

Contribution of Bone and Mineral Abnormalities to Cardiovascular Disease in Patients with Chronic Kidney Disease

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1,25-Dihydroxyvitamin D₃ levels begin to drop early in the course of kidney disease, leading to elevated parathyroid hormone levels and disrupted mineral metabolism. Impaired mineral metabolism seems to be associated not only with bone disease but also with vascular calcification. Animal models have identified molecular mechanisms by which high mineral levels and other uremic substances induce vascular smooth muscle cells to undergo phenotypic changes that initiate the calcification process. Moreover, several epidemiologic and clinical studies showed strong associations between bone loss, arterial calcification, and cardiovascular disease in populations with and without kidney disease. This review discusses evidence that two early complications of chronic kidney disease—vitamin D deficiency and secondary hyperparathyroidism—contribute to bone and cardiovascular disease. New treatment strategies aimed at the prevention of bone loss and parathyroid hyperplasia, such as vitamin D receptor ligand therapy, calcimimetic agents, and noncalcifying phosphate binders, are being investigated for their impact on improving overall outcome in dialysis patients.

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Chronic kidney disease (CKD) is now the ninth leading cause of death, affecting approximately 20 million adults in the United States (1,2). Nearly 80,000 people receive a diagnosis of CKD annually, with diabetes and hypertension being the most common causes (3). More than 8 million Americans have significant impairment of kidney function, and nearly 400,000 receive maintenance dialysis (4–7). Two of the early complications of CKD include deficiency of 1,25-dihydroxyvitamin D₃ (1,25-D) and development of secondary hyperparathyroidism (SHPT), complications that lead to bone loss and, likely, cardiovascular disease (CVD) (8–11). Although bone loss contributes to abnormally high fracture rates in patients with CKD, emerging data also indicate that the disorders of bone metabolism typical of kidney failure contribute to the high rates of CVD observed (12–15). This review identifies recent studies that describe the impact of 1,25-D deficiency, SHPT, and bone metabolism derangements on the development of CVD in patients with CKD and summarizes new treatment strategies that are expected to have a substantial impact on mortality in this patient population.

1,25-D Deficiency in CKD

The progressive effects of CKD lead to a deficiency in serum calcitriol levels, which begin to decline when the GFR drops

below 70 ml/min in stage 2 CKD (16). 1,25-D regulates calcium and phosphate levels in the blood by enhancing calcium and phosphate absorption in the intestine, enhancing calcium reabsorption in the kidney tubules, and suppressing parathyroid hormone (PTH) secretion (17,18). Accordingly, 1,25-D-deficient individuals are hypocalcemic and have elevated serum levels of PTH (19,20). Moreover, 1,25-D deficiency is the probable primary initiating event behind the elevated PTH levels seen in the majority of patients with stage 3 CKD. Indeed, serum levels of calcitriol begin to decline when GFR falls below 70 ml/min, corresponding to the point at which elevated PTH levels are usually first noted (16,20). It is not until much later (GFR <30 ml/min) that hyperphosphatemia, a condition that further inhibits the 1 α -hydroxylase enzyme, and hypocalcemia also become apparent and act additionally to stimulate PTH production and parathyroid gland enlargement (21–23).

The recent finding that vitamin D receptor ligand (VDRL) therapy is crucial in preventing and inducing regression of parathyroid hyperplasia in CKD underscores the importance of low 1,25-D levels in the pathogenesis of this disease (24). These low levels of calcitriol contribute to the development of bone disease in patients with CKD. Decreased VDR activation, caused by low calcitriol levels, is directly responsible for bone loss through decreased osteoblast recruitment (25). Furthermore, 1,25-D deficiency leads to elevated serum PTH levels, which can cause bone loss through the stimulation of excess bone resorption.

