Pathogenesis of vascular calcification in chronic kidney disease

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Background. Hyperphosphatemia and hypercalcemia are independent risk factors for higher incidence of cardiovascular events in patients with chronic kidney disease. In addition to increased calcium-phosphate product, hyperphosphatemia accelerates the progression of secondary hyperparathyroidism with the concomitant bone loss, possibly linked to vascular calcium-phosphate precipitation.

Results. The control of serum phosphate levels reduces vascular calcification not only by decreasing the degree of secondary hyperparathyroidism and calcium-phosphate product, but also by reducing the expression of proteins responsible for active bone mineral deposition in cells of the vasculature. The calcium and aluminum-free phosphate-binders provide a new and effective therapeutic tool in preventing vascular calcifications in chronic kidney disease in animal models and in hemodialysis patients.

Conclusion. Additional investigations are necessary to examine the benefits of different phosphate-binders in reducing mortality from cardiovascular disease.

Cardiovascular events are the most frequent cause of death in patients with chronic renal failure [1, 2]. Calcification of soft tissues and blood vessel walls occurs more frequently in dialyzed patients compared to the nonuremic population [3–5].

In the last decade, large evidence has been accumulated indicating that disturbances in mineral and bone metabolism in patients with chronic kidney disease (CKD) associate with vascular calcification and increased morbidity and mortality. Abnormalities in mineral and bone metabolism are very common in end-stage renal disease (ESRD). In this patient population, parathyroid gland enlargement and high circulating levels of parathyroid hormone (PTH) are major contributors to increased bone resorption, a feature of renal osteodystrophy [6, 7].

Thus, vascular calcification is linked to enhanced bone resorption. In addition, an inverse relationship between arterial calcification and bone density has been documented in uremic patients [8]. In the general population there is an association between osteoporosis and vascular calcification [9].

Recently [10], a multivariate analysis performed in a group of patients maintained on hemodialysis demonstrated that the arterial calcification score was positively associated with age and daily dose of calcium-containing phosphate binders, and an inverse correlation with osteoblastic surfaces. A high arterial calcification score was associated with bone histomorphometry suggestive of low bone activity and adynamic bone disease. Thus, an oversuppression of PTH could also influence the development of vascular calcification.

Vascular calcification involves not only passive calcium-phosphate deposition on atherosclerotic vessels but active “ossification” of vascular structures [11, 12]. Hyperphosphatemia and increased calcium-phosphate product are important contributors to vascular calcifications in uremic patients, and also appear to be associated with increased mortality [13, 14]. In particular, elevated blood levels of phosphate associate with ectopic calcifications and increased risk of calciphylaxis [8, 15–17]. Unfortunately, the pathogenic mechanisms for hyperphosphatemia, high calcium-phosphate product, secondary hyperparathyroidism, or kidney disease in itself in enhancing vascular calcification in CKD are still incompletely understood. Because vascular calcifications cause higher morbidity and mortality, the control of serum phosphate in patients with CKD is crucial in preventing increases in calcium-phosphate product, secondary hyperparathyroidism and, therefore, ectopic calcifications [18]. In the past, the standard treatment for the hyperphosphatemia of CKD consisted of dietary phosphate restriction, efficient dialysis treatment, and administration of phosphate-binders (aluminum salts, calcium carbonate, or acetate). Recent studies proved the limitations of calcium salts as phosphate-binders elevating calcium load in patients with ESRD [19, 20], and with more than 50% of patients not achieving a good control of serum phosphate levels [13, 14].
The development of new phosphate binders that do not contain aluminum or calcium opened new perspectives in preventing vascular calcifications in ESRD in animals and humans [20, 21].

This review presents the current understanding of pathogenic mechanisms for regulation and prevention of ectopic calcification in CKD.

PROTEINS MODULATING ECTOPIC CALCIFICATIONS

In the last decade, several studies have defined calcification of atherosclerotic lesions as an active process similar to bone formation. Different gene products seem to induce or inhibit the process of ectopic calcification (Table 1). In particular, matrix Gla-protein, fetuin, osteoprotegerin, and osteopontin may play a very important role on inhibiting mineral deposition in the vasculature. In fact, these 4 “protective” proteins associate with reduced vascular calcification and may be the regulatory keys in preventing ectopic calcification in renal failure.

