Reducing the Burden of Cardiovascular Calcification in Patients with Chronic Kidney Disease

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Patients with chronic kidney disease (CKD) have a higher burden of atherosclerotic coronary artery disease compared with age- and gender-matched individuals with normal renal function. Cardiovascular calcification (CVC), a marker of atherosclerosis, is also more prevalent in these patients and is associated with serious clinical consequences. The pathogenesis of CVC is complex and includes factors that promote calcification and others that inhibit calcification. Thus, multiple therapeutic interventions should be used simultaneously to reduce the burden of calcification in patients with CKD. Thus far, interventional attempts have focused on curtailing the effects of factors that promote calcification such as management of known traditional factors for atherosclerotic coronary artery disease and on adopting specific approaches to normalize mineral metabolism, deliver adequate dialysis, and control serum cholesterol level. By contrast, interventions that may bolster the effects of inhibitors of calcification have not yet been studied well but are beginning to attract attention. Ideally, the goal of interventions is not only to slow or halt progression of calcification but also to reverse pre-existing calcification. Whether this goal is achievable is not currently known. This review examines the potential of various therapeutic interventions in reducing the CVC burden in patients with CKD. Moreover, the review is intended to stimulate more research in this area because the efficacy of these interventions has not been examined in controlled clinical trials.

Coronary artery calcification (CAC), which is absent in normal vessels, represents an integral part of the atherosclerotic plaque (1). Detection and quantification of arterial calcification now can be easily achieved by the use of newer imaging techniques such as electron-beam computed tomography (EBCT) and multislice computed tomography (2,3). In the general population, coronary artery calcium (CAC) score as measured by EBCT was found to be an independent predictor of subsequent cardiac events in both symptomatic and asymptomatic individuals (3,4).

The pathogenesis of CVC is complex and includes factors that promote calcification and others that inhibit calcification (Tables 1 and 2). Several studies have clearly established that the prevalence and the extent of CVC are increased in patients with ESRD (5–8). The mechanisms that are responsible for CVC in patients with ESRD are still being debated and have been reviewed previously in detail (9). Briefly, cross-sectional studies in dialysis patients have shown a correlation between CAC and a number of uremia-related factors such as dialysis vintage, hyperphosphatemia, high calcium (Ca) × phosphorus (P) product, vitamin D therapy, and the prescribed daily dose of Ca-based phosphate binders (CBPB) (5–9).

Clinical Consequences of CVC

Calcification of the aorta and other large vessels previously has been considered a benign process without serious clinical consequences. However, several clinical studies have shown clearly that calcification of various cardiovascular structures may be associated with increased morbidity and mortality. Calcification of the cardiac valves may lead to heart failure, coronary ischemia, arrhythmias, valve stenosis, increased risk for infective endocarditis, and thromboembolic events (10). Moreover, valve calcification was shown to be independently predictive of increased all-cause mortality as well as cardiovascular death (10). Calciphylaxis or calcific uremic arteriolopathy, a form of medial calcification, is associated with very high risk for death (11). Moreover, medial arterial calcification often leads to stiffening and decreased compliance of blood vessels, which in turn leads to increased systolic BP, reduced diastolic BP, and increased pulse pressure (12). These hemodynamic changes may result in increased afterload, left ventricular hypertrophy, decreased coronary artery perfusion, and increased risk for death (13). Finally, CAC has been linked to increased risk for cardiovascular events such as myocardial infarction, fatal arrhythmia, and congestive heart failure (9,14,15). Given that CVC may lead to serious clinical consequences, it is possible that interventions that are designed to slow or even reverse the process of calcification may lead to improved patient outcomes.

Interventions Designed to Reduce CVC in Patients with CKD

Theoretically, for any intervention to reduce CVC, it should curtail the influence of factors that promote calcification and/or augment the effects of factors that inhibit calcification. Unfortunately, such interventions have not been investigated in controlled clinical trials. Therefore, the potential beneficial role of...
some of these interventions on CVC must be considered speculative at this time. Hopefully, future interventional clinical studies will be designed to examine more carefully the role of these factors in reducing the burden of CVC in calcification-prone CKD patients (Table 3).

