Impact of Treatment with Calcimimetics on Hyperparathyroidism and Vascular Mineralization

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Soft tissue calcification that involves primarily the medial portion of the arterial vasculature is a widely recognized and common complication of chronic kidney disease. Vascular calcification (VC) causes increased arterial stiffness and contributes to the high cardiovascular mortality and morbidity in dialysis patients. The pathogenesis of VC is complex and includes factors that promote calcification and others that inhibit calcification. Studies in dialysis patients have shown a correlation between VC and a number of uremia-related factors. Overall, abnormalities in calcium and phosphate metabolism, such as hyperphosphatemia and a raised serum calcium-phosphorus product traditionally have been thought of as important determinants in patients with chronic renal failure. Common therapeutic interventions in secondary hyperparathyroidism have come under scrutiny for associations with the development of VC. Calcimimetics provide a means of controlling serum levels of parathyroid hormone in secondary hyperparathyroidism without increasing the calcium-phosphorus product and, more important, may lower the risk for VC in these patients.

Secondary hyperparathyroidism (SHPT) generally develops early in chronic kidney disease (CKD), before dialysis is needed; consequently, most patients who have ESRD and are undergoing dialysis will have elevated parathyroid hormone (PTH) and SHPT of variable severity (1–3). Cardiovascular disease accounts for almost half of all deaths in patients with ESRD, with risk being particularly elevated in younger individuals (4). Patients with CKD may develop soft tissue calcification of various types and locations, including vascular calcification (VC). This process starts long before reaching ESRD (5).

Types of VC

There are different types of VC:

1. Intima calcification: Deposits of calcium and phosphate in atheromatous plaques. It is associated with lipid-laden macrophages and intimal hyperplasia.
2. Media calcification: Characterized by diffuse deposits in the media layer of the arterial tree. Occurs in the media of the vessel in conjunction with a phenotypic transformation of smooth muscle cells into osteoblast-like cells (6).
3. Calciphylaxis: Also called calcific uremic arteriolopathy, a much more infrequent, rapidly progressive form of VC.

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 (7). These hemodynamic changes may result in increased afterload, left ventricular hypertrophy, decreased coronary artery perfusion, and increased risk for death (8). Coronary artery calcification has been linked to increased risk for cardiovascular events such as myocardial infarction, fatal arrhythmia, and congestive heart failure (9,10). Therefore, given that cardiovascular calcification 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.

Causes

The causes of calcification in CKD remain to be elucidated. Associated risk factors include age, hypertension, diabetes, male gender, white race, and time on dialysis. Many local factors are involved in the regulation of the calcification process, by either inhibiting or stimulating VC and the associated phenotypic transformation of local vascular smooth muscle cells (VSMC) toward osteoblast-like calcifying cells (11). SHPT is associated with elevated serum calcium and phosphorus, and calcium-phosphorus product (Ca × P), and these elevations have been associated with an increased risk for VC (10,12–14).

Need for Better Control

If the serious consequences of SHPT are to be avoided in patients who are on dialysis, then PTH, phosphorus, and calcium must be managed effectively. However, common therapeutic interventions in SHPT have come under discussion for associations with the development of VC (15,16). The National Kidney Foundation recently published revised targets for PTH, calcium, phosphorus, and Ca × P levels as part of its Kidney Disease Outcomes Quality Initiative (K/DOQI) program (17). It is hoped that these guidelines will help physicians to improve control of SHPT and clinical outcomes, because published observational studies suggest that physicians find it difficult to achieve optimal control of PTH and mineral levels in their patients (18,19). Given that few patients have optimally con-
trolled PTH and mineral levels, it is cause for concern that even these patients do not seem to remain within treatment targets over the long term (20,21,22).

**Current Therapeutic Interventions in SHPT**

Traditional SHPT therapies, particularly vitamin D sterols and calcium-based phosphate binders, have failed to assist the majority of patients to achieve K/DOQI goals. In addition, they can exacerbate mineral imbalances, resulting in hypercalcaemia and further hyperphosphataemia and consequently an increase in the risk for VC.

The severe outcomes that are associated with poorly controlled SHPT emphasize the need for improved pharmacologic management. Several treatment options are available, but many data suggest that these agents do not allow physicians to achieve and sustain new therapeutic targets in the majority of their patients.

Calcium supplementation has several limitations, and concerns about calcium overload have led to the revision of dosing recommendations with an earlier limit of 6 g of elemental calcium per day being reduced to a new maximum of 1 to 2 g/d (23,24).

