Title
Vitamin D receptor activation and survival in chronic kidney disease

Journal
Kidney International, 73(12)

ISSN
0085-2538

Authors
Kovesdy, CP
Kalantar-Zadeh, K

Publication Date
2008-06-01

DOI
10.1038/ki.2008.35

Vitamin D receptor activation and survival in chronic kidney disease

CP Kovesdy[1,2] and K Kalantar-Zadeh[3,4]

[1]Division of Nephrology, Salem Veterans Affairs Medical Center, Salem, Virginia, USA; [2]Department of Medicine, University of Virginia, Charlottesville, Virginia, USA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA and [4]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Replacement of activated vitamin D has been the cornerstone of therapy for secondary hyperparathyroidism (SHPT). Recent findings from several large observational studies have suggested that the benefits of vitamin D receptor activators (VDRA) may extend beyond the traditional parathyroid hormone (PTH)-lowering effect, and could result in direct cardiovascular and metabolic benefits. The advent of several new analogs of the activated vitamin D molecule has widened our therapeutic armamentarium, but has also made therapeutic decisions more complicated. Treatment of SHPT has become even more complex with the arrival of the first calcium-sensing receptor (CSR) agonist (cinacalcet hydrochloride) and with the uncovering of novel mechanisms responsible for SHPT. We provide a brief overview of the physiology and pathophysiology of SHPT, with a focus on vitamin D metabolism, and discuss various practical aspects of VDRA therapy and its reported association with survival in recent observational studies. A detailed discussion of the available agents is aimed at providing the practicing physician with a clear understanding of the advantages or disadvantages of the individual medications. A number of open questions are also analyzed, including the present and future roles of CSR agonists and 25(OH) vitamin D replacement.

Kidney International (2008) **73,** 1355–1363; doi:10.1038/ki.2008.35; published online 20 February 2008

KEYWORDS: hyperparathyroidism; vitamin D; mortality

Correspondence: *CP Kovesdy, Division of Nephrology, Salem Veterans Affairs Medical Center, 1970 Roanoke Blvd., Salem, Virginia 24153, USA. E-mail: csaba.kovesdy@va.gov*

Received 20 September 2007; revised 27 November 2007; accepted 3 January 2008; published online 20 February 2008

Disorders of mineral and bone metabolism are common in patients with chronic kidney disease (CKD)[1] and have been implicated as a novel risk factor in the high mortality seen in this patient population.[2,3] These encompass not only conditions related to the traditionally defined renal osteodystrophy, including secondary hyperparathyroidism (SHPT), disorders of vitamin D metabolism, hyperphosphatemia, and hypo- and hypercalcemia, but also more recently defined disease states related to vascular calcification. Due to this wide range of complications, the more inclusive term CKD mineral and bone disorder (CKD-MBD) is currently favored.[4] Several of the abnormalities characterizing CKD-MBD have been amenable to therapeutic interventions, and have hence become a cornerstone of our day-to-day management of patients with CKD. One of these is SHPT, which is due in part to the progressive decline in activated vitamin D levels with advancing stages of CKD.[1,5] Replacement of activated vitamin D has thus become the main strategy in the treatment of SHPT. The introduction of a number of analogs of the activated vitamin D molecule, together known as vitamin D receptor activators (VDRA), has broadened our therapeutic armamentarium,[6,7] but has also made decisions about which drug to use more complicated. We examine the rationale for the therapeutic use of activated vitamin D, provide an overview of the effects of various available analogs of activated vitamin D, and summarize the available scientific evidence supporting the use of them, alone or in combination with other therapeutic agents such as calcium-sensing receptor (CSR) agonists or 25(OH) vitamin D. In particular, we review the recent observational data on the association of VDRA and survival in CKD and expand our discussion on interpretation of such associative data in the setting of clinical practice and current and anticipated treatment guidelines.

SHPT AND VITAMIN D METABOLISM

SHPT develops early in the course of CKD as a result of a combination of the following events: deficiency of 1,25-dihydroxycholecalciferol (activated vitamin D),[1,5] decreased expression of the vitamin D receptor[8] and the CSR,[9] hyperphosphatemia,[10] hypocalcemia,[11] and PTH resistance.[12]

More recently, fibroblast growth factor 23 has emerged as a new regulator that plays an important role in CKD-MBD.[13] Fibroblast growth factor 23, like PTH, has phosphaturic properties, but, unlike PTH, it inhibits 1-α-hydroxylation and hence leads to lower levels of activated vitamin D and further stimulation of PTH production.[13] Additionally, fibroblast growth factor 23 may have a direct stimulatory effect on the parathyroid glands, hence further contributing to SHPT.[14] As kidney function declines in patients with CKD, their PTH levels become increasingly higher, mirrored by a progressive decline in activated vitamin D levels.[1] It is unclear to what extent these different pathophysiological mechanisms (intrinsic loss of enzymatic activity vs. suppression by fibroblast growth factor 23) contribute to the lower 1-α-hydroxylase activity, but the net effect is a progressive decline in activated vitamin D levels with advancing stages of CKD.[1] Administration of synthetic activated vitamin D to replace physiological levels of this hormone thus appears to be a plausible strategy to treat SHPT. The application of activated vitamin D in physiological doses often fails to correct SHPT, in part due to decreased expression of the vitamin D receptor in the parathyroid gland.[8] This can be overcome by the administration of higher doses of activated $(1,25(OH)_2)$ vitamin D, but such pharmacological doses are more likely to induce side effects. Most relevant of these undesirable side effects are hypercalcemia and hyperphosphatemia,[15] which have themselves been associated with higher mortality in patients on dialysis.[2,3] To circumvent such side effects, new agents have been developed that showed a more selective effect toward suppressing PTH production, with a lesser effect on intestinal and bone absorption of calcium and phosphorus.[16,17] These novel analogs of activated vitamin D (paricalcitol and doxercalciferol in the United States and alpha-calcidol and maxacalcitol outside the United States) appeared to have less effects on the vitamin D receptors in the gastrointestinal tract and bone, thus mitigating calcium and phosphorus absorption and allowing a wider therapeutic margin. Nevertheless, the concept of VDRA selectivity and its utility in clinical practice has been a matter of ongoing debate.[18]

THE CASE FOR VDRA: BENEFITS BEYOND LOWERING OF PTH?

