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Efficacy of early treatment with calcimimetics in combination with reduced doses of vitamin D sterols in dialysis patients

David A. Bushinsky[1] and Piergiorgio Messa[2]

[1]University of Rochester School of Medicine, Rochester, NY, USA and [2]CROFF Policlinico Hospital, Milan, Italy

Abstract

Vitamin D is an important physiologic regulator of bone and mineral metabolism. In chronic kidney disease, reduced renal production of calcitriol contributes to secondary hyperparathyroidism (SHPT). Consequently, supplementation with vitamin D sterols is an important treatment for SHPT and its associated mineral and bone disorders. However, doses of vitamin D sterols required to suppress parathyroid hormone (PTH) secretion often promote hypercalcaemia and hyperphosphataemia. Therefore, there is a trade-off between reduced serum PTH and increased levels of serum calcium, phosphorus and calcium–phosphorus product. It has been suggested that treatment of SHPT with cinacalcet, a type II calcimimetic, with reduced doses of vitamin D sterols could enhance achievement of calcium and phosphorus treatment targets while maintaining goals for PTH. Recent clinical trials have evaluated this hypothesis and demonstrated that treatment with cinacalcet in combination with reduced doses of vitamin D sterols is an effective treatment for the management of SHPT.

Keywords: calcimimetics; calcium; parathyroid hormone; phosphorus; secondary hyperparathyroidism; vitamin D

Biologic role of calcitriol

Physiologic effects

The chief physiologic role of calcitriol (the active form of vitamin D) is the maintenance of bone mineralization and turnover through increased absorption of calcium and phosphorus and suppression of parathyroid hormone (PTH) synthesis. Calcitriol increases calcium and phosphorus absorption from the gut; in excess, it mobilizes calcium from bone; and, in the parathyroid gland, suppresses PTH synthesis [1]. These effects of calcitriol are mediated through the vitamin D receptor (VDR), a ligand-activated nuclear receptor that modulates gene transcription in vitamin D-sensitive tissues through interaction with vitamin D-response elements (VDREs) [2–4]. The VDR is localized not only in target organs involved in mineral homeostasis but also in many other tissues. Nonclassic vitamin D systems and tissues include the immune system [5,6], myeloid tissue [7–9], the heart [10], skeletal muscle [11], the brain, and nerve tissue [12–14]. This wide distribution of the VDR suggests that calcitriol has physiologic roles other than mineral homeostasis. These physiologic roles have been extensively reviewed and, consistent with the nonclassic vitamin D tissues described above, include effects on the haematopoietic system, immune system, skin, muscle and nervous system [1,2,15,16]. Evidence also suggests that calcitriol can mediate nongenomic actions through a cell surface receptor distinct from the nuclear VDR [1].

The synthesis of calcitriol (the most potent endogenously produced vitamin D metabolite) occurs primarily in the kidney but also in a variety of other tissues [17,18]. The renal production of calcitriol is tightly regulated and is thought to account primarily for the level of calcitriol in serum under normal physiologic circumstances [1]. Control of calcitriol is achieved through the coordinated action of the kidneys, intestine, bone and parathyroid glands in response to physiologic calcium and phosphorus requirements [1]. Serum calcium, phosphorus and PTH regulate vitamin D through activation or suppression of the enzymes involved in its synthesis, bioactivation and catabolism [17].

Role of calcitriol in the development of SHPT in chronic kidney disease

A common complication of chronic kidney disease (CKD) is the development of secondary hyperparathyroidism (SHPT) [19]. SHPT begins to develop when reduced renal function results in dysregulation of the complex interactions involved in calcium and phosphorus homeostasis. Reduced renal excretion of phosphorus and synthesis of calcitriol both contribute to the development of hypocalcaemia that, in turn, leads to increased serum PTH [19]. Both the parathyroid gland calcium-sensing receptor (CaR) and VDR are down-regulated in the hyperplastic parathyroid gland, resulting in reduced sensitivity to calcium and vitamin D, respectively [19–22]. This abnormal calcium sensing leads to elevated serum PTH and abnormalities

Correspondence and offprint requests to: Piergiorgio Messa, Nephrology Division–CROFF Policlinico di Milano, Via Della Commenda, 20122 Milano, Italy. E-mail: pmessa@policlinico.mi.it

in divalent ion homeostasis, which have been associated with increased morbidity and mortality [23]. In particular, increased calcium–phosphorus product (Ca × P) is associated with vascular calcification [24,25].

