Medical management of secondary hyperparathyroidism in chronic renal failure

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Abstract
Abnormalities in calcium and phosphorus metabolism are common, and metabolic bone disease develops often in patients with chronic renal failure (CRF). Effective clinical management includes measures to control phosphorus retention and prevent hyperphosphataemia, to maintain serum calcium concentrations within the normal range and to prevent excess parathyroid hormone (PTH) secretion by the judicious use of vitamin D sterols. Certain of these interventions appear to increase the risk of soft tissue and vascular calcification in patients with end-stage renal disease (ESRD), changes that may contribute to the development of cardiovascular disease. Current therapeutic approaches are thus being re-evaluated in an effort to limit these risks. Despite the importance of controlling phosphorus retention and preventing hyperphosphataemia in patients with CRF, current management strategies often are inadequate, particularly in those ingesting diets containing adequate amounts of protein. Results from clinical trials using daily haemodialysis strongly suggest that thrice-weekly haemodialysis regimens are only marginally adequate for achieving weekly phosphorus balance in many patients with ESRD. The safety of large oral doses of calcium as a phosphate-binding agent in patients with ESRD has also been questioned because excess amounts of calcium that are absorbed from the gastrointestinal tract may lead to ongoing calcium retention in those with little or no residual renal function. Arterial calcification and cardiac valve calcification are two serious complications that adversely affect cardiovascular haemodynamics. The use of large, often supraphysiological, doses of calcitriol or other vitamin D sterols to treat secondary hyperparathyroidism may aggravate hypercalcaemia and hyperphosphataemia, further increasing the risk of soft tissue and vascular calcification. Phosphate-binding agents that do not contain calcium, new vitamin D analogues and calcimimetic compounds offer new therapeutic alternatives for managing renal osteodystrophy. The integration of these novel agents into existing treatment regimens may provide safer and more effective methods for controlling secondary hyperparathyroidism and renal bone disease, while limiting the risks of soft tissue and vascular calcification in patients with CRF.

Keywords: calcimimetic agents; non-calcium phosphate-binding agents; renal osteodystrophy; vitamin D analogues

Introduction
Renal osteodystrophy in its broadest context encompasses all the disorders of bone and mineral metabolism caused by chronic renal failure (CRF) [1]. Prominent among these are disturbances in calcium, phosphorus and vitamin D metabolism that ultimately lead to alterations in parathyroid gland function and to various types of renal bone disease [2]. Despite numerous therapeutic advances, the management of renal osteodystrophy remains an ongoing challenge for clinicians [2,3].

Phosphate retention and hyperphosphataemia are extremely common in patients with end-stage renal disease (ESRD). In the USA, serum phosphorus concentrations are elevated in >70% of patients who are treated with regular haemodialysis, despite the use of phosphate-binding medications [4]. Although recognized for many years as a factor than can aggravate secondary hyperparathyroidism [5], recent reports have served to re-emphasize the critical role of this biochemical disturbance in the development of soft tissue and vascular calcification [6–9]. Additional evidence strongly suggests that certain therapeutic strategies designed to control phosphate retention and
to manage secondary hyperparathyroidism increase the risk of soft tissue and vascular calcification in patients with ESRD [6,8]. The adverse consequences associated with the long-term use of supraphysiological amounts of calcium as a phosphate-binding agent and with the administration of pharmacological doses of vitamin D sterols to treat secondary hyperparathyroidism must be recognized, and their importance appreciated fully when formulating therapeutic interventions [2,6,8]. Vascular calcification may represent an independent, and previously inadequately appreciated, risk factor for cardiovascular disease in the ESRD population, and it probably contributes to the very high mortality rate from cardiovascular causes in such patients [7,10,11]. The foregoing considerations suggest that prevailing guidelines for managing renal osteodystrophy be modified in an effort to maximize benefits while minimizing risks.

**Major components of clinical management**

**Hypocalcaemia**. hyperphosphataemia and impaired renal 1,25-dihydroxyvitamin D synthesis with attendant reductions in serum calcium concentrations and decreases in vitamin D receptor expression in the parathyroid glands each contribute to excess parathyroid hormone (PTH) secretion in patients with CRF [5,12]. All represent targets for therapeutic interventions aimed at preventing the development and controlling the progression of secondary hyperparathyroidism.