Matrix gla-protein (MGP)

During the first 8 weeks of life, mice lacking MGP develop osteoporosis and pathologic fractures, as well as diffuse arterial calcification [22]. In addition, MGP is an extracellular matrix protein with high affinity for hydroxyapatite that actively participates in the pathophysiology of osteoporosis and in the prevention of vascular calcification [23]. These data indicate that MGP is required to both promote normal bone formation and inhibit vascular calcification, but its potential role in CKD still needs to be clarified.

Fetuin (Ahsg)

α2-Heremans-Schmid glycoprotein (Ahsg), also known as fetuin-A, is an important inhibitor of ectopic calcification. Serum concentrations of fetuin fall during the cellular immunity-phase of inflammation [24, 25]. In vitro, fetuin inhibits the de novo formation and precipitation of calcium-phosphate, with no effects on hydroxyapatite once it is formed [26, 27]. Ahsg-deficient mice develop extensive soft tissue calcifications in myocardium, kidney, lung, tongue, and skin [28]. Recently, Ketteler et al [29] reported that low serum fetuin levels associate with increased cardiovascular mortality in patients receiving hemodialysis treatment, therefore suggesting that Ahsg could be involved in preventing the accelerated extraskeletal calcification observed in CKD.

Fetuin/MGP complex

In the last 5 years, Price et al [30–33] characterized biochemically and physiologically a high-molecular-mass complex of bone calcium-phosphate mineral and serum fetuin, matrix Gla-protein (MGP), and a new 24-kD protein (spp 24), similar to fetuin and MGP [32]. This high-molecular-mass complex inhibits bone mineralization in vivo [30–32].

Paradoxically, in studies stimulating bone resorption with pharmacologic doses of vitamin D [33], formation of fetuin-mineral complex coincides temporally with increases in bone resorptive activity and arterial calcifications. Furthermore, there is a reduction in serum fetuin in rats with ongoing artery calcification. It is possible that excessive bone resorption generates such massive amounts of fetuin mineral complex that impair fetuin ability to further arrest the growth of the mineral components, which could then induce arterial calcifications. The reduction in serum fetuin associates with clearance of the complex from circulation. In fact, when bone resorption is prevented through administration of bisphosphonates, there is no reduction of serum fetuin. The striking correlation between depletion of serum fetuin and death suggests that exhaustion of serum fetuin is an important pathophysiologic factor [33].

Osteoprotegerin (OPG)

Bucay et al [34] showed low bone density and increased arterial calcification in OPG-deficient mice. Similar to matrix Gla-protein and fetuin, osteoprotegerin appears to inhibit ectopic calcification, playing an important role in both pathologic and physiologic calcification processes [35].

Osteopontin (OPN)

Recently, several authors [36, 37] proposed that OPN acts as an inhibitor of calcification of vascular smooth muscle cell (VSMC) cultures, while Jono et al [38] demonstrated that the phosphorylation of osteopontin was a mandatory step to inhibit VSMC calcification. Thus, osteopontin is both an important modulator of bone mineralization and a potent inhibitor of ectopic calcifications.

In contrast to the protective effects of matrix Gla-protein, fetuin, osteoprotegerin, and osteopontin, a higher expression of osteocalcin, alkaline phosphatase [39], osteonectin [40], and BMP2a [41] was associated with myofibroblasts and vascular smooth muscle cells being diverted to the osteogenic lineage with a concomitant

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**Table 1. Opposite effects of proteins associated with vascular calcification**

<table>
<thead>
<tr>
<th>Inhibitory genes</th>
<th>Inducing genes</th>
</tr>
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<tbody>
<tr>
<td>Osteopontin (OPN)</td>
<td>Alkaline phosphatase (ALP)</td>
</tr>
<tr>
<td>Matrix Gla-protein (MGP)</td>
<td>Osteocalcin (OC)</td>
</tr>
<tr>
<td>Fetuin (Ahsg)</td>
<td>Osteonectin (ON)</td>
</tr>
<tr>
<td>Osteoprotegerin (OPG)</td>
<td>Bone matrix protein 2a (BMP 2a)</td>
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induction of calcification (Table 1). More studies are necessary to clarify the impact of altered expression and function of these gene products in the vascular calcification of end-stage kidney disease.