While the only current indication for the use of activated vitamin D and its analogs in patients with CKD is the treatment of SHPT, the impact of lowering PTH levels may extend beyond the skeletal system and includes potential cardiovascular and metabolic benefits.[2,3,19] This has prompted a number of large observational studies examining outcomes associated with the use of activated vitamin D therapy in patients on maintenance dialysis,[3,20–24] and in patients with CKD not yet on dialysis[25] (Table 1). These studies incorporated data from a very large number of patients and consistently showed that patients treated with any kind of VDRA experienced significantly lower all-cause and cardiovascular mortality rates compared with patients not receiving any treatment.

The most obvious explanation for the observed benefits could be the effects induced by the lowering of PTH level (Figure 1). Elevated PTH has been shown to induce a number of cardiovascular (myocardial fibrosis, left-ventricular hypertrophy, decreased myocardial contractility, increased vascular, and valvular calcification, decreased vasodilatation),[26,27] metabolic (decreased insulin sensitivity and disorders of lipid metabolism),[28–30] hematological (bone marrow fibrosis and decreased erythropoiesis),[31,32] and immunological[33] abnormalities. Treatment of SHPT could thus improve or reverse a number of these abnormalities, potentially translating into a better survival.

On the other hand, the broad benefits observed in the studies shown in Table 1 suggest that the impact of VDRA reaches beyond lowering of PTH levels. Subgroup analyses in these studies indicated that virtually all patients benefited

Table 1 | Observational studies examining outcomes associated with treatment of activated vitamin D compared with no treatment in patients with CKD

Study	Number of patients	Examined treatment	Results	Comments
Shoji *et al.*[22]	242	Oral alpha calcidol vs no treatment	Lower cardiovascular mortality with alpha calcidol treatment	Prevalent HD patients from Japan; all cause mortality similar in the two groups
Teng *et al.*[23]	51 037	Any VDRA vs no treatment	20% lower all-cause mortality in the vitamin D group	Prevalent HD patients from a single for-profit dialysis chain; benefit present in 48 of 49 examined subgroups
Melamed *et al.*[21]	1007	Calcitriol vs no treatment	Lower all-cause mortality associated with calcitriol use	Incident HD and PD patients from CHOICE study
Kalantar-Zadeh *et al.*[3] and Lee *et al.*[20]	58 058	Paricalcitol vs no treatment	Lower all-cause mortality associated with paricalcitol use in time-dependent models	Prevalent HD patients from a single for-profit dialysis chain. Benefit present in all examined subgroups
Tentori *et al.*[24]	7731	Any VDRA vs no treatment	Lower all-cause mortality with activated vitamin D	Prevalent HD patients from a single non-profit dialysis chain
Kovesdy *et al.*[25]	520	Calcitriol vs no treatment	Lower all-cause mortality with calcitriol	CKD stage 2–5, not yet on dialysis. Also showed trend toward lower ESRD incidence with calcitriol

CKD, chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis; VDRA, vitamin D receptor activator.