### Curbing Effects of Factors that Promote Vascular Calcification

**Control of Hyperphosphatemia, Hypercalcemia, and Ca × P Product**

Disturbances in serum P, Ca, and Ca × P product are frequently seen in patients with CKD and have been implicated in promoting CVC as well as in increased risk for death (9,16). High P levels stimulate osteoblastic differentiation of vascular smooth muscle cells and directly enhance extracellular calcification by these cells (17). Given that hyperphosphatemia is common in dialysis patients and that it plays a key role in the increased risk for CVC, it is conceivable that control of serum P may result in reduced burden of CVC in these patients and improve outcomes.

Because dietary restriction of P and intermittent dialysis are not usually effective in controlling serum P, most dialysis patients require dietary phosphate binders (18). CBPB such as Ca acetate and Ca carbonate have replaced aluminum hydroxide as the most widely prescribed phosphate binders. Although cost-effective, recent concern over the possible role of Ca loading from these binders in progression of CVC has led to more frequent use of the considerably more expensive noncalcium, nonaluminum phosphate binder sevelamer hydrochloride (Renagel) (7–10). This concern became more widespread after the publication of the Treat to Goal Study, which showed a 25% increase in the coronary Ca scores among the patients who were treated with Ca salts compared with a 6% increment in the sevelamer group and a similar difference in aortic artery calcification scores. However, the mechanism of the beneficial effect of sevelamer on progression of calcification is unknown. One possible mechanism is reduced Ca loading during treatment with sevelamer. However, reduced cardiovascular calcification may also result from dramatic reductions in total and LDL cholesterol, which occur during treatment with this bile acid sequestrant. Moreover, results of the Calcium Acetate Renagel Evaluation (CARE), a randomized, double-blind trial, demonstrated that Ca acetate is significantly more effective than sevelamer in controlling serum P and Ca × P product to the recom-

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**Table 1. Promoters of vascular calcification**

<table>
<thead>
<tr>
<th>Traditional factors</th>
<th>Uremia-related factors</th>
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<tbody>
<tr>
<td>older age</td>
<td>uremic serum</td>
</tr>
<tr>
<td>male gender</td>
<td>hyperphosphatemia</td>
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<tr>
<td>hypertension</td>
<td>increased Ca × P product</td>
</tr>
<tr>
<td>diabetes</td>
<td>exogenous vitamin D therapy</td>
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<tr>
<td>smoking</td>
<td>elevated parathyroid hormone levels</td>
</tr>
<tr>
<td>high LDL cholesterol</td>
<td>dialysis vintage</td>
</tr>
<tr>
<td>low HDL cholesterol</td>
<td>calcium load and hypercalcemia</td>
</tr>
<tr>
<td>genetic predisposition</td>
<td>chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td>elevated leptin levels</td>
</tr>
</tbody>
</table>

**Table 2. Inhibitors of vascular calcification**

<table>
<thead>
<tr>
<th>Circulating inhibitors</th>
<th>Locally acting inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>fetuin A</td>
<td>matrix Gla protein</td>
</tr>
<tr>
<td>bone morphogenetic protein-7</td>
<td>osteopontin</td>
</tr>
<tr>
<td>PTHrP</td>
<td>pyrophosphate</td>
</tr>
<tr>
<td>HDL</td>
<td>osteoprotegerin</td>
</tr>
<tr>
<td>magnesium</td>
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</tbody>
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| Genetic protection                   |                                          |

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**Table 3. Interventions that may reduce cardiovascular calcification**

<table>
<thead>
<tr>
<th>Control of factors that promote calcification</th>
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</thead>
<tbody>
<tr>
<td>control of serum phosphorus and calcium levels</td>
</tr>
<tr>
<td>control of Ca × P product</td>
</tr>
<tr>
<td>lower LDL cholesterol level</td>
</tr>
<tr>
<td>sevelamer HCl</td>
</tr>
<tr>
<td>treatment of secondary hyperparathyroidism with calcimimetic agents</td>
</tr>
<tr>
<td>use of physiologic doses of vitamin D</td>
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<tr>
<td>calcium channel blockers</td>
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<tr>
<td>avoid treatment with warfarin</td>
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<tr>
<td>renal transplantation</td>
</tr>
<tr>
<td>avoid hypercalcemia</td>
</tr>
<tr>
<td>? lower calcium load</td>
</tr>
<tr>
<td>? frequent dialysis</td>
</tr>
<tr>
<td>? control of chronic inflammation</td>
</tr>
</tbody>
</table>