**INDUCTION OF VASCULAR CALCIFICATION BY HIGH PHOSPHATE LEVELS AND UREMIC TOXINS**

In the last 10 years, several mechanisms have been proposed for phosphate regulation of vascular calcification, involving not only deposition of calcium and phosphate in the vasculature, but also direct activation of genes associated with osteoblastic functions in vascular smooth muscle cells [11]. Jono and Giachelli [42, 43] showed that high phosphorus levels in the incubation media (2 mmol/L) enhanced calcification in human aortic smooth muscle cells (HSMCs). Phosphate-containing mineral deposition was predominant in the extracellular matrix [42]. In vivo studies by Kuro-o et al [44] demonstrated that even in the presence of normal renal function, a 2-fold increase in serum phosphate levels in the KLOTHO-gene mutant mice resulted in increased calcium-phosphate product with the development of vascular calcifications and osteoporosis.

Characterization of the mechanisms involved in phosphate induction of calcification, in vitro studies, indicated that high phosphate increased HSMCs calcification is dependent upon a functional sodium-phosphate cotransporter Pit-1, and involves direct induction of the osteoblast-specific genes Osf2/Cbfa-1 [45]. Moreover, Cbfa-1 regulates the expression of osteocalcin [46], one of the most important genes in osteoblastogenesis. Also, in bovine vascular smooth muscle cells (BVSMCs) incubated with different concentration of phosphate, the expression of osteopontin and alkaline phosphatase increases, and calcification is induced [47].

Importantly for CKD, in BVSMCs, the expression of these proteins critical in bone formation was also induced by uremic serum independently of phosphate concentrations [47]. This finding constitutes the first demonstration of direct induction of vascular calcification by uremic toxins in vitro. Interestingly, changes in phosphate had no further effect on calcification. Of significance was the report by Moe et al [48], demonstrating increased expression of the key transcriptional regulator of osteoblasts differentiation, Osf2/Cbfa1, and osteopontin in the media and intima of calcified epigastric arteries from uremic patients.

Recent studies [49, 50] have demonstrated the role of calcium, per se, in addition to phosphate in the development of vascular calcification in HVSMCs. Yang et al [49] described that elevated calcium stimulated mineralization of HSMC under normal phosphate conditions, and accelerated mineralization under elevated phosphate conditions. The elevated calcium induced the expression of the sodium-dependent phosphate cotransporter, Pit-1. Calcium-induced mineralization was inhibited by phosphonoformic acid (FPA), an inhibitor of the sodium-dependent phosphate cotransporter, in a manner similar to FPA inhibition of phosphate-induced mineralization. This indicates that calcium-induced mineralization was also dependent on the activity of a sodium-dependent phosphate cotransporter. In addition, elevated calcium increased mRNA levels of Cbfa-1 and alkaline phosphatase similar to those observed in elevated phosphate-treated HVSMC. Reynolds et al [50] demonstrated that elevated calcium or phosphate induced HVSMC calcification independently and synergistically, a process that was inhibited by normal serum. The investigators found that in the presence of increased phosphate, even a modest increase in calcium can significantly exacerbate calcification. This process is induced by nucleation of basic calcium phosphate in vesicles that are released from both viable and apoptotic HVSMC. Taken together, the results of these investigations [49, 50] suggest that the abnormal vascular calcification observed in patients with CKD results from reduced capacity of HVSMC to inhibit mineralization via cell-mediated mechanisms.

These in vivo and in vitro findings support a new definition of arterial calcification as an active process, “similar” to bone formation, and suggest that serum phosphate and calcium levels, as well as the uremic state, per se, could directly regulate vascular calcification through modulation of the expression of proteins with bone-forming activity in the vessel walls (Fig. 1).

**PREVENTION OF THE DETERIORATION OF RENAL FUNCTION AND KIDNEY CALCIFICATION BY CONTROLLING SERUM PHOSPHATE IN EXPERIMENTAL KIDNEY DISEASE**

In 1978, Ibelis et al [51] described that in 5/6 nephrectomized rats, dietary phosphate restriction associated
with preservation of renal function. Two years later, the renal toxicity of phosphate in rats was elucidated [52]. Chronic kidney disease causes a reduction in the number of nephrons and consequently in phosphate excretion; different studies have shown that phosphate retention not only induces secondary hyperparathyroidism, but also accelerates renal failure by inducing kidney calcifications [53]. In more than 200 renal biopsies in humans, Gimenez et al [54] showed a correlation between high blood phosphate levels, renal calcium deposition, and the progression of renal failure. In these studies, patients with higher serum calcium-phosphate product, renal calcium content, and histologic calcium deposition were those with serum creatinine levels above 1.5 mg/dL [54]. In experimental renal failure, the accelerated deterioration of renal function induced by high dietary phosphate associates with nephrocalcinosis, as depicted by renal calcium-phosphate precipitation and tubulointerstitial damage [55].