**Calcium metabolism**

Variations in the concentration of ionized calcium in blood modulate the minute-to-minute release of PTH in vivo by affecting the level of activation of the calcium-sensing receptor (CaR) in parathyroid cells [13]. Hypocalcaemia stimulates PTH release directly by inactivating the CaR, and plasma PTH concentrations increase within minutes as the concentration of blood ionized calcium declines [14,15]. Reductions in extracellular calcium concentration that persist for several hours also enhance pre-pro-PTH gene transcription, ultimately making more hormone available for secretion [16]. Sustained periods of hypocalcaemia lasting days, weeks or months promote the development of parathyroid gland hyperplasia, a prominent feature of secondary hyperparathyroidism caused by CRF that markedly increases the mass of parathyroid tissue available for PTH synthesis and secretion [17]. Indeed, signalling via the CaR appears to be a crucial mediator of parathyroid gland hyperplasia [18]. Hypocalcaemia must therefore be avoided, to abrogate several compensatory responses that can lead to excess PTH synthesis and secretion and, ultimately, to overt secondary hyperparathyroidism in patients with CRF.

From a historical perspective, hypocalcaemia was a common biochemical finding in persons with progressive kidney disease and in those first starting dialysis before the widespread use of calcium-containing phosphate-binding medications and active vitamin D sterols [19]. Limitations in dietary calcium intake were partly responsible. Because of the need to restrict dietary phosphorus intake and thereby minimize phosphorus retention, the amount of dairy products contained in most renal diets is quite limited [2]. Dietary calcium intake is typically only 500–600 mg/day, far less than the amount recommended by the World Health Organization to attenuate age-related bone loss [20]. In addition, intestinal calcium absorption is compromised in most patients with renal failure because of reduced renal calcitriol production and decreased vitamin D-dependent intestinal calcium transport [21]. The latter process is particularly important for maintaining intestinal calcium absorption during calcium deprivation [22]. The combined effects of marginal dietary calcium intake and suboptimal intestinal calcium absorption often led to hypocalcaemia unless specific corrective measures were implemented, such as dietary calcium supplementation or treatment with calcitriol.

A seminal change in clinical management occurred during the early 1980s when it was recognized that the sustained use of aluminium-containing, phosphate-binding medications led to tissue aluminium accumulation and to various syndromes of aluminium toxicity including bone disease, encephalopathy and anaemia [23,24]. Calcium-containing compounds subsequently were embraced as a safe alternative to aluminium-containing compounds to manage phosphorus retention. Although effective in diminishing intestinal phosphorus absorption, very large doses of calcium were required [25]. Indeed, early reports document that substantial amounts of calcium were absorbed from the gastrointestinal tract and that total body calcium balance became positive when calcium carbonate was used exclusively as a phosphate-binding medication in patients with ESRD [26]. Increases in serum calcium concentrations were common during calcium carbonate therapy [27]. The relative frequency of this complication led to overall reductions in the calcium concentration of haemodialysis and peritoneal dialysis solutions from earlier standard concentrations of 3.0–3.5 mEq/l to the concentration of 2.5 mEq/l that is now employed most widely [28–30].

The consequences of the long-term use of relatively large doses of calcium as a phosphate-binding medication are only now being recognized. Several reports have implicated the use of calcium-containing compounds in the pathogenesis of calcific uremic arteriolopathy, or calciphylaxis [31,32]. Calcium carbonate therapy has also been associated with coronary artery calcification and with calcifications in other major arteries in patients undergoing regular dialysis [6,8]. Reduction in arterial wall compliance because of medial wall calcification has important adverse haemodynamic consequences, and these disturbances may contribute to the development of cardiovascular disease in patients with ESRD [7]. Indeed, survival in those undergoing regular haemodialysis diminishes as a
function of the extent of arterial calcification as documented by vascular ultrasound [33]. Such findings have led to efforts to design safer, alternative strategies for managing calcium and phosphorus metabolism in patients with renal disease [2,10].

One such approach is to maintain total daily calcium intake at a level sufficient to satisfy nutritional requirements while avoiding the very large amounts of calcium that can induce a positive total body calcium balance [34]. In most patients with advanced renal insufficiency and in those who require dialysis, modest dietary calcium supplementation will be necessary to maintain net intestinal calcium transport by passive mechanisms and to offset deficits in vitamin D-dependent intestinal calcium absorption. A combined intake totalling 1500–1800 mg of elemental calcium from dietary sources and oral calcium supplements should be sufficient to achieve this objective [2]. The use of other agents that do not contain calcium will be required, however, to manage phosphorus retention.