In addition to the effects of reduced calcitriol on serum calcium that contribute to SHPT, a decrease in calcitriol has a number of direct effects that influence the development of SHPT. Calcitriol reduces parathyroid gland synthesis of PTH through the actions of the VDR on two VDREs located in the 5′ promoter region of the PTH gene [1,4]. In animal studies, calcitriol was shown to regulate the CaR in the parathyroid gland. Compared with controls, rats fed a vitamin D-deficient diet had reduced parathyroid gland CaR mRNA content [26]. Administration of calcitriol increased CaR mRNA. Interestingly, rat CaR mRNA was unaffected by diet-induced changes in serum ionized calcium [26].

Vitamin D sterol therapy in patients with CKD

Treatment with vitamin D sterols in CKD patients on dialysis has two principle goals. First, it corrects the vitamin D deficiency that commonly develops as renal function declines [27], and second, treatment with higher doses of vitamin D sterols has been demonstrated to decrease serum PTH [28,29]. Therefore, therapy with vitamin D sterols has become a primary treatment for SHPT [30]. Because vitamin D sterols also act to promote intestinal absorption of calcium and phosphorus and, in excess, mobilize calcium from bone [1], this effect on PTH comes at the expense of increased serum calcium, phosphorus and Ca × P. Indeed, clinical studies have shown that treatment with vitamin D sterols can increase serum calcium [31–34]. In some instances, increases in serum phosphorus [34] and Ca × P have been reported [33,34]. Thus, as with other traditional therapies for SHPT in CKD (such as phosphate binders), there is a trade-off between reduced serum PTH and increased Ca × P [35,36]. Potentially, hypercalcaemia and hyperphosphataemia associated with vitamin D sterol use could result in elevations of calcium and phosphorus and their product, leading to an increased risk of cardiovascular calcification and subsequent mortality [24,37]. Moreover, oversuppression of serum PTH from excessive vitamin D sterol treatment can result in reduced bone turnover (adynamic bone) [38].

The recognition of the hyperphosphataemic and hyercalcaemic effects of vitamin D sterols has led to the development of novel vitamin D sterols, such as paricalcitol, that retain the ability to suppress PTH secretion with reduced calcaemic effects [39]. This benefit was demonstrated in a study comparing paricalcitol with calcitriol in rats [40], yet only a small benefit was observed in a clinical trial [41]. These findings may be attributed to the fact that, although the calcaemic effects of paricalcitol may be reduced in comparison with calcitriol, they are not absent [36]. In patients on haemodialysis, paricalcitol treatment was shown to significantly increase serum calcium and serum phosphorus compared with placebo [28].

Observational studies have investigated the effects of vitamin D sterols, such as paricalcitol, calcitriol and alfacalcidol (1α-hydroxyvitamin D_3) on survival in haemodialysis patients. In a retrospective epidemiologic analysis of a large database of haemodialysis patients [42], those treated with injectable vitamin D sterols (>95% receiving paricalcitol or calcitriol) were shown to have a 2-year survival advantage of 20% compared with those not receiving vitamin D sterol treatment (hazard ratio, 0.80; 95% confidence interval, 0.76–0.83). Cardiovascular mortality was also lower in the vitamin D sterol-treated group (7.6/100 person-years) compared with the control group (14.6/100 person-years; $P < 0.001$). Similarly, in an observational study of 242 haemodialysis patients with stage 5 kidney disease, patients receiving alfacalcidol had a significantly lower risk of cardiovascular death compared with nonusers (hazard ratio, 0.287; $P = 0.003$) [43]. However, not all studies have demonstrated a survival benefit associated with vitamin D sterol treatment. In the observational Dialysis Outcomes and Practice Patterns Study, no association between vitamin D sterol use and mortality was observed [44]. The results of a retrospective study investigating the relative effects of paricalcitol and calcitriol on survival are also controversial. Patients treated with paricalcitol had a 16% lower mortality rate than patients treated with calcitriol [45]. It should be noted that all of these studies are observational, not randomized, and thus there was a fundamental difference in patients selected/not selected to receive vitamin D. In addition, the two groups were not matched with respect to a number of baseline characteristics, including comorbidities and demographics and, pre-study treatment data were not collected. Thus, that a difference in outcome was found is not unexpected. Prospective, randomized trials will be necessary to conclusively demonstrate if there is a survival benefit associated with vitamin D sterol treatment and whether the potential reduced calcaemic effects of paricalcitol compared with calcitriol translate into lower mortality rates.