Vitamin D and analogue supplementation and, eventually, active vitamin D therapy are the mainstay of treatment for SHPT. Unfortunately, a substantial proportion of patients do not respond to vitamin D therapy (25–27), most likely those with advanced SHPT, in whom nodular hyperplasia has reduced expression of vitamin D receptors and calcium-sensing receptors (CaR). In addition to its effects on PTH synthesis, vitamin D has an indirect effect on PTH through facilitating the intestinal absorption of calcium, and it may induce episodes of hyperphosphatemia and/or hypercalcaemia (25,26). Accordingly, vitamin D therapy may add to the risk for extraskeletal calcification (28). It has been suggested that newer vitamin D analogues are less calcemic than calcitriol, although hypercalcemic episodes also have been. As such, vitamin D and its analogues are contraindicated in patients with high calcium or phosphorus levels, and episodes of hypercalcaemia and/or hyperphosphatemia may necessitate dosing adjustments or temporary withdrawal of therapy (29–31).

Finally, it has become apparent that sustained treatment with high-dosage vitamin D can cause oversuppression of PTH, leading to the onset of adynamic bone disease. Further administration of vitamin D may induce hypercalcaemia, thereby increasing the risk for VC in affected patients (23). A second mechanism for inducing VC is that the active vitamin D sterol calcitriol may act on specific vitamin D receptors that are constitutively expressed by VSMC (32). Calcitriol has been shown to increase expression of several proteins that are involved in calcification (e.g., alkaline phosphatase) and to decrease expression of proteins that inhibit calcification (e.g., PTH-related peptide [28,33]).

Among other treatment options that are available as SHPT therapies for those in whom dietary restriction is not sufficient to control serum phosphorus levels, phosphate-binding agents must be prescribed. Of the currently available phosphate-binding agents, the majority of patients with hyperphosphataemia now receive either calcium-based phosphate binders or the noncalcium, nonaluminum agent sevelamer HCl, which have been shown to be similarly effective in clinical trials (34). Calcium-based agents unfortunately can add to systemic calcium load and have been associated with increased risk for cardiovascular calcification by a number of authors (14,35).

The most recently approved phosphate binder is lanthanum carbonate. Lanthanum carbonate has been shown to reduce serum phosphorus levels. However, because of similarities to aluminum, concerns about long-term safety with lanthanum have been voiced (36). Although recently presented preliminary evidence suggests that there are no aluminum-like effects on bone in the clinic (37), the long-term effects remain to be elucidated. The efficacy of these agents also is compromised in that they are able to bind only dietary phosphate and not phosphorus that is released from skeletal stores.

Calcimimetics are small, orally active organic compounds that increase CaR sensitivity to extracellular calcium, thus maximizing the suppressive effect of calcium on PTH secretion and production (38). In SHPT, the CaR-mediated balance between PTH and calcium often is skewed in that inappropriately low levels of PTH are released on the basis of serum calcium levels. This suggests that increasing the sensitivity of the parathyroid gland to extracellular calcium through the modulation of the CaR may have therapeutic potential.

**Impact of Treatment with Calcimimetics on HPT**

The utility of cinacalcet in the treatment of SHPT has been demonstrated in several clinical trials (39–42). In an early study, patients who had SHPT and were on hemodialysis were administered cinacalcet that ranged from 10 to 50 mg/d or placebo for 8 d. Treatment with the higher dosages of cinacalcet resulted in reductions in plasma PTH, Ca × P, calcium, and phosphorus (39). Two additional 18-wk studies explored the efficacy and the safety of cinacalcet in dialysis populations with uncontrolled SHPT. Patients who were enrolled in these studies were required to have a minimum PTH of 300 pg/ml, but no upper limit was established. These trials consisted of two phases: A 12-wk dosage-titration phase to establish an efficacious dosage of cinacalcet and a 6-wk maintenance phase to explore the sustainability of the therapeutic effect. Patients were treated with a range of dosages (20 to 50 mg/d [41] or 25 to 100 mg/d [40]). During the maintenance phase, the mean PTH, Ca × P, calcium, and phosphorus were reduced after treatment with cinacalcet.

These positive data were supported and reinforced by a report that combined two major Australian, European, and United States phase 3 trials (42). Patients who had SHPT and were undergoing dialysis were treated with standard-of-care therapy (vitamin D analogues and/or phosphate binders) or standard-of-care therapy plus cinacalcet (30 to 180 mg/d) for a total of 26 wk (12-wk titration phase and 14-wk efficacy assessment phase). Patients responded well to cinacalcet treatment, with significant reductions in the four key K/DOQI laboratory target guidelines during the efficacy assessment phase. Signif-
bicent differences in PTH and Ca × P between groups occurred by 2 wk after the start of treatment. In addition to the reduction in PTH overall, a significant portion (43%; P < 0.001) of cinacalcet-treated patients achieved mean PTH levels ≤250 pg/ml, the primary study end point. An even more substantial proportion (64%) achieved a ≥30% reduction in PTH. Similar achievement of the iPTH ≥30% reduction occurred regardless of baseline PTH level (300 to 500 pg/ml, 501 to 800 pg/ml, and >800 pg/ml). Changes in vitamin D dosage seemed to have no significant effect on the cinacalcet-induced reductions in PTH and Ca × P. Of note, the significant improvement in Ca × P (−14.6%; P < 0.001) resulted from significant improvements in both serum calcium (−6.8%) and phosphorus (−8.4%) levels (both P < 0.001) after treatment with cinacalcet in relation to placebo (0.5, 0.4, and 0.2%, respectively). These data suggest that cinacalcet treatment could be an effective therapeutic option in patients regardless of disease severity of SHPT or vitamin D analogue status.