Phosphorus metabolism

Hyperphosphataemia promotes the development of parathyroid gland hyperplasia, and high ambient phosphorus concentrations facilitate PTH synthesis by stabilizing PTH mRNA and facilitating message translation [35–38]. Persistent hyperphosphataemia may also diminish the effectiveness of treatment with calcitriol in patients with established secondary hyperparathyroidism [39]. Adequate control of serum phosphorus concentrations is important, therefore, in the prevention and management of excess PTH secretion in CRF.

Apart from its role as a contributor to hyperparathyroidism, hyperphosphataemia represents an independent risk factor for death in patients treated with haemodialysis even after adjusting for other co-morbid conditions [4]. Death from cardiovascular causes largely accounts for the excess mortality [11]. The mechanism responsible for this relationship remains uncertain, but vascular calcification may play a role. In a recent study that documented the presence of coronary artery calcification in young adults undergoing long-term dialysis, serum phosphorus concentrations tended to be higher and the calcium–phosphorus ion product in serum was greater in patients with coronary calcification than in those without this abnormality [6].

Efforts to manage phosphorus retention in patients with ESRD almost always entail the use of phosphate-binding medications together with dietary phosphorus restriction [5]. Adequate control of serum phosphorus concentrations is difficult to achieve, however, because of limitations in the cumulative amount of phosphorus that can be removed during the week with either thrice-weekly haemodialysis or various peritoneal dialysis regimens. In this regard, alternative dialysis regimens, such as daily nocturnal haemodialysis and short-duration haemodialysis done 6 days per week, provide much better control of serum phosphorus concentrations than conventional thrice-weekly haemodialysis [40]. Indeed, most patients undergoing nightly haemodialysis maintain normal serum phosphorus concentrations without ongoing treatment with phosphate-binding agents [40]. Such findings strongly suggest that current dialysis regimens are only marginally adequate for achieving weekly phosphorus balance in patients who have little or no residual renal function, even when used together with dietary phosphorus restriction and phosphate-binding medications. Ongoing efforts to maintain adequate protein nutrition, although necessary and appropriate, make it even more difficult to achieve weekly total body phosphorus balance in patients undergoing regular dialysis because of the amounts of phosphorus contained in protein-rich foods. New strategies for dialysis management may be required to control phosphorus metabolism effectively and to avoid phosphorus retention in many patients with ESRD.

Given the limitations of current dialysis strategies, the ongoing use of phosphate-binding medications represents the primary intervention to manage phosphorus retention in patients with ESRD [5]. Agents that do not contain either calcium or aluminium have the distinct advantage of allowing wide-ranging adjustments in dosage without incurring dose-related side effects. This issue is particularly relevant for calcium-containing compounds that often cause hypercalcemia at the doses required to control serum phosphorus concentrations effectively in patients undergoing dialysis, particularly when given together with vitamin D sterols. The potential role of exogenous calcium loading as a contributor to the development and progression of vascular calcification argues strongly against the sustained administration of supraphysiological doses of calcium to patients with little or no residual renal function and to those treated with regular dialysis [6,8]. The adverse consequences of aluminium ingestion for extended periods in patients with ESRD have been documented [23,24].

For patients with marked hyperphosphataemia in whom modest doses of calcium are inadequate to control serum phosphorus concentrations, aluminium hydroxide can be used for periods limited to a few weeks, with little risk of aluminium retention or aluminium toxicity. This approach may be particularly useful in patients with overt hypercalcaemia. Care must be taken, however, to avoid the concurrent administration of compounds such as citrate that can facilitate intestinal aluminium absorption [41,42]. Sevelamer, or poly-allyl-amine hydrochloride, is an ion exchange resin that effectively binds phosphorus in the lumen of the gastrointestinal tract and prevents its absorption [43,44]. It contains neither calcium nor aluminium. Sevelamer can be given alone or together with modest oral doses of calcium to reduce intestinal phosphorus absorption. Adjustments to the dose of sevelamer can be made as tolerated to control serum phosphorus concentrations without affecting overall calcium intake. This therapeutic approach may favourably influence the process of vascular calcification in
patients with ESRD. Thus, coronary artery calcification scores and the extent of calcification in the thoracic aorta, as measured by electron beam computed tomography, did not change after 12 months of follow-up in haemodialysis patients given sevelamer to control serum phosphorus concentrations [45]. In contrast, coronary artery and aortic calcification increased substantially from baseline values after 12 months in those treated with calcium-containing, phosphate-binding medications [45]. Such findings suggest, but do not prove definitively, that lowering cumulative oral calcium intake in patients with ESRD can slow the progression of vascular calcification.