Combining cinacalcet and vitamin D sterols to maximize control of SHPT

Because the therapeutic window for treatment with vitamin D sterols is narrow, it is difficult to determine an optimal dose that will sufficiently suppress PTH secretion without also increasing calcium and phosphorus absorption. Cinacalcet has a novel mechanism of action, acting on the CaR to simultaneously reduce serum PTH, calcium, phosphorus and Ca × P [46]. A new treatment paradigm has been proposed in which cinacalcet is used in combination with conventional therapies, such as vitamin D sterols and phosphate binders, for the treatment of SHPT. Phase 2 and phase 3 registrational studies were designed to compare cinacalcet in combination with traditional therapies with placebo and traditional therapies. In these studies, strict protocol-defined rules were followed to maintain the dose of vitamin D sterols at a constant level throughout the study period. These trials demonstrated that cinacalcet enabled significantly more haemodialysis patients with SHPT to achieve individual and combined National Kidney Foundation Kidney Disease Outcomes Quality Initiative

Table 1. Early-use cinacalcet/vitamin D sterol combination trials: study design

	CONTROL	OPTIMA
Study design	Titration phase: Weeks 1–8; Assessment phase: Weeks 8–16	Dose optimization phase: Weeks 1–16; Assessment phase: Weeks 16–23
Patients	($n = 53$); PTH controlled (biPTH: 80–160 pg/mL), elevated Ca × P at baseline	($n = 552$); Baseline PTH elevated (iPTH: 300–800 pg/mL)
Objective	Evaluate KDOQI^{TM} target achievement	Compare treatment strategy with conventional therapy for KDOQI^{TM} target achievement
Treatment	Cinacalcet: titrate to optimum at 8 weeks; vitamin D sterol dose reduced at day 1 to levels equivalent to ≤2 μg paricalcitol	Algorithm to optimize combination of cinacalcet, vitamin D sterols and phosphate binder or use best conventional methods; vitamin D sterol dose adjusted according to algorithm to a minimum 2 μg paricalcitol equivalent

(KDOQI^{TM}) targets and that cinacalcet induced simultaneous reductions in PTH and Ca × P [47–50].

It has been postulated that treatment with cinacalcet in combination with doses of vitamin D sterols sufficient for replenishment might limit the hypercalcaemia and hyperphosphataemia associated with vitamin D sterol therapy while maintaining control of SHPT. The following section of this review describes the results of two trials that investigated the effects of reduced-dose vitamin D combined with cinacalcet therapy on the achievement of KDOQI^{TM} goals: Cinacalcet Open-Label Study to Reach KDOQI^{TM} Levels (CONTROL) [51] and An Open-Label, Randomized Study Using Cinacalcet to Improve Achievement of KDOQI^{TM} Targets in Patients With End-Stage Renal Disease (OPTIMA) [52–55].