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Hyperparathyroidism in CKD

Parathyroid gland cells express receptors for the ionic form of calcium and proliferate in response to low serum calcium levels, resulting in an overall enlargement of the glands and elevation of circulating levels of PTH (19). In addition, 1,25-D deficiency and hyperphosphatemia can further stimulate secretion of PTH. In healthy individuals, PTH regulates serum calcium levels by increasing bone remodeling, decreasing the renal reabsorption of phosphates, elevating the renal reabsorption of calcium, and increasing renal production of calcitriol. In turn, increasing levels of calcium suppress PTH levels in healthy individuals in an autoregulatory manner. In CKD, both calcium and phosphorus serum levels may rise as bone tissue is remodeled in response to the PTH action, although phosphate levels also rise as a result of loss of renal function (26). Importantly, hyperphosphatemia lowers the ability of the parathyroid gland to detect changes in serum calcium levels by interacting with free calcium ions, hence indirectly promoting PTH synthesis (8). In addition, high levels of phosphates have been shown to lead to downregulation of calcium-detecting receptors in parathyroid gland cells, inducing resistance of the parathyroid glands to respond to high levels of serum calcium (8). Thus 1,25-D deficiency and renal dysfunction both promote SHPT, resulting in adverse impacts on bone tissue *via* decreased osteoblast recruitment, decreased formation of bone tissue, and increased breakdown of bone tissue by osteoclasts (26).

Renal Failure–Associated Bone Disease

The most frequently encountered types of bone disease in patients with CKD are high-turnover and adynamic bone disease (ABD) with a minority of patients showing a combination of the two. High-turnover bone disease is characterized by excessive rates of bone resorption and formation that occur in response to high levels of PTH (9,26). In this condition, both osteoblast and osteoclast activity is increased and the extremely rapid remodeling rate prevents adequate mineralization of newly formed bone (9). This results in a structurally weak bone with decreased overall density. In contrast, ABD is characterized by decreased rates of bone formation as a result of decreased osteoblast recruitment and activity and defects in bone mineralization (9,27). This type of bone anomaly often occurs in patients with relatively low levels of PTH (<150 pg/ml) and may result in part from 1,25-D deficiency (18).

The most prevalent metabolic bone abnormality in patients with CKD is high-turnover bone disease. In predialysis CKD, more than 90% of patients have this form of bone histology, whereas fewer than 5% have the adynamic variety of bone histology (28). In dialysis patients, however, the percentage with ABD is often larger (20 to 40%), although this is highly dependent on the type of dialysis and on the extent of calcium loading in any given patient (27–30). Although it is clear that high bone turnover contributes to bone loss and fractures, it is less clear that ABD is associated with an increased fracture risk because of a paucity of bone biopsy data in large prospective studies (11,31–34). Excess calcium loading, often seen in ABD, has been proposed as a risk factor for bone loss in dialysis

patients as shown by the reduction of bone mineral density (BMD) measured by sequential quantitative computed tomography (35). The purported mechanism for such paradoxical effect is the suppression of the pulsatile release of PTH induced by constant administration of calcium supplements. This in turn suppresses bone remodeling. Recent data suggest that ABD may also constitute a risk for CVD if there is concomitant aluminum or calcium overload, because of the inability of bone to buffer calcium (36,37). Whether the induction of ABD by low PTH levels, without evidence of aluminum or calcium overload, is related to increased CVD morbidity and mortality remains a point of debate. Recent studies of dialysis patients who underwent parathyroidectomy showed a long-term survival benefit after parathyroid gland removal (38). Although controversial, this finding lends support to the notion that PTH levels lower than those recommended by recent consensus guidelines may be preferable for dialysis patients (4). Further prospective studies will be needed to confirm the survival benefit associated with lower PTH levels, particularly in light of the findings reported by Avram *et al.* (39); a 14-yr prospective observational study of more than 600 dialysis patients showing that very low levels of PTH (<65 pg/ml) are associated with increased mortality.

CVD in CKD

Within the Medicare population, CVD is twice as common and advances at twice the rate in patients with CKD (40). Moreover, there is a 40-fold higher CVD death rate in dialysis patients compared with the general population (41). This extraordinary burden of disease can be only partially explained by the presence of traditional risk factors for CVD and suggests that other mechanisms may be involved (42). A growing body of evidence indicates that abnormalities of mineral metabolism may contribute to the development of cardiovascular disease, with the most likely link being the development of vascular calcification. It is now clearly established that vascular calcification is closely associated with cardiovascular events in non-CKD populations, and evidence is building rapidly in the CKD population (43–48). In advanced stages of CKD, arterial calcification occurs both in the subintimal space, where it is associated with classic atherosclerosis, and in the medial muscular layer of the vessel wall. It is interesting that patients with ESRD do not seem to have a greater amount of atherosclerotic plaques but, instead, qualitative differences in plaque composition (49). In fact, histologic studies of coronary arteries reveal that hemodialysis patients have an increased thickness of the medial layer of the coronary arteries, a marked increase in the number of calcified plaques, and an increased severity of calcification when compared with control subjects without CKD (49).