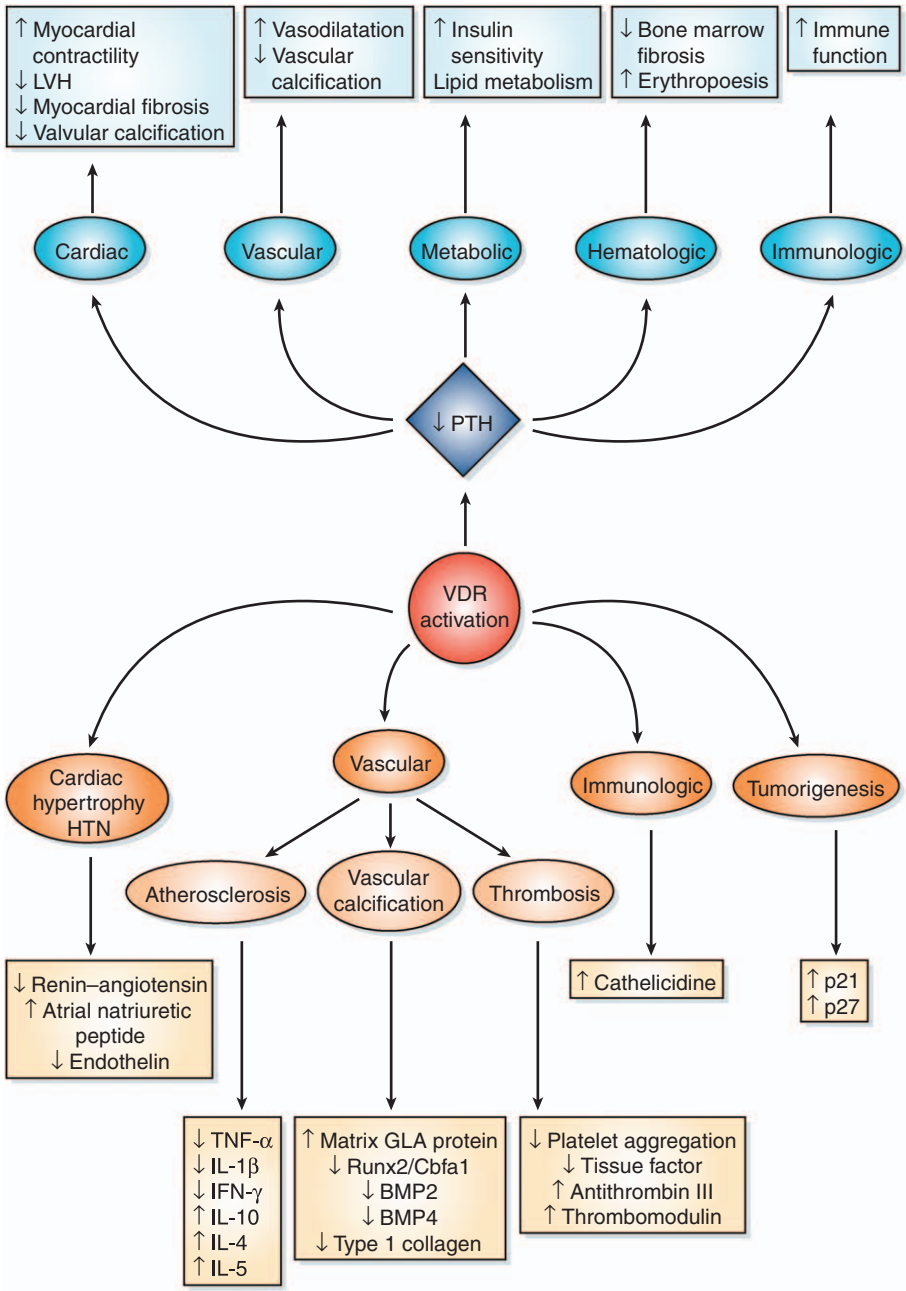

Figure 1 | Putative mechanisms of action responsible for the lower mortality associated with vitamin D receptor activation.

from activated vitamin D therapy, including patients with lower PTH or higher calcium or phosphorus levels.[20,23] Furthermore, vitamin D deficiency was associated with higher all-cause and cardiovascular mortality in a large cohort of hemodialysis patients,[34] and lower $1,25(OH)_2$ vitamin D levels have been associated with worsened coronary calcification,[35] also suggesting a PTH-independent link between vitamin D and survival.

The vitamin D receptor is ubiquitous, and its stimulation has been shown to have wide-ranging effects.[6] Some of the many physiological effects of vitamin D receptor activation could explain how the administration of activated vitamin D could directly impact on the cardiovascular system: by regressing cardiac hypertrophy,[36] by decreasing the activation of the renin–angiotensin system,[37] by inhibiting the production of proteins implicated in arterial calcification,[38–40] by stimulating the production of proteins that are inhibitors of arterial calcification,[38,41] by inhibiting the production of cytokines that are involved in calcification and atheroma formation[42,43] and stimulating the production of cytokines that are inhibiting it,[44,45] and by preventing thrombosis[46] (Figure 1). Non-cardiovascular effects related to stimulation of vitamin D receptor include increased production of cathelicidine[47] (suggesting anti-tuberculosis properties) and

anticancer effects.[48] Such effects could explain the broad benefit seen with activated vitamin D therapy in observational studies, independent of the abnormalities of CKD-MBD.

All the above putative mechanisms of action form a plausible explanation for why the administration of VDRA was associated with lower mortality in observational studies. Since the vast majority of the studies elucidating the mechanism of action of VDR activation come from non-human experimental studies, their extrapolation to clinical practice will have to wait for proof by randomized controlled trials (RCTs).

VDRA AND SURVIVAL IN CKD: ASSOCIATION OR CAUSALITY?

Examining therapeutic interventions in observational studies is always subject to confounding bias, no matter how rigorous the statistical adjustments are. Recent examples where the results of observational studies were refuted by RCTs[49–51] serve as a cautionary tale against using observational data as final proof of a beneficial effect. A set of criteria for making the leap from association to causation was systematically presented in the 1965 article of Sir Austin Bradford Hill, 'The Environment and Disease: Association or Causation'.[52] As shown in Table 2, applying Hill's criteria to the available evidence on activated vitamin D therapy shows that six of the nine criteria appear to be satisfied. One (dose response) is not (although the reason for this could be confounding by the higher PTH levels seen in those receiving higher doses of activated vitamin D[3]), one needs more research (specificity), and one (experimentation) requires controlled trials. There also are novel epidemiological techniques such as structural nested modeling, marginal structural modeling, propensity-based matching, or instrumental variable analysis that can better account for time-varying confounders and that are sometimes called 'causal models'.[53–56] Such methodology was applied in the study by Teng *et al.*,[23] the results of which were concordant with the studies' that applied more conventional methodologies. Nevertheless, a conclusive answer could only be provided by an RCT.

WHICH VITAMIN D ANALOG IS THE BEST?

Disorders of CKD-MBD are complex and incorporate conditions such as hyperphosphatemia and disorders in calcium metabolism beside SHPT. Higher phosphorus and calcium levels have been associated with increased mortality in patients on dialysis;[2,3] hyperphosphatemia has also been associated with higher mortality[57,58] and more progression of kidney disease[58–60] in patients with earlier stages of CKD. Treatment with the native VDRA calcitriol effectively suppresses SHPT, but can have less salutary effects by inducing hyperphosphatemia and hypercalcemia. This has prompted the development of several activated vitamin D analogs that can suppress PTH production, with a lesser concomitant hypercalcemic and hyperphosphatemic effect.[7,61–63]

One question that arises is whether the salutary side effect profile of these activated vitamin D analogs translates into superior outcomes compared to patients receiving calcitriol? If the benefit of activated vitamin D therapy is indeed broad ranging and extends to patient groups with hyperphosphatemia and hypercalcemia,[3,23] the favorable side effect

Table 2 | Hill's criteria for causal inference in epidemiological studies. The causality criteria are examined for treatment with activated vitamin D

Criterion	Definition/comments	Applied to vitamin D treatment in CKD
1. Temporal relationship	Exposure always precedes the outcome	Treatment with activated vitamin D is followed by improved survival
2. Strength of association	The stronger the association, the more likely it is that the relation is causal	Most studies indicate a strong association with better survival
3. Dose response	Increasing amount of exposure increases the risk proportionally	Higher doses of paricalcitol and calcitriol not associated with better survival compared with lower doses
4. Consistency of results	The association is consistent when results are replicated in studies in different settings using different methods	Consistent results in incident and prevalent patients, in for-profit and not-for-profit dialysis chains, and in patients from different countries
5. Biological plausibility	The association agrees with currently accepted understanding of pathological processes. However, studies that disagree with established understanding of biological processes may force a re-evaluation of accepted beliefs	The effects of vitamin D receptor activation on lowering PTH and on various cardiovascular and metabolic processes provide a plausible explanation for the beneficial effect of activated vitamin D therapy
6. Experimentation	The condition can be altered (prevented or ameliorated) by an appropriate experimental regimen	Randomized controlled trials examining the benefit of activated vitamin D therapy are missing
7. Specificity	If possible, a single putative cause produces a specific effect	It is currently unclear which one of the potential effects of activated vitamin D is responsible for the observed benefits
8. Biological coherence	The association is consistent with the natural history of the disease	An improved cardiovascular risk profile (such as seen with activation of the vitamin D receptor) should result in lower mortality
9. Analogy	There are similar associations in other populations or under different settings	Treatment with 25(OH) vitamin D of patients with normal kidney function is beneficial. Activated vitamin D is only used therapeutically in patients with CKD

CKD, chronic kidney disease; PTH, parathyroid hormone.