The CONTROL study

The CONTROL study was a 16-week open-label trial in 72 adult haemodialysis patients in the United States with controlled biointact PTH (biPTH) levels (80–160 pg/mL) and uncontrolled Ca × P (>55 mg^2/dL^2) (Table 1) [51]. At study entry, all patients were receiving moderate to high doses of intravenous vitamin D sterols (paricalcitol, doxercalciferol or calcitriol; mean ± standard deviation paricalcitol equivalent dose, 14.1 ± 7.8 μg/week) and phosphate binders. Doses of vitamin D sterols were reduced on day 1 of the dose-titration phase (to 2 μg paricalcitol equivalent dose per dialysis session) but could be increased during the 8-week titration phase if serum calcium was <8.4 mg/dL or if biPTH was >270 pg/mL and Ca × P was <70 mg^2/dL^2 and cinacalcet could not be titrated further. The vitamin D sterol dose could be decreased after reaching two consecutive biPTH values of <80 pg/mL. During the 8-week titration phase, cinacalcet doses were titrated in stepwise increments from 30 to 180 mg/d (when biPTH was >160 pg/mL or when biPTH was 80–160 pg/mL and Ca × P was >55 mg^2/dL^2) to reach treatment targets. Cinacalcet dose adjustments were allowed during the assessment phase, and dose reductions were allowed at any time during the study. The primary efficacy measures were the achievement of biPTH ≤160 pg/mL and Ca × P ≤55 mg^2/dL^2.

Although the dose of vitamin D sterols was reduced, the introduction of cinacalcet enabled PTH control to be maintained (85% achieved their biPTH target versus 91% of patients at baseline, P = not significant), and Ca × P control was markedly improved (72% versus 21% at baseline; $P < 0.0001$). Serum calcium and phosphorus levels were simultaneously reduced by 9.7% and 11.1% from baseline, respectively. More patients treated with cinacalcet achieved both biPTH and Ca × P goals at assessment compared with baseline (47% versus 17%; $P < 0.01$) (Figure 1A). At the assessment phase, vitamin D sterol use was discontinued in 21% of patients, and in the other patients, the dose was reduced by 49% (to 6.9 μg/week) compared with baseline (Figure 1B). Taken together, these results demonstrate that cinacalcet and reduced-dose vitamin D sterols can simultaneously address all four KDOQI^{TM} targets.

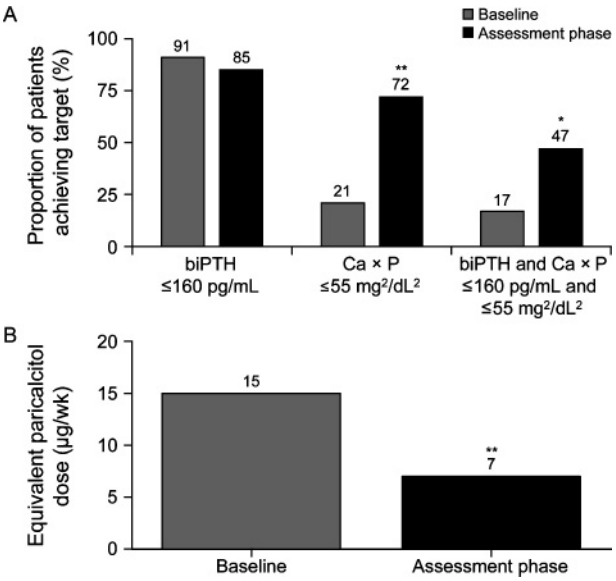

Fig. 1. CONTROL trial: comparison of standard care with cinacalcet; (**A**) percentage of patients achieving KDOQI^{TM} targets and (**B**) dose of paricalcitol at baseline and endpoint. Note that the biPTH target in this study was ≤160 pg/mL. The KDOQI^{TM} target range is approximately 80–160 pg/mL. $^*P < 0.01$, $^{**}P < 0.001$. Adapted with permission from Chertow *et al.* [51].

The OPTIMA study

The OPTIMA trial was a 23-week, randomized, standard care-controlled, multicentre, open-label study in 552 dialysis patients in Europe (Table 1) [52–55]. This study used a predefined algorithm designed to optimize the combination