Calcification is associated with CVD *via* multiple mechanisms; atherosclerotic calcification is obviously a marker of inflammatory vascular disease that typically is seen in the general population as well as the CKD population. As such, coronary calcification has been linked with atherosclerosis-related events in the general population and all-cause mortality in dialysis patients (45,50,51).

Intimal and medial calcification is also closely associated

with reduced vascular compliance, resulting in reduced coronary perfusion and increased rates of heart failure and ultimately death (11,52,53). Increased vascular stiffness causes increase in peripheral radiation of a perfusion pulse (increased pulse wave velocity) and accelerated return of the so-called reflective waves. Whereas reflective waves are timed to return in diastole in individuals with a healthy vascular system, helping the retrograde filling of the coronary arteries, their early return in patients with reduced vascular compliance causes an increase in afterload with increases in myocardial stress, oxygen consumption, and reduced coronary perfusion (53). Ultimately, this causes left ventricular hypertrophy, increased myocardial fibrosis, myocyte death, and heart failure often secondary to isolated diastolic dysfunction and preserved systolic function (47,54–56). The development of left ventricular hypertrophy, however, is likely driven by additional factors besides vascular calcification and stiffness, such as alteration of the renin-angiotensin system, anemia, and elevated PTH (57). Other forms of cardiovascular calcifications, demonstrated by simple imaging tests, have also been linked with unfavorable outcome in dialysis patients (58–60).

In addition to intimal and media calcification, patients with advanced CKD may experience calcific uremic arteriopathy (CUA), a rare condition characterized by extensive calcification of the vessel wall of subcutaneous arterioles often not associated with obstructive disease of capacitance arteries (61). CUA typically causes cutaneous ischemia and necrosis and may eventually lead to death as a result of severe complicating infections. The pathogenesis of CUA remains largely unknown, although excessive calcium supplementation, especially in patients with diabetes, has been associated with its occurrence (61,62). Some investigators reported symptom resolution after parathyroidectomy, which suggests a link between excessive PTH secretion and CUA (63,64). Evidently, more research is required to elucidate its relationship with bone disease, mineral metabolism, and CVD in patients with CKD.

Pathogenesis and Molecular Mechanisms of Vascular Calcification in Patients with CKD

Multiple factors have been shown to contribute to vascular calcification in patients with CKD. Studies have found that the use of calcium-based phosphate binders, episodes of hypercalcemia and hyperphosphatemia, and elevated PTH levels all are associated with the progression of vascular calcification, whereas the use of non-calcium-based phosphate binders and the control of serum mineral levels attenuate calcification (65–67). In addition, diabetes, age, inflammation, and BMI all correlate positively with the extent of calcification in patients with CKD, whereas bone density is inversely correlated with high levels of calcification (68).

Active processes that involve cells and enzymes that normally are responsible for bone formation seem to be instrumental for the initiation and progression of vascular calcification (69–74). Genetic mouse models have identified vascular smooth muscle cells (VSMC) as being central to the pathogenesis of arterial wall calcification. In addition, endogenous inhibitors of calcification may be lacking in the uremic state

(75,76). It is now believed that arterial calcification is an active process that involves the phenotypic transformation of VSMC into bone-forming osteoblast-like cells that are capable of expressing the bone matrix proteins that are necessary to support the calcification process (77). Genes that are specific to osteoblasts are upregulated and VSMC genes become downregulated during this transition, including bone morphogenetic protein-2, osteopontin, matrix Gla protein, and osteoprotegerin (78–81).