Table 3 | Observational studies comparing outcomes associated with the use of various activated vitamin D products in patients on dialysis

Study	Number of patients	Examined treatment	Results	Comments
Teng *et al.*[70]	67 399	Paricalcitol vs calcitriol	16% lower all-cause mortality with paricalcitol	Prevalent HD patients from a single for-profit dialysis chain, benefit also present in patients who switched treatments
Tentori *et al.*[24]	7731	Calcitriol vs paricalcitol vs doxercalciferol	No difference in all-cause mortality between the three groups after multivariable adjustment	Prevalent HD patients from a single non-profit dialysis chain

HD, hemodialysis.

profile of the more selective drugs may not be that important. On the other hand, the activated vitamin D analogs may be different from calcitriol in ways other than their lesser intestinal effects.[64–66] The activation of the VDR is a complex process that involves recruitment of a multitude of coactivators and corepressors.[67] Differential recruitment of such elements distinguishes the gene activation profile seen with VDR stimulation from paricalcitol and calcitriol,[65] which could translate into significant differences in their clinical effects. Supporting an advantage from activated vitamin D analogs are animal models showing that paricalcitol induced significantly less vascular calcification compared to calcitriol.[68,69]

A more complicated picture is suggested by another experimental model of 5/6 nephrectomized rats, showing that animals treated with paricalcitol displayed significant reductions in endogenously produced activated vitamin D (calcitriol) levels and showed increased perivascular fibrosis, but also a higher density of intramyocardial capillaries.[66] These results suggest that calcitriol and activated vitamin D analogs may differ significantly in their ancillary effects. While some of these ancillary effects (such as the effect on calcium, phosphorus, vascular calcification and capillary density) seem to favor the analogs (or rather specifically paricalcitol), others may be beneficial to calcitriol (such as the more severe perivascular fibrosis seen with paricalcitol treatment). What is unclear from these pre-clinical results is the effect of the various activated vitamin D molecules on clinical outcomes in patients with CKD. Teng *et al.*[70] examined such outcomes in a historical cohort of 67 399 patients on maintenance hemodialysis, and found that treatment with paricalcitol was associated with a 16% lower all-cause mortality compared to treatment with calcitriol (Table 3).

Contrasting the foregoing findings, Tentori *et al.*[24] compared outcomes in patients receiving paricalcitol, doxercalciferol, and calcitriol in 7731 maintenance hemodialysis patients, and found no differences between the three groups after adjustment for potential confounders. The reason for the discrepant findings of these observational studies is unclear; RCT are needed to settle this issue. Other benefits of activated vitamin D analogs were suggested by studies showing lower hospitalization rates in patients treated with paricalcitol vs calcitriol.[71] This may be one of the reasons why a cost analysis suggested that the use of paricalcitol provided cost-savings compared with calcitriol, in spite of its higher price.[72,73] Limitations inherent of observational data apply to these studies as well, and short of an RCT their results can also be only viewed as hypothesis-generating.

A different concern arises in patients with CKD who are not yet on dialysis, where progressive loss of kidney function represents an important outcome. Pharmacological doses of calcitriol may hasten loss of kidney function through induction of hypercalciuria or hyperphosphatemia;[60,74] this effect is not seen with lower doses of calcitriol,[25,75,76] which also have been associated with a trend toward slower progression of kidney disease in patients with CKD stages 3 and 4.[25,76] Hypercalciuria is also a lesser concern with activated vitamin D analogs,[77,78] of which paricalcitol has also been shown to reduce proteinuria in patients with CKD stages 3 and 4,[79] and to attenuate renal interstitial fibrosis in experimental obstructive nephropathy.[80]

For the time being, our clinical practice will have to be directed by what the approved indications of these medications are (treatment of SHPT), and hence the choice of agent (calcitriol vs analog VDRA) will continue to be driven by patient tolerance, individual side effect profiles, and cost considerations. In patients with CKD who are not yet on dialysis, physiological doses of calcitriol may be able to adequately control the less severe SHPT, without deleterious side effects and with a potentially renoprotective effect;[25,76] if higher doses are necessary, activated vitamin D analogs (especially paricalcitol) may be safer.

The second practical question pertains to the choice of particular activated vitamin D analog. The two agents available in the United States (paricalcitol and doxercalciferol) were approved on the basis of their ability to lower PTH with a more favorable side effect profile compared with that of calcitriol,[77,78,81–86] but they have different pharmacological characteristics. There are currently very few head-to-head comparison studies between these two agents. Paricalcitol may have a more favorable side effect profile in experimental animals, with lower calcium and phosphorus absorption,[61] and lower vascular calcification.[69,87] Doxercalciferol may hold an advantage due to its longer half-life, leading to more consistent bioavailability.[7] The available clinical studies comparing paricalcitol and doxercalciferol were underpowered and have suboptimal study designs. One study found

similar serum calcium and phosphorus levels with equivalent doses of the two agents in a before–after design of 27 dialysis patients.[88] A second study, a 36-h crossover study in 13 dialysis patients, showed comparable PTH suppression with high doses of these two agents, but significantly higher serum phosphorus levels and calcium × phosphorus products in those receiving doxercalciferol.[89]

Regarding survival benefits, the only study comparing the two agents was observational and found no difference in outcomes between patients on maintenance hemodialysis treated with the two drugs.[24] Thus, there is currently insufficient evidence to clearly distinguish one activated vitamin D analog from the other in clinical practice, and decisions about which one to use will be based most likely on individual patient characteristics or practitioner preference. Due to the complexity of VDR activation, it is possible that differences between the various activated vitamin D analogs are substantial and go beyond their immediately obvious effects on serum PTH, calcium, and phosphorus. Better-designed and head-to-head conducted clinical comparisons are needed to determine which drug is superior in terms of clinical end points, especially survival.