Several preliminary reports have described the long-term efficacy of cinacalcet in patients who had SHPT and entered extension trials after the successful completion of one of a number of cinacalcet trials. Briefly, these studies suggested that cinacalcet can assist patients to reduce their PTH and Ca × P with these reductions sustained for up to 1 yr after the initiation of therapy (43), control their PTH and Ca × P levels for >3 yr (44), and assist a substantial proportion of patients to achieve the K/DOQI targets for PTH and Ca × P (45). Cinacalcet was reported to be well tolerated in all of these studies. It should be borne in mind that the patients who entered these trials previously had completed successfully another cinacalcet trial, although they could have received placebo in this earlier trial. These data are encouraging for the long-term efficacy and safety of cinacalcet in patients with SHPT.

Interim data from two ongoing studies, Treatment Strategies to Achieve Recommended K/DOQI Goals in ESRD Subjects on Cinacalcet (TARGET) and Cinacalcet Open Label Study To Reach K/DOQI Levels (CONTROL), support the ability of cinacalcet to maintain or improve K/DOQI variables within target ranges with reduced dosages of vitamin D analogues. In TARGET, cinacalcet assisted patients to achieve target PTH while lowering Ca × P (46). Similarly, in CONTROL, patients with PTH within the target range but with elevated Ca × P exhibited maintenance of PTH and achievement of Ca × P goal (47).

**Cinacalcet and VC**

Because calcimimetics reduce PTH levels without the induction of hypercalcemia, it is likely that patients who have advanced CKD and are treated with a calcimimetic may show less risk for VC than patients who are treated with vitamin D sterols. To explore this concept better, Henley et al. (48) in a rat model of SHPT (five-sixths nephrectomy) studied the administration of cinacalcet HCl, 1,25-dihydroxyvitamin D3, or the combination. Calcitriol-treated rats had moderate to marked aortic calcification, whereas no significant calcification was observed in vehicle- or cinacalcet HCl only–treated groups. Cinacalcet HCl and calcitriol both effectively reduce PTH, albeit via different mechanisms, but unlike calcitriol, cinacalcet HCl did not produce hypercalcemia, an increased Ca × P, or VC. However, calcitriol-produced aortic VC was unaffected by concomitant treatment with cinacalcet HCl.

Lopez et al. (49) studied the effect of the calcimimetic R-568 alone or in combination with calcitriol on the development of VC and other soft tissue calcifications in a rat model of uremia-associated SHPT. They studied both calcitriol and R-568. Treatment with calcitriol induced significant VC (aortic Ca increased) and with R-568 did not induce VC. Concurrent administration of R-568 with calcitriol reduced the aortic Ca in relation to calcitriol alone. Soft tissue calcifications mirrored aortic mineralizations. They concluded that in uremic rats, R-568 reduces elevated PTH levels without inducing VC and prevents calcitriol-induced VC.

The calcitriol-induced VC was localized consistently in the media of the aorta of uremic rats. The mineralizing effect of calcitriol can be explained by the increase in the serum Ca and P observed after its administration, although other smooth muscle–based mechanisms also may play a role (28). This kind of calcification is independent of lipids and seems to be related to phenotypic transformation of smooth muscle cells into bone-producing cells (6).

How can the anticalcification effect of the calcimimetic be explained? The most valuable explanation is related to the control of PTH levels without increasing the Ca × P. Lopez et al. (49), in addition, pointed to a direct action of calcimimetic at the cellular level on the arterial wall. Vessels express CaR (50), and some investigators have demonstrated the presence of CaR using a polyclonal antibody to the CaR (51), whereas other preliminary studies have failed to detect CaR in bovine and human VSMC using RNase protection assays (52). Calcium modulates the function of vessels, and it is of considerable importance the findings that calcimimetics influence BP profile.

**Conclusion**

VC contributes to the high cardiovascular mortality and morbidity in dialysis patients. SHPT often is associated with elevated serum calcium and phosphorus and Ca × P, and common therapeutic interventions in SHPT have come under scrutiny for associations with the development of VC. Calcimimetics provide a means of controlling serum levels of PTH in SHPT without increasing the Ca × P and, more important, may lower the risk for VC in these patients.

**References**


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