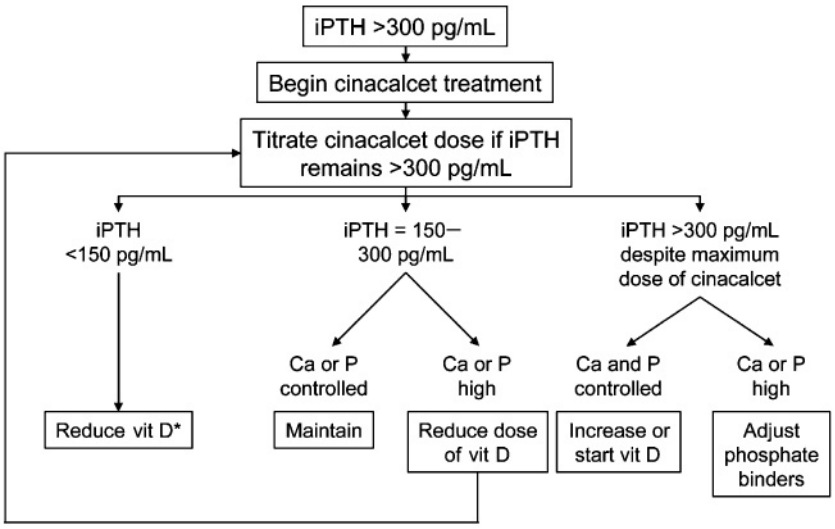

Fig. 2. OPTIMA treatment algorithm. Ca, calcium; P, phosphorus; vit D, vitamin D. Adapted with permission from Messa *et al*. [53].

Table 2. OPTIMA study efficacy outcomes

	Best conventional treatment		Cinacalcet	
	iPTH 300–500 pg/mL ($n = 92$)	iPTH >500–800 pg/mL ($n = 89$)	iPTH 300–500 pg/mL ($n = 193$)	iPTH >500–800 pg/mL ($n = 167$)
iPTH, % change, mean ± SD	2.0 ± 46.2	1.8 ± 42.5	−39.9 ± 33.7	−53.4 ± 27.7
Ca × P, % change, mean ± SD	3.5 ± 27.3	5.9 ± 31.2	−11.1 ± 27.4	−13.0 ± 26.0

SD, standard deviation.
Adapted with permission from Messa *et al.* [53].

of cinacalcet and existing treatments of vitamin D sterols and phosphate binders to control intact PTH (iPTH) and reduce serum calcium and phosphorus (Figure 2). Patients were assigned to cinacalcet or conventional therapy in a 2:1 ratio. Conventional therapy gave investigators full freedom to administer vitamin D sterols and phosphate binders as appropriate to maximize target achievement. Cinacalcet was titrated from a starting dose of 30 mg/d until an iPTH of 150–300 pg/mL was achieved. Dose reductions related to patient safety were allowed at any time during the 23-week study. Vitamin D sterol dose was reduced in patients with calcium $\geq$9.5 mg^2/dL^2 or phosphorus $\geq$5.5 mg^2/dL^2. The dose of vitamin D sterols was reduced by 50% in sequential steps until a minimum dose (calcitriol, 0.5 μg three times per week [TIW] intravenous or 0.25 μg TIW oral; alfacalcidol, 1 μg TIW intravenous or 0.25 μg daily oral; paricalcitol, 2 μg TIW intravenous) was prescribed. Efficacy as measured by achievement of KDOQI^{TM} targets was evaluated during Weeks 17–23.

More patients achieved the primary endpoint of iPTH control ($\leq$300 pg/mL) with cinacalcet compared with standard care (71% versus 22%; $P < 0.001$). Cinacalcet reduced iPTH levels irrespective of the baseline PTH level (Table 2). When patients were stratified into a less severe SHPT group (baseline iPTH, 300–500 pg/mL) and more severe SHPT group (baseline iPTH, 500–800 pg/mL), the greatest reduction in serum iPTH was achieved in patients with more severe SHPT (Table 2). However, the proportion of patients in the cinacalcet group reaching the primary endpoint of iPTH $\leq$300 pg/mL was greater in the less severe SHPT group (Figure 3). Additionally, the median dose of cinacalcet was lower in the less severe SHPT group (30 mg/d) than in the more severe SHPT group (60 mg/d).

Compared with the best standard care, the cinacalcet-based algorithm used in the OPTIMA study provided superior control of SHPT. Attempts by physicians to maximize therapy with standard care to attain the recommended targets were generally unsuccessful, with just 30% of patients in the less severe SHPT group achieving the primary endpoint (iPTH $\leq$300 pg/mL) and 20% of patients reaching the composite endpoint (iPTH $\leq$300 pg/mL and Ca × P $<$55 mg^2/dL^2). In contrast, 80% of cinacalcet-treated patients in the less severe SHPT group reached the primary endpoint, and 64% reached the composite endpoint (Figure 3).