In 1980, Walser [56] described the association between calcium salt (calcium carbonate) administration to ESRD patients and elevated serum creatinine concentration after 2 to 4 weeks of treatment. More recently, Hsu et al [57] pointed out that dialysis patients are in a positive calcium balance, and that the excess calcium is present in soft tissues. In addition, there is evidence that calcium deposition in dialysis patients may be triggered by inflammation [58].

The control of serum calcium-phosphate product is critical in preventing ectopic calcification in chronic renal failure. Recently, Nagano et al [59, 60] examined whether sevelamer hydrochloride, a noncalcemic phosphate-binder, could slow deterioration of renal function in rats with progressive renal insufficiency. In sevelamer-treated rats, serum phosphorus, calcium-phosphate product, and PTH levels were greatly decreased compared to untreated animals. Sevelamer not only prevented the decrease in creatinine clearance and elevations in kidney calcium content, but also reduced glomerular and tubulointerstitial histologic lesions of the kidney [60].

Using the 5/6 nephrectomy model of CKD in rats, we compared the effects of sevelamer and calcium carbonate in the control of serum phosphate, secondary hyperparathyroidism, and kidney calcifications [61]. Sevelamer was as effective as calcium carbonate in reducing serum phosphate and PTH levels, and in controlling parathyroid gland growth. Moreover, sevelamer treatment controlled serum phosphate independent of increases in serum calcium, thus reducing serum calcium-phosphate product, and preventing further deterioration of renal function (Fig. 2). Sevelamer-treated rats showed reduced renal calcium deposition compared to untreated uremic animals or rats taking calcium carbonate as phosphate-binder. Importantly, the degree of tubular-interstitial fibrosis was also markedly lower when rats were treated with sevelamer [61].

Both studies provide enough evidence that in experimental chronic renal failure in rats, sevelamer not only reduces serum phosphate and PTH levels but prevents kidney calcium deposition and tubulointerstitial fibrosis, thus preserving renal function.

PREVENTION OF CARDIOVASCULAR CALCIFICATION IN EXPERIMENTAL KIDNEY DISEASE

In chronic kidney disease, severe complications, including secondary hyperparathyroidism, ectopic calcification, and increased cardiovascular morbidity and mortality are associated with increased serum phosphate levels [13, 14]. Therefore, prevention of vascular calcification through a strict control of phosphate and calcium-phosphate product is a major goal for new therapeutic agents.

Recently, 2 studies examined the efficacy of sevelamer in preventing ectopic calcification of soft tissues in experimental renal failure. In rats with adenine-induced renal failure, Katsumata et al [62] showed that serum phosphate, calcium-phosphate product, and PTH levels were reduced by treatment with sevelamer compared with the untreated uremic animals. More importantly, therapy with sevelamer was accompanied by reduced aortic calcification and ameliorated renal osteodystrophy in this animal model [62]. In addition, in our study using the 5/6 nephrectomized model in rats, treatment for 6 months with either calcium carbonate or sevelamer demonstrated that the phosphate-binder sevelamer controls serum phosphate and secondary hyperparathyroidism as well as calcium salts, but greatly attenuates vascular calcification and, as mentioned earlier, the deterioration of kidney function (Fig. 3) [63]. Despite the similar efficacy of sevelamer and calcium carbonate to maintain serum levels of phosphorus,
onset of renal failure. Calcifications within the myocardium, aorta, and kidney were found in the sevelamer treated group of uremic animals [63]. Sevelamer also induced less deterioration in renal function, as indicated by higher creatinine clearance and lower urinary protein excretion.