UNANSWERED QUESTIONS

Should all patients receive treatment with activated vitamin D?

Observational studies are unanimous in their findings that patients receiving any kind of activated vitamin D have lower mortality compared with those who do not (Table 1).[3,20–25] This benefit may or may not be related to lowering of PTH, but because treatment of SHPT is the only approved indication for the different VDRA, it is unclear what an optimal regimen would be to maximize patient survival. On the basis of their PTH levels, a significant proportion of patients do not receive treatment with VDRA because of concerns related to over-suppression of PTH levels and adynamic bone disease.[90] Observational studies in patients receiving maintenance dialysis support the current PTH target levels recommended by the K-DOQI guidelines,[91] in that PTH levels below the recommended 150–300 pg ml^{-1} seem to be associated with poorer survival.[3] Complementing these findings, however, patients with low PTH levels who were treated with VDRA in the same study had lower mortality compared with those who did not.[3] It is possible that the higher mortality that is in general associated with states of lower PTH level (and adynamic bone disease) is the result of confounding by a state of malnutrition and inflammation,[92–94] in which case treatment with VDRA would not necessarily lead to worsened outcomes, in spite of further lowering of their PTH levels. This question could only be answered satisfactorily by a clinical trial; short of such a trial, the current practice of only administering VDRA therapy for treatment of SHPT has to be favored.

What is the role of 25(OH) vitamin D replacement?

The natural precursor of activated vitamin D (that is, 1,25$(OH)_2$) is 25(OH) vitamin D, and hence a deficiency of the latter can play a role in the low activated vitamin D levels seen in patients with CKD.[95] Low 25(OH) vitamin D levels are very common in patients with CKD,[96] but while activated vitamin D levels appear to decline progressively with worsening kidney function, 25(OH) vitamin D levels do not.[1] This suggests that 1-α-hydroxylation in the kidneys may be a more important determinant of activated vitamin D levels rather than the availability of its precursor. 25(OH) Vitamin D is able to suppress PTH production *in vitro* by virtue of direct stimulation of the VDR and a slow tissue-level 1-α-hydroxylation;[97] the low affinity of 25(OH) vitamin D to the VDR is presumably counterbalanced by its higher plasma concentration. Indeed, a small observational study examined the effect of 25(OH) vitamin D (ergocalciferol) replacement on PTH levels in patients with stage 3 and 4 CKD and found this strategy to be somewhat successful only in the subgroup with stage 3 CKD.[98] Similar studies in patients on dialysis have also questioned the effectiveness of 25(OH) vitamin D therapy in achieving suppression of SHPT and resolution of bone histological changes.[99]

It is yet unclear what the longer-term outcomes of 25(OH) vitamin D replacement might be. Lower 25(OH) vitamin D levels were associated with significantly higher mortality in an observational study of incident hemodialysis patients, but subsequent treatment with activated vitamin D nullified this association; replacement of 25(OH) vitamin D was not performed and thus its effect could not be analyzed.[34] Studies examining replacement of 25(OH) vitamin D in patients with no kidney disease support a beneficial effect on survival,[100] but the results of these studies cannot be extrapolated to patients with CKD, due to the differences in activated vitamin D levels between these two populations. It is possible that the benefits of 25(OH) vitamin D replacement are partially independent of activated vitamin D, if 25(OH) vitamin D indeed has roles other then being a mere precursor to activated vitamin D.[101–105] In this case, replacement of both components could be beneficial, but this idea needs to undergo formal testing. Such a combined application may especially be beneficial in patients treated with activated vitamin D analogs, the selectivity of which may prevent them from compensating for abnormalities brought about by 25(OH) vitamin D (and consequently, calcitriol) deficiency.[106]

Can CSR agonists circumvent the need for VDRA in CKD?

The advent of CSR agonists has not only added another weapon to our armamentarium against SHPT, but also has made therapeutic decisions more complicated. The only CSR agonist currently available for clinical use is cinacalcet; this agent has been shown to effectively lower PTH levels and to lower the risk of parathyroidectomy, fracture, and cardiovascular hospitalization, along with improvements in self-reported physical function and diminished pain.[107,108] Patients treated with cinacalcet may develop hypocalcemia, which has been severe in about 5% of dialysis patients enrolled in a clinical trial examining the efficacy and safety of this drug.[108] Although the majority of the hypocalcemic

episodes seen with cinacalcet therapy are asymptomatic,[108] it is unclear what its long-term consequences are.

While cinacalcet was only approved in the United States for SHPT treatment in patients on dialysis, its use in patients with CKD not yet on dialysis has also been examined. Findings from a clinical trial in this population indicated that patients treated with cinacalcet developed not only hypocalcemia but also significant hyperphosphatemia (possibly related to the diminished phosphaturic effect of the lower PTH levels).[109] Additional concern in patients with earlier stages of CKD is the impact on kidney function of the hypercalciuria that can be expected from an agonist of CSR, this receptor being expressed in the thick ascending limb of the loop of Henle and the distal nephron.[110] These concerns have prompted the recent cessation of the manufacturer's efforts to pursue an indication to treat SHPT with cinacalcet in patients with CKD who are not yet on dialysis in the United States, and to withdraw this indication in Canada.

Finally, still little is known about the impact of cinacalcet on outcomes requiring longer follow-up, such as mortality. A recently initiated clinical trial will be examining this question in hemodialysis patients with SHPT, but its results are probably a few years away.[111] Given all these uncertainties, we believe it is premature to think that CSR agonists can take over the role of VDRAs in the treatment of SHPT. Cinacalcet could be a valuable addition in patients who are not responding adequately to or who are intolerant of higher doses of VDRA.