As previously discussed, treatment with vitamin D sterols is often associated with hypercalcaemia and hyperphosphataemia, with consequent risk of increased mortality [24,37,45]. Importantly, in this study, treatment with cinacalcet in combination with vitamin D sterols enabled

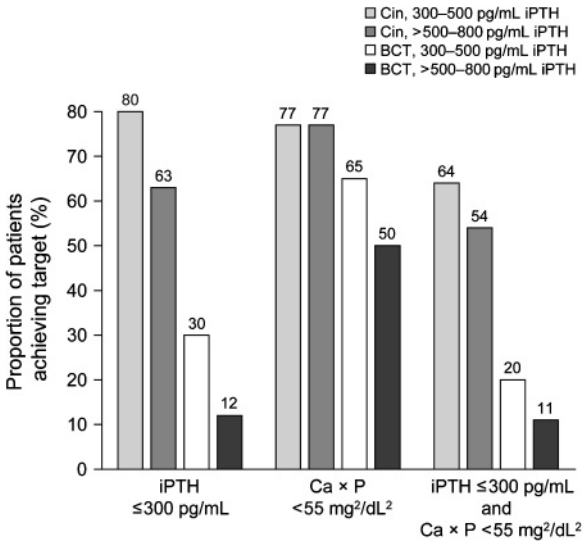

Fig. 3. OPTIMA trial: percentage of patients achieving endpoint targets by baseline iPTH level. BCT, best conventional treatment. Adapted with permission from Messa *et al*. [53].

approximately a 24% reduction in the dose of vitamin D sterols compared with baseline.

Summary and conclusions

Overall, evidence from the CONTROL and OPTIMA trials demonstrates the clinical utility of treatment with cinacalcet in combination with reduced doses of vitamin D sterols. These treatment regimens allowed for both replenishment of vitamin D and improved control of SHPT. Compared with conventional therapy, an increased proportion of CKD patients were able to achieve their individual KDOQI™ targets, as well as combined targets of reduced iPTH, calcium, phosphorus and Ca × P. Furthermore, in the OPTIMA trial, this treatment regimen improved control of both PTH and Ca × P in patients with moderate (300–500 pg/mL PTH) and severe (500–800 pg/mL PTH) SHPT. Given the potential risks involved in therapy with vitamin D sterols, including vascular calcification and adynamic bone, the ability to lower vitamin D sterol doses while maintaining, and indeed improving, KDOQI™ target achievement is an exciting development. Prospective, long-term clinical trials will be necessary to definitively evaluate the effects of this treatment on mortality, cardiovascular calcification and other outcomes.