Several new molecular markers, including adipokines such as leptin and resistin, which are tightly regulated by the kidney, were recently investigated as a link between CKD and CVD (82). The decreased GFR characteristic of CKD may dramatically alter the clearance of these adipokines, contributing to the progression of CVD (82). Leptin has been shown to be associated with coronary artery calcification (CAC) and increased carotid intima-media thickness (83–85). Furthermore, prospective studies have shown links between elevated leptin levels and an increased risk for CVD events (86,87). The role of leptin in calcification could potentially be the strong osteogenic differentiation capacity demonstrated by this adipokine, coupled with the fact that leptin receptors are expressed in human atherosclerotic arteries and that the hormone was shown to contribute to vascular calcification in mice (88,89); however, these are recent findings, and further research is still needed.

Relationship between Bone Loss and CVD

Several clinical studies reported strong associations between bone loss, arterial calcification, and CVD (90–92). Using lumbar spine and hand radiographs in 364 women and 190 men from the Framingham Heart Study over a 25-yr study period, Kiel *et al.* (90) noted that the metacarpal relative cortical area decreased by 22% in women and 13% in men. The aortic calcification score increased concomitantly, eight-fold in women and six-fold in men, and there was a significant association between the percentage change in metacarpal relative cortical area and the change in aortic calcification index in women.

In a retrospective analysis of ambulatory patients who underwent dual-energy x-ray absorptiometry (DEXA) bone scans and coronary angiography, 56% had clinically significant coronary artery disease as defined by a >50% luminal stenosis (93). The finding of osteoporosis of the proximal femur, ultradistal radius, and one-third distal radius correlated with coronary artery stenosis of $\geq 50\%$. This was the first study to report an association between angiographically documented coronary artery disease and low BMD predominantly in women. In a population-based study by van der Klift *et al.* (94), low BMD of the femoral neck but not the spine correlated with the existence of peripheral arterial disease; findings that were also observed by Aksoy *et al.* (95) and Schulz *et al.* (96).

Similar findings are less readily available in CKD populations, although low BMD is a common finding in dialysis patients (31). Taal *et al.* (97) demonstrated that dialysis patients with bone loss (osteopenia or osteoporosis) have higher rates of cardiovascular death compared with patients with normal BMD. The first observation that many dialysis patients experience CAC was reported by Braun *et al.* (98) in a longitudinal

assessment of dialysis patients. They found a 2.5- to five-fold higher prevalence of CAC compared with matched nondialysis patients. In addition, calcification of the aortic and mitral valves was present in more than 50% of the dialysis patients. Although there was no correlation of serum calcium, phosphate, or PTH levels with the extent of CAC, bone mass did correlate inversely with coronary calcium (98). Matsuoka *et al.* (51) recently reported that patients with aluminum bone deposition and high oral calcium intake had more extensive arterial calcification in conjunction with lower PTH levels and low bone turnover. Finally, Raggi *et al.* (85) showed that patients who were treated long term with calcium-based phosphate binders calcify their cardiovascular system while they progressively lost vertebral BMD.

Importantly, several of these studies used either plane x-rays or DEXA scans of the extremities or hip to establish an inverse association between vascular calcification and bone demineralization. The use of DEXA for bone density measurement of the spine is fraught with the frequent occurrence of vascular calcification, particularly in the dialysis population, rendering DEXA of little utility in this particular scenario (100).

Recent Findings and Therapeutic Advances

The previous discussion highlights the complex interplay among the skeletal, vascular, and renal systems (Figure 1). The mainstay of therapy in dialysis remains the use of phosphate binders. For the past two decades, calcium-based phosphate binders represented the therapeutic gold standard for treatment of hyperphosphatemia. They replaced aluminum salts that were found to cause long-term toxic effects such as encephalopathy, ABD, and microcytic anemia (101). Still widely used, often in large doses, calcium-containing binders provide a substantial calcium load, leading to progressive cardiovascular calcification (102,103). In hemodialysis patients with evidence of metastatic calcification, the use of calcium-based phosphate binders should be carefully monitored, and the use of calcium- and aluminum-free phosphate binders is recommended (104). Sevelamer hydrochloride is one of two calcium-free phosphate binders available on the market and the one with the most extensive clinical experience. Beyond the effects on mineral