**Augmenting the effects of factors that inhibit calcification**

| matrix Gla protein                      |
| osteoprotegerin                        |
| fetuin-A                               |
| bone morphogenetic protein-7           |
| osteopontin                            |
| pyrophosphate                          |
| genetic factors                         |

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*PTHrP, parathyroid hormone-related peptide.*
mended goal levels (19). Thus, it is conceivable that Ca acetate might in fact reduce the risk for CVC and mortality in dialysis patients as a result of better control of both serum P and Ca × P product. Clearly, more studies on the role of Ca loading from CBPB in progression of CVC are needed before prematurely abandoning these cost-effective binders.

Control of Hyperlipidemia

Hyperlipidemia, particularly increased LDL, has been implicated in progression of CAC (20–23). In addition, the beneficial effect of lowering LDL cholesterol levels on progression of calcification in the general population has been reported by several groups (21–23). Callister et al. (22) demonstrated that treatment with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors can reduce the volume of calcified plaque in the coronary arteries (Figure 1). At the follow-up EBCT scans, a net reduction in the Ca-volume score of 7% was observed only in patients whose the final LDL cholesterol levels were <120 mg/dl \( (P < 0.01) \). Moreover, in the only prospective study on the effect of lipid-lowering therapy on the progression of CAC, Achenbach et al. (23) found that treatment with the cholesterol-synthesis enzyme inhibitor cerivastatin significantly reduced coronary artery Ca progression in patients with LDL cholesterol levels >130 mg/dl (Figure 2). The median annual relative increase in coronary Ca was 25% during the untreated period versus 8.8% during the treatment period \( (P < 0.0001) \).

Results of the Treat to Goal Study (8) suggest that lowering the LDL level in patients with ESRD may also result in amelioration of progression of CVC. Patients who were treated with sevelamer had a significant decrease in their plasma LDL cholesterol levels from 102 to 65 mg/dl during the study period, whereas the LDL levels did not change in patients who were treated with CBPB. Therefore, it is possible that the slower rate of progression of cardiovascular calcification observed in the Treat to Goal Study may have resulted from the significant lowering of the LDL level by sevelamer. Two other studies underscore the role of dyslipidemia in the pathogenesis of CVC in patients with CKD. Nitta et al. (24) reported the results of their preliminary study from Japan, which showed that progression of aortic calcification in patients with ESRD was significantly retarded during treatment with colistimide (a bile acid sequestrant similar to sevelamer) in combination with atorvastatin compared with the period before treatment was initiated. Tamashiro et al. (25) reported that rapid progression of CAC in hemodialysis patients was associated with higher triglycerides and lower HDL cholesterol levels.

Control of Secondary Hyperparathyroidism: Vitamin D versus Calcimimetic Agents

The current treatment of secondary hyperparathyroidism (SHPT) in dialysis patients includes suppression of parathyroid hormone secretion with supraphysiologic doses of vitamin D or its analogues. Unfortunately, vitamin D may predispose to vascular calcification. Rats that were treated with high-dose vitamin D developed calcification in the aorta, carotid, hepatic, mesenteric, renal, and femoral arteries (26). Clinical studies have also reported an association between vascular calcification and use of vitamin D therapy in hyperphosphatemic patients with renal failure (27,28). Vascular smooth muscle cells (VSMC) have been shown to express vitamin D receptors (29). Although vitamin D inhibits VSMC proliferation by enhancing Ca flux into cells, it induces VSMC to exhibit an osteoblastic phenotype.