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References

1. Brown AJ, Dusso A, Slatopolsky E. Vitamin D. *Am J Physiol* 1999; 277: F157–F175
2. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocrine Rev* 2005; 26: 662–687
3. Nishishita T, Okazaki T, Ishikawa T *et al*. A negative vitamin D response DNA element in the human parathyroid hormone-related peptide gene binds to vitamin D receptor along with Ku antigen to mediate negative gene regulation by vitamin D. *J Biol Chem* 1998; 273: 10901–10907
4. Demay MB, Kiernan MS, DeLuca HF *et al*. Sequences in the human parathyroid hormone gene that bind the 1,25-dihydroxyvitamin D_3 receptor and mediate transcriptional repression in response to 1,25-dihydroxyvitamin D_3. *Proc Natl Acad Sci USA* 1992; 89: 8097–8101
5. Manolagas SC, Hustmyer FG, Yu XP. 1,25-Dihydroxyvitamin D_3 and the immune system. *Proc Soc Exp Biol Med* 1989; 191: 238–245
6. Yang S, Smith C, Prahl JM *et al*. Vitamin D deficiency suppresses cell-mediated immunity *in vivo*. *Arch Biochem Biophys* 1993; 303: 98–106
7. Yetgin S, Yalcin SS. The effect of vitamin D_3 on CD34 progenitor cells in vitamin D deficiency rickets. *Turk J Pediatr* 2004; 46: 164–166
8. Yetgin S, Ozsoylu S. Myeloid metaplasia in vitamin D deficiency rickets. *Scand J Haematol* 1982; 28: 180–185
9. Bastie JN, Balitrand N, Guidez F *et al*. 1alpha,25-dihydroxyvitamin D_3 transrepresses retinoic acid transcriptional activity via vitamin D receptor in myeloid cells. *Mol Endocrinol* 2004; 18: 2685–2699
10. Wu J, Garami M, Cheng T *et al*. 1,25$(OH)_2$ vitamin D_3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. *J Clin Invest* 1996; 97: 1577–1588
11. Boland R. Role of vitamin D in skeletal muscle function. *Endocr Rev* 1986; 7: 434–448
12. Cai Q, Tapper DN, Gilmour RF Jr *et al*. Modulation of the excitability of avian peripheral nerves by vitamin D: relation to calbindin-D28k, calcium status and lipid composition. *Cell Calcium* 1994; 15: 401–410
13. Cantorna MT, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D_3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. *Proc Natl Acad Sci USA* 1996; 93: 7861–7864
14. Garcion E, Wion-Barbot N, Montero-Menei CN *et al*. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab* 2002; 13: 100–105
15. Staud R, Vitamin D. More than just affecting calcium and bone. *Curr Rheumatol Rep* 2005; 7: 356–364
16. DeLuca HF, Zierold C. Mechanisms and functions of vitamin D. *Nutr Rev* 1998; 56: S4–S10; discussion S54–S75
17. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005; 289: F8–F28
18. Zehnder D, Bland R, Williams MC *et al*. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab* 2001; 86: 888–894
19. Rodriguez M, Nemeth E, Martin D. The calcium-sensing receptor: a key factor in the pathogenesis of secondary hyperparathyroidism. *Am J Physiol* 2005; 288: F253–F264
20. Fukuda N, Tanaka H, Tominaga Y *et al*. Decreased 1,25-dihydroxyvitamin D_3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. *J Clin Invest* 1993; 92: 1436–1443
21. Kifor O, Moore FD Jr , Wang P *et al*. Reduced immunostaining for the extracellular Ca^{2+}-sensing receptor in primary and uremic secondary hyperparathyroidism. *J Clin Endocrinol Metab* 1996; 81: 1598–1606
22. Gogusev J, Duchambon P, Hory B *et al*. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. *Kidney Int* 1997; 51: 328–336
23. Block GA, Klassen PS, Lazarus JM *et al*. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; 15: 2208–2218
24. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478–1483