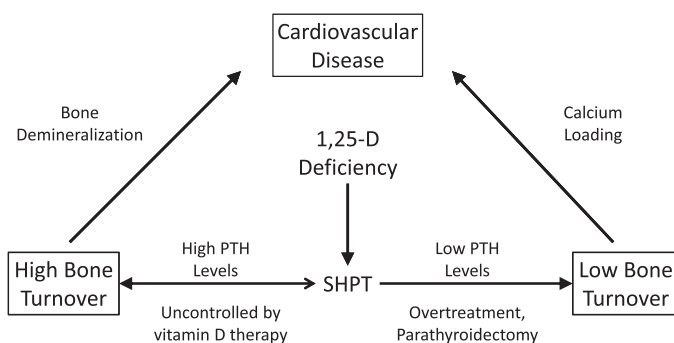


Figure 1. Overview of the relationships between bone disease and cardiovascular disease. 1,25-D, 1,25-dihydroxyvitamin D₃; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

metabolism, sevelamer has other potentially favorable cardiovascular effects, such as reduction in serum uric acid, improvement in lipid profile, and anti-inflammatory activity (105–107).

In two randomized clinical trials, sevelamer controlled serum phosphate to a degree similar to calcium-based binders without causing hypercalcemia and arrested the progression of coronary, aorta, and valvular calcification in hemodialysis patients (102,103,108). In the recent study by Block *et al.* (50), randomization to sevelamer treatment as opposed to calcium salts significantly reduced the mortality rate in incident hemodialysis patients; however, in a larger randomized trial of prevalent hemodialysis patients, such a survival advantage was not seen in the overall cohort, although a survival benefit was noted in older patients (109).

Whether VDRL therapy contributes directly to reduced cardiovascular mortality in dialysis patients still remains to be determined. Although it was suggested in one uncontrolled study that calcitriol treatment promotes adynamic bone, the study was confounded by the inclusion of patients who had a high oral intake of calcium and underwent dialysis with high dialysate calcium concentrations (110). This level of calcium intake may have contributed to the change in bone histology, because Raggi *et al.* (35) recently showed that calcium loading was associated with bone loss.

In contrast, several observational reports showed that dialysis patients who received injectable VDRL therapy had a 20% adjusted survival benefit compared with those who did not receive VDRL therapy and that patients who received intravenous paricalcitol had a 16% survival advantage compared with those who received intravenous calcitriol (111,112). This observation was corroborated by Kalantar-Zadeh *et al.* (66), who showed that patients who were treated with intravenous paricalcitol had a 25 to 40% adjusted survival benefit compared with those who did not receive any paricalcitol. Tentori *et al.* (113) suggested that the survival benefit afforded by the two forms of VDRL therapy that are available on the market may be equivalent. Conversely, a recent meta-analysis by Palmer *et al.* (114) failed to prove a definite survival benefit with these drugs. Although promising, the survival benefits of VDRL therapy should be evaluated in randomized trials to corroborate these findings further. Because VDRL therapy suppresses bone loss in CKD, future research should include prospective evaluations of VDRL therapies in the treatment of CKD to verify whether a beneficial effect on bone is associated with amelioration of CVD (115,116).

Calcimimetic agents are another class of drugs that have been investigated in the treatment of CKD and SHPT complications. Acting on the calcium receptor at the level of the parathyroid gland, drugs such as cinacalcet have been shown to reduce PTH secretion while minimizing hypercalcemia and hyperphosphatemia (117). Although approved for use in patients with stage 5 CKD, the long-term safety and efficacy of cinacalcet in predialysis patients have not been well established (88). Because the effects of cinacalcet on bone loss have not yet been reported, it should be evaluated in studies that measure bone disease markers and markers of vascular health (118).

Conclusions

Bone loss is a common complication seen in CKD, caused primarily by high bone turnover but increasingly by ABD as well. Vascular calcification, another common complication, presents an increased risk to patients with CKD and may be linked to the high rates of bone loss commonly observed with elevated PTH levels, although some evidence indicates that adynamic bone states may also be responsible for calcification development (37). On the basis of the recent evidence that vascular calcification is an active process within the arterial wall, an improved understanding of the pathologic changes that occur in patients with CKD may prove valuable in the development of strategies to reduce vascular calcification. Novel treatments will need to address the complexity of factors that contribute to CVD in CKD, and VDRL therapies seem to be important treatment options in this environment.

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