64–66] and thus serves as an endogenous inhibitor of calcification. In particular, production of PPi by smooth muscle may be an important defense against medial vascular calcification. Rat aortas do not calcify in culture unless the PPi is removed[31] and humans lacking ectonucleotide pyrophosphorylase (Enpp1), the enzyme that synthesizes extracellular PPi, develop severe medial arterial calcification at an early age.[67–69] Mice lacking this enzyme or that have a defect in PPi transport also develop vascular calcification.[70] Plasma levels of PPi may be reduced in hemodialysis patients[71] and correlate inversely with vascular calcification in patients with ESRD and advanced CKD.[72] Alkaline phosphatase, which hydrolyzes PPi, is upregulated in uremic aortas could contribute to vascular deficiency of PPi.

Studies over four decades ago showed that PPi inhibits medial arterial calcification in vitamin D-toxic rats.[73] However, rapid hydrolysis of PPi *in vivo* limited this therapy and prompted the development of nonhydrolyzable analogs, such as bisphosphonates that were subsequently shown to inhibit vascular calcification in the same model, but at much lower doses.[66] More recently, bisphosphonates have been shown to prevent aortic calcification in uremic rats[33,74,75] but at doses much higher than those used clinically to treat osteoporosis. In humans, bisphosphonates provide lifesaving therapy for vascular calcification in Enpp1 deficiency,[15] but have not shown any effect on coronary artery or aortic calcification in the general population.[76,77] Studies in CKD and ESRD patients are limited to small studies that suggest a beneficial effect of etidronate,[78–81] but not alendronate[82] on vascular calcification and case reports of successful treatment of CUA with etidronate or pamidronate,[83,84] but larger clinical trials are underway. The fact that the doses of bisphosphonates necessary to inhibit vascular calcification in uremic rats also inhibit bone formation[33] is not surprising based on their mechanism of action and raises serious concerns about their clinical use. Indeed, the positive results with etidronate and negative results with alendronate are consistent with the relative potencies in inhibiting bone formation.[85] Larger clinical studies are underway, but are likely to show no effect based on the type of bisphosphonate and dosage. An additional concern is that bisphosphonates are cleared by the kidneys and will accumulate in CKD and ESRD. Because of potential effects on bone formation and accumulation in renal failure, bisphosphonates should be used with extreme caution for the treatment of uremic vascular calcification.[86]

A recent study presented only in abstract form showed that PPi inhibits vascular calcification in uremic rats without any adverse effects on bone.[87] The differential effects of PPi and bisphosphonates on bone formation can be explained by the high level of tissue-nonspecific alkaline phosphatase (TNAP) in bone, which serves to remove PPi and allow bone formation at physiological PPi concentrations.[70] This is the basis for the skeletal abnormalities in hypophosphatasia, which is due to TNAP deficiency. However, TNAP

would not protect bone from the nonhydrolyzable bisphosphonates. Its selectivity for vascular calcification and the fact that it does not accumulate in renal failure make PPi a promising therapy.

Thiosulfate

The use of thiosulfate to treat vascular calcification stems from reports that it prevents nephrolithiasis in humans.[88] A subsequent study showed that it reduced tumoral calcifications in renal failure[89] and this was followed almost two decades later by several reports of successful treatment of CUA with thiosulfate.[90,91] However, many of these patients received other therapies and there have been no randomized or controlled studies, so the efficacy of thiosulfate is uncertain. Recently, thiosulfate was shown to inhibit medial vascular calcification in uremic rats[92] and a confirmatory study has been presented in abstract form.[93] In a preliminary report in abstract form, thiosulfate slowed the progression of CAC in a very small cohort of dialysis patients,[94] and additional clinical trials are underway. Thiosulfate therapy does not alter circulating calcium or phosphorus levels[88,90,92] and the therapeutic mechanism remains unknown. The finding that thiosulfate also prevents nephrolithiasis in rats[95] and appears to do the same in humans[88] points to a direct effect on calcium crystallization. Despite statements to the contrary, thiosulfate does not chelate calcium ions though it does interact with calcium to form ion pairs.[96] This interaction is too weak to have any significant effect on calcium-dependent reactions at clinically relevant concentrations, including the formation of hydroxyapatite (WC O'Neill and KA Hardcastle, unpublished data). A disconcerting finding in rats was a decrease in bone strength,[92] raising the possibility that calcification is also inhibited in bone. Although thiosulfate has been used to treat nephrolithiasis in humans for periods of several years without apparent adverse effects,[88] these patients did not have renal failure and potential effects on bone were not examined.