25. London GM, Guerin AP, Marchais SJ *et al*. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; 18: 1731–1740
26. Brown AJ, Zhong M, Finch J *et al*. Rat calcium-sensing receptor is regulated by vitamin D but not by calcium. *Am J Physiol* 1996; 270: F454–F460
27. Ishimura E, Nishizawa Y, Inaba M *et al*. Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. *Kidney Int* 1999; 55: 1019–1027
28. Martin KJ, Gonzalez EA, Gellens M *et al*. 19-nor-1-alpha-25-dihydroxyvitamin D_2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 1998; 9: 1427–1432
29. Berl T, Berns AS, Hufer WE *et al*. 1,25-Dihydroxycholecalciferol effects in chronic dialysis. A double-blind controlled study. *Ann Intern Med* 1978; 88: 774–780
30. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–S201
31. Khajehdehi P, Taheri S. Effect of oral calcitriol pulse therapy on the lipid, calcium, and glucose homeostasis of hemodialysis-patients: its safety in a combination with oral calcium carbonate. *J Ren Nutr* 2003; 13: 78–83
32. Koshikawa S, Akizawa T, Kurokawa K *et al*. Clinical effect of intravenous calcitriol administration on secondary hyperparathyroidism. A double-blind study among 4 doses. *Nephron* 2002; 90: 413–423
33. Moe SM, Zekonis M, Harezlak J *et al*. A placebo-controlled trial to evaluate immunomodulatory effects of paricalcitol. *Am J Kidney Dis* 2001; 38: 792–802
34. Akizawa T, Ohashi Y, Akiba T *et al*. Dose-response study of 22-oxacalcitriol in patients with secondary hyperparathyroidism. *Ther Apher Dial* 2004; 8: 480–491
35. Goodman WG. Recent developments in the management of secondary hyperparathyroidism. *Kidney Int* 2001; 59: 1187–1201
36. Tentori F, Hunt WC, Stidley CA *et al*. Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; 70: 1858–1865
37. Raggi P, Boulay A, Chasan-Taber S *et al*. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002; 39: 695–701
38. Malluche HH, Monier-Faugere MC, Koszewski NJ. Use and indication of vitamin D and vitamin D analogues in patients with renal bone disease. *Nephrol Dial Transplant* 2002; 17(Suppl 10): 6–9
39. Martin KJ, Gonzalez EA. Vitamin D analogues for the management of secondary hyperparathyroidism. *Am J Kidney Dis* 2001; 38: S34–S40
40. Takahashi F, Finch JL, Denda M *et al*. A new analog of 1,25-$(OH)_2D_3$, 19-nor-1,25-$(OH)_2D_2$, suppresses serum PTH and parathyroid gland growth in uremic rats without elevation of intestinal vitamin D receptor content. *Am J Kidney Dis* 1997; 30: 105–112
41. Sprague SM, Llach F, Amdahl M *et al*. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; 63: 1483–1490
42. Teng M, Wolf M, Ofsthun MN *et al*. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. *J Am Soc Nephrol* 2005; 16: 1115–1125
43. Shoji T, Shinohara K, Kimoto E *et al*. Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D_3 users in a haemodialysis population. *Nephrol Dial Transplant* 2004; 19: 179–184
44. Young EW, Albert JM, Satayathum S *et al*. Predictors and consequences of altered mineral metabolism: the dialysis outcomes and practice patterns study. *Kidney Int* 2005; 67: 1179–1187
45. Teng M, Wolf M, Lowrie E *et al*. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; 349: 446–456
46. Steddon SJ, Fan SL, Cunningham J. New prospects for the management of renal bone disease. *Nephron Clin Pract* 2005; 99: c1–c7
47. Moe SM, Chertow GM, Coburn JW *et al*. Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. *Kidney Int* 2005; 67: 760–771
48. Block GA, Martin KJ, de Francisco AL *et al*. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004; 350: 1516–1525
49. Lindberg JS, Culleton B, Wong G *et al*. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. *J Am Soc Nephrol* 2005; 16: 800–807
50. Quarles LD, Sherrard DJ, Adler S *et al*. The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 2003; 14: 575–583
51. Chertow G, Blumenthal S, Turner S *et al*. Cinacalcet hydrochloride (Sensipar) in hemodialysis patients on active vitamin D derivatives with controlled PTH and elevated calcium × phosphate. *Clin J Am Soc Nephrol* 2006; 1: 305–312
52. Gonzalez M, Hutchison A, Girndt M *et al*. Secondary hyperparathyroidism (HPT) in patients receiving peritoneal dialysis (PD) can be effectively managed with cinacalcet (Mimpara/Sensipar) [Abstract SP359]. Presented at: ERA-EDTA Congress, 15–18 July 2006, Glasgow, UK
53. Messa P, Villa G, Braun J *et al*. The OPTIMA study: lower doses of cinacalcet (Mimpara/Sensipar) are required to achieve KDOQI secondary hyperparathyroidism (HPT) targets in patients with less severe disease [Abstract and Presentation MP324]. Presented at: ERA-EDTA Congress, 15–18 July 2006, Glasgow, UK.
54. Wilkie M, Salvadori M, De Meester J *et al*. The OPTIMA study: optimising the dose of vitamin D (vit D) in the presence of cinacalcet (Mimpara/Sensipar) to obtain maximum clinical benefit [Abstract SP358]. Presented at: ERA-EDTA Congress, 15–18 July 2006, Glasgow, UK.
55. Locatelli F, Macario F, Brink H *et al*. The OPTIMA study; efficacy of cinacalcet (Mimpara/Sensipar) treatment algorithm to treat dialysis patients with elevated PTH and calcium–phosphorus product (Ca × P) [Abstract SP357]. Presented at: ERA-EDTA Congress, 15–18 July 2006, Glasgow, UK.

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