Figure 1. Reduction of LDL cholesterol to <120 mg/dl resulted in halting progression of coronary artery calcification (CAC). \( \square \), Initial values; ■, final values for coronary artery Ca volume scores. As can be seen, patients in group 1 who were not treated with 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitor had significant progression of CAC. Similarly, patients in group 2 who were also treated but their average LDL cholesterol levels remained >120 mg/dl had significant progression of calcification. Patients in group 3 who were treated with HMG-CoA reductase inhibitor and their average LDL cholesterol levels were successfully reduced to <120 mg/dl had no progression of calcification. Reprinted from reference (29), with permission.
(35–37). In the PREVENT study, the CCB amlodipine was found to reduce intimal medial thickness in type 2 diabetes (37). More recently, Motro and Shames (38) compared the effect of nifedipine and diuretics on progression of CAC in 201 hypertensive patients over a 3-yr period. They showed that CAC score increased by 40% in patients who were treated with nifedipine versus 78% on diuretics (P = 0.02). The effect was more pronounced in patients who had higher CAC scores at baseline. No similar studies have been reported in patients with CKD. Clearly, the effect of CCB on progression of CVC deserves further study, particularly in patients with CKD.

Role of Renal Transplantation

Cardiovascular mortality is clearly lower in renal transplant recipients than in dialysis patients (39,40). Moreover, the prevalence of CVC is also lower in renal transplant recipients than in dialysis patients (41). A preliminary study by Moe et al. (42) showed that CAC can be slowed or arrested after renal transplantation (Figure 3). A study by Stompor et al. (43) also showed no progression of CAC in renal transplant recipients compared with peritoneal dialysis patients. There are a number of potential mechanisms by which renal transplantation reduces the burden of CVC: First, renal transplantation restores renal function and therefore eliminates the role of uremic toxins in promoting CVC. Second, because baseline CAC scores in renal transplant recipients are dependent on the duration of dialysis (44), transplantation may reduce the burden of calcification by shortening the duration of dialysis. Third, renal transplantation may improve some disorders of mineral metabolism. Indeed, hypophosphatemia, rather than hyperphosphatemia, may develop in renal transplant recipients with normal graft function. Further studies designed to examine the role of renal transplantation in ameliorating CVC are clearly needed.

Augmenting Effects of Factors that Inhibit Vascular Calcification

Although CVC is very common in patients with CKD, it is conspicuously absent in approximately 17% of patients despite similar exposure to factors that promote calcification (45). Moreover, patients who do not have detectable vascular calcification rarely develop calcification on follow-up studies (46). Because the physiologic concentrations of Ca and P in human serum, particularly in patients with ESRD, are far above their solubility product and therefore should precipitate immediately, inhibitors of precipitation of these ions must be playing a major role in preventing extrasosseous calcification.

Several animal knockout models have shown that the Ca regulatory factors matrix Gla protein (MGP), osteoprotegerin (OPG), and fetuin-A (α2-Heremans-Schmid glycoprotein-Ahs) may be protective from vascular calcification (46–49). Mice deficient in MGP or OPG develop spontaneous vascular calcification (48). Similarly, mice deficient in fetuin-A also develop severe ectopic calcification when fed a mineral- and vitamin D–rich diet or when fed a normal diet when combined with a DBA/2 genetic background (49). Unfortunately, the therapeutic potential of these inhibitors of calcification has not been explored in clinical trials. However, because MGP requires vita-
min K for γ-carboxylation, acquired vitamin K deficiency, as with the use of warfarin, may predispose to vascular calcification (50). It is interesting that calciphylaxis, or calcific uremic arteriolopathy, has been reported with increasing frequency in patients who are treated with warfarin therapy (11). Thus, it is possible that by avoiding the use of warfarin in patients with CKD, the risk for CVC may be reduced by not interfering in the production of MGP.

Similarly, OPG knockout mice develop osteoporosis and severe vascular calcification (48). This observation indicates that OPG is an important inhibitor of calcification of blood vessel walls. Paradoxically, serum OPG levels are associated with the extent of vascular calcification in hemodialysis patients (46,51). This may be a compensatory, protective response to the progression of vascular calcification or due to the effect of OPG on decreasing bone turnover, thus impairing the ability of bone to buffer Ca load (46). It is interesting that a study by Price et al. (52) showed that subcutaneous doses of OPG that inhibited bone resorption in rats were effective in inhibiting arterial calcification induced by warfarin or vitamin D.