Vitamin K

Vitamin K is the common name for phylloquinone (vitamin K_1) and several menaquinones (vitamin K_2) and serves as a cofactor for modifying glutamate into γ-carboxylated glutamate (Gla) residues in certain proteins, including an important inhibitor of vascular calcification, matrix gla protein (MGP). Deletion of MGP causes massive aortic calcification and death in mice.[97] Vascular calcification is also observed in humans lacking MGP, but is much less extensive.[98] Warfarin, which blocks vitamin K-dependent γ-carboxylation of MGP, promotes vascular calcification in aortas *in vitro*[99] and in rats *in vivo*,[100] which is prevented by dietary vitamin K.[24] Warfarin has been associated with valvular calcification[101–103] and CUA[104] (in abstract form only) in humans, but in the largest study to date, warfarin use was not associated with increased CAC.[105] The relationship between vitamin K intake and vascular calcification is unclear. Menaquinone intake was strongly and inversely correlated with aortic calcification in one study,[106] whereas no correlation was found between dietary vitamin K_1 intake and CAC in another study.[107] The disparate results with vitamin K_1 and vitamin K_2 are surprising, as vitamin K_1 may be transformed into menaquinone *in vivo*.

The role of vitamin K deficiency in vascular calcification is difficult to determine because the assessment of vitamin K status is challenging and appropriate dosing is unclear. A recent comprehensive study of 174 patients with CKD stage 3–5 found a high prevalence of subclinical vitamin K deficiency manifest as an increased fraction of circulating under-carboxylated osteocalcin in 60% of patients or elevated levels of undercarboxylated prothrombin in 97% of patients.[108] It is of note that the vitamin K1 (phylloquinone) levels were reduced only in 6% of patients, suggesting that vitamin K1 levels may not be sensitive for detection of subclinical deficiency or that the biochemical abnormalities are not due to vitamin K deficiency. Higher prevalences of subclinical vitamin K deficiency and lower

levels of phylloquinone have also been reported in hemodialysis[109] and peritoneal dialysis patients.[110] Other studies have reported normal phylloquinone levels in ESRD patients,[111] indicating the importance of biochemical markers of vitamin K deficiency rather than plasma phylloquinone levels. As the optimum levels of these markers is unclear, the point at which supplementation should be given and the appropriate dose are unknown. A daily intake of 1 mg of phylloquinone was needed in young adults to maximize carboxylation of osteocalcin,[112] but the equivalent dose for MGP is unknown. To date, there are no data to indicate whether the treatment of apparent vitamin K deficiency in CKD or ESRD is beneficial or carries any risk.

Acidosis

There is experimental evidence that acidosis may reduce vascular calcification. In uremic rats fed a high phosphorus diet and treated with calcitriol, aortic calcification was prevented by metabolic acidosis that was induced by dietary ammonium chloride.[113] An alkaline pH augments calcification of rat aortas in culture[28] and even transient increases in pH equivalent to those occurring during hemodialysis significantly increased calcification. This raises the possibility that the practice of alkaline loading during hemodialysis may contribute to vascular calcification.

Other potential therapies

Bone morphogenic protein-7 reduces vascular calcification in a mouse model of atherosclerosis and CKD.[114] This is primarily because of a reduction in the serum phosphate concentration, although there may be some direct effect on VSMCs.[115] MGP appears to be an important endogenous inhbibitor of vascular calcification, but its extreme insolubility precludes it as a therapeutic agent. Although deficiency of the circulating protein fetuin in mice does not cause vascular calcification, it does promote calcification in uremia and a high phosphate diet.[116] Its correlation with vascular calcification in clinical studies has been variable and its use as a therapy in animal models has not been reported. Osteopontin is a potent inhibitor of hydroxyapatite formation[117] that inhibits calcification of VSMCs in culture.[118] No *in vivo* studies have been reported, but osteopontin can inhibit calcification of other tissues when implanted in osteopontin-deficient mice.[119,120] Other actions of osteopontin that promote inflammation[121] and cancer metastasis[122] probably preclude it as a therapy for vascular calcification. Additional, but as yet unexplored strategies against vascular calcification include altering smooth muscle phenotype to reduce its osteogenic potential, and targeting osteoclastic cells to the sites of calcification.

CONCLUSIONS

Vascular calcification is common in advanced CKD and likely contributes to cardiovascular events and death. However, there are few controlled studies on which to base therapeutic decisions, and these studies do not distinguish between medial and intimal calcification, which may show different responses to therapies. The current state of knowledge indicates that treatment should be preventative and based on reducing hyperphosphatemia and minimizing serum calcium concentrations. Other therapies should be considered experimental and used with extreme caution pending an evaluation of simultaneous effects on bone metabolism, as well as other safety issues. A better understanding of the biology and chemistry of vascular calcification should lead to more specific therapies in the future.

Acknowledgments

The authors thank Paolo Raggi for critical review of the paper and helpful suggestions.

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