SUMMARY

Pharmacological administration of activated vitamin D has become the main strategy in the treatment of SHPT. There is a large volume of observational evidence suggesting a broader beneficial effect of such treatments, which could be the result of multiple non-skeletal functions modulated by the vitamin D receptor. The lack of RCTs means that a broadening of the indication of use for activated vitamin D is not yet possible. Due to insufficient clinical data, no single activated vitamin D product can claim to be uniformly superior to the others, although a wider therapeutic window often prompts the use of activated vitamin D analogs in patients requiring higher doses of these medications. Currently available evidence favors individualized treatment decisions when choosing a particular type of activated vitamin D, where detailed knowledge of each of the available agents allows the tailoring of the therapeutic regimen to the individual patients' needs.

DISCLOSURE

Dr Kovesdy has received honoraria from Genzyme Inc. and from Amgen Inc., and has received grant support from Abbott Laboratories. Dr Kalantar-Zadeh has received honoraria and grants from Genzyme Inc. and has received honoraria and grants from Abbott Laboratories.

REFERENCES

1. Levin A, Bakris GL, Molitch M *et al.* Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007; **71**: 31–38.
2. Block GA, Klassen PS, Lazarus JM *et al.* Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; **15**: 2208–2218.
3. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; **70**: 771–780.
4. Moe S, Drueke T, Cunningham J *et al.* Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). *Kidney Int* 2006; **69**: 1945–1953.
5. Portale AA, Booth BE, Tsai HC *et al.* Reduced plasma concentration of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. *Kidney Int* 1982; **21**: 627–632.
6. Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int* 2006; **69**: 33–43.
7. Brown AJ, Slatopolsky E. Drug insight: vitamin D analogs in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 134–144.
8. Korkor AB. Reduced binding of [3H]1,25-dihydroxyvitamin D3 in the parathyroid glands of patients with renal failure. *N Engl J Med* 1987; **316**: 1573–1577.
9. 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.
10. Kates DM, Sherrard DJ, Andress DL. Evidence that serum phosphate is independently associated with serum PTH in patients with chronic renal failure. *Am J Kidney Dis* 1997; **30**: 809–813.
11. Yamamoto M, Igarashi T, Muramatsu M *et al.* Hypocalcemia increases and hypercalcemia decreases the steady-state level of parathyroid hormone messenger RNA in the rat. *J Clin Invest* 1989; **83**: 1053–1056.
12. Llach F, Massry SG, Singer FR *et al.* Skeletal resistance to endogenous parathyroid hormone in patients with early renal failure. A possible cause for secondary hyperparathyroidism. *J Clin Endocrinol Metab* 1975; **41**: 339–345.
13. Fukagawa M, Kazama JJ. FGF23: its role in renal bone disease. *Pediatr Nephrol* 2006; **21**: 1802–1806.
14. Kazama JJ, Gejyo F, Shigematsu T *et al.* Role of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism. *Ther Apher Dial* 2005; **9**: 328–330.
15. Sprague SM, Lerma E, McCormmick D *et al.* Suppression of parathyroid hormone secretion in hemodialysis patients: comparison of paricalcitol with calcitriol. *Am J Kidney Dis* 2001; **38**: S51–S56.
16. Chertow GM, Burke SK, Lazarus JM *et al.* Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 1997; **29**: 66–71.
17. Martin KJ, Gonzalez EA, Gellens M *et al.* 19-Nor-1-alpha-25-dihydroxyvitamin D2 (paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 1998; **9**: 1427–1432.
18. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. *Kidney Int* 2007; doi:10.1038/sj.ki.5002287.
19. Ganesh SK, Stack AG, Levin NW *et al.* Association of elevated serum PO(4), CaxPO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; **12**: 2131–2138.
20. Lee GH, Benner D, Regidor DL *et al.* Impact of kidney bone disease and its management on survival of patients on dialysis. *J Ren Nutr* 2007; **17**: 38–44.
21. Melamed ML, Eustace JA, Plantinga L *et al.* Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006; **70**: 351–357.
22. Shoji T, Shinohara K, Kimoto E *et al.* Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant* 2004; **19**: 179–184.
23. 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.
24. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; **70**: 1858–1865.
25. Kovesdy CP, Ahmadzadeh S, Anderson JE *et al.* Association of treatment with activated vitamin D and mortality in chronic kidney disease. *Arch Intern Med* 2008 (in press).