Finally, fetuin-A has also been shown to be a potent systemic inhibitor of calcification, accounting for approximately 50% of the precipitation inhibitory capacity of serum (49,53). Hemodialysis patients have lower levels of fetuin-A compared with control subjects with normal renal function (53). The effect of restoring fetuin-A levels in dialysis patients on progression of CVC has not been reported but potentially could represent an attractive therapeutic modality.

**Inhibitors of Bone Resorption**

Clinical and experimental studies have consistently established an association between arterial calcification and bone resorption (54–56). Consequently, it can be hypothesized that treatment strategies that reduce bone resorption and increase bone mineralization may simultaneously decrease the risk for vascular calcification. Indeed, several preliminary studies have shown a beneficial effect of bisphosphonates and other inhibitors of bone resorption on vascular calcification (54,57).

Etidronate was shown previously to inhibit vitamin D–induced arterial calcification in rats (58,59). Other bisphosphonates, such as ibandronate and alendronate, also inhibited arterial and cardiac valve calcification after 2 and 4 wk in a warfarin-induced ectopic calcification model (50,54). The effect of intermittent etidronate therapy on progression of vascular calcification was recently reported in 35 hemodialysis patients (Figure 4) (59). In that study, three courses of etidronate, 200 mg/d for 14 d every 3 mo, significantly suppressed CAC progression with no change in bone mineral density. This effect was associated with a decrease in both C-reactive protein and serum OPG levels.

**Other Interventions**

Aged garlic extracts (AGE), which have antioxidant properties, have the ability to reduce several cardiovascular risk factors, such as BP, serum cholesterol, and platelet aggregation and adhesion, while stimulating nitric oxide generation in endothelial cells (60). As a result, these may improve peripheral circulation. Thus, it has been claimed that AGE impart cardiovascular benefits. It is interesting that a recent small pilot study

![Figure 3. Change in coronary artery calcium score over time.](image1)

The changes in CAC in transplant recipients (A) and hemodialysis patients (B) are plotted for individual patients who had calcification at baseline. Reprinted from reference (53), with permission.

![Figure 4. Axial cross-section obtained by spiral computed tomography in a 73-yr-old patient at baseline (A) and after cyclic intermittent etidronate therapy (B).](image2)

Reprinted from reference (59), with permission.
by Budoff et al. (60) showed that, compared with placebo, AGE may inhibit the rate of progression of CAC in the general population. The mechanism is probably related to their ability to inhibit atherosclerosis (61).

**Genetic Susceptibility or Immunity**

Limited evidence suggests that CAC has strong genetic determinants (62). Possibly, some genes are procalcification genes, whereas others are anticalcification (protective) genes. Little is known about these CAC susceptibility genes, and it is vitally important to identify and characterize these genes by identifying the chromosomal regions that harbor them. The identification of susceptibility genes for CAC should increase the knowledge about CVD risk for a given patient and help to identify those for whom intensive preventive or therapeutic measures may be most beneficial.

**Can Cardiovascular Calcification Be Reversed?**

So far, the goal of most interventional studies has been to slow or halt progression of CVC. However, whether calcification can realistically be reversed, particularly in patients with CKD, is not known at the present time. It is interesting that several studies have indicated that reversal of calcification may indeed be possible. Callister et al. (29) reported regression of Ca volume score in 63% of 65 patients with LDL levels <120 mg/dl. In another study of 102 symptomatic patients with CAC, Schmermund et al. (20) reported that standard therapy for coronary artery disease resulted in regression of calcification in 15% of patients with suspected or known coronary artery disease on follow-up EBCT scans. Although it is possible that regression of calcification may be due to interscan variability, these authors speculated that reduction of calcification may be the result of shrinkage and increased density of the calcified lesions. Given that CAC may be predictive of cardiovascular events and death from CVD, interventions designed to induce regression of calcification may help to reduce the risk for death in patients with CKD and coronary artery disease.

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