Many factors, including high phosphate, calcium, and vitamin D therapy are associated with the development of vascular calcification. In the treatment of secondary hyperparathyroidism, 1,25(OH)2D3 has been used because of its efficacy in suppressing PTH synthesis and secretion through a mechanism similar to other steroid hormones, which involves its receptor, the vitamin D receptor [6, 64, 65]. However, the hypercalcemia and hyperphosphatemia that results from increased intestinal calcium and phosphate absorption or bone resorption often precludes the therapeutic use of 1,25(OH)2D3 in chronic kidney disease patients. Because of the potent effects of 1,25(OH)2D3 in increasing intestinal calcium absorption, and calcium and phosphate mobilization from bone, vitamin D therapy further increases the risk of development of soft tissue calcification in patients with an already enhanced calcium-phosphate product, especially in those receiving calcium salts as phosphate binders [15]. As a result, analogues of 1,25(OH)2D3 that suppress PTH synthesis and secretion in uremic rats with secondary hyperparathyroidism at doses that do not increase either serum calcium or phosphate levels were developed [66, 67]. The mechanisms responsible for the decreased calcemic and phosphatemic activities of these new 1,25(OH)2D3 analogues are incompletely elucidated.

A recent study by Hirata et al [68] compared the efficacy of 22-oxacalcitriol (OCT), a 1,25(OH)2D3 analogue with lesser calcemic activity than 1,25(OH)2D3, in suppressing secondary hyperparathyroidism and soft tissue calcifications in 5/6 nephrectomized rats. Despite a similar control of serum PTH levels, kidney, myocardial, and aortic calcifications were more severe in the 1,25(OH)2D3-treated group than in the animals receiving OCT. In addition, the deterioration of the residual renal function, tubular-interstitial changes, and nephrocalcinosis were significantly lower in OCT-treated rats compared to animals receiving 1,25(OH)2D3 [68].

More importantly, a 16% survival advantage was recently reported in a retrospective study of over 60,000 chronic hemodialysis patients throughout the United States treated with the vitamin D analogue paricalcitol compared to those treated with calcitriol [69]. This report demands validation from controlled prospective studies. Several mechanisms could contribute to the survival advantage of paricalcitol. In addition to the milder elevations in serum phosphate and calcium levels with analogue therapy compared to those induced by calcitriol, there could be a higher potency of paricalcitol to display nonclassic calcitriol actions, such as in the down-regulation of the renin-angiotensin system [70], or in the inhibition of smooth muscle proliferation [71]. The actual role of these processes in vascular calcification is only speculative at present.

**NONCLASSIC CARDIOVASCULAR RISK FACTORS IN CKD PATIENTS**

Patients with chronic renal failure develop atherosclerotic vascular disease more frequently and earlier than the general population [4, 5]. Several elements need to be added to the classic risk factors, such as hypertension, diabetes, dyslipidemia, obesity, gender, smoking, and family history, in uremia-induced cardiovascular disease. In particular, advanced-glycation end products (AGEs), oxidative stress, and nitric oxide (NO), asymmetric dimethylarginine (ADMA), homocysteine, phosphate, and calcium-phosphate product, are all potential culprits in uremia (Table 2).

**Table 2. Risk factors for cardiovascular disease in chronic renal failure patients**

<table>
<thead>
<tr>
<th>Classic</th>
<th>Nonclassic</th>
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<tr>
<td>Hypertension</td>
<td>Advanced glycation end products (AGEs)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Oxidative stress and nitric oxide (NO)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Asymmetric dimethylarginine (ADMA)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Smoking</td>
<td>Phosphate and calcium-phosphate product</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<td>Family history</td>
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**Advanced glycation end products (AGEs)**

Both CKD and dialysis treatment are associated with oxidative and carbonyl stress and, therefore, with an increased microinflammatory status [72]. Inflammation and oxidative/carbonyl stress damage may act synergistically...
on inducing accelerated atherosclerosis and increasing cardiovascular morbidity and mortality in CKD [73].

Oxidative stress, nitric oxide (NO), and asymmetric dimethylarginine (ADMA)

Nitric oxide is a vasodilator compound that participates in regulation of endothelial function and inhibits atherosclerotic process [74]. In addition, NO synthesis can be blocked by endogenous inhibitors, such as ADMA [75]. Recent clinical studies demonstrated that increased blood ADMA levels correlate with endothelial dysfunction and cardiovascular mortality in patients with chronic kidney disease [76].