26. Massry SG, Smogorzewski M. Mechanisms through which parathyroid hormone mediates its deleterious effects on organ function in uremia. *Semin Nephrol* 1994; **14**: 219–231.
27. Mazzaferro S, Coen G, Bandini S *et al.* Role of ageing, chronic renal failure and dialysis in the calcification of mitral annulus. *Nephrol Dial Transplant* 1993; **8**: 335–340.
28. Chiu KC, Chuang LM, Lee NP *et al.* Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. *Metabolism* 2000; **49**: 1501–1505.
29. Gadallah MF, el-Shahawy M, Andrews G *et al.* Factors modulating cytosolic calcium. Role in lipid metabolism and cardiovascular morbidity and mortality in peritoneal dialysis patients. *Adv Perit Dial* 2001; **17**: 29–36.
30. Wareham NJ, Byrne CD, Carr C *et al.* Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. *Metabolism* 1997; **46**: 1171–1177.
31. Meytes D, Bogin E, Ma A *et al.* Effect of parathyroid hormone on erythropoiesis. *J Clin Invest* 1981; **67**: 1263–1269.
32. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N Engl J Med* 1993; **328**: 171–175.
33. Massry SG, Alexiewicz JM, Gaciong Z *et al.* Secondary hyperparathyroidism and the immune system in chronic renal failure. *Semin Nephrol* 1991; **11**: 186–201.
34. Wolf M, Shah A, Gutierrez O *et al.* Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007; **72**: 1004–1013.
35. Watson KE, Abrolat ML, Malone LL *et al.* Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 1997; **96**: 1755–1760.
36. Kim HW, Park CW, Shin YS *et al.* Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. *Nephron Clin Pract* 2006; **102**: c21–c29.
37. Li YC, Kong J, Wei M *et al.* 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 2002; **110**: 229–238.
38. Bellows CG, Reimers SM, Heersche JN. Expression of mRNAs for type-I collagen, bone sialoprotein, osteocalcin, and osteopontin at different stages of osteoblastic differentiation and their regulation by 1,25 dihydroxyvitamin D3. *Cell Tissue Res* 1999; **297**: 249–259.
39. Drissi H, Pouliot A, Koolloos C *et al.* 1,25-(OH)2-vitamin D3 suppresses the bone-related Runx2/Cbfa1 gene promoter. *Exp Cell Res* 2002; **274**: 323–333.
40. Virdi AS, Cook LJ, Oreffo RO *et al.* Modulation of bone morphogenetic protein-2 and bone morphogenetic protein-4 gene expression in osteoblastic cell lines. *Cell Mol Biol (Noisy-le-Grand)* 1998; **44**: 1237–1246.
41. Fraser JD, Otawara Y, Price PA. 1,25-Dihydroxyvitamin D3 stimulates the synthesis of matrix gamma-carboxyglutamic acid protein by osteosarcoma cells. Mutually exclusive expression of vitamin K-dependent bone proteins by clonal osteoblastic cell lines. *J Biol Chem* 1988; **263**: 911–916.
42. Panichi V, De PS, Andreini B *et al.* Calcitriol modulates *in vivo* and *in vitro* cytokine production: a role for intracellular calcium. *Kidney Int* 1998; **54**: 1463–1469.
43. Staeva-Vieira TP, Freedman LP. 1,25-dihydroxyvitamin D3 inhibits IFN-gamma and IL-4 levels during *in vitro* polarization of primary murine CD4+ T cells. *J Immunol* 2002; **168**: 1181–1189.
44. Barrat FJ, Cua DJ, Boonstra A *et al. In vitro* generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *J Exp Med* 2002; **195**: 603–616.
45. Boonstra A, Barrat FJ, Crain C *et al.* 1Alpha,25-dihydroxyvitamin D3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol* 2001; **167**: 4974–4980.
46. Aihara K, Azuma H, Akaike M *et al.* Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. *J Biol Chem* 2004; **279**: 35798–35802.
47. Liu PT, Stenger S, Li H *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; **311**: 1770–1773.
48. Hansen CM, Binderup L, Hamberg KJ *et al.* Vitamin D and cancer: effects of 1,25(OH)2D3 and its analogs on growth control and tumorigenesis. *Front Biosci* 2001; **6**: D820–D848.
49. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
50. Singh AK, Szczech L, Tang KL *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–2098.
51. Jamison RL, Hartigan P, Kaufman JS *et al.* Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *JAMA* 2007; **298**: 1163–1170.
52. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58**: 295–300.
53. Greenland S, Brumback B. An overview of relations among causal modelling methods. *Int J Epidemiol* 2002; **31**: 1030–1037.
54. Maldonado G, Greenland S. Estimating causal effects. *Int J Epidemiol* 2002; **31**: 422–429.
55. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11**: 550–560.
56. Stukel TA, Fisher ES, Wennberg DE *et al.* Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; **297**: 278–285.
57. Kestenbaum B, Sampson JN, Rudser KD *et al.* Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 520–528.
58. Voormolen N, Noordzij M, Grootendorst DC *et al.* High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant* 2007; **22**: 2909–2916.
59. Norris KC, Greene T, Kopple J *et al.* Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. *J Am Soc Nephrol* 2006; **17**: 2928–2936.
60. Schwarz S, Trivedi BK, Kalantar-Zadeh K *et al.* Association of disorders in mineral metabolism with progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2006; **1**: 825–831.
61. Slatopolsky E, Cozzolino M, Finch JL. Differential effects of 19-nor-1,25-(OH)(2)D(2) and 1alpha-hydroxyvitamin D(2) on calcium and phosphorus in normal and uremic rats. *Kidney Int* 2002; **62**: 1277–1284.
62. Finch JL, Brown AJ, Slatopolsky E. Differential effects of 1,25-dihydroxy-vitamin D3 and 19-nor-1,25-dihydroxy-vitamin D2 on calcium and phosphorus resorption in bone. *J Am Soc Nephrol* 1999; **10**: 980–985.
63. Coyne DW, Grieff M, Ahya SN *et al.* Differential effects of acute administration of 19-Nor-1,25-dihydroxy-vitamin D2 and 1,25-dihydroxy-vitamin D3 on serum calcium and phosphorus in hemodialysis patients. *Am J Kidney Dis* 2002; **40**: 1283–1288.
64. Issa LL, Leong GM, Sutherland RL *et al.* Vitamin D analogue-specific recruitment of vitamin D receptor coactivators. *J Bone Miner Res* 2002; **17**: 879–890.
65. Wu-Wong JR, Nakane M, Ma J *et al.* Effects of vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. *Atherosclerosis* 2006; **186**: 20–28.
66. Repo JM, Rantala IS, Honkanen TT *et al.* Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol. *Kidney Int* 2007; **72**: 977–984.
67. Slatopolsky E, Finch J, Brown A. New vitamin D analogs. *Kidney Int* 2003; **63**: S83–S87.
68. Cardus A, Panizo S, Parisi E *et al.* Differential effects of vitamin D analogs on vascular calcification. *J Bone Miner Res* 2007; **22**: 860–866.
69. Mizobuchi M, Finch JL, Martin DR *et al.* Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. *Kidney Int* 2007; **72**: 709–715.
70. 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.
71. Dobrez DG, Mathes A, Amdahl M *et al.* Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings. *Nephrol Dial Transplant* 2004; **19**: 1174–1181.
72. Gal-Moscovici A, Sprague SM. Comparative cost-benefit analyses of paricalcitol and calcitriol in stage 4 chronic kidney disease from the perspective of a health plan. *Clin Drug Investig* 2007; **27**: 105–113.
73. Rosery H, Bergemann R, Marx SE *et al.* Health-economic comparison of paricalcitol, calcitriol and alfacalcidol for the treatment of secondary hyperparathyroidism during haemodialysis. *Clin Drug Investig* 2006; **26**: 629–638.
74. Goodman WG, Coburn JW. The use of 1,25-dihydroxyvitamin D3 in early renal failure. *Annu Rev Med* 1992; **43**: 227–237.
75. Bertoli M, Luisetto G, Ruffatti A *et al.* Renal function during calcitriol therapy in chronic renal failure. *Clin Nephrol* 1990; **33**: 98–102.