Because sevelamer contains no calcium, most patients with CRF who use this compound exclusively as a phosphate-binding agent are likely to require modest dietary calcium supplementation to maintain adequate calcium nutrition. Other agents that do not contain either calcium or aluminium, such as lanthanum carbonate and various iron-containing compounds, have also been shown to be effective phosphate-binding medications, but they are not yet available for use clinically [46].

**PTH secretion**

Interventions aimed at controlling secondary hyperparathyroidism in CRF are directed toward three distinct steps that ultimately determine the biochemical severity of the disorder, namely PTH secretion, PTH synthesis and parathyroid gland hyperplasia.

As mentioned previously, CaR activity modulates the immediate release of PTH from parathyroid cells. Hypocalcaemia thus represents the most proximate stimulus to PTH secretion and, if present, will raise the plasma PTH concentration. Modest oral calcium supplementation and treatment with small doses of vitamin D sterols, such as calcitriol, are useful in correcting hypocalcaemia and eliminating any calcium-dependent stimulus to PTH secretion both in patients with CRF and in those treated with dialysis. These two interventions are necessary and appropriate for patients whose serum calcium concentrations are below the lower limit of normal as defined by local clinical laboratory standards. Hypercalcaemia during treatment should be avoided, however, in order to limit the potential for aggravating soft tissue or vascular calcification.

In the past, it was often recommended that serum calcium concentrations be maintained at modestly elevated levels to suppress PTH secretion optimally in patients with secondary hyperparathyroidism [47–49]. Such guidelines were based on the concept that the set point for calcium-regulated PTH release was abnormally high in secondary hyperparathyroidism caused by CRF. Several carefully controlled in vivo studies have demonstrated, however, that the set point does not differ from normal in most patients with the disorder [15,50,51]. In contrast, there is evidence that the set point for calcium-regulated PTH release is modestly elevated in persons with advanced secondary hyperparathyroidism in whom medical management has proven unsuccessful [50,52,53]. The changes in parathyroid gland function in patients with severe secondary hyperparathyroidism, or tertiary hyperparathyroidism, are qualitatively similar to, but less marked than, those observed in individuals with primary hyperparathyroidism. Nevertheless, substantial increases in non-suppressible or basal PTH secretion in both disorders underscore the limited effect of high blood ionized calcium concentrations in lowering plasma PTH levels in patients with marked parathyroid gland enlargement [50]. Overall, currently available data do not support the use of therapeutic strategies that purposefully elevate serum calcium concentrations in an effort to suppress PTH secretion. Maintaining serum calcium concentrations within the normal range should be sufficient to eliminate any calcium-dependent stimulus to PTH secretion.

As noted previously, phosphorus retention promotes PTH mRNA translation and enhances PTH synthesis. Perhaps more importantly, however, both vitamin D and calcium negatively regulate the rate of gene transcription for pre-pro-PTH. The various vitamin D analogues, including calcitriol, or 1,25-dihydroxyvitamin D₃, act by binding to the vitamin D receptor (VDR) in target tissues, including the parathyroid glands. After binding to its ligand, the VDR interacts with a vitamin D response element (VDRE) located 100–125 bases upstream from the gene for pre-pro-PTH, and diminishes gene transcription [54]. Calcium ions also inhibit pre-pro-PTH gene transcription by interacting with a calcium response element (CaRE) located ~3.6 kb upstream from the transcriptional start site [55]. The administration of vitamin D thus lowers plasma PTH concentrations in patients with secondary hyperparathyroidism not only by reducing pre-pro-PTH gene transcription directly but also by indirectly raising the blood concentration of ionized calcium, which in turn diminishes pre-pro-PTH gene transcription and inhibits PTH release via CaR activation.