Homocysteine

Hyperhomocysteinemia strongly correlates with cardiovascular disease both in general population and in uremic patients [77]. Furthermore, the decrease in blood homocysteine levels in hemodialysis patients rarely reaches “normal” values of general population [78]. However, the role of hyperhomocysteinemia as a nonclassic cardiovascular risk factor for atherosclerosis in chronic kidney disease patients needs to be better clarified [79].

CARDIOVASCULAR CALCIFICATIONS IN CKD PATIENTS

Calcification of blood vessel walls occurs frequently with advanced age, atherosclerosis, and diabetes mellitus. Some autopsies [4, 5] and clinical studies [8] have documented a higher prevalence of coronary plaques in dialyzed patients compared to the nonuremic population. In contrast, Sharples et al [80] recently observed that coronary artery calcification quantified by electron-beam computed tomography (EBCT) does not correlate with obstructive coronary lesions detected by angiography in single arteries in dialysis patients. However, a zero calcification score had a negative predictive value of 87.5% [80]. In the general population, there was no direct correlation between plaque by angiography and vascular calcification by EBCT. The risk factors contributing to the higher prevalence of atherosclerotic lesions in chronic renal failure include high blood pressure, diabetes, dyslipidemia, hyperhomocysteinemia, and endothelial dysfunction [81].

Vascular changes in ESRD are associated with increased atherosclerosis, ischemic heart disease, and vascular stiffening [82]. In a recent study, London et al [83] observed that intimal and medial arterial calcification is common in young and middle-age dialysis patients who do not have conventional atherosclerotic risk factors. Moreover, arterial medial calcification increased arterial stiffness, both strong markers of cardiovascular mortality clearly associated with months of dialysis and calcium load [83]. Moreover, left ventricular hypertrophy and aortic stiffness are major determinants of cardiovascular mortality in hemodialysis patients, in which aortic pulse wave velocity (PWV) index can greatly correlate with the cardiovascular and overall mortality risk. In fact, Blacher et al [84] demonstrated that aortic PWV index, like age of dialysis, represents a strong and important predictor of mortality in end-stage kidney disease patients. Both accelerated atherosclerosis and calcification of arterial intima and media caused arterial stiffness and consequent hemodynamic changes, with elevated systolic blood pressure [85].

Increases in serum levels of phosphate and calcium-phosphate product have been associated with arterial calcification in renal failure, but a clear correlation between cardiovascular calcification and mortality needs to be better clarified [86]. Recent evidence demonstrates that calcium-containing phosphate-binders can increase calcium load [83]. In patients with CKD there are many factors involved in the pathogenesis of cardiovascular disease: hypertension, dyslipidemia, left ventricular hypertrophy, arterial stiffness, inflammation, and hyperhomocysteinemia [86]. In addition, altered phosphate and calcium-phosphate product levels may worsen cardiovascular events in this population by causing a progressive increase in calcium deposition in the coronary arteries and cardiac valves. A study of adolescent and young adult hemodialysis patients by Goodman et al [15] noted a correlation between coronary artery calcification detected by EBCT and duration of dialysis, serum phosphorus and calcium-phosphate product levels, and daily intake of calcium. Another study in 200 hemodialysis patients by Chertow et al [11] showed that sevelamer attenuated the progression of coronary and aortic calcification better than calcium-based phosphate binders after 12 months. Subjects treated with sevelamer had lower serum calcium, total cholesterol, and low-density lipoprotein (LDL) levels compared to subjects treated with calcium-based phosphate binders.

Thus, in the past 5 years, several investigators have demonstrated a potential role of an increased “calcium load” as a pathogenic mechanism in the development of vascular calcification. Total body calcium can be quite positive and contributes to vascular calcification without overt increases in serum calcium concentrations in patients undergoing dialysis. Long-term prospective studies are necessary to address the actual role of calcium overload in the etiopathogenesis of vascular calcification and increased morbidity and mortality due to cardiac events in CKD.

CONCLUSION

Cardiovascular calcifications are very common in patients with CKD. The contribution of high serum phosphate, calcium-phosphate product, and PTH levels to vascular calcification is still incompletely understood. In
addition to the classic alterations in bone and mineral metabolism, an active process has been reported in which vascular cells elicit features of osteoblasts. Multiple factors in kidney disease, including uraemic toxins, were associated to increased extraskeletal calcification. However, prospective, controlled studies are mandatory for proper elucidation of their relative contribution to cardiovascular complications in CKD.

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