76. Coen G, Mazzaferro S, Manni M *et al.* No acceleration and possibly slower progression of renal failure during calcitriol treatment in predialysis chronic renal failure. *Nephrol Dial Transplant* 1994; **9**: 1520.
77. Coburn JW, Maung HM, Elangovan L *et al.* Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004; **43**: 877–890.
78. Coyne D, Acharya M, Qiu P *et al.* Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. *Am J Kidney Dis* 2006; **47**: 263–276.
79. Agarwal R, Acharya M, Tian J *et al.* Antiproteinuric effect of oral paricalcitol in chronic kidney disease. *Kidney Int* 2005; **68**: 2823–2828.
80. Tan X, Li Y, Liu Y. Paricalcitol attenuates renal interstitial fibrosis in obstructive nephropathy. *J Am Soc Nephrol* 2006; **17**: 3382–3393.
81. Maung HM, Elangovan L, Frazao JM *et al.* Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hydroxyvitamin D(2)) in dialysis patients with secondary hyperparathyroidism: a sequential comparison. *Am J Kidney Dis* 2001; **37**: 532–543.
82. Tan Jr AU, Levine BS, Mazess RB *et al.* Effective suppression of parathyroid hormone by 1 alpha-hydroxy-vitamin D2 in hemodialysis patients with moderate to severe secondary hyperparathyroidism. *Kidney Int* 1997; **51**: 317–323.
83. Frazao JM, Elangovan L, Maung HM *et al.* Intermittent doxercalciferol (1alpha-hydroxyvitamin D(2)) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 2000; **36**: 550–561.
84. Martin KJ, Gonzalez EA, Gellens M *et al.* 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 1998; **9**: 1427–1432.
85. Lindberg J, Martin KJ, Gonzalez EA *et al.* A long-term, multicenter study of the efficacy and safety of paricalcitol in end-stage renal disease. *Clin Nephrol* 2001; **56**: 315–323.
86. Sprague SM, Llach F, Amdahl M *et al.* Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney Int* 2003; **63**: 1483–1490.
87. Wu-Wong JR, Noonan W, Ma J *et al.* Role of phosphorus and vitamin D analogs in the pathogenesis of vascular calcification. *J Pharmacol Exp Ther* 2006; **318**: 90–98.
88. Zisman AL, Ghantous W, Schinleber P *et al.* Inhibition of parathyroid hormone: a dose equivalency study of paricalcitol and doxercalciferol. *Am J Nephrol* 2005; **25**: 591–595.
89. Joist HE, Ahya SN, Giles K *et al.* Differential effects of very high doses of doxercalciferol and paricalcitol on serum phosphorus in hemodialysis patients. *Clin Nephrol* 2006; **65**: 335–341.
90. Malluche HH, Monier-Faugere MC. Risk of adynamic bone disease in dialyzed patients. *Kidney Int Suppl* 1992; **38**: S62–S67.
91. Eknoyan G, Levin A, Levin N. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42**: 1–201.
92. Carlstedt E, Ridefelt P, Lind L *et al.* Interleukin-6 induced suppression of bovine parathyroid hormone secretion. *Biosci Rep* 1999; **19**: 35–42.
93. Nielsen PK, Rasmussen AK, Butters R *et al.* Inhibition of PTH secretion by interleukin-1 beta in bovine parathyroid glands *in vitro* is associated with an upregulation of the calcium-sensing receptor mRNA. *Biochem Biophys Res Commun* 1997; **238**: 880–885.
94. Sanchez-Gonzalez MC, Lopez-Barea F, Bajo MA *et al.* Serum albumin levels, an additional factor implicated in hyperparathyroidism outcome in peritoneal dialysis: a prospective study with paired bone biopsies. *Adv Perit Dial* 2006; **22**: 198–202.
95. Pitts TO, Piraino BH, Mitro R *et al.* Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 1988; **67**: 876–881.
96. Saab G, Young DO, Gincherman Y *et al.* Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clin Pract* 2007; **105**: c132–c138.
97. Ritter CS, Armbrecht HJ, Slatopolsky E *et al.* 25-Hydroxyvitamin D(3) suppresses PTH synthesis and secretion by bovine parathyroid cells. *Kidney Int* 2006; **70**: 654–659.
98. Zisman AL, Hristova M, Ho LT *et al.* Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol* 2007; **27**: 36–43.
99. 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.
100. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; **167**: 1730–1737.
101. Borges AC, Feres T, Vianna LM *et al.* Recovery of impaired K+ channels in mesenteric arteries from spontaneously hypertensive rats by prolonged treatment with cholecalciferol. *Br J Pharmacol* 1999; **127**: 772–778.
102. Borges AC, Feres T, Vianna LM *et al.* Effect of cholecalciferol treatment on the relaxant responses of spontaneously hypertensive rat arteries to acetylcholine. *Hypertension* 1999; **34**: 897–901.
103. Wakasugi M, Noguchi T, Inoue M *et al.* Vitamin D3 stimulates the production of prostacyclin by vascular smooth muscle cells. *Prostaglandins* 1991; **42**: 127–136.
104. London GM, Guerin AP, Verbeke FH *et al.* Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. *J Am Soc Nephrol* 2007; **18**: 613–620.
105. Bordier P, Zingraff J, Gueris J *et al.* The effect of 1alpha(OH)D3 and 1alpha,25(OH)2D3 on the bone in patients with renal osteodystrophy. *Am J Med* 1978; **64**: 101–107.
106. Hernandez JD, Wesseling K, Boechat MI *et al.* Osteomalacia in a hemodialysis patient receiving an active vitamin D sterol. *Nat Clin Pract Nephrol* 2007; **3**: 227–232.
107. Cunningham J, Danese M, Olson K *et al.* Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism. *Kidney Int* 2005; **68**: 1793–1800.
108. 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.
109. Charytan C, Coburn JW, Chonchol M *et al.* Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. *Am J Kidney Dis* 2005; **46**: 58–67.
110. Ba J, Friedman PA. Calcium-sensing receptor regulation of renal mineral ion transport. *Cell Calcium* 2004; **35**: 229–237.
111. Chertow GM, Pupim LB, Block GA *et al.* Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. *Clin J Am Soc Nephrol* 2007; **2**: 898–905.