Until the late 1980s, active treatment of secondary hyperparathyroidism in patients undergoing regular haemodialysis relied predominantly on the use of daily oral doses of vitamin D sterols. Calcitriol, or 1,25-dihydroxyvitamin D₃, was used in the USA, whereas alphacalcidol, or 1-α-hydroxyvitamin D₃, was employed in Europe [56–58]. Parenteral preparations of each agent subsequently became available, and most haemodialysis patients in the USA are now managed with thrice-weekly intravenous doses of calcitriol or other vitamin D analogues. This approach ensures patient compliance, allows larger cumulative doses of vitamin D to be given each week and produces very high plasma sterol concentrations shortly after bolus intravenous injections. Although pharmacokinetic considerations suggest that intermittent parenteral therapy should be more effective than treatment with daily oral doses of calcitriol for controlling excess PTH secretion and reducing plasma PTH concentrations, recent clinical studies have failed to...
demonstrate substantive differences between the two therapeutic approaches [59, 60]. The frequency of episodes of hypercalcaemia and/or hyperphosphataemia also does not differ between treatment regimens.

Because serum calcium and phosphorus concentrations often rise during treatment with calcitriol, new vitamin D analogues have been developed with the objective of diminishing the frequency of dose-limiting side effects such as hypercalcaemia and hyperphosphataemia [56]. Two compounds currently available for clinical use in the USA are 19-nor-1,25-dihydroxyvitamin D$_2$, or paricalcitol, and 1α-hydroxyvitamin D$_3$, or doxercalciferol [61, 62]. Both are vitamin D$_3$ derivatives. Another vitamin D$_3$-derived compound, 22-oxacalcitriol or 22-oxa-1,25-dihydroxyvitamin D$_3$, is now available for clinical use in Japan. All three compounds have been shown to lower PTH concentrations effectively in patients with secondary hyperparathyroidism caused by ESRD. Plasma PTH concentrations decreased by an average of 25–30% during the first few weeks of treatment with either paricalcitol or doxercalciferol, and values fell by ~60% after 12–16 weeks. It remains uncertain, however, whether the frequency of episodes of hypercalcaemia and/or hyperphosphataemia is less during treatment with new vitamin D analogues than with calcitriol. Despite the limitations of currently available data, new vitamin D analogues may ultimately provide a way of managing secondary hyperparathyroidism while diminishing the risk soft tissue and vascular calcification during vitamin D therapy.

Calcimimetic agents are small organic molecules that activate the CaR in the membrane of the parathyroid cell, thereby inhibiting PTH release. They represent a novel approach to managing excess PTH secretion because their mechanism of action is distinct from that of the vitamin D sterols [63], and their efficacy in lowering plasma PTH concentrations in haemodialysis patients with secondary hyperparathyroidism has been documented in several clinical trials [64].

In contrast to treatment with vitamin D analogues, serum calcium concentrations remain unchanged or decrease modestly during calcimimetic therapy, whereas serum phosphorus concentrations often decline [65, 66]. Thus, several biochemical abnormalities that have been associated with the development of soft tissue and vascular calcification in patients with ESRD improve as plasma PTH concentrations fall. Because their mechanisms of action differ, the combined use of calcimimetic agents and vitamin D sterols may provide a highly effective therapeutic strategy for patients with moderately severe or advanced secondary hyperparathyroidism.

Apart from their immediate effect on PTH secretion, studies in rats with renal failure suggest that calcimimetic compounds retard the development of parathyroid gland hyperplasia [67]. Signalling through the CaR by maintaining serum calcium concentrations within the normal range by dietary manoeuvres is also sufficient to prevent the development of parathyroid gland hyperplasia in mice with inactivating mutations of the VDR [18, 68]. Thus, calcium per se, acting through the CaR, appears to be more important than vitamin D as a modifier of parathyroid gland hyperplasia.

**Conclusion**

The risks associated with persistent hyperphosphataemia and with the use of large doses of calcium and vitamin D to manage renal osteodystrophy in patients with ESRD are now widely appreciated. New strategies for managing phosphorus retention are being implemented, and alternative phosphate-binding agents have been developed. Vitamin D analogues with a purportedly greater therapeutic effect are also available for clinical use. The availability of calcimimetic compounds in the future may further augment therapeutic strategies for controlling excess PTH secretion and provide a means for retarding the development of parathyroid gland enlargement in patients with ESRD.

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